Economic landscapes of human tissues and cells for clinical application in the EU

Final Report

EAHC/2012/Health/19

Contract nº 20126301

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ABSTRACT

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Economic landscapes of human tissues and cells for clinical application in the EU

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Contract no. 20126301: EAHC/2012/Health/19

Time period

December 2013 – May 2015

Scope

The safe and sustainable supply of tissues and cells is an essential pillar in modern EU healthcare and a priority for national and EU-level health authorities alike. While tissues and cells are usually donated by citizens without any payment, they still require some further processing and handling before they can be applied as therapy. Many of these activities are undertaken by public actors, while others are undertaken by private actors. In both cases, costs are involved and different options exist to recover (part of) these costs.

Understanding the economic aspects of the tissues and cells sector can help Member States in taking, increasingly difficult, decisions on how to organize this essential service of public healthcare at best. This is in particular important as the tissues and cells sector is subject to continuous technological innovation and globalization, and as a consequence to changing economics and organisational setups.

The EU health contracting agency CHAFEA therefore called for a study aimed at producing an overview on EU wide economic landscapes of human tissues and cells for transplantation, covering three medical sectors:

- Replacement tissues: mainly bone, cornea, skin and cardiovascular tissues (RT)
- Hematopoietic progenitor cells from bone marrow, peripheral blood and cord blood (HPC)
- Gametes and tissues for assisted reproductive technology (ART).

The study maps the three domains across all EU-28 Member States by identifying key activities and costs, key players in public and private sectors, legislative and reimbursement schemes across Member States, and finally emerging technological trends and associated ethical, legal, and social issues.

Methodology and research design

The research involved extensive document-gathering and analysis via desk research (including literature study, secondary analysis of existing datasets and registries, online searches); fieldwork consisting of semi-structured interviews and conference attendance; a survey to National Competent Authorities for the Safety and Quality of Tissues and Cells (NCATC) in the EU-28 Member States and production of country factsheets; questionnaires to tissue establishments in cardiovascular, cornea and musculoskeletal (mostly bone) banking; and finally, a forecast to identify novel therapies in the tissue and cell sector and an outlook on emerging techno-legal issues in the EU context.

Research team and contract

This study was performed by a consortium of three main organizations: the Rathenau Instituut-Royal Netherlands Academy of Arts and Sciences (RI-KNAW, NL), the Foundation of European Tissue Banks (SEGB, DE), and the Dutch Foundation for Hemovigilance and Biovigilance (TRIP, NL). The study followed a call for tender No EAHC/2012/Health/19 concerning an 'EU-wide economic overview of the markets of tissues and cells for transplantation' launched by the Consumers, Health and Food Executive Agency (CHAFEA, formerly EAHC). The contract started in December 2013, and ended in May 2015.

EXECUTIVE SUMMARY

Economic landscapes of human tissues and cells for clinical application in the EU

1 Outline and aim of the study

1.1 The safe and sustainable supply of tissues and cells is an essential pillar in modern EU healthcare and a priority for national and EU-level health authorities alike. While tissues and cells are usually donated by citizens without any payment, they still require some further processing and handling before they can be applied as therapy. Many of these activities are undertaken by public actors, while others are undertaken by private actors. In both cases, costs are involved and different options exist to recover (part of) these costs.

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For each sector the study brings a field description, a view on organisational set-up, on economic aspects and a future perspective. The study also covers horizontal aspects relevant for each of these three medical sectors and a forward looking chapter covering impact of related sectors and general factors that will influence the future of the tissue and cell landscape.

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1.7 The content of this report represents the views of the authors and can in no way be taken to reflect the views of the European Commission and/or Chafea or any other body of the European Union, nor of the National Competent Authorities for Safety and Quality for Tissues and Cells (NCATC) who have contributed with their expertise.

2 Horizontal aspects: economics factors for all tissue sectors

2.1 The set-up of a tissue establishment requires equipment, know-how and appropriate facilities. These call for significant investment, in particular to build clean-rooms offering the environmental conditions to safely process tissues and cells, as required by EU-law. Building a high-grade clean-room (grade A in B) at least costs €250,000, and more regularly require amounts of over 1 million EUR.

2.2 The consequent operational costs of tissue establishments are defined along four major activities needed to transform a tissue from a donor into a therapy for a recipient:

1. Donor procurement: to identify a donor, obtaining consent, verification of suitability to donate and obtain the tissues or cells.
2. Testing: to identify and avoid the risk of transmitting diseases
3. Processing and storage: to transform the procured tissue/cell into a substance ready to be applied as treatment

4. Distribution: to ship the final graft towards the clinician or hospital where the tissue/cell will be applied on a patient.

2.3 The relative importance of each of these activities varies between the 3 sectors and along tissue type. E.g., for bone marrow transplants (HPC) processing and storage is relatively limited, but a reliable and fast distribution mechanism is of utmost importance.

2.4 General overhead costs, such as management, or the need for a 24/7 presence, can add significantly to the budget. The high discard rates for quality reasons, like for heart valves, and the often short shelf-lives, like for corneas, add further challenges and significant costs. The stock of transplantable tissues should be high enough to cover direct demand, but low enough to prevent expiration, this is a challenge in itself.

2.5 The surveys performed within this study indicate a limited cost-awareness on the real costs made by tissue establishments. The legal structure and funding model of the tissue establishment may play a role when it comes to this, in particular where tissue establishments are hosted in public hospitals, or where funding is based on charity.

2.6 This limited cost-awareness is also reflected by the high variability in prices/fees charged for tissue and cells over the EU. These prices are often fixed at national level, and do not necessarily reflect costs, but rather reflect a national policy like ensuring self-sufficiency or avoiding commercialization of the human body. They do not really take account of the real cost or the volumes needed to cover all costs and come to a financial break-even.

2.7 All these factors led to the conclusion that there is no real single EU market for tissues and cells, which is the reason why the authors prefer to title this study rather as an 'economic landscape'.

2.8 Four funding models can be seen for tissue establishments in the EU. Tissue establishments can either have (1) a public model, with all costs carried by a public budget and the eventual tissue/cell provided without charge to the users. Alternatively, (2) public, (3) non-profit or (4) for-profit tissue establishments do recover their costs by charging a fee to the users. The (3) non-profit and (4) for-profit tissue establishments do also aim to obtain a financial surplus for investments, for building a reserve or for obtaining a profit in case of (4). Public tissue establishments can usually rely on public budgets or on charity to make investments.

3 Replacement tissues

3.1 Replacement tissues allow to replace some damaged tissues and therewith their biological functions. The majority of EU tissue establishments focus on four categories of replacement tissues: cardiovascular, musculoskeletal, ocular and skin.

Category	**Cardiovascular**	**Ocular**	**Musculoskeletal**	**Dermatological**
Indications	Congenital, endocarditis, & alternative for mechanical valves	Idiopathic cell loss, cut- & burn-accidents	Bone loss, trauma, cancer, tear & break of tendons	Burns, reconstructive surgery
Tissue types	Heart valves (vascular graft)	Cornea (Sclera)	Bone Demineralised Bone Matrix (DBM) Tendons	Skin grafts
Donors	Deceased	Deceased	Deceased + Living	Deceased
Main costs	Much discard	Much discard, easy expiry	High procurement costs with high yield for DD, end-irradiation reduces processing costs	Easy procurement, some storage cost
Average price/fee (min-max) reported by sample of TEs	2600€ (950€-5250€) for a heart valve	1420€ (250€-3500€) for a cornea graft	520€ (340€-900€) for a 30CC cancellous chip	1.2-1.4€ per cm2 skin
Tissue establishments	77, small scale, mainly public	141, small scale, mainly public	386, half are private, from local to large international scale	57, mainly local and public, few large international player
Import, export and cross-border exchange	I/+, E/- Informal networks for cross-border exchange	I/+, E/+ Informal networks for import/export	I/ +++, E/ - International partnerships	I/ - E/ - Some international partnerships

3.2 In addition there are 181 tissue establishments authorized to process other tissue grafts like amniotic membrane or pancreatic islets, and 166 to process multiple tissue types.

3.3 Price comparisons for the different types of replacement tissues reveal strong difference between Member States. These differences do not reflect real costs made, but rather are a consequence of different factors including the price-setting process, policy objectives (non-commercialisation, self-sufficiency), the relative high presence of public tissue establishments, limited cost-awareness and intra-EU differences in salaries and purchasing power.

3.4 The absence of a single EU 'market' for tissues and cells is in particular true for the replacement tissue sector and driven by some additional thresholds at national borders:

- Several Member States have set-up prior authorization schemes for export and (outward) cross-border exchange, in order to ensure local supply and self-sufficiency.
- Many Member States require additional national requirements on safety and quality including donor screening, testing or processing (in addition to EU legal requirements). These are not always clear for tissue establishments.
- Some Member States apply national legal frameworks for pharmaceuticals or medical devices on replacement tissues, which can for example lead to the need for prior administrative authorizations to supply tissues to that Member State.
- Administrative procedures in different Member States are to be addressed in different languages.
- Fees are set at different levels by different national authorities, often reflecting a more general policy objective (non-commercialisation, self-sufficiency).
- Some Member States recently changed VAT taxation policies for tissues and cells distributed within their borders, which impacts the fees to be charged.

All these factors hinder a free distribution of grafts across borders of EU Member States. Also, only few Member States have an overview of the distribution and cross-border exchange of different tissue grafts. More importantly, these thresholds also lead to situations where surpluses in some EU Member States exist in parallel to shortages in other EU Member States. Eventually, clinicians/surgeons cannot access the optimal replacement tissue graft matched to their patients' individual needs.

3.5 Overcoming these thresholds at the border, and supplying tissues to multiple countries, requires dedicated regulatory know-how, which is expensive and usually not available for small-scale, public-funded tissue establishments with limited resources. This prevents many EU tissue establishments from supplying hospitals/clinicians in a larger area and from growing their activities. This puts an important limitation to their development as, for reasons of efficiency a larger scale of activities might be increasingly needed to obtain economies of scale, and eventually to break-even or remain profitable.

3.6 Over time, a few larger tissue establishments in the EU have built alliances cross borders to overcome these barriers. Several of them are described in the report. These agreements allow for more efficient procurement, processing or distribution.

In addition, some US-based tissue establishments seem to be able to overcome that barrier as well. They are usually private and well-funded, sometimes even through public listing on the financial markets, and therewith can acquire the resources and know-how to overcome these barriers and supply multiple EU countries. High quantities of surplus musculoskeletal tissues, some corneal grafts and specific sizes of heart valves, are exported to, and distributed into Europe. They often do this by building partnerships with or acquiring major EU-based tissue establishments to do so. This can raise some competitive challenges for the local/smaller-scale establishments. It also brings a need to verify equivalency of safety and quality of the imported substances and to reflect on EU self-sufficiency and dependency on imports.

3.7 Exports out of the EU to third countries seem to be limited. It mainly concerns cornea grafts, which have a limited shelf life and are therefore rather exported than expired, usually during seasonal holiday periods in the EU.

3.8 When it comes to the long term continuity of individual tissue establishments in Europe, there are signs that, given the fact that many of them are small entities, there may be a consolidation or shake-out of tissue establishments in the next five years. It is expected that not all of the small entities will be able to continue processing and supplying a critical mass of tissues large enough to cover the increasing costs of regulatory quality requirements, and many of them may therefore not be able to survive.

3.9 A strengthened collaboration between Member State authorities to facilitate cross-border exchange of tissues within the EU might therefore be a key factor for success for the future of many EU based (replacement) tissue establishments. The fragmented availability of activity data and the need for a common vision on optimal demand and supply for replacement tissues at EU level are priorities to be addressed.

4 Hematopoietic stem cell transplantation (HPC)

4.1 Transplantation with hematopoietic progenitor cells (HPC) has become a standard of care procedure for the treatment of haematological malignancies, immune-deficiencies, and metabolic diseases. Stem cells, donated by either unrelated or family donors or collected from the patient, can be obtained from bone marrow (HPC-BM, under general anaesthesia) or peripheral blood (HPC-A, after administration of hematopoietic growth factors). Umbilical cord blood (HPC-CB) donated to public banks is a third stem cell resource.

4.2 Since genetic markers for tissue typing and matching (Human Leukocyte Antigen, HLA) are inherited from both parents, approximately one third of patients only will find a matching HLA identical donor within their family. The remainder are dependent on finding an acceptable match in the global inventory of voluntary unpaid donors. The chance to find an HLA-identical donor depends on the genetic background of the patient, and varies from 1 in 12 000 to 1 in 50 000.

4.3 Worldwide, currently over 25 million donors and cord blood units are registered with unrelated donor registries, the majority from north western European and north American origin. As a direct result, the access to hematopoietic stem cell transplantation (HPCT) is unequally divided among patients. The main limiting, non-clinical, factor for patients with a non-Caucasian background for not receiving an HPC transplantation, is the lack of donors from ethnic groups that are in a minority in Western countries. Further maximizing the numbers of donors in the common (European) HLA groups will not improve their chances of finding a match. The likelihood of being selected from a registry to give a donation is already rather small: annually, stem cells are collected from only 0.07% of all registered donors for the treatment of approximately 13 000 patients.

4.4 In 2012 there were 33 donor registries active in 24 EU Member States, with a total of 7 499 769 registered donors. The registries are classified as small (< 20 000 donors, n=11) or medium sized (20 000-100 000 donors, n=13), large (>100 000, n=8) or very large (>1 million, n=1). All registries are searchable through Bone Marrow Donors Worldwide, an online search tool, established in 1989, that was designed to simplify international search activities. The main investments in maintaining a donor registry are the recruitment of new donors (including HLA-typing and registration), as well as the costs of an ICT infrastructure. The availability of internationally-compatible ICT systems and software are crucial for the search of suitable HPC donors or products. The ongoing development of a protocol to exchange information between registries in which over 30 registries worldwide participate, has showed the importance of Information and Communication Technology (ICT), and international collaboration.

4.5 In Europe, 33 donor registries were active in 2012 but approximately 80% of all European patients in need of a HPCT received a product donated by a German donor. The German Registry (ZKRD), and in particular their donor centre DKMS, registered over 4 million donors and not only dominate the European field in terms of stem cell provision, but also internationally: 30% of patients outside the EU Member States were also transplanted with a HPC donation of German origin. In terms of self-sufficiency, over 80% of German patients receive products from their

fellow citizens, followed by Poland (45%), Portugal (45%) and the United Kingdom (39%).

4.6 The overall probability of obtaining an eventual HPC transplant depends on a couple of factors, which also define the success of donor registries and cord blood units:

a. Finding a matching donor within the family of the patient. The probability of finding such match is expected to increase significantly with the uptake of new techniques like haplo-identical donations.
b. Finding a matching HLA-profile of an unrelated donor within one of the globally accessible registries.
c. The availability of the candidate donor at moment of a possible request. Availability ratios in the EU vary between 27-100% (on average 74%). Donor registries therefore need to organize regular binding to keep in touch with their candidate donors.
d. The medical screening of the candidate donor to donate HPC on request in order to ensure donation does not harm donor or recipient.
e. The access to transplant programs and sufficient resources. The overall cost of an allogenic HPC transplantation varies from €50,000 (family related HPC) to €250,000 (use of unrelated cord blood unit(s)).

4.7 The costs for donor registries are mainly driven by recruitment activities, HLA typing, IT (database costs) and binding activities to keep donor coordinates up to date. Procurement costs (and eventually transplant costs) are made only when a donation is requested for a specific patient. The costs for cord blood banks relate mainly to collection and storage, and need to take account of a very high discard rate of collected units which are of insufficient quality to store. Many of the public registries and banks have no clear view of their costs, so it is unclear whether costs are effectively covered by the fees.

4.8 Provision of stem cell products is the main source of income for Donor Registries; hospitals or insurance companies are charged between €12 000 and €25 000 per HPC donor product. It remains unclear to what extent this fee covers the total cost of managing a donor registry, since insight from the registries in the breakdown of the real expenses is often not published. However, it is often assumed that it does not fully cover the cost of initial investments and registry maintenance. The costs of donor care management and collection might differ between registries and is also dependent on the scale of activities carried out. Since the majority of HPC donations in Europe are provided by one extra-large scale organisation, the income of small,

medium, and even large size European registries is at risk, due to decreasing numbers for donation and distribution.

4.9 Increasing interest and success of using haplo-identical donors (using HPC from non-matched relatives) is reducing the need and demand for unrelated/allogenic HPC grafts from registries and cord-blood banks. Economic and practical factors, like HPC transplantation with related donors is faster and costs less, may also play a role. If the clinical outcome of transplantation with HPC of haplo-identical donors is equal to full matched donors, it is expected to substantially reduce the demand for unrelated donors. This trend adds further pressure on the more expensive cord blood banks and registries.

4.10 Given that the costs are usually incurred a long time before the income is received, donor registries have to carefully manage their liquidity and cash situation. Those organisations therefore also need to reflect on other sources of income, such as from charitable organisations. Without the necessary financial income, registries report that they struggle to improve the quality of their services with just the funding from units distributed, and that they need to seek additional financial support from local government, insurance companies and, gifts, subsidies or charitable funds. Sometimes donors are asked to contribute financially to help cover the cost of registration and HLA typing.

4.11 Cord blood as a source of stem cells is used for specific indications (e.g. in the paediatric setting) or when no suitable adult donor is available. These are often patients from an ethnic minority background, or mixed ethnic background or patients with rare or uncommon HLA typing. Since for the use of HPC-CB, match grade criteria are less strict, it is often possible to identify an HPC-CB for a patient lacking an unrelated or family donor. After donation to a public bank, cord blood units are processed and cryopreserved and are almost immediately available for treatment. In 2012, worldwide over 640 000 cord blood units were stored in public banks, of these 196 997 cord blood units were registered in 23 Cord Blood Registries in 18 EU Member States.

4.12 The establishment of a cord blood bank requires large initial investment. They are often funded by public bodies like blood banks or governments. Cord blood Registries, often representing the interests of more than one cord blood bank, have large infrastructural maintenance costs, and face an additional financial burden, since only 10-15% of the donated material is compliant with the strict quality criteria. In general, cord blood units containing high numbers of total nucleated cells (TNC) are more sought after, since the success of transplantation with HPC-CB depends largely on this indicator. Currently, more than half the global stock of cord

blood units are low-cell-count products, which is cost ineffective. Cord blood units are more expensive than adult donor derived HPC, and can sometimes double the price (€15 000-40 000), but still the income of public cord blood banks does not balance with the overall costs. Given that the costs are, again, usually incurred a long time before the income is realised, issues of liquidity and cash flow become more challenging.

4.13 Cord Blood Registries contribute to patient care in particular by providing HPC-CB to patients lacking an unrelated or family donor. Since the probability to deliver a rare HLA typed unit from an adult registry is relatively low, collecting these rare/unique products fulfils a medical need. It is however very expensive, at least from a perspective standalone of the Registry.

4.14 There is an opportunity to look for different opportunities for cost effectiveness. For example, costs for ICT equipment and staff are a heavy burden for small and medium sized registries, but it is usually not an option to work without ICT personnel. Intensifying collaboration in this area could reduce costs, and be of direct benefit for the smaller and medium sized registries.

4.15 The HPC donor registries and cord blood bank are a public provision, and since it is based upon HLA selection it prevents it from exploiting a normal business model. In the current situation there is a very strong dependency on German donors, and the majority of EU Member States are not self-sufficient in terms of providing national HPC products to their own patients. This has raised some concerns on governance and public accountability of this non-public registry on which a large number of EU patients and healthcare systems are dependent. Furthermore, collaboration between HPC Donor Registries could enhance the efficiency and quality of services, which will be an advantage for patients and take away the need to compete between Donor Registries.

4.16 Besides donating their child's cord blood to a public Cord Blood Bank, in many European countries parents are offered the opportunity to store it in a private Cord Blood bank, as a means for potential lifesaving treatment in the future. These services are offered by commercial enterprises that are charging the parents upfront for the costs of storage (approximately €2 000 – €2 500 for processing and storage for 20 years). Contrary to the public banks, private cord blood banks are paid immediately for their service rather than having to wait for the income until the units are selected for treatment for a specific patient. A combination of public and private banking, the so-called hybrid model, is still rare. This is partly due to the differences in ethical, regulatory and quality issues between the public and the commercial activities, and as such creating hurdles for the establishment of hybrid

banks. In Europe there are over 120 cord blood banks active in private or family-directed cryopreservation of cord blood. It is estimated that the number of private stored cord blood is at least five times more than the world wide public inventory. To the contrary, the number of distributed grafts is far less.

5 Assisted reproductive technologies (ART)

5.1 ART refers to all treatments that include in vitro handling of human reproductive cells (gametes) and embryos to establish a pregnancy. This includes, but is not limited to, in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI), intra-uterine insemination (IUI), and cryopreservation of gametes and/or embryos. These treatments are performed with reproductive cells from a man and a woman in an intimate physical relationship (partner donation), or with gametes or embryos from another person apart from the couple (non-partner donation). A couple of establishments are focusing on collection, banking and distribution of sperm and egg cells (so-called sperm and egg banks).

5.2 The total number of tissue establishments dedicated to ART in the EU-28 is unclear; ranging from 772 (of which 69% private and 31% public) according to the EC implementation survey (2011), to 1519 in EUROCET128 (2013). The largest countries have the highest absolute numbers. However Spain, Denmark and Belgium have a relatively high number of clinics compared to the number of females in the reproductive age (however, a high amount of clinics does not necessarily mean a high amount of activity).

5.3 These TE's are supplied by a few large multinational pharmaceutical corporations, in particular to supply hormone therapies to stimulate female patients undergoing an IVF cycle. Merck Sereno is leading this market with 40% share, followed by Ferring Pharmaceuticals. There is a trend that these companies also offer packages combining pharmaceuticals (hormone therapy) with accompanying equipment, disposables, testing and training of professionals, hence supporting the entire set-up and operations of an ART tissue establishment.

5.4 Furthermore, some intermediary organizations (or brokers) have emerged in the sector to bring together intended parents and clinics, sometimes facilitating travel across borders (Spain or third countries like the US or Northern Cyprus), and offering additional services such as travel and insurance. Additional innovative models exist to facilitate uptake of fertility services like egg sharing (donating part of the collected egg cells in return for a rebate on the costs of the IVF cycle) or social fertility preservation (freezing egg cells for use at a later, more convenient time).

5.5 More than 550,000 IVF cycles were initiated in the year 2011. According to the European professional society for reproductive medicine (ESHRE), one in six couples experience infertility problems of some sort at least once during their reproductive years. The increasing demand for ART is driven by age and lifestyle factors (including stress, obesity, smoking, substance abuse). Also new technological possibilities, like storing gametes for future use, and the desire for genetically related children amongst gay and lesbian couples, are further drivers for growth in the ART sector.

5.6 Access to ART is strongly related to national legislations, which are less or more strict in factors like maximum age (relatively high in EE, ES and CR), family composition (e.g. taken into account in IT, LV, PT and SE) or the possibility to use donated gametes (strict in AT, DE, LU and until recently IT). Reimbursement is another important factor that defines access and is less or more strictly stipulated in national laws (e.g., with 6 reimbursed IVF cycles BE has a relatively large reimbursement). Reported fees vary from €210 to €9900 per IVF cycle, but it differs widely what is covered as part of the procedure.

5.7 These national differences are drivers for cross-border ART services. Women and couples of Member States with stricter access and/or reimbursement criteria travel to ART establishments abroad. CZ, EE and ES seem to be countries attracting foreign citizens for ART treatment in facilities that announce their activities online in multiple languages.

5.8 Within the EU, DK is the leading country for sperm collection, banking, distribution and sale. The two largest EU sperm banks (Cryos and European Sperm Bank) are both located in DK and ship sperm to multiple other EU Member States. BE is an important destination for sperm. Only IE and UK report import of sperm from the US, while it is however also possible that part of the sperm distributed by DK banks is collected outside the EU.

5.9 The selection of donors contains an extensive selection for medical criteria (in line with Directive 2004/23/EC) as well as for social criteria. Once accepted, sperm donors are requested to make several donations within a few months. DK sperm banks compensate donors with €30-70 per donation. The more personal information the donor is willing to share with candidate recipients, the closer this amount is to the higher end. Higher compensations are however not thought to increase the overall donor pool.

5.10 Tissue establishments in ES and CZ are the most active in collecting donor egg cells. However these egg cells are hardly distributed across borders. Rather egg cell

donors as well as recipients are travelling to these countries to make donations or undergo ART treatments with donated egg cells.

5.11 Egg cell banks in ES and CZ announce their search for donors in multiple languages, which indicates they are attracting donors from different countries. Several clinics recruit oocyte donor online in PL, offering compensation for travelling to other countries. Egg cell donation is an invasive and long process requiring multiple injections with stimulating hormones and eventually a (minimally invasive) surgery to pick-up the egg cells. Reported compensations are around €900. Another approach to obtain donated egg cells is the so-called 'egg-sharing' scheme applied in the UK, where women get a significant reduction in the fee for their own IVF treatment if they agree to donate part of the collected egg cells to another woman (or to research).

5.12 Embryo donation is mainly reported in CZ, EE, and ES. Embryos are however hardly shipped across borders but, as for egg cells, it is rather recipients that travel to these countries to undergo ART treatments with donated embryos. IE has organized an oocyte donation program in collaboration with a non-EU country, to which sperm is exported and from which consequent embryos are reimported.

5.13 Overall fees/prices paid for donated gametes are usually not set in function of the cost of collection and storage, but are rather set in function of the demand for specific donor profiles.

6 Forward look: novel therapies

6.1 Innovation in the tissues and cells sector is advancing continuously by progress in immunology, microsurgery and cryopreservation. More recently developments in tissue engineering, gene and somatic therapies add to this progress. These innovations are therefore ongoing within and outside the legal framework of Directive 2004/23 of Tissues and Cells.

6.2 In replacement tissues, growth trends vary per type of tissue, each one being subject to different factors. Overall, the use of ophthalmologic grafts is expected to increase due to higher needs of our ageing population, while the use of bone grafts is expected to grow due to an increased commercialisation, evidenced by the entry of private operators. The growth trends in use of skin and cardiovascular grafts are less clear due to different, partly opposing, factors.

6.3 Annual transplantation numbers of allogeneic HPC in Europe have tripled between 1998 and 2013, and are likely to continue increasing. Some new techniques like using haplo-identical (i.e. family-related) donors might decrease this need, while

others, like the development of new HPC-based therapies like tumor-infiltrating vaccines, might increase the need for HPC.

6.4 The continuing growth for assisted reproductive technologies (ART) is driven by medical (increasing infertility rates), social (e.g., new family compositions), technological (e.g. freezing of genetic material for future use) and commercial (e.g., online and cross-border services) factors.

6.5 The development of the tissue and cells sector might also be affected by the developments in neighboring sectors like advanced therapy medicinal products (ATMP) and medical device industry. This might in first place impact demand and possible competition by commercial actors for allogenic human tissues and cells. However, so far ATMP developments seem mainly to take place with autologous cell products. Whenever novel therapies bring significant benefits in terms of efficacy, safety and quality, they might replace traditional transplant therapies. It seems however difficult to have a central overview on this, as oversight on the traditional tissues and cells sector is organised at national level, and as many ATMPs are currently offered within the decentralized setting of hospital exemptions.

6.6 The developments in the ATMP sector offer opportunities for tissue establishments to supply not only starting materials, but also infrastructure and expertise in GMP-cleanrooms or dedicated cell culture facilities. Several public banks, like NHS Blood and Transplant (UK) have set up such cell culture facilities, and also the research for several of the (5) centrally approved ATMPs has been initiated in tissue establishments within academic hospitals.

6.7 However the developments of ATMP also bring challenges, including due to legal uncertainties and borderline issues which make it difficult for professionals and companies to know which safety and quality requirements to apply: those under the Tissue/Cells legislation or those under the (Advanced Therapy) Medicinal Product legislation. Classifications often depend on technical details and the Committee on Advanced Therapies (CAT) makes scientific recommendations on whether products fall within the definition of ATMP. However these recommendations are not binding at EU level, leading to different Member States to apply different legal frameworks for similar products. Tissue establishments regularly complain on classifications which force them to stop preparing well-established therapies. In parallel, pharmaceutical companies complain of a lack of level playing field, forcing them to undergo costly clinical trials and marketing authorization procedures, which translate into the need to charge high prices which are hard to obtain reimbursement for.

6.8 Future developments of the tissue and cell sector will also reflect general economic trends related to the entry of the private sector and the need for efficiency. Private sector entry is driven a.o. by the possibility of direct-to-consumer activities (e.g., internet sales of sperm), of organizing large-scale processing (e.g., to make bone powder) and by changes in societal demand (e.g., ageing or delaying childbirth). In order to ensure supply of all types of tissues/cells, public actors will have to focus on economically less interesting activities and will have to undertake some actions to increase their cost-efficiency, like cost-sharing or consolidation of establishments.

6.9 The strong involvement of clinicians, and significant data-collection efforts led by professional societies, are an important facilitator for innovation in the sector. These data will allow authorities to monitor and ensure safety, quality and functionality of novel therapies. In times of financial constraints, these data will also be helpful to justify public investments to ensure overall availability of tissue and cell therapies.

6.10 Media play an increasingly important role to ensure public awareness and willingness to donate, without which this sector cannot exist. While there is an overall public support for this sector, thrust can easily erode when there is coverage of (monetary) scandals, and with it donation rates go down. Media will therefore require specific attention, also to help leverage the possibilities of social media, and to manage often premature coverage and expectations on novel therapies.

6.11 With new therapies come new ethical concerns and hopes, which require dedicated political debates. Ethical opinions can oppose strongly, in particular as each comes with valid arguments. It is therefore important that a good basis of facts and sector-knowledge is available to support policy makers in these difficult ethical discussions. Some of the ethical discussions that are needed, concern directly some important preconditions for the sector like the need for donor protection and the possibility of patenting (or not) therapies based on human materials.

6.12 The future development of the sector also depends a lot on enabling technologies, like the availability of new testing technologies. Some of these new technologies can however be very expensive, in particular for EU Member States with lower GDP rates. Their added value therefore needs to be assessed within the (national) context of existing safety and quality measures, which will require dedicated (health) technology assessment (HTA) knowledge.

TABLE OF CONTENTS

ABSTRACT 5

EXECUTIVE SUMMARY 7

TABLE OF CONTENTS 22

LIST OF FIGURES 26

LIST OF TABLES 27

LIST OF ABBREVIATIONS 28

1 INTRODUCTION: ECONOMIC LANDSCAPES HUMAN TISSUES AND CELLS 32

1.1 OBJECTIVE AND AIM 32

1.2 DATA SOURCES 33

1.3 TISSUE AND CELL SECTORS COVERED 34

1.4 METHODOLOGY AND RESEARCH DESIGN 35

1.4.1 LITERATURE REVIEW 35

1.4.2 ANALYSIS OF EXISTING DATASETS 35

1.4.3 REGISTRIES 35

1.4.4 SURVEY TO NATIONAL COMPETENT AUTHORITIES (NCATC) 36

1.4.5 COUNTRY FACT SHEETS 39

1.4.6 TISSUE ESTABLISHMENTS SURVEY 40

1.4.7 INTERNET SEARCH OF ART ESTABLISHMENTS 41

1.4.8 INTERVIEWS AND FIELDWORK 43

1.4.9 ADVISORY PANEL 44

1.4.10 LOOKING FORWARD 44

1.5 RESEARCH TEAM AND AUTHORSHIP 44

1.6 CONCLUDING REMARKS AND SUMMARY INTRODUCTION 46

2 HORIZONTAL ASPECTS OF ECONOMIC FACTORS IN TISSUE AND CELL BANKING 47

2.1 INVESTMENT, FUNDING AND COSTS OF TISSUE ESTABLISHMENTS 47

2.1.1 INVESTMENT 47

2.1.2 FUNDING 50

2.1.3 OPERATIONAL COSTS 52

2.1.4 DONOR RECRUITMENT AND SELECTION, AND TISSUE PROCUREMENT COSTS 53

2.1.5 COSTS OF TESTING FOR SAFETY 54

2.1.6 COSTS OF PROCESSING AND STORAGE 54
2.1.7 COSTS OF DISTRIBUTION 54
2.1.8 ALLOCATION OF FINANCIAL SURPLUSES 55
2.2 MANAGING VOLUMES AND THE RELATED COST FOR TISSUE ESTABLISHMENTS 55
2.3 VALUE AND FEES CHARGED FOR TISSUES AND CELLS 56
2.4 CROSS-BORDER EXCHANGE, IMPORT AND EXPORT 57
2.5 IMPACT OF TAX AND VAT REGULATIONS 59
2.6 CONCLUDING REMARKS AND SUMMARY HORIZONTAL ASPECTS 60
3 REPLACEMENT TISSUES 62
3.1 FIELD DESCRIPTION (INCLUDING ECONOMIC ASPECTS) 62
3.1.1 CARDIOVASCULAR TISSUES 62
3.1.2 OCULAR TISSUES 68
3.1.3 MUSCULOSKELETAL TISSUES 75
3.1.4 SKIN GRAFTS 83
3.1.5 AMNIOTIC MEMBRANE 88
3.1.6 PANCREATIC ISLETS 88
3.1.7 OTHER TISSUES AND CELLS 89
3.2 ORGANISATION OF THE SECTOR 89
3.2.1 ASSOCIATIONS AND FOUNDATIONS OF REPLACEMENT TISSUE ESTABLISHMENTS 91
3.3 FUTURE PERSPECTIVES IN REPLACEMENT TISSUES 95
3.3.1 CARDIOVASCULAR TISSUES 95
3.3.2 OCULAR TISSUES 96
3.3.3 MUSCULOSKELETAL TISSUES 96
3.3.4 SKIN 97
3.4 CONCLUDING REMARKS AND SUMMARY REPLACEMENT TISSUES 97
4 HEMATOPOIETIC PROGENITOR CELLS (HPC) 100
4.1 FIELD DESCRIPTION 100
4.1.1 AN INTRODUCTION TO HEMATOPOIETIC STEM CELL TRANSPLANTATION 100
4.1.2 DESCRIPTION OF THE PRODUCT GROUPS 102
4.2 ORGANISATION OF THE SECTOR 105
4.2.1 ORGANISATIONAL STRUCTURES IN THE FIELD OF HPCT 105
4.2.2 LEVELS OF ACTIVITY IN STEM CELL TRANSPLANTATION 108
4.2.3 THE EUROPEAN DONOR REGISTRIES 110
4.2.4 CORD BLOOD BANKING 112
4.2.5 INTERNATIONAL CORD BLOOD REGISTRIES AND NETWORKS 113
4.2.6 DESCRIBING THE CHAIN: FROM DONOR RECRUITMENT TO STEM CELL INFUSION 115
4.2.7 TRANSPLANTATION ACTIVITY IN EU MEMBER STATES 118

4.2.8 MANAGING A DONOR REGISTRY: KEY FACTORS TO CONSIDER 123
4.3 ECONOMIC ASPECTS IN HPC 125
4.3.1 GENERAL ASPECTS 125
4.3.2 ECONOMICS OF STEM CELL DONOR REGISTRIES 126
4.3.3 ECONOMICS OF CORD BLOOD BANKS 131
4.3.4 INCOME FOR STEM CELL DONOR REGISTRIES AND CORD BLOOD BANKS 133
4.3.5 HPC DISTRIBUTION BETEEN, IMPORT TO AND EXPORT FROM EU MEMBER STATES 135
4.3.6 ORIGIN OF HPC PRODUCTS 136
4.4 FUTURE PERSPECTIVES IN HPC 138
4.4.1 CONSOLIDATION OF EUROPEAN REGISTRIES? 138
4.4.2 THE FUTURE OF CORD BLOOD BANKING 139
4.4.3 FUTURE APPLICATIONS OF STEM CELL PRODUCTS 140
4.5 CONCLUDING REMARKS AND SUMMARY HPC 142
5 ASSISTED REPRODUCTIVE TECHNOLOGIES (ART) 146
5.1 FIELD DESCRIPTION 146
5.1.1 REPRODUCTIVE TECHNOLOGIES AND TREATMENTS 146
5.1.2 DRIVING FACTORS INFLUENCING THE USE OF INFERTILITY TREATMENTS 147
5.1.3 ART ESTABLISHMENTS IN THE EU 149
5.1.4 PROFESSIONAL SOCIETIES IN REPRODUCTIVE HEALTH 152
5.1.5 FERTILITY MONITORING 152
5.1.6 FERTILITY DRUGS AND PRODUCERS 152
5.1.7 BROKERS 154
5.2 ORGANISATION OF THE ART SECTOR 154
5.2.1 METHODOLOGICAL CONSIDERATIONS IN ART 154
5.2.2 MAIN SUPPLIERS FOR NON-PARTNER GAMETE DONATION 155
5.2.3 ORGANISATION OF THE SECTOR: SPERM DONATION AND BANKING (INCLUDING ECONOMIC ASPECTS) 157
5.2.4 ORGANISATION OF THE SECTOR: EGGS AND EMBRYOS (INCLUDING ECONOMIC ASPECTS) 185
5.2.5 PRICING OF ART TREATMENTS IN THE EU 204
5.3 FUTURE PERSPECTIVES IN ART 215
5.3.1 INCREASING DEMAND FOR FERTILITY TREATMENTS 215
5.3.2 CHANGES IN FERTILITY TREATMENT OFFERS AND SERVICES 215
5.4 CONCLUDING REMARKS AND SUMMARY ART 216
6 FORWARD LOOK: NOVEL THERAPIES 219
6.1 INTRODUCTION 219
6.2 EMERGING INNOVATIONS AND TRENDS IN THE TRADITIONAL TISSUES AND CELL SECTORS 219
6.2.1 REPLACEMENT TISSUES 219

6.2.2 HEMATOPOIETIC PROGENITOR CELLS (HPC) 220
6.2.3 ASSISTED REPRODUCTIVE TECHNOLOGIES (ART) 221
6.3 OPPORTUNITIES AND CHALLENGES FOR THE TISSUE AND CELL SECTOR 221
6.3.1 IMPACT 222
6.3.2 OPPORTUNITIES: DEVELOPING AND MANUFACTURING ATMPS 225
6.3.3 CHALLENGES 227
6.4 FACTORS WITH IMPACT ON FUTURE DEVELOPMENTS IN THE TISSUE AND CELL SECTOR 229
6.4.1 ECONOMIC FACTORS: ENTRY OF THE PRIVATE SECTOR AND THE DRIVE FOR EFFICIENCY 229
6.4.2 MEDICAL FACTORS: GROWING NEED FOR SYSTEMATIC DEMONSTRATION OF CLINICAL FUNCTIONALITY 231
6.4.3 SOCIAL FACTORS: MEDIA, ALTRUISM AND TRUST 232
6.4.4 ETHICAL FACTORS 233
6.4.5 NEW TECHNOLOGIES AND THEIR IMPACT ON THE T&C SECTOR 235
6.5 CONCLUDING REMARKS AND SUMMARY NOVEL THERAPIES 235
7 ANNEX 1: BIBLIOGRAPHY 238
7.1 BIBLIOGRAPHY HORIZONTAL 238
7.2 BIBLIOGRAPHY REPLACEMENT TISSUES 240
7.3 BIBLIOGRAPHY HPC 245
7.4 BIBLIOGRAPHY ART 256
7.5 BIBLIOGRAPHY FORWARD LOOK 267
8 ANNEX 2: TABLES 274
8.1 TABLES REPLACEMENT TISSUES 274
8.2 TABLES HPC 274
8.3 TABLES NOVEL THERAPIES 286
8.4 TABLES ART 287
8.4.1 TABLE A1: PRICES SPERM BANKS 287
8.4.2 TABLE A2: PRICES SPERM AND DELIVERY 2 289
8.4.3 TABLE A3: PRICES OF RESERVATION DEPOT (STORAGE FOR FUTURE USE) 291
8.4.4 TABLE A4: VOLUMES EMBRYO 293
8.4.5 TABLE A5: VOLUMES OOCYTE 297
8.4.6 TABLE A6: VOLUMES SPERM BANKS 300
8.4.7 TABLE A7: DONOR COMPENSATION 306
8.4.8 TABLE A8: DONOR ANONYMITY 317
8.4.9 TABLE A9: PRICES OF ART TREATMENTS FROM INTERNET SEARCH PER MEMBER STATE (N=180) 321
9 ANNEX 3: COUNTRY CLASSIFICATION ACTIVITY ART 345
10 ANNEX 4: GLOSSARY 351

List of figures

Figure 1 Data sources and research design 34
Figure 2 Core processes and cost in tissue establishments 52
Figure 3 Cross-border distribution, import and export 58
Figure 4 Bone Marrow Puncture & Apheresis Chart 102
Figure 5 Overview of product source provided by unrelated donors 109
Figure 6 Patient age as a factor of influence over years 109
Figure 7 Autologous/allogeneic transplantations/10 million inhabitants in EU 110
Figure 8 Two-compartment cryopreservation of cord blood 113
Figure 9 Stem cell transplant process from donation to infusion 116
Figure 10 Cord blood search process 118
Figure 11 Global transplantation activity 119
Figure 12 Allogeneic unrelated transplantation activity in EU-28 120
Figure 13 Trends in autologous and allogeneic HPCT since the start 121
Figure 14 Transplant rates in Europe 122
Figure 15 Export and import of cord blood units 126
Figure 16 HPC donor density in EU28 Member States 136
Figure 17 Origin of HPC products 137
Figure 18 the 2012 export flows HPC 139
Figure 19 Number of tissue establishments in ART 151
Figure 20 Total ART tissue establishments per 1 million women of reproductive age (15-45) 151
Figure 21 Main suppliers of gametes and embryos non-partner donation 156
Figure 22 Main suppliers of gametes and embryos; public, private status 157
Figure 23 Development of Cryos sperm bank (DK) 160
Figure 24 Donor recruitment pyramid CCB (US) 162
Figure 25 Sperm donation related activity Europe 167
Figure 26 Donor benefits Cryobank (US) 173
Figure 27 Donor benefits Birmingham Sperm Bank (UK) 173
Figure 28 Anonymous donation and identity disclosure ART 176
Figure 29 Donor selection Cryos (DK) 178
Figure 30 Extended profile Cryos (DK) 179
Figure 31 Donor information European Sperm Bank (DK) 180
Figure 32 Donor information Spermbank International (CZ) 180
Figure 33 Look-a-like sperm (US) 181
Figure 34 Maximum number of families/children per sperm donor 182
Figure 35 Delivery prices Cryos (ex VAT) (DK) 184
Figure 36 Prices International sperm bank (CZ) 185
Figure 37 Travelling donors and clients (PL) 188
Figure 38 Oocyte donation related activity 190
Figure 39 Embryo donation related activity 195
Figure 40 Donor compensation in Europe 198
Figure 41 Cost table egg donation (US) 200
Figure 42 Compensation of oocyte donors 201
Figure 43 Compensation of sperm donors 201
Figure 44 Pricing of ART treatment and gametes in the EU 205
Figure 45 Gamete donation 209
Figure 46 Maximum age of the woman to access treatment 211
Figure 47 Maximum age of the woman as limitation for reimbursement 212
Figure 48 Heterosexual partnership as a condition for access to treatment 213
Figure 49 Infertility diagnosis requirement for reimbursement 214

LIST OF TABLES

Table 1 Responses to the survey per Member State and per sector 38
Table 2 Member States' response to the country factsheet and preliminary findings 39
Table 3 Responses to the tissue establishment survey 41
Table 4 Sampling strategy: internet search of 180 ART establishments in EU 42
Table 5 Classification of cleanroom levels 48
Table 6 Investment cost of GMP cleanrooms 49
Table 7 Number of tissue establishments with cost calculation 53
Table 8 Volumes of heart valves 63
Table 9 Cost divisions in cardiovascular tissue establishments 65
Table 10 Fee of cardiovascular grafts 66
Table 11 Volumes of corneas 68
Table 12 Cost division in cornea tissue establishments 70
Table 13 Number of corneal grafts and cost 71
Table 14 Fee of ocular and amnion tissues to local end-users 72
Table 15 Fee determination of cornea 73
Table 16 Cross-border distribution, import, export and shortages of cornea 74
Table 17 Donation, distribution, import and export of musculoskeletal tissue 77
Table 18 Cost division in a musculoskeletal tissue establishment 79
Table 19 Fee determination of musculoskeletal tissues 81
Table 20 Import, export and reported shortages of musculoskeletal tissues 82
Table 21 Export of musculoskeletal tissue from US to EU in units 83
Table 22 Skin graft donations, distribution, import and export 84
Table 23 Need for donor skin in EU Member States 88
Table 24 Number of tissue establishments for replacement tissues 89
Table 25 Public/Private Status of EU tissue establishments 91
Table 26 Total number of TE in ART and number of IVF clinics 150
Table 27 Key players in sperm banking 159
Table 28 Cost-structure of a sperm bank 165
Table 29 Cost-structure of an egg-bank 189
Table 30 Compensation for sperm and oocyte donors 203
Table 31 ART treatment prices 205
Table 32 Treatment reimbursement levels of ART treatments 210
Table 33 Provision of HPC-M products in 2012 274
Table 34 Provision of HPC-A products in 2012 274
Table 35 Provision of HPC-CB products in 2012 275
Table 36 Overview Growth European HPC Donor Registries[$] 276
Table 37 Overview growth European Public Cord Blood Registries[$] 278
Table 38FACT/Netcord accredited HPC-CB banks in Europe 279
Table 39Percentage of population registered as donor, availability rate and number of donations per EU MS in2012 280
Table 40 EBMT registered patients receiving 1st allogeneic and autologous HPCT (2012) 281
Table 41 Allogeneic HPCT – donor source in 2012 281
Table 42 Allogeneic and autologous HPCT – stem cell source in 2012 281
Table 43 Allogeneic HPCT with unrelated donors/cord blood (2012) 281
Table 44 Average cost for HPCT with autologous donor, sibling donor, unrelated donor and unrelated cord blood in euros 282
Table 45 BMDW fees, actual November 2014 282
Table 46 WMDA fees, actual May 2015 282
Table 47 Fee schedules actual November 2014* 283
Table 48 Examples of financial funding 284
Table 49 Cost of processing umbilical cord units 284
Table 50 Some major private cord blood banks active in EU MS 285
Table 51 Licensed ATMP in Europe (EMA) 286

LIST OF ABBREVIATIONS

AATB	American Association of Tissue Banks
ACI	Autologous Chondrocyte Implantation
APHP	Assistance Publique des Hôpitaux Paris
ART	Assisted reproductive technology
ASHI	American Society for Histocompatibility and Immunogenetics
ASRM	American Society for Reproductive Medicine
AT	Austria
ATMP	Advanced Therapy Medicinal Product
BE	Belgium
BG	Bulgaria
BISLIFE	Foundation Bio Implant Services Foundation
BM	Bone Marrow
BMDW	Bone Marrow Donors Worldwide
BMP	Bone Morphogenetic Protein
BSE	Bovine Spongiform Encephalopathy
BST	Banc de Sanq I Teixits Barcelona
CA	Competent Authorities (see also NCA)
CAGR	Compound Annual Growth Rate
CARs	Chimeric Antigen Receptors
CAT	Committee for Advanced Therapies
CB	Cord Blood
CBB	Cord Blood Bank
CBR	Cord Blood Registry
CBU	Cord Blood Unit
CC	Collection Centre
CCB	California Cryobank
CE	Marquage Conformité Européenne (conformity with EU law)
CFU	Colony-Forming Units (cfu)
CHAFEA	Consumers, Health and Food Executive Agency
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CT	Clinical trial
CT	Confirmatory Typing
CV	Cardiovascular
CY	Cyprus
CZ	Czech Republic
DBM	Demineralized Bone Matrix
DC	Donor Centre
DE	Germany
DG	Directorate General
DGfG	Deutsches Gesellschaft für Gewebetranplantation
DG SANCO	Directorate General for Health and Consumers
DG SANTE	Directorate General for Health
DHZB	Deutsches Herzzentrum Berlin
DIZG	Deutsches Institut für Zell- und Gewebeersatz
DK	Denmark
DKMS	Deutsche Knochenmark Spenderdatei / German Bone Marrow Donor Centre
DLI	Donor lymphocyte infusion
DR	Donor Registry
EATB	European Association of Tissue Banks
EAHC	Executive Agency for Health and Consumers
EBMT	European society for Blood and Marrow Transplantation
EC	European Commission
ED	Embryo donation
EE	Estonia

EEBA	European Eye Bank Association
EFI	European Federation for Immunogenetics
EGE	European Group on Ethics in Science and New Technologies
EHB	European Homograft Bank
EIM	the European IVF Monitoring Program from ESHRE
EL	Greece
EMA	European Medicines Agency
EMDIS	European Marrow Donor Information System
ES	Spain
ESB	European Sperm Bank
ESHRE	European Society of Human Reproduction and Embryology
EU	European Union
EUTCD	European Union Tissue and Cells Directive
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration (US)
FET	Frozen Embryo Transfer
FI	Finland
FR	France
FSH	Follicle Stimulating Hormone
G-CSF	Granulocyte Colony Stimulating Factor
GDP	Gross Domestic Product
GEMS	Group European Medium Sized Registries
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
GTP	Good Tissue Practice
GvHD	Graft versus Host Disease
HE	Hospital Exemption
hESC	Human Embryonic Stem Cells
HFEA	Human Fertilisation and Embryology Authority
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
HPC	Hematopoietic progenitor cells
HPC-A	Peripheral blood stem cells (i.e. HPC collected through aphaeresis)
HPC-BM	Bone Marrow
HPC-CB	Cord Blood
HR	Croatia
HSCT	Hematopoietic stem cell transplantation
HTA	Health Technology Assessment
HU	Hungary
ICMART	International Committee for Monitoring Assisted Reproductive Technology
ICSI	Intracytoplasmic Sperm Injection
ICT	Information and Communication Technology
IDM	Infectious Disease Markers
IE	Ireland
IP	Intellectual Property
iPS	Induced pluripotent stem cell
ISCT	International Society for Cellular Therapy
ISSCR	International Society for Stem Cell Research
IT	Italy
IUI	Intra-Uterine Insemination
IVF	In-Vitro Fertilization
JACIE	Joint Accreditation Committee ISCT and EBMT
LMDP	Luxemburg Marrow Donor Program
LT	Lithuania
LU	Luxembourg
LV	Latvia
MAR	Medically Assisted Reproduction
MD	Medical Device

MS	Member State(s)
MSC	Mesenchymal Stromal Stem Cells
MSK	Musculoskeletal
MT	Malta
MTF	Musculoskeletal Transplant Foundation
NA	Not Available
NAT	Nucleic Acid Test
NCATC	National Competent Authorities for Safety and Quality of Tissues and Cells
NGS	Next Generation Sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NL	Netherlands
NMDP	National Marrow Donor Program
OC	Ocular
OD	Oocyte donation
OR	Operating Room
PBSC	Peripheral Blood Stem Cells
PGD	Pre-implantation Genetic Diagnosis
PL	Poland
PKP	Penetrating Keratoplasty
PT	Portugal
RI	Rathenau Instituut
RO	Romania
RT	Replacement tissues
SARE	Serious Adverse Reactions or Events
SARS	Severe Acute Respiratory Syndrome
SE	Sweden
SEGB	Foundation of European Tissue Banks
SI	Slovenia
SK	Slovakia
SMEs	Small and Medium Sized Enterprises
TC	Transplant Center
TC-T	Therapeutic cells
T&C	Tissues and Cells
TE	Tissue establishment
TESA	Testicular Sperm Aspiration
TNC	Total Nucleated Cells
TRIP	Hemovigilance and Biovigilance Office
UCB	Umbilical Cord Blood
UK	United Kingdom
US(A)	United States (of America)
VAT	Value Added Tax
vCJD	Variant Creutzfeldt-Jakob disease
VUD	Voluntary Unpaid Donation
VUDTC (survey)	Voluntary Unpaid Donation of Tissues and Cells (survey)
WBMT	Worldwide network for blood and marrow transplantation
WHO	World Health Organization
WMDA	World Marrow Donor Association
ZKRD	Zentrales Knochenmark Register Deutschland

1 INTRODUCTION: ECONOMIC LANDSCAPES HUMAN TISSUES AND CELLS

This section describes the objective and aim, data sources and scope of the study, the research design and methods used, and it introduces the research team.

1.1 OBJECTIVE AND AIM

The safe and stable supply of tissues and cells for patients requiring transplantation is a key priority for national health authorities and the European Commission alike.

Many of the activities in the tissue and cells landscape are undertaken by public actors, while others are undertaken by private actors. In both cases, costs are involved and different options exist to recover these costs, at least partly, through an income. Understanding these economic aspects can help Member States in taking, increasingly difficult, decisions on how to organize this essential part of their healthcare system. Many of these actors abide to the principle of voluntary and unpaid donation (VUD) which is strongly encouraged by the e EU legislation (Directive 2004/23/EC) and international organisations such as the WHO and Council of Europe.

Currently, a variety of economic activities have emerged that may jeopardize these health priorities and governing principles, both within the EU and on a global level, given the increasing import and export of human tissues and cells.

In order to gain better insight into the dynamics and economic characteristics of these activities, CHAFEA called for a study aimed at producing an overview on EU wide economic landscapes of human tissues and cells for transplantation. The specific features and types of activities in three medical sectors are investigated:

- Replacement tissues, such as bone, cornea, skin and cardiovascular tissues (RT)
- Hematopoietic progenitor cells from bone marrow, peripheral blood and cord blood (HPC)
- Gametes and tissues for assisted reproductive technology (ART)

This study maps the economic landscapes and key players in the field of transplantation medicine across the three respective domains across all EU-28 Member States. The study focuses on identifying current and emerging economic practices, key players in public and private sectors, legislative and reimbursement schemes across Member States, and finally on providing a forecast of technological trends and of associated ethical, legal, and social issues.

The main deliverable of the study is a report, which provides insight into the following key aspects:

- The characteristics of the EU tissues and cells economic landscape, such as steps from donor recruitment through donation, procurement/collection, testing, processing, storage, distribution to clinical application. This covers quantities, prices, the extent and ratio of VUD versus paid donations, concerns and conflicts, supply and demand volumes and other elements in order to better understand the economic parameters and dynamics;

- The main actors involved in the different steps from donor recruitment to transplantation, for the EU-28 Member States, but also at the EU level, covering public and private actors in this sector;

- Regulations on reimbursement and financing in the EU Member States to better understand the various models of organization of reimbursement, the overall costs for tissue transplantation, including transplant tourism. This includes compensation schemes for donors;

- A forecast for the EU economic landscape and trends for tissue and cells for transplantation and assisted reproduction for the next years, with respect to technological, scientific, economic, medical, social, political and ethical evolutions in the different sectors. This includes the impact of future technological developments and their respective needs for legal provisions to warranty safety and quality of tissue transplantation.

The report therefore starts with a chapter on horizontal economic aspects (chapter 2) which are relevant for all sectors.

Consequently a chapter is dedicated to each of the medical sectors. Chapter 3 covers the specifics of replacement tissues. Chapter 4 covers the specifics of hematopoietic progenitor cells. And chapter 5 covers the specifics of assisted reproductive technologies. Each of these three chapters covers the key aspects laid out above, through a description of the field, the organisational set-up, economic aspects and future perspectives.

A final chapter 6 is looking forward not only to the expected developments within each of these 3 sectors, but also in related sectors and ends with general factors that will impact the future of the tissue and cells sector.

1.2 DATA SOURCES

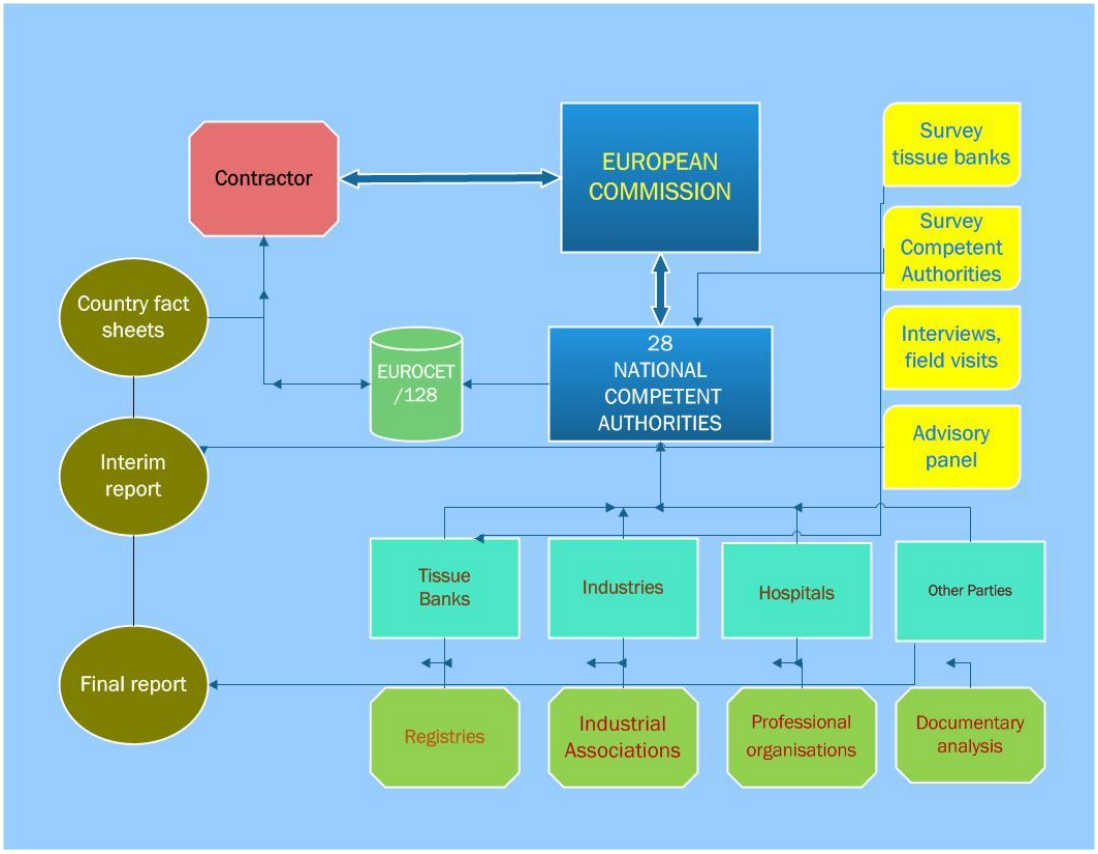
The research strategy builds on existing data sets and bodies of literature as well as on newly developed data from surveys and interviews.

The research involved extensive document-gathering and analysis via desk research (including literature study, secondary analysis of existing datasets and registries, online searches), as well as fieldwork consisting of semi-structured interviews and conference attendance. The consortium designed an economic landscape survey for the national competent authorities for the safety and quality of tissues and cells in the EU-28 Member States[1] and questionnaires to tissue establishments in the cardiovascular, cornea and bone banking sectors which were used as basis for producing country factsheets. In the reproductive field, an extensive internet search was performed of 180 fertility clinics in the EU for additional information on fertility treatments and services.

Datasets from professional associations were used to cross-reference the findings of this study, and National Competent Authorities for Tissues and Cells were given the opportunity to validate and cross-check the results. Finally, the research team was supported via advisory panel meetings and high-level expert meetings, in order to discuss outcomes of the study and for quality review. The figure below provides an overview of data sources used.

[1] These authorities are designated following Article 4 of Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. While these authorities were consulted for their expertise in the field, they are not, and cannot be seen to be, responsible for the economic organization of the tissue and cells sector within their countries.

Figure 1 Data sources and research design



1.3 TISSUE AND CELL SECTORS COVERED

Different sectors and specific tissue and cell types were covered in the research. These include:

Replacement tissues (RT)

- Cardiovascular tissues
- Cornea
- Musculoskeletal tissue, including bone
- Skin
- Other (e.g. amniotic membrane, pancreatic islets, adipose tissue)

Hematopoietic progenitor cells (HPCs)

- Bone marrow
- Blood (PBSCs)
- Umbilical cord blood (CB)
- Other (e.g. donor lymphocyte infusion/DLI)

Gametes and embryos for assisted reproductive technologies (ART)

- Oocytes
- Sperm
- Embryos

1.4 METHODOLOGY AND RESEARCH DESIGN

1.4.1 Literature review

The desk research includes searches in the scientific and medical literature (PubMed); policy analysis of legal and regulatory documents, including Commission reports and legislative instruments; previous EU-funded project reports (such as those by AGORA, EUSTITE, EURO-GTP, SOHO V&S, DOMAINE, EQSTB); social scientific and economic literature review on transplantation medicine' and assisted reproductive technologies and information regarding the healthcare reimbursement approaches for this sector, as provided by associations and advisory panel members. All scientific articles were saved and managed via the online data reference system Zotero.

1.4.2 Analysis of existing datasets

The initial part of the desk research focused on an analysis of current datasets in the field of tissue and cell transplantation and assisted reproductive technologies. These data were used for cross-reference and provided the baseline for the survey submitted to the National Competent Authorities for Tissues and Cells and for producing country fact sheets for all Member States (see also below).

As a main source, EUROCET[2] was considered to facilitate the analysis of data on donations, tissue banking activities and the distribution of grafts in the EU Member States.

The year of reference was 2012 for RT and HPC, and 2011 for ART as more recent data were not available at the time of research. In addition, datasets collected by the European Commission in 2010 and 2014 during the Voluntary Unpaid Donation (VUD) and implementation surveys were also consulted. These datasets and reports are based on the inputs from National Competent Authorities for the Safety and Quality of Tissues and Cells in the EU-28 Member States.

In addition, the following (online) sources were consulted:

- EUROCET128
- Eurostat
- Registries (see also below)
- European Medicines Agency (EMA) and Committee on Advanced Therapies (CAT)
- World Health Organisation (WHO) website.

1.4.3 Registries

Registries were mostly relevant for the HPC sector, where organisations were actively requested to provide data, or information was retrieved from the internet. The following organisations were consulted:

- World Marrow Donor Association (WMDA) and Group of European Medium Sized Registries (GEMS)

[2] EUROCET is an EU-funded project (2003-2007) under e-TEN programme, coordinated by the Italian Transplantation National Centre, aiming at setting up a registry on organ, tissue and cell donation and transplantation activity shared by Member States. After its completion, EUROCET continues hosting a database on tissue and cell donation and transplantation activities based on voluntary data submissions by EU national competent authorities.

- Bone Marrow Donors Worldwide (BMDW)
- European Society for Blood and Marrow Transplantation (EBMT)
- Joint Accreditation Committee-ISCT & EBMT (JACIE)
- Foundation for the Accreditation of Cellular Therapy (FACT)
- NetCord Foundation
- Anthony Nolan (UK)
- Cord Blood Europe
- Parent's Guide to Cord Blood Foundation (USA)
- German Bone Marrow Donor Center (DKMS)
- Stefan Morsch Stiftung (DE)

For RT, the following registries were consulted:

- Annual Directory of the European Eye Bank Association (EEBA)
- Directory of Cardiovascular Tissue Banks, issued by the Foundation of European Tissue Banks.

For ART, mostly ESHRE data were used:

- European Society of Human Reproduction and Embryology (ESHRE), e.g. European IVF-monitoring group (EIM).

1.4.4 Survey to National Competent Authorities (NCATC)

An online survey was used to get insights from the National Competent Authorities for the Safety and Quality of Tissues and Cells in the EU-28 Member States (NCATC)[3], in order to fill gaps in data that were not otherwise available. These variables were then excluded from the survey design, in order to avoid duplication and to make filling out the survey less time consuming. Variables included in the survey for the different sectors are detailed below:

Regulatory framework: EU distribution, import and export

- Binding legislative requirements in addition to the requirements of the EU legislation or non-binding guidelines regarding distribution of tissues and cells in the EU
- Binding legislative requirements in addition to the requirements of the EU legislation or non-binding guidelines regarding import and/or export from/to third countries.

Regulatory framework: cost and pricing

- Institution/organisation that determines the purchase price for the end users
- Description of the process of determining the purchase price for the end user
- Binding legislative requirements regarding the determination of the purchase price for the end user
- Pricing part of or separate from a price of a transplant procedure
- Prices centrally determined at national level versus prices locally established by tissue establishments
- Prices for different subcategories of tissues and cells

[3] These authorities are designated following Article 4 of Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. While these authorities were consulted for their expertise in the field, they are not responsible for the economic organization of the tissue and cells sector within their countries. While these authorities could contribute to the research, their specific mandate is also an important reason why they could not respond to all questions of the survey.

Regulatory framework for HSCs:

- Forms of storage allowed (and therefore accessible) for cord blood

Regulatory framework for ART:

- Access to ART treatments
- Limitations on getting access to ART treatments
- Reimbursement of ART treatments
- Limitations on reimbursement of ART treatments

Main organisations

- Main organisations in each sector
- Main organisations in HLA typing
- Main organisations in testing

Volumes[4]

- For replacement tissues: number of donors, number of donations, grafts issued to stock, distribution in own Member State, cross-border distribution (within EU), import and export (from/to third countries).
- For HPC: potential donors of BM/PBSC, donation in own country, search activity in donor registries, units stored; number of cord blood units (CBU) stored, available, newly added and distributed; total patients transplanted; cross-border distribution of HPCs.
- For ART: number of donors, donations and donated gametes, number of units distributed in own Member State, cross-border distribution (within EU), import and export (from/to third countries). Number of ART treatments (partner and non-partner donation).
- Shortages and their potential explanation/sector.

In order to establish how the use of human tissues and cells as starting material for products may influence their availability for consolidated transplantation procedures, information on advanced therapy medicinal products (ATMP) was also requested:

- National availability of ATMPs based on hospital exemption and of ATMPs that are centrally authorized;
- Price and reimbursement process for ATMPs per Member State.

A methodologist was consulted for advice on the structure of the survey questions and the order of the questions, and an in-house test panel tested the routing of the survey. Finally the survey was piloted with two members of NCATCs in two different Member States (NL and PL).

The survey was programmed using the online tool Qualtrics. This allowed for extensive routing in the survey to the relevant questions or sections. The survey was accessible through an online link and could be accessed from different computers and stopped and stored at different times, enabling more people to work in the same survey. Sharing the survey between different authorities or experts was also enabled in this way, as many countries have more than one authority per sector.

After piloting and testing in the summer of 2014, the survey was circulated in August 2014. An overview of the responses to the survey is below.

[4] For volumes (e.g. number of donors, donations, treatments etc.) data from the EUROCET database were used for the ART sector, and for the HPC sector data from the WMDA were used. These data were pre-programmed so NCATC could verify, adjust or complement the information. For replacement tissues, no data were preprogrammed as new categories for tissues were introduced.

Table 1 Responses to the survey per Member State and per sector

Member State	Replacement tissues	HPC	ART
Austria	V	V	V
Belgium	V	V	V
Bulgaria	V	V	V
Cyprus	X	X	X
Czech Republic	V	V	V
Germany	V	V	X
Denmark	V	V	V
Estonia	V	V	V
Greece	X	X	X
Spain	X	X	X
Finland	X	X	X
France	X	X	X
Croatia	X	V	V
Hungary	V	V	X
Ireland	V	V	V
Italy	V	V	V
Lithuania	V	V	X
Luxembourg	V	V	V
Latvia	X	X	X
Malta	V	V	V
Netherlands	V	V	V
Poland	V	V	X
Portugal	V	V	V
Romania	X	X	X
Sweden	V	V	V
Slovenia	V	V	V
Slovakia	V	V	V
United Kingdom	V	V	V

V = response, x = no response

1.4.5 Country fact sheets

Data from the survey were integrated with the other data sources (as mentioned above) into country factsheets in order to provide an overview per sector (RT, HPC and ART) for each Member State. Furthermore, tables were produced to integrate findings from different Member States. These were analysed and preliminary findings were described in bullet points which were also discussed with DG SANTE. These country factsheets and preliminary findings were then sent to the NCATCs in order to verify, adjust, complement or comment on. The full table of responses is below.[5]

Table 2 Member States' response to the country factsheet and preliminary findings

Member State	Response to country factsheets	Response to preliminary findings
Austria	Full response, final version not submitted	Full response, final version not submitted
Belgium	Full response	Full response
Bulgaria	No response	No response
Cyprus	No response on country factsheet	Response on preliminary findings
Czech Republic	Full response	Full response
Germany	Partial response (response on replacement tissues and HPC, not ART)	Partial response (response on replacement tissues and HPC, not ART)
Denmark	Response on country factsheet	No response on preliminary findings
Estonia	Full response	Full response
Greece	No response	No response
Spain	Full response	Full response
Finland	No response on country factsheet	Response on preliminary findings
France	No response	No response
Croatia	No response	No response
Hungary	No response on country factsheet	Response on preliminary findings
Ireland	Full response	Full response
Italy	Full response	Full response
Lithuania	Partial response (response on replacement tissues and HPC, not ART)	Partial response (response on replacement tissues and HPC, not ART)
Luxembourg	Full response	Full response
Latvia	No response on country factsheet	Response on preliminary findings

[5] Spain and Romania did not respond to the survey but did verify the country factsheets and the preliminary conclusions (please note the country factsheets for these Member States included data from registries, Eurocet128, implementation survey and VUDTC survey). Cyprus, Finland and Latvia did not respond to the survey but did respond to the preliminary findings (but not on the country factsheet). Bulgaria, Croatia and Slovenia did respond to the survey but did not respond to the country factsheets and preliminary findings. Germany, Croatia, Hungary, Lithuania and Poland did respond to the survey but not to all three tissue and cells sectors of the survey (e.g. replacement tissues, HPC and ART). Germany and Lithuania did not respond to the ART part of the survey and also gave no response to the ART country factsheet and the ART preliminary findings. Hungary did not respond to the ART part of the survey but did respond to the preliminary findings (not to the country factsheet). Poland responded to the replacement tissue and HPC part of the survey, not to the ART part. Poland did give a response to the preliminary findings for replacement tissues and ART but not for HPC and also gave a response to the country factsheets for replacement tissues but not for ART and HPC.

Malta	Full response	Full response
Netherlands	Full response	Full response
Poland	Partial response (response on replacement tissues not ART and HPC)	Partial response (response on replacement tissues and ART, not HPC)
Portugal	Full response	Full response
Romania	Full response	Full response
Sweden	Full response	Full response
Slovenia	No response	No response
Slovakia	Full response	Full response
United Kingdom	Full response	Full response

The country fact sheets were compiled between November 2014 and February 2015 and sent out for final verification by the end of March. Final results were received in April 2015 and included in the final report.

1.4.6 Tissue establishments survey

In parallel to the economic landscape survey to the NCATCs, questionnaires were also sent out to tissue establishments active in three specific domains of replacement tissue: cardiovascular, ocular, and musculoskeletal tissues (mostly bone).

During the period February 2014 to February 2015, questionnaires were sent to:

- 28 EU cardiovascular tissue banks,
- 53 EU eye banks,
- 46 EU musculoskeletal tissue banks,
- one eye bank in Switzerland with close relations to several eye banks in the EU,
- two musculoskeletal organisations in the US with significant export activity to EU Member States.

The addresses of cornea and cardio-vascular tissue banks were, with the permission of the respective professional organisations, obtained from the Directories of the EEBA (European Eye Bank Association, 2014), and the SEGB (Foundation of European Tissue Banks, 2013). During the survey period, several reminders, by email and in person, were addressed to those who hadn't yet responded. The survey of musculoskeletal tissue establishments was sent out to 46 organisations, mostly in Europe (and two in the US).

Overall, by early 2015, replies were received from 43 tissue establishments (10 EU, one in Switzerland and two from the US). The responses are in the table below.

Table 3 Responses to the tissue establishment survey

Tissue establishments	Total number of tissue establishments in the survey	Number of responses
Cardiovascular	28	12
Cornea	53	15
Bone	46	16
Total	**127**	**43**

1.4.7 Internet search of ART establishments

In order to cross-reference data and for additional data collection in the ART sector, an additional data search strategy was developed.

The focus of the internet search was to understand the internationalisation of activities for assisted reproductive technologies, so the search was narrowed down to establishments for assisted reproductive technologies (ART establishments) that addressed potential patients from abroad, by including clinics with a multi-language internet webpage.[6] The internet search is thus not meant to be representative for ART activities (such as number and size of clinics) within a Member States but to get additional information on the movements between Member States and cross-border reproductive care. The internet search was conducted in the period 1 July 2014-15 October 2014, with final data cleaning performed in April 2015.

The sample size was relatively large in order to provide adequate coverage in the EU and relevant third countries. Websites of 180 ART establishments in the EU-28 Member States were analysed. A sample of 20% of the total number of IVF-clinics per Member State was taken, with a minimum of five clinics. The table below provides an overview. As a reference point for the total number of ART establishments per Member State, a list of authorised tissue establishments was used. This list included ART establishments licensed under the Tissue and Cell Directive (2004/23/EC) mainly from the EUROCET128 database.[7]

[6] In most cases one of the other languages was English, but this was not a set criterion. Multi-language websites from which English was not one of the languages were included, for example Polish clinics that were also available in German. Several exceptions were made to the inclusion criteria of having a multi-language website. English language websites from Great Britain and Ireland not available in any other language were also included as these websites are accessible to people from other Member States. Furthermore, we included websites that were only available in the language of the Member State in which the clinic was situated in cases where this language is also an official language (or very similar language) in a neighboring Member State. This included: Dutch clinics with a website only in Dutch; Belgian clinics with a website in Flemish; Belgian clinics with a website in French; French clinics with a website in French; German clinics with a website in German, and Austrian clinics with a website in German. Finally, we included websites from clinics that were only available in the language of the Member State if these clinics were part of a chain organisation from which the main website of the chain was a multi-language website, for instance in Sweden.

[7] There are several possible reasons why clinics offering fertility treatments are not on the EUROCET128 list. One reason is that they are not subject to having to be licensed under the national implementation of the Directive. Furthermore, at the time of the internet search, the EUROCET128 list was in its final stage but still under revision; possibly these clinics were included in the final EUROCET128 list. For five countries no clinics were included on the EUROCET128 list. These countries are Estonia, Greece, Lithuania, Malta and Poland. For these we set a target loosely related to the size of the Member State: 5 for Estonia, Greece 16, Lithuania 5, Malta 5 and Poland 10. In several cases we included more or fewer clinics than the target (20% of the EUROCET128 list with a minimum of five). In Luxemburg and Slovenia, the total number of clinics is fewer than five. Furthermore, we included fewer clinics than the target if no further clinics with multi-language websites

Table 4 Sampling strategy: internet search of 180 ART establishments in EU

Member State	ART establishments EUROCET 128 database	20%	Total of websites analysed	On EUROCET 128 list	Not on EUROCET 128 list
Austria	29	6	6	6	0
Belgium	60	12	12	12	0
Bulgaria	32	6,5	7	6	1
Croatia	12	2,4	3*	3	0
Cyprus	9	1,8	5	2	3
Czech Republic	39	8	8	6	2
Denmark	63	12,6	13	12	1
Estonia	Not on list	-	3*	0	3
Finland	23	5	3*	3	0
France	188^	38	4**	2	2
Germany	180	36	12**	7	5
Greece	Not on list	-	16	0	16
Hungary	13	2,6	5	1	4
Ireland	11	2,2	5	5	0
Italy	196	39	5**	2	3
Latvia	6	1,2	5	4	1
Lithuania	Not on list	-	5	0	5
Luxembourg	1	0,2	1	0	1
Malta	Not on list	-	1**	0	1
Poland	Not on list	-	11	0	11
Portugal	26	5	2*	2	0
Romania	23	5	5	3	2
Slovenia	3	0,6	0*	-	-
Slovakia	8	1,6	2*	2	0
Spain	18	3,6	13	0	13
Sweden	15	3	5	5	0
The Netherlands	78	15	10**	6	4
United Kingdom	±100***	20	13**	10	3

* No further multi-language websites found ** Point of saturation reached after clinic *n*
*** List does not distinguish ART centers ^ Figure provided by DG SANTE

Source: EUROCET128 (provided by DG SANTE), Internet fertility search Rathenau Instituut (2014)

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could be found through the google search. This was the case for Finland, France, Italy, Portugal Estonia and Malta. In Slovenia, none of the total number of three clinics had a multi-language website and therefore no clinics in Slovenia were analysed. For France also, websites only in French can be included according to the inclusion criteria, but since adding new clinics did not add new information (point of saturation was reached) no more clinics were added. For Germany, The Netherlands and United Kingdom, fewer than the target of 20% were analysed for this same reason. For Spain, more than the target of 20% were analysed as significantly more clinics offer fertility treatments with a multi-language website than the number listed on the EUROCET128 list. On the EUROCET128 list, 18 clinics are listed against the target of 5 clinics to analyse. To have a more comprehensive view, we included 13 clinics in our analysis for Spain. For Cyprus we only included clinics from the EU part of the island. For comparison we analysed three more websites of clinics on the Turkish part of the island, which will be described separately.

Data collection and analysis in the ART sector was difficult, which is why caution is in place in interpreting the findings. Data on gamete donors, ART treatment with non-partner donations and flows of gametes are incomplete. There are various factors hindering collecting a complete database on ART. In this section we reflect on a few of those.

As part of the research for this report, National Competent Authorities for Tissues and Cells were asked to complement existing data on, for instance, the number of sperm, oocyte and embryo donors and treatments with donor sperm or oocytes. From EUROCET and ESHRE no data was available on flows between Member States and between Member States and third countries (except for limited data reported in the Implementation Survey, also incorporated in this report). The National Competent Authorities for Tissues and Cells were asked to provide this data. The most common response by the National Competent Authorities for Tissues and Cells was that data was not collected at national level, or collecting these data not mandatory.

Another hindering factor is the variability between Member States as to how data is collected at the national level. For some Member States, the implication is that the template used for data collection does not match the way data is collected at national level. Spain, for example, makes no distinction between IVF and ICSI when collecting data; in the EUROCET template, IVF and ICSI are asked separately. Also, some Member States do collect data on total number of treatments but do not separate treatment with partner donation from treatment with non-partner donation as specified in the EUROCET template, making it difficult for those Member States to provide data. Finally, Member States differ in how the number of treatments are counted, which makes it hard to compare the number of treatments between Member States. France, for instance, collects data on the number of aspiration cycles for IUI, while Finland only reports the number of cycles started, and Sweden only the number of couples treated.

1.4.8 Interviews and fieldwork

Semi-structured interviews were conducted with key actors in the field in order to gain inside knowledge into local practices or to discuss trends and issues in transplantation and reproductive medicine. Some interviews were clustered per country or sector, some were group interviews and several meetings took place during international conferences where many of the experts were present, such as the meetings of the European professional associations in 2014 and 2015[8].

Thirty experts were actively engaged in the meetings and interviews. These experts were selected from clinics and hospitals, tissue establishments, academic centres, industry (including commercial developers, spinoffs, brokers), regulatory organisations and related committees (e.g. HTA, EMA, CAT), and professional associations and registries (e.g. EATB, EEBA, WMDA, EBMT, ESHRE).

For the semi-structured interviews, topic lists and informed consent forms were developed. Notes were taken during the interviews but not transcribed verbatim or coded. Informal conversations took place during conferences and meetings or during expert and advisory meetings.

[8] EATB meetings Brussels 2013 and Lund 2014, AATB meeting San Diego USA 2014, ESHRE annual meeting Munich 2014, Brocher summer school ART Geneva 2014, ATMP meeting Dresden 2014, EBMT meeting Istanbul 2015

1.4.9 Advisory panel

High-level experts from different medical sectors and professional associations were included as members of an advisory panel during the research process. Their specific tasks were:

- To provide support in getting data access on an ad hoc basis, on request by individual team members (via phone or email) or in local arrangements for interviews, and/or to provide support in accessing local (language) documents and interpretation of data.
- Review of the draft final report before finalizing the last version, during working meetings in Brussels.
- To discuss key messages and draft conclusions per medical sector during working meetings in Brussels.

Members of the advisory panel were selected taking into account expertise (e.g. tissue and cell banking, legal-regulatory, health technology assessment, clinical expertise in tissue/cell transplantation and ART), membership/board management position to a European professional association, and geographic coverage.

The meetings of the advisory panels took place in April 2015 at DG SANTE in Brussels. Experts present were:

- Dr. Sergio Querol, Director of the Hematopoietic Progenitor Cell Unit and Cord Blood Bank of Banc Sang i Teixits in Barcelona (ES)
- Lydia Foeken, Executive Director World Marrow Donor Association WMDA (NL)
- Dr. Claudia Rutt, Former Executive director and co-Founder of DKMS (DE)
- Timothy Fox, Commercial Director of Anthony Nolan (UK)
- Dr. Anna Veiga, director stem cell bank Barcelona, past chair ESHRE (ES)
- Dr. Stine Willum Adrian, social scientist researching sperm banking (DK)
- Prof. dr. Sjoerd Repping, Professor in human reproductive medicine AMC (NL)
- Dr. Kersti Lundin, Reader Obstetrics and Gynecology Göteborg, chair ESHRE (SE)
- Dr. Veerle Goossens, Science manager ESHRE (BE)
- Hannah Verdin, Head of regulatory affairs HFEA (UK)
- Prof. dr. Iva Dekaris, medical director eye hospital Zagreb, former president EEBA (HR)
- Dr. Artur Kaminski, tissue bank expert Warsaw, president of EATB (PL)
- Prof. dr. Klaus Lindgaard Høyer; professor department of public health, University of Copenhagen (DK)
- Dr. John-Paul Pirnay, skinbank, Queen Astrid Military Hospital Brussels (BE)
- Luc Noël, transplantation expert WHO (FR)
- Josie Godfrey, associate director NICE (UK)

1.4.10 Looking forward

Additional research was performed for the development of the "looking forward" chapter. This included interviews with several experts in the clinical and regulatory field, attendance to an expert workshop on advanced therapies organised by CAT/EMA and reporting from desk research of ongoing EU-funded projects. Clinical trial databases, both covering (centrally authorised) medicines and other therapies, were also consulted in order to get a better understanding of the pipeline of new therapies based on tissues and cells.

1.5 RESEARCH TEAM AND AUTHORSHIP

This study was performed by a consortium of three main organizations: the Rathenau Instituut-Royal Netherlands Academy of Arts and Sciences (RI-KNAW, NL), the

Foundation of European Tissue Banks (SEGB, DE), and the Dutch Foundation for Hemovigilance and Biovigilance (TRIP, NL). A small part was contracted to the German Heart Institute Berlin (DHZB, DE). The study followed a call for tender No EAHC/2012/Health/19 concerning an 'EU-wide economic overview of the markets of tissues and cells for transplantation' launched by the Consumers, Health and Food Executive Agency (CHAFEA, formerly EAHC). The contract started in December 2013, and ended in May 2015. The chapters were written by the following authors:

Chapter 1: Introduction

Ingrid Geesink

Marjolijn Heerings

Chapter 2: Horizontal economic aspects of tissue establishments

Theo de By

Ingrid Geesink

Arlinke Bokhorst

Jürgen Ehlers (on VAT)

Chapter 3: Replacement tissues

Theo de By

Marjan Happel

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Chapter 4: Hematopoietic progenitor cells

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Suzanna M van Walraven

Marjoleine Bergers

Chapter 5: Assisted reproductive technologies

Ingrid Geesink

Marjolijn Heerings

Judith Weeda (internet search)

Anna van de Haar (research support)

Chapter 6: Forward look

Arlinke Bokhorst

Ingrid Geesink

1.6 CONCLUDING REMARKS AND SUMMARY INTRODUCTION

- The safe and sustainable supply of tissues and cells is an essential pillar in modern EU healthcare and a priority for national and EU-level health authorities alike. While tissues and cells are usually donated by citizens without any payment, they still require some further processing and handling before they can be applied as therapy. Many of these activities are undertaken by public actors, while others are undertaken by private actors. In both cases, costs are involved and different options exist to recover (part of) these costs.

- Understanding the economic aspects of the tissues and cells sector can help Member States in taking, increasingly difficult, decisions on how to organize this essential part of public health at best. This is in particular important as the tissues and cells sector is subject to continuous technological innovation and globalization, and as a consequence to changing economics and organisational setups.

- The EU health contracting agency CHAFEA therefore called for a study aimed at producing an overview on EU wide economic landscapes of human tissues and cells for transplantation, covering three medical sectors:
  - Replacement tissues: bone, cornea, skin and cardiovascular tissues (RT)
  - Hematopoietic progenitor cells from bone marrow, peripheral blood and cord blood (HPC)
  - Gametes and tissues for assisted reproductive technology (ART).

- For each sector the study brings a field description, a view on organisational set-up, on economic aspects and a future perspective. The study also covers horizontal aspects relevant for each of these three medical sectors and a forward looking chapter covering impact of related sectors and general factors that will influence the future of the tissue and cell landscape.

- The study maps the three domains across all EU-28 Member States by identifying key activities and costs, key players in public and private sectors, legislative and reimbursement schemes across Member States, and finally emerging technological trends and associated ethical, legal, and social issues.

- The research involved extensive document-gathering and analysis via desk research (including literature study, secondary analysis of existing datasets and registries, online searches); fieldwork consisting of semi-structured interviews and conference attendance; a survey to National Competent Authorities for the Safety and Quality of Tissues and Cells (NCATC) in the EU-28 Member States and production of country factsheets; questionnaires to tissue establishments in cardiovascular, cornea and musculoskeletal (mostly bone) banking; and finally, a forecast to identify novel therapies in the tissue and cell sector and an outlook on emerging techno-legal issues in the EU context.

2 HORIZONTAL ASPECTS OF ECONOMIC FACTORS IN TISSUE AND CELL BANKING

Tissue establishments, regardless of whether they focus on replacement tissues, assisted reproductive tissues and cells, or hematopoietic stem cells, share some common, horizontal economic aspects.

It is widely accepted and encouraged in the EU Member States that donation of human tissues and cells for transplantation is unpaid. According to the EU Directive on quality and safety of human tissues and cells (2004/23/EC), the philosophy of voluntary unpaid donation (VUD) should be a guiding principle, and Member States are urged to take steps to encourage a strong public and non-profit sector involvement in the provision of tissue and cell application services (2004/23/EC:18).

However, it is important to note that economic factors do have an impact on the broad range of tissue banking activities. Every activity undertaken comes with a cost, regardless whether they are undertaken within a public or private setting. As such these factors have an impact on the availability to patients of safe tissue and cell therapies. This section focuses on costs and incomes for tissues and cells produced and delivered by tissue establishments.

If tissues or cells are needed for a patient in a hospital or clinic, either that organisation or the appropriate health (insurance) institution[9] is charged by a tissue establishment.[10] Although tissue was donated altruistically and free of charge, costs of labour and services necessary to transform the donor material into a usable and safe transplant add up, and need to be covered. For tissues aimed at autologous treatments after processing or storage in the tissue establishment, costs are equally applicable.

Throughout the European Union, the process of establishing the fees necessary to cover the costs incurred in tissue and cell banks is regulated and influenced in many ways. This chapter provides an indication of which costs are generated in the different steps of the process from donation to transplantation.

2.1 INVESTMENT, FUNDING AND COSTS OF TISSUE ESTABLISHMENTS

2.1.1 Investment

The demand for tissue or cellular allografts can be intermittent (incidental) or structural. For example, if a hospital or clinic uses donor tissue only a few times per year, it may not be feasible to invest in the construction of a tissue bank. If the demand is structural (e.g. daily use in orthopaedics or ophthalmology), setting up a tissue or cell bank can guarantee a continuous flow of tissue, of which the specifications should correspond with the demand from one or more hospitals. Many tissue and cell banks have been set up to cover a specific local demand. The bone/musculoskeletal sector is a good example of

[9] In research undertaken as part of this study, three cases were found where the tissue establishment provided grafts free of charge. These tissue establishments were located in a university hospital which compensates the total costs of these tissue establishments.

[10] In the UK, hospitals currently pay no processing fee for corneas or sclerae from the Bristol and Manchester Eye Banks. There is a charge levied by NHSBT to cover transportation and a contribution towards the cost of the NHSBT Eye Retrieval Scheme, which provides funds for eye retrieval staff in 10 hospitals around the UK. The eye banks run as NHSBT-commissioned services with the salary and other running costs funded through an agreed budget with NHSBT. This is all changing and full cost recovery is due to be introduced by NHSBT starting April 2015.

this. In the EU, there are hundreds of local tissue establishments providing femoral heads, procured in the OR, for the benefit of recipients in the same hospital. However, in parallel larger tissue establishments supply bone (and other multiple tissues) on a regional or national level or even across borders.

Initiating a tissue establishment compliant with the requirements of EU Directives (Directive 2003/94/EC), particularly with relation to the processing facility requirements, requires investment. Not only for the construction of a cleanroom and adjacent service rooms, but also for special instruments, education and training of personnel, quality system and certification, as well as for putting in place the appropriate ICT solutions. The table below shows the following range of costs per m^2 of a GMP laboratory.

Table 5 Classification of cleanroom levels

	Maximum permitted number of particles/m^3 equal to or above				Recommended limits for microbial contamination			
Grade	At rest**		In operation		Air sample cfu/m^3	Settle plates cfu/4 hours	Contact plates cfu/plate	Glove print 5bfingers cfu/glove
	0.5µm	5µm	0.5µm	5µm				
A	3,500	0	3,500	0	<1	<1	<1	<1
B*	3,500	0	350,000	2,000	10	5	5	5
C*	350,000	2,000	3,500,000	20,000	100	50	25	-
D*	3,500,000	20,000	not defined	not defined	200	100	50	-

Source: Camfil Farr (via Advantage Business Media, Controlled Environments, 2013)

*(a) In order to reach the B, C and D air grades, the number of air changes (i.e. a measure of how many times the air within a defined space per hour is replaced) should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for grades A, B and C.

**(b) The guidance given for the maximum permitted number of particles in the "at rest" condition corresponds approximately to the US Federal Standard 209E and the ISO classifications as follows: grades A and B correspond with class 100, M 3.5, ISO 5; grade C with class 10 000, M 5.5, ISO 7 and grade D with class 100 000, M 6.5, ISO 8.

Indeed, one of the main drivers for initial investment relates to the level of environmental air quality and related cleanroom conditions required to process tissues and cells. Depending on the tissue grafts that will be processed, different levels of airborne particulate classification can be defined, based on the EU guide to GMP, which is also used by the Directive 2006/86/EC to define the requirements of the environment during processing of tissues and cells in a tissue establishment.[11] These so called cleanrooms are necessary to prevent microbial contamination of the tissues during

[11] Directive 2006/86/EC. Annex D. "3. Unless specified in point 4, where tissues or cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality with particle counts and microbial colony counts equivalent to those of Grade A as defined in the current European Guide to Good Manufacturing Practice (GMP), Annex 1 and Directive 2003/94/EC is required with a background environment appropriate for the processing of the tissue/cell concerned but at least equivalent to GMP Grade D in terms of particles and microbial counts.
A less stringent environment than specified in point 3 may be acceptable where: (a) a validated microbial inactivation or validated terminal sterilisation process is applied; (b) or, where it is demonstrated that exposure in a Grade A environment has a detrimental effect on the required properties of the tissue or cell concerned; (c) or, where it is demonstrated that the mode and route of application of the tissue or cell to the recipient implies a significantly lower risk of transmitting bacterial or fungal infection to the recipient than with cell and tissue transplantation; (d) or, where it is not technically possible to carry out the required process in a Grade A environment (for example, due to requirements for specific equipment in the processing area that is not fully compatible with Grade A).

processing. The requirements for a certain level also depend on the processing steps (debridement, cutting, sizing) after the work in the clean room has been completed. To achieve this, a certain level of absence of particles in the air must be maintained (see table below). For a Class A clean room, a level of maximal 3 500 particles of a size of 0.5 µm and 0 (zero) particles of 5 µm is permitted (Commission Regulation (EC) No 1234/2008).[12] A Class A environment requires continuous monitoring of particle counts (FDA 2004; 91/356/EEC Annex 1 Revised 2008). Under Class D these values are 3 500 000 and 20 000 per m3 respectively.

Although legislation, guidelines and standards exist, in general best practice translates into aseptic tissue processing within environmentally controlled facilities, as it is up to each establishment to determine and establish the qualification of their facility in relation to cleaning and sanitation (AATB, 12th Edition; Nair et al, 2012). As such, musculoskeletal and cardiovascular tissues may be processed in Grade A clean rooms (A laminar Flow Cabinet against in a grade B environment), but a lower grade (A with C or D background) is also still common practice. Skin and corneal grafts, depending on the final graft that is to be produced, may be processed in a Grade A Laminar Flow Cabinet, with an environment of Grade C or D. HPC processing usually takes places in Grade C or D environment in a Grade A Laminar Flow Cabinet. If the grafts are not processed in a Grade A clean room, and the tissue allows it, terminal sterilisation is applied or required by local authorities. The investment for a clean room facility can be considerable as shown in the table below.

Table 6 Investment cost of GMP cleanrooms

	€ price m2	€ price m2
	Minimum	**Maximum**
Class A	12,331	14,061
Class B	9,730	11,178
Class C	7,452	8,746

Source: Advantage Business Media 2013

As indicated, since facilities with Grade A clean rooms must be entered from Grade B, and assuming that the minimum Grade A surface area is $16m^2$, and the Grade B room is $8m^2$, the minimum investment in this facility (without service and office space) would be about €275 000. Assuming a ten-year depreciation period, the annual costs would be €27 500. If the tissue establishment in this example were to distribute 1,000 tissue grafts per year, a cost of €27.50 per graft could be included (in addition to other costs, see below) in the calculation of the final fee to the end user, in order to recover this investment. It might be assumed therefore, that it is in the interest of tissue establishments with high investment costs to process as many grafts as possible to achieve an economy of scale in which these costs per tissue are as low as possible.

In a typical processing unit, multiple environmental Grades are required. For instance, a clean room complex can consist of 20 m² Grade A, 100 m² Grade B, 20 m² Grade C and

[12] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

800 m² Grade D. A typical investment in a cleanroom facility therefore costs easily over €1 million.

Maintaining and running clean rooms also incur high operational costs, including:

- Electricity to provide clean air and temperature control
- Regular change of hepa-filters
- Sterile personnel suits
- Microbiological control and environmental monitoring
- Sterile materials and agents
- Cleaning after each donor

Additionally, before the tissue establishment can start using its clean rooms for processing tissues, there will be a non-productive, preparatory, testing and validation period required for the qualification of the facility. The cost of this non-productive period and the investment in construction of the tissue establishment during a phase without income should be taken into account.

2.1.2 Funding

There are multiple options for financing a new, state of the art tissue establishment:

- Donation such as a subsidy by a government, a charity or the general public
- Grant or financial injection by the hospital or the university, primarily to create a solution for the demand for tissues or cells in that specific clinic/hospital
- Bank loans (from financial institutions)
- Private party investment
- A combination of two or more of the above.

The source of investment may very well influence the fees that tissue establishments ask for their services, either within or outside the location where they are situated.

In the case of subsidies, grants or injections by public actors, charities or governments, there is usually no necessity for a return on investment. So it may very well be that the investment and operational costs are not reflected in the fee or price. When banks or private investors have contributed, standalone or in a combination with other modalities, there is a necessity for a return on investments through interests, and/or a dividend to the investor(s) and eventually return of the investment itself.

The modality of investment also influences the legal entity under which the tissue establishment is operating. The nature of the legal entity may influence the fees tissue establishments are charging. Tissue establishments are set-up in different ways. As a result, the following broad funding models can be observed in tissue establishments in the EU.

1) *Public sector: centrally allocated operating budget; tissues and cells provided to the user without charge*

This was the typical model for a hospital based tissue bank, supplying only to users in its own hospital, and fully hosted and financially supported by the hospital. Although common in the past, this model is now much less frequently seen. It does however still exist in a number of Member States for some tissue and cell types. It avoids any kind of competitive market, any disincentive for hospitals to use tissues and cells, and any pressure on tissue establishments to distribute a particular volume of tissues or cells for clinical use. However, it is often challenging for centrally-funded tissue establishments to obtain the funding needed for investment in new or improved facilities or for preparation

process developments (depending on who is the centrally funding entity, e.g., a hospital or government). In this model, many essential internal steps are carried out by public sector players also without charging, e.g. donor testing or microbiological testing of tissues or cells, and total service costs are often not well defined, which can be performed by other horizontal hospital services. Salaries and benefits of employees are tightly controlled as in all public sector health service units.

2) *Public Sector: cost recovery from user hospitals, clinics, patients or health insurance schemes*

This health service 'internal market' model is increasingly common in the field of tissue and cell services, as is it is in the entire public health sector. It requires a full costing activity that includes identification and quantification of fixed and variable costs, including capital depreciation and the costs of all third party contracts. The fee charged for each unit of tissues or cells distributed should equal the total unit cost so that income from tissues or cells supplied provides adequate funds for a sustainable service. The fee charged might include a small percentage for service development and for contingency planning in the event of emergency. Salaries and benefits of employees are also controlled in this model, as in all public sector health service units.

In this model, there is a 'break-even' point when the tissue establishment is supplying a sufficient number of finished tissues or cells to cover all costs; a so-called critical mass. The need to achieve a 'break-even' point could be seen as putting pressure on the tissue establishment to compete with other (private or public) tissue establishments for orders; their service might not be economically sustainable otherwise and hospitals might become dependent on commercial providers. However, in this model, there is usually more opportunity for leading tissue establishments to carry out thorough cost-assessments and to obtain adequate funds for service developments and facility improvements. Commonly, this model exists in the context of tissue establishments that are established within other public sector health organisations such as blood transfusion services. In some cases, tissue establishments operating in this funding model might obtain an injection of 'start-up' funding from the central health service or cross-subsidisation from the parent organisation for an initial period until well established.

3) *Independent: non-profit; cost recovery from user hospitals, clinics, patients or health insurance schemes*

The establishment of independent foundations or other types of non-profit organisations has been observed in this sector over a number of years. This model is characterised by cost-recovery based on a full-cost analysis as in the previous model and the same pressure exists to achieve a threshold level of supply activity to ensure adequate income to cover all costs. The independence of these organisations, however, means that there is less (or no) health service financial governance and aspects such as employee salaries, and benefits and the margins included for developments or other contingencies, can be much higher. The greater flexibility provided in this model often allows a tissue establishment to achieve a high level of efficiency and rapid development but the model raises concerns regarding the sustainability of services if the owners choose to move to another activity. Many independent non-profit organisations achieve success through supplementing their income by achieving charity status and organising fund-raising programmes; this applies notably to a number of independent bone marrow donor registries.

4) *Independent: for profit companies*

This purely commercial model involves accurate costing of activities but no requirement to ensure that fees or prices equal costs. In the EU, this model exists in the field of assisted reproduction (private ART establishments), private cord blood banks for family use and some replacement tissues, particularly bone. In the case of commercial bone banking and supply, most commercial actors are subsidiaries of US companies.

Traditionally, tissue banking in the EU has been organised under one of the models described above. Some commercial players are quoted on the stock exchange, bringing the added feature that their strategy for tissue and cell processing and supply can be determined by shareholders, not in any way involved in the field.

The levels or sources of the investments were not studied for this report.

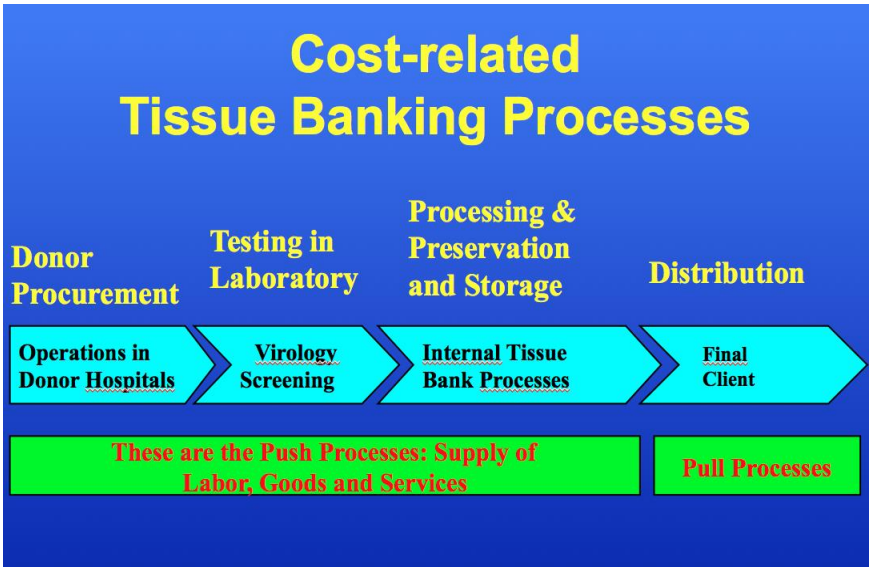
2.1.3 Operational costs

In order to understand how tissue establishments have calculated their costs, four main activities (processes) are recognised in any tissue establishment. In terms of micro-economics, these may be indicated as cost-centres. This division in four major activities doesn't differ from similar structures in any productive organisation:

- Donor recruitment and selection; tissue procurement or cell collection (acquisition of raw materials)
- Testing and quality control (quality management)
- Processing and storage of tissues or cells (production into end products)
- Distribution (customer relations and physical distribution to end users - hospitals, health professionals or recipients directly).

Overhead costs such as management costs, public relations, software, etc. are allocated over the four main activities by means of 'activity-based costing'. This means that these costs are divided according to a factor representing the level of activity (work) taking place in these four activities.

Figure 2 Core processes and cost in tissue establishments



Source: Theo de By (2013)

The costs, generated in these four main processes, add up to the total costs of the tissue establishment. The tissue establishment management needs to recover these costs from the revenue for the number of finalised tissue/cell grafts that are distributed during one year, in order to financially break-even. Also, the investment costs might also need to be recovered from these revenues, over a period of years of depreciation, depending on the funding model.

It is therefore important that tissue establishments have a good understanding of their cost-structure. Cardiovascular and ocular tissue establishments were asked in research

for this report whether they have cost calculation information, specified for the four main processes. Replies are summarised in the table below.

Table 7 Number of tissue establishments with cost calculation

	Cost calculation made	No cost calculation made	No answer	Total
Cornea Banks*	12	3		**15**
Cardiovascular Banks**	6	5	1	**12**
Total	**18**	**8**	**1**	**27**

Sources: * Survey to ocular tissue establishments (2015), data from 2012 ** Survey to cardiovascular tissue establishments (2014), data from 2012

Respondents who did not calculate the costs, were mostly tissue establishments where the price is determined by either the government or by another authority. Only three cornea banks, and no cardiovascular tissue establishments, specified the costs in line with the core processes.

2.1.4 Donor recruitment and selection, and tissue procurement costs

Direct and indirect costs occur when a tissue establishment recruits donors and donations. The direct costs are the costs of the procurement that can vary significantly in complexity. Obtaining sperm cells from a living donor is relatively simple, while obtaining heart valves from a deceased donor requires invasive surgery. Appropriately-trained staff, sterile instruments and materials for tissue retrieval, and transportation of tissues and/or retrieval teams are the main direct costs.

Frequently, tissue has to be discarded after procurement due to quality and safety reasons such as medical contraindications to transplantation, microbiological contamination, and tissue quality. For example, in cornea banking the percentage of discarded tissues is approximately 40% on donor related, serological, microbiological or morphological grounds (EEBA Annual Directory, 22nd edition). In cardiovascular tissue banking, many valves are rejected because of calcification, fenestrations or other anatomical abnormalities.

Thorough donor selection based on the donor history, professional procurement techniques, as well as donor testing (see Chapter 2) is therefore essential. Obviously these are easier with living donors. A set of well thought-out questions, with cross references and an assessment by qualified and trained healthcare professionals is therefore of upmost importance in order to pre-select donors well and minimize later discard rates. The donor retrievals that result in discarding of tissue grafts are still a direct cost burden that contributes to the overall running cost of a tissue establishment.

The indirect costs include maintenance of an infrastructure for recruitment and initial selection of donors. In the case of regional post-mortem donation, the infrastructure includes such necessities as: maintenance of a stock of materials, trained staff and a 24/7 duty desk.

Tissue establishments providing bone marrow, Peripheral Blood Stem Cells (PBSC) or sperm present a specific situation of donor recruitment and banking. These activities are based on an inventory of potential donors. Having a register of potential donors is an essential asset for providing an adequate number of donations for medical purposes. The effort that goes into recruiting donors, but also in retaining and keeping track of them, is a substantial part of the costs in these establishments. For stem cell registries, it also means that because of the unique HLA typing, an enormous number of potential donors

is needed to provide for a limited number of effective donations and eventual grafts (0.01-0.1% of the registered donors actually donate per year) (WMDA report, 2012).

2.1.5 Costs of testing for safety

To minimise the risk of serious adverse reactions (SARE) due to the infection of the recipient with contaminated material from the donor, various tests are carried out in all tissue establishments. EU legislation lays down a set of minimum testing requirements (Directive 2006/17/EC Annex II), while in several countries, there are additional tests designed to address the local epidemiological situation.

The composition of the test regimen may therefore be different from country to country and from bank to bank, however a minimum set of tests to be performed is mandatory. In addition to blood tests for markers of transmissible diseases, tissue establishments sometimes include blood cultures or the determination of absence of malignancies by a pathologist. Emerging infectious diseases or changes in the prevalence or incidence of existing viruses require that new tests be added to the existing regimen.

Testing techniques are continually developing. Contaminant micro-organisms that could not previously be detected may be detectable in the future; e.g. nucleic acid technology (NAT) tests, which enable tissue establishments to determine the presence of specific donor-related viruses, and/or to confirm the negative outcome of other tests. The existing regimen and the necessity to add additional tests can influence the final fee for the tissues.

2.1.6 Costs of processing and storage

Processing is the activity in which the donated tissue is prepared as a graft for storage and subsequent transplantation. Processing can be more or less intensive, depending on the kind of tissue as well as on the chosen decontamination method. For example, the preparation of corneas involves cleaning and disinfection of the whole eye, dissection of the cornea, placement in storage medium (with or without subsequent microbiological testing) and an assessment of tissue quality. On the other hand, the processing of bone may involve different steps, including terminal sterilisation by gamma-irradiation. Many tissue establishments perform microbiological testing during processing and and/or apply methods aimed at eliminating any micro-organism. These activities generate high costs. Processing requires trained personnel with appropriate expertise who process the tissue in cleanrooms.

Depending on the kind of tissue and the packaging and storage method, the storage time after processing can vary from a few days to many years. Short-term storage has the risk that tissue or cell grafts expire more quickly, while long-term storage has the risk that revenues may be obtained years after the costs have been incurred, possibly leading to financial liquidity problems.

The costs for equipment and organisation of storage also depend on how the tissue is stored; e.g. by room temperature on shelves (glycerol-preserved skin); in incubators (cornea); at -80^{o}C (musculoskeletal tissue); or in liquid or vapour phase nitrogen (heart valves). Monitoring storage temperatures by continuous logging and alarm systems add to the cost of storage.

2.1.7 Costs of distribution

In the distribution process, which aims to provide finalised tissue/cell grafts to the end-user (surgeon, patient or hospital) of the tissue establishment, there are direct and indirect costs. The direct costs include packaging and transportation. The indirect costs

consist of the administration of logistics in relation to final destination, recipient data and costs to be charged.

Distribution costs vary significantly. There are tissue establishments which process tissue/cells mainly for local use, for example, tissue establishments related to a hospital. At the other end of the scale are tissue establishments that ship tissues/cells to clinics/healthcare professionals across borders, as is often the case in the HPC sector.

2.1.8 Allocation of financial surpluses

In order to guarantee long-term continuity, all organisations, both for-profit and non-profit, must at least generate sufficient income to cover their costs. Financial surpluses occur when there is more income than costs.

Whereas for-profit organisations focus at maximising profits and will use (part of) these surpluses to compensate shareholders or other providers of risk capital, organisations that are not aimed at making profit might allocate any financial surplus as 'reservations' to the financial balance, or might transfer them to the centrally funding entity. Where reservations are made, these can be earmarked to compensate future losses, or investments, for example. As in tissue banking, donations fluctuate from year to year, and therefore income fluctuates accordingly, such reservations are important to guarantee the continuity of the services provided.

2.2 MANAGING VOLUMES AND THE RELATED COST FOR TISSUE ESTABLISHMENTS

The main purpose of banking human materials for transplantation is to satisfy the clinical demand for tissues and cells. In many cases, a tissue/cell transplant is the best or only therapeutic option for patients. Tissue establishments in general have a complex serious of tasks: to correctly estimate the demand for tissue transplants; plan the number of donations needed accordingly; purchase procurement and processing materials; and finally, produce transplantable allografts.

Tissue establishments have an additional challenge: they depend on the willingness of the general public to donate tissues and cells before or after death. The return on investment of donor recruitment is uncertain. Donor shortage is frequently reported (WHO, 2014); NTS, 2014), and can be absolute or relative (insufficient donors of a specific type of tissue). In a situation of absolute donor shortage, the tissue establishment cannot satisfy the medical demand, nor can it cover its projected costs. The nationally defined donor consent system plays a role in this, and is often related to organ donation, although consent systems fall outside the scope of this report.

A different scenario is when tissue establishments are very successful in recruiting donors. In such situations the stock of grafts, for which no recipients can be found (yet), becomes a financial burden. For the management of the tissue or cell bank, it might be difficult to explain why, after many years of publicity about the need to donate, donations from the public are refused because there is a surplus.

In situations where tissue establishments distribute relatively few tissues, it may be that the total financial proceeds received by distributing tissues to the end-users (hospitals or surgeons) is not enough to compensate exploitation and investment costs. In such cases, without other financial resources, the tissue establishment may have insufficient 'critical mass' for innovation and investments for improvements and ultimately, the continuity and sustainability of the tissue establishment may become uncertain (as was demonstrated in the case of *Bayerische Gewebebank* and *Bislife* in the Netherlands). The

'critical mass' is difficult to estimate however, since tissue establishments are organised in different ways, as described above.

In conclusion, the supply and demand in banking of human materials is a management task in which medical, financial and additional social aspects must be constantly balanced in order to strive for the continuity of the organisation and its acceptance in society.

2.3 VALUE AND FEES CHARGED FOR TISSUES AND CELLS

There is a great variety in the way prices or fees of tissues are calculated. Moreover, in many instances the fee charged to the end-user is determined on grounds other than the costs generated in the tissue establishment. Referring to the 'fee' for tissues rather than to the 'price' is therefore more appropriate.

EU Directive 2004/23/EC states: "As a matter of principle, tissue and cell application programmes should be founded on the philosophy of voluntary and unpaid donation, anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient. Member States are urged to take steps to encourage a strong public and non-profit sector involvement in the provision of tissue and cell application services and the related research and development".

Since the tissue of donors is donated for altruistic reasons, and free of charge, some state that the tissue has a socio-medical value before it gets a financial value. Some speak of the production of bio-value in this respect (Waldby, 2002). The value of altruism is the result of people being concerned for the welfare of others (Rodriguez and Leon, 2002). The socio-medical value cannot be expressed in monetary terms, since it is literally the value of life. If only the economic value of donated tissue or cells is appraised, serious concerns can be raised that, through the creation of a market for body parts, there is the potential to devalue human life. It would imply that an individual's worth is based on the material value of their body rather than that of a human being (Boo et al, 2011).

Donation of tissue and cells is estimated to be cost-effective and potentially cost saving, since the final resulting therapies are often live-saving and/or enabling patients to return to work and therefore reduce the reliance on social or medical support (Committee on Increasing Rates of Organ Donation Board on Health Sciences Policy, 2006). In other areas of healthcare, for example, pharmaceuticals, this value is often estimated through dedicated bodies working on health technology assessments (HTA). Such value-based pricing-mechanisms do not explain how the prices or fees for tissues and cells are determined, however. Tissue and cell therapies are relatively low priced on a cost-basis, or sometimes even below costs in a public funding model. It is said that fees just 'cover the costs', but this does not entirely explain the differences between the fees charged by tissue establishments. Fees partly depend on the cost of procurement, and take into account the additional tests required to safeguard the potential recipient (Epstein, 2009). These fees may differ per laboratory (Hoeyer, 2013).

In order to protect the system of altruistic donation and the socio-medical value of the cells and tissues that is based on principles of subsidiarity and solidarity, many countries have installed (semi, or quasi) governmental organisations to regulate tissue and cell banking. The tasks of these organisations are among others, to prevent financial over-compensation or the commercialisation of tissue and cell grafts, and to safeguard the interest of the general public from mishandling donations of human tissue and cell grafts (WHO Guiding Principles on human cell, tissue and organ transplantation).

The work of the tissue establishments in executing the four major processes as explained earlier in this chapter results in an economic value of the grafts.

2.4 CROSS-BORDER EXCHANGE, IMPORT AND EXPORT

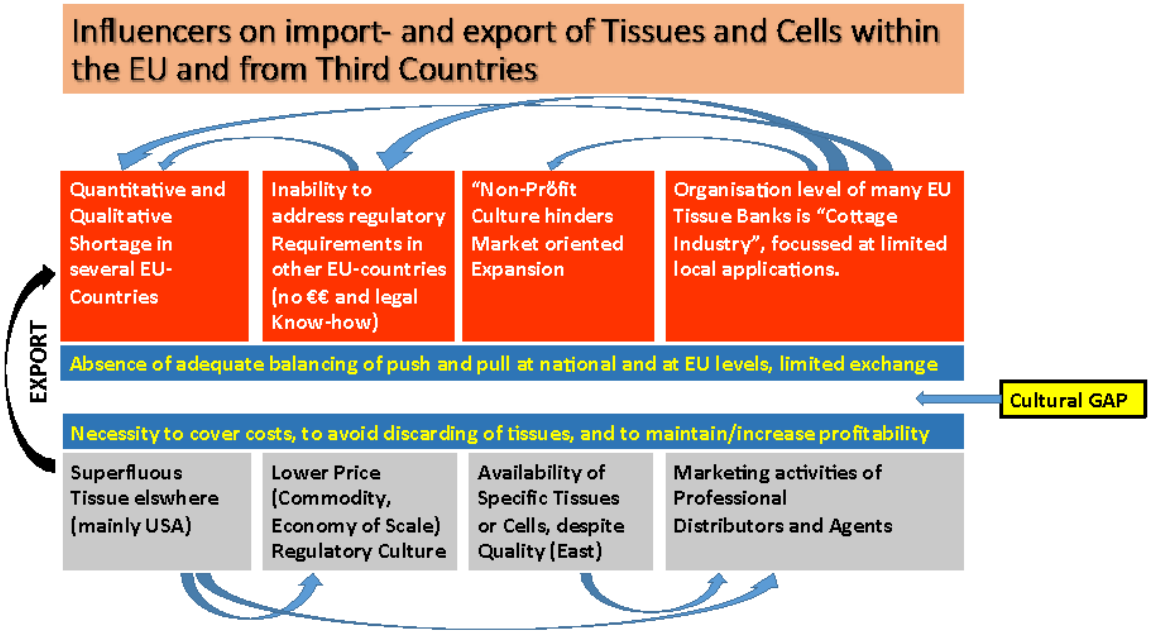
A market is a physical or a virtual place where the demand and supply of goods or services meet to trade. In free markets, the economic reality is that given a high demand and a low supply of a certain product, the price of that product will undergo an upward pressure. However the tissue and cell "market" is not fully subject to these dynamics given the fact that these are not typical products and authorities often determine their price or the fee charged by the tissue establishment. Contrary to free markets for other goods, the flow of tissues and cells is controlled by authorities. In some countries, policies are in place to prevent tissues being the subject of free market forces in order to ensure that no profit is made from the donated material itself. Only in a few instances is a higher fee charged to international (including non-EU) recipients.

The cross-border distribution (within the EU), as well as import and export of tissues from/to third countries, are influenced by a number of factors (see also figure 3 below). One factor could be the introduction by some Member States of more stringent quality and safety requirements (than those laid down in the EU Directives), which may lead to the fact that a tissue establishment in one Member State does not necessarily meet the more stringent requirements in another Member State. An important obstacle for tissue establishments in freely distributing tissue grafts throughout the EU, relates to the different national implementations of EU legislation, and consequent differences in administrative and regulatory procedures which have to be overcome to get access to another Member State. EU legislation lays down only minimum requirements, and many Member States add a significant number of requirements (and procedures). An overview of these additional requirements is not available for the actors in the field (unless costly consultants can be paid for). It is therefore very difficult for a single tissue establishment in one Member State, in particular with limited resources, to address demands in other EU Member States. From this point of view, it may be considered that the European 'market' for tissues and cells is restricted.

Imports from third countries, specifically from the USA, seem to be needed to cover the needs of European patients. However, since most EU Member States do not have a sufficiency policy and/or do not collect data on cross-border distribution (within the EU) and import/export of tissues and cells from/to third countries, it is impossible to understand if these imports are absolutely needed or could be covered from other sources (e.g. EU tissue establishments). In some countries the import takes place on a structural basis.

Compared to EU, US developed a completely different model. Donor recruitment is well organised and organ and tissue procurement organisations in USA are rewarded for tissue donor referrals, which results in a sufficient quantity of tissue. For US tissue establishments, Europe is an attractive market where they can distribute their surpluses and generate additional income. In particular musculoskeletal tissues and cornea are imported from the US.

Figure 3 Cross-border distribution, import and export



Source: Theo de By (2013)

Alliances between US tissue establishments and European partners have been created to ensure the continuity of the flow of tissues to Europe. These alliances also allow getting the necessary know-how to address (national) administrative procedures in EU Member States. As these US tissue establishments are usually larger, they also have resources to acquire insights into regulations and administration of different Member States, and hence facilitate access. Some US tissue establishments have assigned managers to facilitate distribution (in the US the term 'sales' is used) of their tissues in Europe. A few Member States report these imports to be important in order to address local shortages.

Some EU countries have organised their tissue banking structure in such a way that self-sufficiency is enabled. In some countries (IT, UK, NL) a mandatory allocation system is in place. This guarantees the supply to cover the national demand. In other countries, such as Germany (DE), Spain (ES) and France (FR), voluntary networks strive to achieve optimal allocation of available grafts.

The situation of being able to satisfy the national need for tissue grafts, which is the result of this structure, prevents dependency on other countries. As we have seen over time, this dependency could interrupt the availability of tissue grafts for patients, e.g. in situations where import from areas with a high incidence of viral contamination is prohibited. Such was the case when an epidemic of SARS (Severe Acute Respiratory Syndrome) broke out in April 2003. The result of the epidemic was that tissue establishments outside the geographical area of contamination could not accept tissues from tissue establishments in that area. Moreover, donors from Europe, who had travelled in those areas, could (if they died after return) not be accepted as tissue donors in Europe. Safety criteria are also the reason why, for many years, the donor-acceptance criteria of tissue establishments forbid import of tissue originating from donors in the UK and Ireland (IE). The reason for this was the risk for variant Creutzfeldt-Jakob disease transmission. For example, IE does not procure from IE donors, nor does it accept UK donors. Therefore IE is strongly reliant on US import.

The factors mentioned above have a significant impact on the underlying discussion whether the EU should strive for self-sufficiency, and whether the exports to countries outside the EU could have (partly) compensated for the imports from the US.

2.5 IMPACT OF TAX AND VAT REGULATIONS

Increasingly, non-profit organisations active in the field of donation, banking and distribution of human tissue for transplantation, are confronted with contradictory policies between healthcare authorities and finance authorities.

In the EU, in line with the EU and national legislation and WHO and Council of Europe recommendations, health care authorities consider tissue banking as an activity which should take place in non-profit organisations. In some countries this principle is strictly enforced via different instruments, such as centrally made price decisions (e.g. by the Ministry of Health or other governmental bodies), and control measures (e.g. inspections/audits and border-control, etc.). Moreover, the non-profit character of tissue banking is comparable to that of other health services such as the provision of blood. If not exempted, then a zero VAT tariff would be compatible with the non-profit approach.

In EU treaties, and subsequent Directives with respect to Value Added Tax (VAT), human organs, blood and breast milk are exempted from being charged with VAT. Even though human tissues and cells are not mentioned, taking into account also the WHO guiding principles (where it is emphasised that the term 'organ' has to be interpreted widely and therefore include any type of human tissue), it is the authors' view that tissues and cells should also be exempted from VAT. Several Member States used this globally accepted understanding when they transposed the provisions of the VAT Directive 2006/112/EC into their national law and mentioned concretely tissues and cells for therapeutic purpose as to be exempted from VAT to avoid any misinterpretation of the "exemptions for certain activities in the public interest" and to clarify the meaning of the written words "organs, blood and milk" (Article 132 (1)d of Council Directive 2006/112/EC of 28 November 2006 on the common system of value added tax).

Recently, finance authorities in some national regions and EU countries have considered that human tissues should be subject to VAT. VAT charging Member States include DE, IT, ES and PT, while for example NL has a 0% VAT. Charging tax on human tissue may conflict with the principles in the EU Directive and also seems contradictory to the interpretation by these same finance authorities in the past. Besides decisions of tax authorities to charge VAT, it has been reported by some non-profit organisations that tax authorities charge them for profits and first national finance courts confirmed such decisions with the argument, that fair competition to commercial companies that could offer comparable activities would be harmed.

In parallel, local and national health authorities request from tissue establishments to continue to strive for and to stay close to state-of the-art methods (e.g. for screening and processing methods with the aim of further developed safety for patients) and to do clinical studies and research to bring evidence of such activities. The financial burden of such requests from health authorities can only be financed by making surpluses in advance or finding other resources. Taxes on these surpluses directly limit the cash ability of tissue establishments and their capacity to fulfil the above mentioned requests from health authorities.

In conclusion, various interpretations of the VAT Directive 2006/112/EC within the EU create inequality between regions or countries, with tissue establishments required to charge VAT, while others do not. This inequality may disrupt the level playing field, putting in difficulty those who have to charge taxes to the end-user. At the same time, end-users, usually non-profit hospitals, are confronted with higher costs. This may give

the general public the impression that altruistically donated tissues are commercialised, which in turn could potentially harm future willingness to donate organs and tissues.

2.6 CONCLUDING REMARKS AND SUMMARY HORIZONTAL ASPECTS

- The set-up of a tissue establishment requires equipment, know-how and appropriate facilities. These call for significant investment, in particular to build clean-rooms offering the environmental conditions to safely process tissues and cells, as required by EU-law. Building a high-grade clean-room (grade A in B) at least costs €250,000, and more regularly require amounts of over €1 million.

- The consequent operational costs of tissue establishments are defined along four major activities needed to transform a tissue from a donor into a therapy for a recipient:
  1. Donor procurement: to identify a donor, obtaining consent, verification of suitability to donate and obtain the tissues or cells.
  2. Testing: to identify and avoid the risk of transmitting diseases
  3. Processing and storage: to transform the procured tissue/cell into a substance ready to be applied as treatment
  4. Distribution: to ship the final graft towards the clinician or hospital where the tissue/cell will be applied on a patient.

- The relative importance of each of these activities varies between the 3 sectors and along tissue type. E.g., for bone marrow transplants (HPC) processing and storage is relatively limited, but a reliable and fast distribution mechanism is of utmost importance.

- General overhead costs, such as management, or the need for a 24/7 presence, can add significantly to the budget. The high discard rates for quality reasons, like for heart valves, and the often short shelf-lives, like for corneas, add further challenges and significant costs. The stock of transplantable tissues should be high enough to cover direct demand, but low enough to prevent expiration, this is a challenge in itself.

- The surveys performed within this study indicate a limited cost-awareness on the real costs made by tissue establishments. The legal structure and funding model of the tissue establishment may play a role when it comes to this, in particular where tissue establishments are hosted in public hospitals, or where funding is based on charity.

- This limited cost-awareness is also reflected by the high variability in prices/fees charged for tissue and cells over the EU. These prices are often fixed at national level, and do not necessarily reflect costs, but rather reflect a national policy like ensuring self-sufficiency or avoiding commercialization of the human body. They do not really take account of the real cost or the volumes needed to cover all costs and come to a financial break-even.

- All these factors led to the conclusion that there is no real single EU market for tissues and cells, which is the reason why the authors prefer to title this study rather as an 'economic landscape'.

- Four funding models can be seen for tissue establishments in the EU. Tissue establishments can either have (1) a public model, with all costs carried by a public budget and the eventual tissue/cell provided without charge to the users. Alternatively, (2) public, (3) non-profit or (4) for-profit tissue establishments do recover their costs by charging a fee to the users. The (3) non-profit and (4) for-profit tissue establishments do also aim to obtain a financial surplus for investments, for building a reserve or for obtaining a profit in case of (4). Public

tissue establishments can usually rely on public budgets or on charity to make investments.

3 REPLACEMENT TISSUES

This chapter starts with a description of the field of replacement tissues, followed by the organisational structures and collaborations; it provides current and future perspectives and conclusions on the most common replacement tissues: cardiovascular, ocular, musculoskeletal tissue and skin.

3.1 FIELD DESCRIPTION (INCLUDING ECONOMIC ASPECTS)

Tissue grafts that replace a recipient's existing tissue(s) in order to take over the functionality of damaged tissue are generally referred to as replacement tissues. In the large majority of cases, such tissue grafts are obtained from a donor who is different from the recipient, through an allogeneic donation. Although the donor and recipient can, in some cases, be the same person (autologous use), this chapter focuses on allogeneic donation.

Replacement tissues are mostly procured after death, but can also be donated by living donors (e.g. femoral heads removed during primary hip replacement). They consist of a wide variety of types. In this chapter the focus will be on the tissues that are used most commonly:

- cardiovascular tissue
- ocular tissue
- musculoskeletal tissue
- skin

Besides these, many other tissues can be transplanted, such as pancreatic islets, amnion, fascia and nerves, but the numbers donated and transplanted are much lower compared to the four categories listed above. Composite tissues such as hands or faces are transplanted on very rare occasions and are not addressed in this chapter. The procurement and transplantation of organs is beyond the scope of this study.

The substances, processes and therapies described below are largely established practice in the tissue sector. However, these substances, processes and therapies are subject to continuous innovations in processing or clinical application, some of which might lead to a classification as Advanced Therapy Medicinal Products (ATMPs). In these cases, the products are not only subject to the tissues and cell legislation for the donation, procurement and testing steps but also to the pharmaceutical legislation (ATMP Regulation) for all subsequent steps in the process. The legal classification and the different legal requirements fall outside the remit of this study, but for tissue establishments that are active in those fields, the economic implications are important.

This chapter describes the different types of replacement tissue grafts and tissue establishments for replacement tissues and mentions ATMPS where they may, in the future, have a significant impact on the demand, and therefore the economic landscape, for a particular tissue as a starting material for ATMP manufacture.

3.1.1 Cardiovascular tissues

Cardiovascular tissues include heart valves (pulmonary and aortic), conduits, arterial vessels (in different forms), veins and pericardium.

Clinical application

Surgical heart valve replacement is an effective treatment for patients with damaged heart valves. The first clinical reports on the transplantation of cardiovascular tissue date back to 1962. While artificial heart valves were still in development and industrial

engineering failures emerged, the human tissue allograft turned out to be an alternative for those patients suffering from severe and irreparable regurgitation, congenital heart diseases or endocarditis. For replacement of the damaged valve, current options include a prosthetic (synthetic) valve or a biological valve (of human or animal origin). As innovation has led to better artificial heart valves with fewer disadvantages and the availability of human hearts has decreased, the surgical use of human donor heart valves has declined and is now important for two main indications: children and adolescents suffering from congenital heart defects and patients suffering from endocarditis (TRIP Annual Report 2012, Biovigilance). Transplantation of human heart valves requires specific surgical skills, which not all thoracic surgeons have acquired during their training.

The use of vascular tissue in surgery also developed in the 20th century. Autografts and allografts, as well as artificial vessels, are used for repairing and replacing damaged or defective vessels. Vascular allografts are used to repair or replace large and medium-sized arteries or veins. They are used in cardiovascular, reconstructive and solid-organ transplantation surgery. Vascular allografts are sometimes used to create a shunt to enable access for dialysis (Inston, 2015). For transplant purposes, mostly arterial vessels and conduits are used. They are indicated for aortic disease that leads to slackening of the vessel wall (aneurism) and in patients who suffer from vascular infection or infected synthetic blood vessel prostheses.

Patches are prepared from the pulmonary artery or aortic artery and are used for reconstructions of congenital malformations in paediatric cardiac surgery.

Recently, development of endovascular stent-grafts has reduced reliance on conventional grafts to replace diseased arteries and it is likely that this trend will continue in the future. Aortic grafts are recently also used as a biological matrix for extensive airway reconstruction (Martinod et al, 2013).

Pericardium is a membrane tissue that can be used for cardiovascular anastomosis, dental and ocular replacement procedures (Fehily et al, 2012).

Activity level in the EU

In 2012 in the European Union, a total of 77 cardiovascular tissue establishments were active. In 2012, Member States reported the donation of 1,974 hearts, processing of 3890 heart valves and discard of 1008 heart valves, resulting in 2,882 heart valves issued for transplantation.

Table 8 Volumes of heart valves

	Donation	Recovered	Tissues available 1-1-2012	Processed	Discarded	Total Import	Total Export
AT							
BE	274	549	170	549	12		188
BG							
HR	19	9	12	31	10	1	
CY							
CZ	53	90	407	72	42		
DK							
EE							
FI		231					
FR	326	368	494	272	196	76	1
DE	296		141	277	124	128	
EL							

HU		20	14	14	6		
IE							
IT	231	366		364			
LV							
LT							
LU							
MT							
NL	220			452			47
PL	179	358	145	230	78		5
PT	22	54	75	10	35		
RO							
SK	11	15		15			
SI	1	1					
ES	192	350		350	102		65
SE	150	323		323	136		
UK		985	814	931	267	37	37
Total	**1,974**	**3,719**	**2,272**	**3,890**	**1,008**	**242**	**343**

Source: EUROCET 2012, Economic landscape survey NCATC (2015), data from 2012

The import and export is the total of cross-border distribution and to/from third non-EU countries.

Besides valves, depending on the demand, and the 'defined graft-range' of the tissue establishment, several other vascular and non-vascular tissues can be procured from a single donor.

Procurement, processing and storage of cardiovascular tissues

Donations of cardiovascular tissues originate from three different sources:

- Organ donors, where the heart is not suitable for heart transplantation;
- Domino donors, i.e. living recipients of transplanted hearts where the removed heart can provide transplantable tissues;
- Deceased non-organ donors, from whom multiple tissues can be removed.

For the procurement of heart valves, the complete human heart is procured and subsequently the heart valve establishment performs dissection and preparation of heart valve grafts. The valves used for transplantation are the pulmonary and the aortic valve. Besides valves, depending on the demand, and the 'defined graft-range' of the tissue establishment, several other vascular and non-vascular tissues can be procured from a single donor.

Processing of cardiovascular tissues takes place in cleanrooms which are often Grade A in a Grade B background. Minimum requirement is Grade A in Grade D. Valves are prepared from the heart and macroscopically evaluated (e.g. measured, tested for function, examined for defects). The valves are temporarily stored in a mixture of antibiotics and cryopreserved in a container with medium that contains cryoprotectant. Vessels are similarly treated (Fehily et al, 2012).

Cardiovascular tissues are cryopreserved and stored in liquid or vapour phase nitrogen. This preservation technique has enabled the storage of donated cardiovascular allografts in heart valve establishments for years in order to create a stock of different sizes. Pericardium can be freeze-dried before storage.

Heart valves are matched between donor and recipient based on type and size. In general, pulmonary valves are in much higher demand compared with aortic valves. This has partly to do with a specific technique for the treatment of congenital valve abnormalities called the Ross operation in which pulmonary allografts are needed. Small size valves for newborns are rare and require donation by infants that die young. Larger sizes also have a limited availability.

Cost structure

Three cardiovascular tissue establishments provided a breakdown of costs over different activities for this study, including staffing dedicated to these processes, such as costs for donor procurement, additional testing, processing, and distribution. Unlike the removal of an eye, or a cornea from an eye, a cardiectomy requires a small operation team.

The differences in cost structure of these three cardiovascular tissue establishments (TEs) find their origin in the way they organise their processes. TE 1 receives the donor hearts free of charge from organ donation teams or from organ donor organisations. Costs of the surgical removal of the heart (cardiectomy) are therefore not invoiced. TE 3 has outsourced the donor screening to a commercial laboratory. The different aspects contributing to the costs of cardiovascular tissue banking are elaborated below.

Table 9 Cost divisions in cardiovascular tissue establishments

	TE 1	TE 2	TE 3
Donor procurement	2%	15%	23%
Testing	14%	2%	30%
Processing	70%	75%	47%
Distribution	14%	7%	Not specified*
Total	**100%**	**99%**	**100%**

Source: Survey to cardiovascular tissue establishments (2014), data from 2012

*Distribution costs of TE 3 are separately charged to the requesting hospital

The cost of procurement of cardiovascular tissue is mainly dependent on the donor source (organ donors, domino donors or non-organ donors).

An important factor, negatively contributing to the cost/benefit ratio, is the high discard rate of retrieved donor hearts. This high discard rate finds its origin in the morphology of the donor hearts as well as in the incidence of contamination of the tissue when it arrives in the tissue establishment. As a result, discard rates for reasons of morphology of 44% and microbiology up to 9.7% have been reported (De By, May 2013). One tissue establishment reported a total of 68% and 70% discard rate respectively for 2012 and 2013 (Heart Valve Bank Rotterdam, Annual Report 2013).

Another important factor to take into account is the cost of donor operations, specifically those in non-organ donors with cardiac arrest. To enable these donations a well-trained team and accompanying logistics must be available.

The cryopreservation method enables cardiovascular tissue establishments to extend shelf life over many years. However, to safeguard preservation in the cryo-containers, the levels of liquid nitrogen must be constantly monitored and kept on a level sufficient to keep the temperature of the tissue grafts at an adequate level. Other costs relate to the maintenance and daily operations of clean room facilities.
The costs for retrieval, transport, materials and initial testing for all procured hearts must be calculated into the fee of the limited number of eventual grafts for transplantation.

A final aspect to be mentioned relates to financial liquidity: the relatively long shelf-life for cardiovascular grafts means that, at least for some (less frequently used) outlier graft sizes, it may take several years before the costs can be recuperated by a fee. In some instances, tissues have to be discarded after the shelf life expiration date.

Fee structure

The table below reflects the fees that cardiovascular tissue establishments charge to local recipient hospitals. It may be the case that different fees are charged to different hospitals as opposed to its 'own' hospital, where the tissue establishment is located, in the same country, or other countries. Where the costs of tissue establishments are compensated by the public health system, no fees are charged to hospitals, e.g. in Italy and in France. When tissues are distributed to other Member States, the fees in the table apply.

Table 10 Fee of cardiovascular grafts

	Fee charged to local recipient hospitals						
Country	**Heart-valves**	**Conduits**	**Arteries**	**Aortic bifurcations**	**Veins**	**Peri-cardium**	**Po patch**
Belgium	3,895	2,269	2,647	2,647			
Germany	3,500						
Italy CVB 1	2,800						
Italy CVB 2	2,800		1,200	1,200	1,200		
Italy CVB 3	3,200	1,750	1,250	2,300		8	
Netherlands	5,230		2,820				1920
Poland CVB 1	2,250					160	
Poland CVB 2	1,823		939			944	
Poland CVB 3	1,900						
Portugal	1,925		1,405		1,405		
Spain CVB 1	0						
Spain CVB 2	3,300						
Spain CVB 3	940						
Spain CVB 4	1,336	1,336	1,336	1,336	1,336		
UK	3,691	2,541	2,541				1,452
Average fee	**2,573**	**1,974**	**1,767**	**1,871**	**1,314**	**371**	**1,686**

Source: Survey to cardiovascular tissue establishments (2014), data from 2012

The table shows a remarkable difference in the fees charged to local hospitals. The one cardiovascular tissue establishment that does not charge anything nevertheless incurs costs; this can be an indication that the hospital management may have chosen not to work with cost-centres. It also has to be mentioned that this cardiovascular tissue establishment processes only three heart valves per year; the quantitative costs are thus a minimal part of the total university hospital budget.

It needs to be noted that in the Netherlands, as for corneas, the fees charged to the local and national hospitals cover more than just the processing in the tissue establishments; it includes overhead charges of the National Transplant Foundation, and other costs.

The difference in pricing between the cardiovascular tissue establishments has several causes:

- The fee to the end user is often determined by outside parties (authorities, insurance) and not based on calculations in which all costs are integrated into a price or fee that covers the real costs.
- A systematic difference in organisational embedding. Some tissue establishments are "stand alone", meaning that they are responsible for balancing the costs and the revenues. Others are part of a larger structure, usually a (university) hospital, in which this larger structure carries (part of) the costs.
- Fee differences may also occur due to differences in the level of salaries and of other costs in the EU countries.

Fees determined by the tissue establishment itself are higher than those determined by a Ministry of Health or by a regional government though this is not to imply that in those cases, fees are too high. As explained elsewhere in this report, the economics of tissue banking are complex and depend on many factors.

Cross-border exchange and import/export of cardiovascular tissue

Cardiovascular tissues are occasionally exchanged between EU Member States. In some countries, specifically with 'opting in' donation systems, there is a shortage of donations (or procurements) rather than a shortage of donors. Organising permission and consent for the donation requires additional efforts, and always entails the possibility of a refusal to donate by the next of kin. To cover the shortage, tissues are distributed from other Member States and imported from the USA.

In the experience of the tissue establishments there are several hurdles to be overcome when tissues are to be distributed cross-border to other EU Member States.

- Verifying that tissues, selected for cross-border distribution or export, are not needed for national patients. Such a system is present in some Member States (like NL and IT), but lacking in most.
- Complying with (often unclear) additional donor selection and testing criteria in the country of destination or importing country, other than required in the exporting country.
- Complying with administrative and regulatory requirements, in particular when tissues are to be distributed to Germany, where there is the greatest demand.[13]
- Complying with criteria requires extended knowledge, sometimes about pharmaceutical regulations for those countries such as Germany where tissues are classified as medicinal products. Such knowledge isn't available in most tissue establishments, and only those who can afford to pay consultancy fees to supporting experts, can – after going through an approval process that may take several years - achieve compliance with the criteria and regulations of some countries.
- Differences in price or fee structure and of reimbursement systems.
- Differences in VAT rates, if applicable.

[13] For the import of tissues and/or certain tissue preparations an import permit pursuant to Section 72b (1), AMG, from the competent regional authority is required. Also, a certificate from the state of origin pursuant to Section 72b (2), AMG, that confirms that the standards observed during the extraction and processing of the tissue/tissue preparations are at least equivalent to the standards of good practice laid down by the European Union (Good Manufacturing Practice - GMP). Pursuant to Section 21a (9) of the AMG, a certificate from the Paul-Ehrlich-Institut is required for first introduction of tissue preparations from Iceland, Liechtenstein or Norway, to Germany.

Many of the alliances mentioned earlier aim to create mutual support between tissue establishments financially (sharing the costs of regulatory consultants, for example) and also by sharing expertise. Such alliances include: BISlife (NL)-TSF (now Banco de Tejidos) (ES)-Homograftlabor DHZB; and EHB (BE) with the Homograftlabor in Zagreb (HR) (see also section 3.2.1 for international alliances).

3.1.2 Ocular tissues

Ocular tissues include corneas and sclera. The cornea is the clear anterior part of the eyeball which permits light to enter into the eye. A corneal transplant is indicated when eyesight is decreased due to corneal disease and provided that other parts of the eye are functional. The sclera is the outermost part of the eyeball and is partly visible as the whites of the eyes.

Clinical application

The most common indications for corneal transplant are opacity, deformation or scarring following infection or injury of the cornea. Often a transplant is the only available option for improving eyesight in these patients. In a small sub-group of patients the matching of HLA type between donor and recipient is indicated when the recipient has an atopic constitution or had previous rejection of a cornea graft. A large number of cornea donors need to be HLA typed in order to identify a suitable match a single patient because of the low probability of finding a match. Sometimes the HLA typing costs can be shared with the organ transplantation organisation in the case of an organ and tissue donor.

The affected cornea is (partly) replaced by the cornea of a deceased donor. Two types of corneal transplant techniques are used: penetrating and lamellar keratoplasty. In penetrating keratoplasty (PKP) the full thickness of the cornea is replaced by a donor cornea. There are some disadvantages of the PKP technique such as graft rejection, slow healing and irregular astigmatism. In lamellar keratoplasty (LKP) only the affected layer is replaced. Lamellar keratoplasty is subdivided according to the replaced layer, anterior or posterior. The disadvantages described for PKP are fewer. But the lamellar technique requires specific skills of the technician in the TE or the surgeon. Besides that, additional investments have to be made in devices to assist the cutting of the lamellas. The preparation of the lamellas can either be done in the operating theatre or at the cornea TEs (pre-cut lamella).

Donor sclera is used in reconstructive surgery of eyes and eyelids. Sclera can be preserved and stored for several years.

Activity level in the EU

In Europe, in 2012, 141 corneal tissue establishments were active.

The table below shows the recovering of 40,185 corneas. From these, 30,428 corneas were distributed.

Table 11 Volumes of corneas

	Donors	Recovered	Distributed in own MS	Distributed to other MS	Exported to third country	Received from other MS	Import from third country
AT*	200	NA	188	3	0	0	0
BE	413	973	906	0	0	45	0
BG	73	145	119	0	0	0	0
HR	178	374	133	0	0	1	53
CY	0	0	0	0	0	0	0

CZ	502	998	676	46	81	0	0
DK*	202	NA	356	0	207	23	0
EE	42	48	46	0	0	0	0
FI	134	273	NA	0	0	4	0
FR**	9,893	9,918	4,372	145	0	0	0
DE	NA	8,435	5,458	405*	68*	188	0
EL	NA	NA	NA	NA	NA	NA	NA
HU	287	302	536	0	0	0	0
IE***	0	0	NA	0	0	0	175
IT	7,529	15,071	6,575	400*	178*	12	0
LV	13	26	NA	0	0	0	0
LT	29	58	53	0	0	0	0
LU***	2	0	0	0	0	0	0
MT	NA	NA	NA	NA	NA	NA	NA
NL	1,635	3,239	2,603	291	43	1*	0
PL	559	1,104	855	0	0	0	0
PT	448	905	NA	0	0	136	0
RO	48	48	NA	0	0	89	0
SK	99	186	118	0	0	0	0
SI	56*	146	110	0	0	0	0
ES	2,735	4,808	2,743	10	0	70	0
SE	516	859	829	21*	0	0	0
UK	3,031*	7,040	3,752	0	0	74	615
Total	**37,059**	**40,185**	**30,428**	**1,321**	**577**	**643**	**841**

Sources: EUROCET 2012 unless stated otherwise:

***The European Eye Bank Association, EEBA Directory, Twenty-Second Edition, January 2014;**

****Agence de la Biomédecine, Rapport Annuel 2012**

***** Data by IE NCATC. No procurement in IE due to vCJD disease**

Procurement, processing and storage of ocular tissues

Ocular tissues are obtained from deceased donors. Retrieval of ocular tissue is performed in the mortuary, in the hospital or at home. For cornea and sclera the complete eyeball is procured. For corneas only, the corneal disc can be removed at the donor procurement site; processing is done in ocular tissue establishments (Bredehorn-Mayr et al, 2009).

The preservation of the (living) endothelial cells is significant in cornea banking. If the corneal disc has not been removed at the procurement site, the eyeball is washed and in the cleanroom the cornea is removed. After evaluation and decontamination, the cornea is stored in preservation media. Preventing contamination is extremely important and antibiotics are used and microbiological cultures taken. Storage in organ culture medium is preferred for the endothelial cells as these will be more vital and there is more time for obtaining the results of donor testing and of microbiological cultures and, where relevant, HLA typing (Fehily et al, 2012). Some cornea banks distribute pre-cut lamellar cornea for LKP. The cornea is cut with a microkeratome by hand. New laser technics however can also be used and even enable cutting multiple lamellas from one cornea.

The shelf life of corneas is limited to four weeks for storage in organ culture medium at 30-37^{o}C. When stored under hypothermic conditions cornea's can be stored up to 14 days (Wilhelmus et al 1995), though in practice tissue establishments usually store grafts up to 5 days as endothelial cells will decrease in viability during storage. After evaluation of cell quality and quantity, the grafts can be released for transplantation. For reasons of

quality, storing corneas in culture medium at body temperature is the most common technique applied in Europe, contrary to the US where cold storage is the standard method.

Sclera are stored separately in 70% ethanol. Distribution may be in segments of 10x15 mm, in quadrants or complete sclera (TRIP Annual Report, Biovigilance, 2012; Haase-Kromwijk et al, 2007; Rijneveld, 2010).

Cost structure

In an additional survey, performed in the context of this study, three cornea tissue establishments (TEs) provided a breakdown of the costs of the major processes, while one cornea establishment could provide its processing costs. They have calculated the cost division per process (note: all TEs reported that donor procurement includes a ±40% discard rate). In this overview, while cornea TE1 had specified its costs in great detail, cornea TE 2 has not separated processing costs from distribution costs.

Table 12 Cost division in cornea tissue establishments

	TE 1	TE 2	TE 3
Donor procurement	24%	25%	30%
Testing	22%	10%	8%
Processing	30%	65%	38%
Distribution	24%	NA	23%
Total	**100%**	**100%**	**99%**

Source: Survey to cornea tissue establishments (2014), data from 2012

One of the cornea tissue establishments indicated that the total costs couldn't be recovered from the income; the difference is covered by fundraising. The other two tissue establishments indicated that National Health Insurance compensated for most of the costs. An example mentioned elsewhere is the investments in the Lions Cornea Banks (Germany), which are mainly provided by the Lions service clubs.

An important cost factor in these calculations, recognized by all cornea tissue establishments, is the high discard rate of donor corneas (Bredehorn et al, 2009). Reports show that the discard rate can reach levels of over 50% (BIS Foundation, Annual Report 2007). This discard rate has several causes and is a challenge to address. One of the main reasons is that many suitable donors are of older age, and, the older the eye, the higher the rate of idiopathic endothelial cell loss. This can however only be diagnosed in the tissue establishment after completion of procurement. Thus, many donated corneas do not fulfil the minimum cell count per mm^2 of 2 000-2 500 according to the criteria of the European Eye Bank Association and have to be discarded.

Sundmacher and Reinhard (2009) reported that, to provide 300 transplantable grafts, an annual budget of almost €600 000 is needed to achieve a break-even between expenses and revenues (Sundmacher and Reinhard, 2009). The fixed expenses include a minimum of two technicians and two MDs on call to cover a 24/7 service. In the study of Sundmacher and Reinhard, 600 corneas had to be recovered to provide 300 transplantable grafts to hospitals. To cover the total costs of €600 000, each distributed cornea would cost around €2 000. If the number of distributed grafts were higher than the necessary 300, the economy of scale could cause a favourable effect on the fee charged to the recipient hospitals, or to the health insurance responsible for reimbursement.

In our survey organized within the context of this report, two tissue establishments that indicated distribution of over 1 000 corneal grafts per year, processing cost per graft are shown to be lower as compared to those which processed fewer than 1 000 grafts per year. A decrease in number of corneas processed would mean that such a cornea tissue establishment would have to find financial support to cover the expenses, increase the price charged per cornea or else reduce its service level, which may lead to being unable to address donor calls or other service cut-backs.

The table below shows the correlation between the number of distributed grafts and the processing costs of four cornea tissue establishments that could provide data with respect to their processing costs. It demonstrates the effect of the economy of scale.

Table 13 Number of corneal grafts and cost

	Number of distributed grafts	Processing costs per graft in €
Cornea TE 1	59	825
Cornea TE 2	989	643
Cornea TE 3	1386	471
Cornea TE 4	2702	315

Source: Survey to cornea tissue establishments (2014), data from 2012

The cost for a cornea also differs per preservation technique. The use of the preservation method should have no influence on the costs of procurement, testing, or distribution. However there are large differences in costs when it comes to comparison of the two storage methods. When using the organ culture method, there's need for a clean room environment in which establishments usually process under a class A cabinet with a background of class B. Moreover, the need to operate an incubator, the necessary change of medium before transportation and the regular microbiology tests of that medium contribute to additional costs. It can therefore be assumed that the culturing method generates more costs than the alternative 'cold storage' method. For cold storage industrially provided closed systems are available, negating the need for clean rooms. This can be a cost-effective solution where economic resources are limited

On the other hand, the culture medium method has a significant positive impact on discard rates due to the longer shelf life, thus contributing to the number of transplantable grafts and a better balance between costs and revenues. Overall, most European cornea tissue establishments have chosen to apply this preservation method based on quality arguments. This method enables evaluation of the quality of the cells, the presence of micro-organisms in the culture, as well as extended possibilities to screen donor material for the presence of transmittable diseases and viruses.

Fee structure

Table 14 reflects the fees TEs charge for different tissue grafts to local end-users. Different fees may be charged to hospitals outside the region. Again, different fees may be invoiced to hospitals in another EU country or to countries outside the EU.

Table 14 Fee of ocular and amnion tissues to local end-users

	Cornea PKP	Cornea emergency	Anterior cornea lamella	DMEK[14]	Sclera	Amnion
AT	1901	1901	2480	2319	479	210
BE	1349	1349			95	1092
BG	500*					
CZ	790	790	1160	1160	790	190
DK	2078		2480		2078	429
DE	1875	1875	1875	1875	560	560
HU	250					
IE	2988	2988	2988	2988	523	497
IT	3465*	875*	3130*	3130*	300	500
NL	2250*	2250*	2250*	2250*	100*	400*
PL	663*		840*			
PT	671					
RO						
SK						
SI						
ES	1030*	1670*	825*		464*	203*
SE	1235	1235			107	
UK	738					
Minimum	250	790	825	1160	95	190
Maximum	3465	2988	3130	3130	2078	1092
Average	**1420**	**1659**	**2003**	**2287**	**567**	**453**

Source: Survey to cornea tissue establishments (2014), data from 2012; Economic landscape survey NCATC (2015), data from 2012

The difference in pricing, as shown in the table, leads to the following observations:

- Fees for all types of ocular tissue vary remarkably from one TE to another. For PKP corneas the range is €250-3465. Though this may partly be explained by differences in the technique used. When considering the differences in degree to which real costs are taken into account for price-setting as well as the difference in healthcare wages in the responding EU-countries, some of these fees include more than the costs of tissue establishment processes. In the Netherlands, for example, the fee includes the costs of HLA-typing of the recipient, but most importantly it must cover the overhead of the National Transplant Foundation and the imbalance between costs and income of several tissue establishments.
- The differences in fees, specifically for those tissue establishments that have the freedom to determine the fee to the end-user, may be explained from the point of 'critical mass'. The greater the number of distributed tissue grafts, the better that fixed costs, such as infrastructure and personnel, can be covered by income (Reinhard and Sundmacher, 2009). As mentioned, the break-even point would be expected at 300 transplantable corneas.
- Emergency corneas are grafts which are in the tissue establishment to be allocated in urgent cases (rather than scheduled operations) in which the patient

[14] DMEK = Deep lamellar endothelial keratoplasty

may lose an eye if he/she doesn't receive a graft. These emergency cases often occur at night or during weekends. Most cornea establishments have a small stock that is ready and prepared (to save time) for immediate shipping. Usually, the quality of these emergency corneas is lower than grafts for elective operations when it comes to the number of viable cells.

- The fee of sclera, which are in fact a by-product from cornea processing, varies from €95 to €2078. In some countries, sclera are considered to be a medicinal product (e.g. in Germany), the registration of which requires intensive legal-administrative application processes, but the observed differences cannot solely be explained from that point of view.
- While sclera are procured from deceased donors, amniotic membranes are donated by living donors. They serve the same purpose in ophthalmology surgery, namely providing a natural support to the eye globe that can easily be sutured. It may be expected that the cost structure for obtaining and processing amnion membranes are quite different from the collection of sclera. The observed differences in fees can otherwise not be explained.

Authorities and health insurance organisations may influence the fee for the end-user. Table 15 provides an overview of legal status and fees in which the decision-makers are listed per EU country. Given the fact that only 15 out of 60 cornea TEs responded to the questionnaire for this research, no conclusions can be drawn concerning the correlation between legal status, the determination of the fee and the fee to the end-user.

Table 15 Fee determination of cornea

	Legal status of organisation	Determination of fee by	Fee of cornea PKP
Hungary	Private foundation	TE itself and insurance	250
Czech Republic	University Hospital	Insurance	790
Italy	Private Foundation	TE itself	1100
Sweden	University Hospital	Regional Council	1140
Belgium	University Hospital	Government	1349
Spain	National Health	TE itself	1425
Germany, TE 1	University Hospital	Hospital	1850
Germany, TE 2	Private foundation	TE itself	1900
Germany, TE 3	University Hospital	TE itself	2000
Austria	University Hospital	Hospital	1901
Denmark	University Hospital	TE itself	2078
Ireland*	National Health	TE itself	2988
Netherlands TE 1	Private Foundation	Insurance	2250
Netherlands TE 2	Private Foundation	Insurance	2250

Source: Survey to cornea tissue establishments (2014), data from 2012

* Ireland imports all corneas from the US (because of vCJD in Ireland and the UK)

Cross-border exchange, and import/export of corneas

For cornea TEs, the international exchange shows different dynamics of cross-border distribution and import/export. In some Member States there is a surplus and corneal grafts are distributed to other Member States or exported, while in other countries there is a shortage and numerous grafts are ordered from other Member States or imported. Imports are mostly from the USA.

Table 16 shows that there is only one tissue establishment (in Hungary) that clearly indicates that there is no donor shortage. One cornea tissue establishment from Germany remarked that there shouldn't be a donor shortage if donor referral and procurement were well organised. One tissue establishment from Germany reported an estimated national shortage of 5 000 corneas per year. One indicator for measuring a donor shortage is whether there is a waiting list for cornea recipients. Such a waiting list could also report the average and maximum waiting time for patients to receive a transplant. Clearly, there is a donor shortage in different EU countries. Several respondents (BE, DE) reported that in the absence of such waiting lists, it is hard to determine the real level of this shortage.

The table below shows the exchange of tissue grafts, as reported by 14 responding tissue establishments. The reporting cornea TEs distributed 919 grafts to other EU countries, and exported 367 to third countries. All in all, more corneas were imported (772) from outside the EU than exported (367) to these third countries. Greece has 5 ocular tissue establishments but as shown in the table, no data is available on number of donors, distribution and import and export. The donated cornea from donors in Luxembourg are processed and stored in another Member State.

Table 16 Cross-border distribution, import, export and shortages of cornea

	Shortage of donors	Cross-border from MS	Cross-border to MS	Import from third country	Export to third country	Countries
Austria	yes	1	11			
Belgium	yes		45			
Czech Republic			47		78	
Denmark	300	23		207		from USA
Germany TE 1	5,000					
Germany TE 2						
Germany TE 3	yes	188		405	68	from USA
Hungary	no		80			to RO
Ireland				160		from USA
Italy		12	400		178	
Netherlands	yes	1	291		43	
Portugal	yes	136				
Spain	100	70	10			
Sweden	150		35			to DK
Total	**>5,550**	**431**	**919**	**772**	**367**	

Source: Survey to cornea tissue establishments (2014), data from 2012

At the same time, the table also shows that there are substantial imports from outside the EU. The reporting cornea tissue establishments purchased 772 grafts from the United States; in this survey this represents a large part of the distributed volume reported.

The export to countries outside the EU may be, partly, explained by the fact that during European holiday periods (e.g. Christmas–New Year) there is a reduced activity in ophthalmology clinics. As the preserved corneas in the tissue establishments have a short expiration period of about four weeks, corneas may expire if they are not transplanted. Corneas, which would otherwise expire, are therefore offered to countries that do not observe the same holiday periods. Often, these corneal grafts are offered at reduced fees.

Some EU countries have organised their tissue banking structure in such a way that self-sufficiency is enabled. In some countries (IT, UK, NL) a mandatory allocation system is in place. This guarantees the supply to cover the national demand. In other countries, such as Germany, Spain and France, voluntary networks strive to achieve optimal allocation of available grafts.

3.1.3 Musculoskeletal tissues

Musculoskeletal tissues include bone and related soft tissue such as tendons and ligaments.

Clinical application

The need for bone grafts is determined by a number of medical indications:

- To substitute the loss of a patient's own bone caused by trauma
- To replace a patient's resected bone or joint because of malignancy
- To fortify the host's bone mass to enable the placement of an artificial joint, usually in re-operations of the (replaced) hip or acetabulum
- To fortify the spine after trauma, for correction of spinal defects caused by congenital disease (scoliosis, lordosis), or severe wear of the vertebrae for other reasons
- To reconstruct dental or maxillofacial bone loss, and to support artificial dental implants by filling the cavity around the implant-base with demineralized bone powder or gel.

The main indications for tendons and ligaments are injuries, such as tearing, of the patient's own tendon, usually the patella or Achilles tendon. Typically in the case of a revision of a previous reconstruction with an autologous tendon (Anterior Cruciate Ligament (ACL) and Posterior Cruciate Ligament (PCL) reconstruction with the patients' own hamstring or other hemi tendon), allografts are needed (Robertson and Nutton, 2006). Other musculoskeletal tissues include cartilage, fascia and menisci from deceased donors. In exceptional cases a graft coming from a donor can replace a ruptured meniscus.

Chondrocytes are mainly used in autologous settings. This treatment involves in vitro culturing of cartilage cells after a harvesting procedure; the cultured cartilage cells are transplanted in a second procedure. The cartilage cells adhere to the bone surface and start forming new cartilage. The in vitro growing of cartilage is a sophisticated, recently developed technique (Bugbee et al, 2015). This cultured cartilage can be classified as ATMP; it was the first authorised product under this regulation.

Demineralized Bone Matrix (DBM) is produced from cortical bone. Cortical bone is harder than the above-mentioned cancellous chips, which, because of their open structure, allow faster ingrowth of the host bone. Thus, cortical bone is less in demand for orthopaedic surgery. DBM is frequently used in dental applications, specifically to support the base of implants in the mandibular or in the upper jaw. Tissue establishments have developed DBM into several products, such as bone-gel with glycerol or hyaluronic acid, also

called hydrogel, bone-flex, bone-putty etc. Bone-gel is often used for implantation along spinal fusion devices. The osteo-induction, caused by the DBM, results in a more rapid bone growth in the recipient the spinal implant/the spine will obtain stability more rapidly. By removing the minerals from the cortical bone, the tissue becomes osteo-inductive, rather than osteo-conductive. The absence of minerals exposes the endogenous growth hormones which then stimulate the host bone to grow into the DBM. Since the removal of minerals causes the loss of weight bearing capacity of the bone structure, DBM is not suitable for grafting in recipient sites that need weight-bearing capacities. DBM is used as bone filler in cavities that need fast restoration.

During the last 10 years there is a clear trend of combining, in a package, CE-marked orthopaedic hardware, such as surgical instruments and/or industrially produced implants with bone tissue. The combination of tissue and hardware is offered to the surgeons to increase the efficiency of their operations. By making use of innovative technologies, musculoskeletal tissue can be combined with antibiotics. The argument for this approach is that it can prevent or eliminate the contamination of bone tissue, respectively prophylactic (in trauma patients with high risk for infection) or in patients who undergo a re-operation because of the failure of an industrial or of a tissue implant.

In the past, combinations of bone tissue grafts with growth factors, bone morphogenetic proteins (BMPs), have been seen. Although this combination has not resulted in successful clinical application, it may be expected that in the future, new combinations of bone and cells, and/or pharmaceuticals, aimed at stimulating bone healing, will be introduced.

Activity level in the EU

In 2012 there were 400 authorised musculoskeletal tissue establishments within the EU. There are several types of bone tissue establishment. Hospitals and orthopaedic centres often operate a bone tissue establishment to provide the required donor bone from their own patients. There are tissue establishments that focus on living bone donation and those that focus on processing deceased donor bone and other musculoskeletal tissues. Other tissue establishments focus on import of musculoskeletal tissue and/or storage and distribution.

Table 17 shows an overview over donation and distribution of musculoskeletal tissues. Though the number of living donors (of femoral heads) is 8 times as high as the number of deceased donations, the yield of tissue grafts coming from living donations is limited as compared to deceased donations. Depending on the number and size of donated bone tissues from a deceased donor, these can be cut and shaped into many units of transplantable grafts. Specifically when grinded into small particles of DBM, the number of units can reach 100 or more.
87% of the distribution of musculoskeletal tissues processed by EU based tissue establishments takes place in the own Member State. In addition musculoskeletal tissue is imported with a quarter of all tissues coming from third countries. The import from third countries, outside the EU, is about ten times as high as the cross border exchange between Member States, inside the EU.

Table 17 Donation, distribution, import and export of musculoskeletal tissue

	Deceased Donors	Living Donors	Total Distri-buted	Distributed in own MS	Cross-border to other MS	Exported to third country	Cross-border from other MS	Import from third country
BE	192	5595	14653	14243	275	1		135
BG	137							
CZ	121	111	3344	3344				
DE*		21372	64358	64358		144373		41648
EE	3	27	98	102			4	
FR	60		31310	30130	1184		3796	
HR	75	165	156	156				
HU	20	458	623	623				
IT	304	3540	16824	16824				
LV	18		0					
LT	4	82	67	67				
LU	2							
NL	128		36649	10027	19977	6645	257	110
PL	242	123	9657					
PT	28	20	121	121			91	
RO	10	127	89	89				
ES	672	1451	14630	13731			900	1
SE	3	1893	1201	1164			58	
SK	309	102	294	127	167			
UK			28851	38384		2452		11985
Total	**4326**	**35076**	**222925**	**193490**	**21603**	**153470**	**5106**	**53879**

Source: EUROCET 2012. Please note that total numbers don't add up as not all countries reported

***** The total distribution in Germany has been interpreted as "Distributed in own Member State". The import and export from third countries refer to a relation of one single tissue establishment.

Procurement, processing and storage of musculoskeletal tissues

Bone is obtained both from deceased and from living donors, who may donate a femoral head at hip replacement surgery. The femoral heads donated during hip replacement can only be used for non – structural purposes due to the brittleness of the bone (TRIP Annual Report 2012, Biovigilance).

It must be collected aseptically into a suitable container and frozen. The donor must have been screened for mandatory markers using traditional serological tests plus either a repeat test 180 days after donation (unless Nucleic Acid testing (NAT) for the mandated markers was performed at donation). Testing for bacterial and fungal contamination must also be performed on samples taken from the tissue itself.

Surgically removed femoral heads are usually provided to the clinical user without further processing.

A significantly larger quantity of bone, and range of bone types, can be procured from deceased tissue donors. It can be processed to prepare a wide range of shaped bone allografts (e.g. ground bone, cubes, demineralised bone paste and putty etc.). From 50-300 units of bone/tendon can be prepared from one donation (Gillan et al, 2014). Often the bone donation is part of a multiple tissue donation including other musculoskeletal tissues, such as tendons and meniscus, and also other tissues such as skin and heart

valves. The processing of bone is performed in a clean room suite to GMP standards, usually Grade A. The bone is then terminally sterilised using irradiation.

Procurement of musculoskeletal tissues requires a surgical approach. Preventing contamination is one of the main challenges. Cleaning, disinfecting and working in a local sterile field is necessary for procuring the grafts. Culturing samples for microbiological contaminants is an important step in guaranteeing the safety of the bone. Procurement of musculoskeletal tissues therefore usually takes place in an operating theatre (OR), particularly in those programmes where the tissue is not subsequently terminally sterilised. Depending of the number of grafts taken, an operation on a deceased donor may take up to three hours or more in which the OR cannot be used for other purposes. Some tissue establishments have therefore invested in dedicated operation theatres at their site, while others use the hospital facilities outside working hours.

Processing of bone may consist of several steps depending of the type of material and the use of the grafts. In general the following steps are applied (Veen, 1994):

a) Cleaning and removal of debris
b) Washing or rinsing to remove debris and bacteria
c) Cutting and shaping
d) Disinfection with different kind of disinfectants or by heating
e) End sterilisation by Gamma or E beam radiation
f) Freeze drying or freezing for storage.

While cleaning and washing with desinfective agents (processing steps a and b) are aimed at reducing the level of micro-organisms, the techniques used in the process steps d and e, are intended to remove or destroy all living micro-organisms. In order to achieve elimination of micro-organisms, the following sterilization and decontamination methods can be applied by musculoskeletal tissue establishments (Veen 1994):

- Heat-sterilization
- Gas-sterilization
- Gamma-irradiation
- Ethanol
- Beta-propiolactone (Lo Grippo et al, 1956)
- Merthiolate (Arde, 1956)

Some musculoskeletal tissues (e.g. femoral heads from living donors) are frozen directly after procurement and distributed after microbiological cultures and donor tests are confirmed negative.

Decalcification (demineralization) of cortical bone is widely used to remove the nonorganic matrix and expose the organic matrix, with subsequent release of osteoinductive growth factors. This kind of bone implant stimulates renewing of bone and is primarily used where bone is implanted in a site that does not have bone mass, e.g. in dental implantation.

Bone can be cut and shaped into a large number of forms and sizes. Some of the most commonly used musculoskeletal tissue grafts are: femoral heads (from living and from deceased donors); cancellous chips, patella tendon whole, and patella tendon or hemi patella tendon); proximal tibia or distal femur frozen, cortical struts or rings demineralized bone powder and osseous gel (putty).

Cost structure

Depending on the donor source (living or deceased), the cost structure of bone banking varies considerably. The response to the survey into cost structures of musculoskeletal tissue establishments didn't result in any information, either because the tissue establishments didn't have the required data, or they didn't want to provide it. Only one reliable source was available (table 18). Depending on factors such as organisation of the procurement teams, the distance to the donor site, the required virology and microbiology testing regiment, the method of processing, the costs of a post-mortem donation can reach a level of around €5000 in some tissue establishments, while other tissue establishments may be able to carry out these tasks at more reduced cost levels. The procurement of a femoral head from a living donor occurs additional costs such as swabbing, microbiology testing, packaging, labelling and transportation to the tissue establishment. Depending on organisational factors the total costs are a few €100.

The following division of processes and related costs can be recognized.

Table 18 Cost division in a musculoskeletal tissue establishment

	Post mortem donors	Living donors
Donor procurement	16.20%	39.00%
Testing	4.30%	49.20%
Processing	42.00%	0.00%
Distribution	37.50%	11.80%
Total	**100%**	**100%**

Source: BIS Foundation Annual Financial Report 2008 and Netherlands Bone Bank Foundation 2008. Percentages based on financially audited costs of 111 deceased donors and 1145 femoral heads. Survey to musculoskeletal tissue establishments (2014)

Procurement from living donors

As a femoral head is removed from the donor to place an artificial implant, there are only costs of the surgical recovery procedure (which takes place anyway, despite of the donation). After training and instruction of the staff, donor screening of medical suitability is executed in the hospital. The orthopaedic surgeon signs the screening form. Packaging of the graft is done in the operating room. Some tissue establishments offer compensation for administration and packaging. The fees, known to the authors, vary from €40 to €70 per donated femoral head. Additionally, there are transport costs, depending on distance from the tissue establishment, and of transport circumstances (cooled, frozen or otherwise).

Procurement from deceased donors

Deceased tissue donors can be organ or non-organ donors. In both cases, there is a limit with respect to the time during which musculoskeletal tissues can be removed after cardiac arrest. In case of a donor referral, a team with on average three trained professionals (MDs and/or technicians) travels to the donor site and carries out the donor operation. In this process, a variety of costs are incurred:

Compared to other tissue procurements (cornea, skin) the costs of musculoskeletal tissue donations are much higher. This is caused by the higher quantity of team members, more sterile materials for packaging of the tissues, a larger instrument set and a multitude of microbiology swabs for the procured tissues. A 24/7 on-call service, executing an initial screening, requires many elements to be organised including:

- A well trained donor team which is on stand-by
- Instruments and sterile materials to operate and package the tissues
- Stock of tubes/swabs for virology and microbiology testing
- Travel to the donor site and back
- Using the OR of the donor hospital or dedicated OR from Tissue establishment
- Carrying out the donor operation. The time depends on the circumstances (waiting for organ donation to finish y/n) and experience of the operating team.
- Administration of donor clinical details and operating report
- Transport costs, depending on distance from the tissue establishment, and of transport circumstances (cooled, frozen or otherwise)
- Virology and bacteriology testing. Virology testing is done with the post mortem blood (preferably also with the pre-mortem blood) of the donor. Bacteriology as well as virology tests are carried out by contracted laboratories, which are certified for these tests;

Donor detection and family interviews is organised in different ways throughout the EU Member States. In some Members States there are no costs reported for such activities, which may be related to an opting-out system, while in other Member States these services are part of the organ network structure and no costs are forwarded to the tissue establishments. In some countries hospitals have dedicated officers for donor recognition and in-house coordination of procedures.
Since bone donation comes with a large number of contra-indications, and to avoid procurements resulting in discards, thorough donor selection (before starting the procurement) is of utmost importance to avoid unnecessary costs. Discard rates of over 11.3 % have been reported (EUROCET 2013). These discards are caused e.g. by contra-indications of the donor, by virology and microbiology results as well as by the morphology of the donated tissue.

Further processing and distribution

- Cutting the bones and tendons into shapes and sizes matching with the expected demand from surgeons.
- Processing of the bone. The costs are dependent on the method which is chosen, and which leads from almost no costs (when the bone is not cut, not macroscopically cleaned, e.g. by removing cartilage) to hundreds of euros per bone piece if intensive cleaning, cutting and processing is applied. Depending on the (terminal) sterilization method, and whether tissues are cryopreserved or freeze-dried, the processing costs can be higher or lower.
- Without processing, grafts are released after negative virology and bacteriology tests and approval of the donor's medical screening.
- Cleaning of the bone by removing attachments such as cartilage, sawing and soaking in an antiseptic such as alcohol. Usually irradiation afterwards.
- Sterilisation by means of irradiation.
- Cleaning by means of critical CO^2 method, irradiation afterwards.
- Freeze drying or freezing, packaging and labelling.
- Storage and administration.
- Distribution.

Additional cost factors to consider relate to the maintenance and daily operations of clean room facilities. The freeze-drying and cryo-preservation methods enable tissue establishments to extend shelf life over many years. However, to safeguard preservation in the cryo-containers, the levels of liquid nitrogen must be constantly monitored and kept on a level sufficient to keep the temperature of the tissue grafts at an adequate level.
In the case of musculoskeletal tissue establishments it is a challenge for the management to balance demand and supply. Because of the fact that grafts are applied in a great variety of specific interventions, depending on the different shapes and forms into which they have been processed. Management should be aware of the demand in

such medical-specialist areas such as orthopaedic surgery, traumatology, neurosurgery, maxillofacial surgery and plastic surgery. The difficulty for the tissue establishment management is to optimize and process the donations in such a way that the demand is completely covered, while stock size is adequately kept and expiration of grafts is prevented.

Fee structure

The fee determination for musculoskeletal tissues reflects the relationship between the legal status of the organisation, determination of the fee and the fee charged to local end-users. As explained elsewhere in this chapter and in this report, the economics of tissue banking are complex and depend on many factors. This is one of the reasons for the observed differences in fees. On top of the factors already mentioned, the fee charged to the end-users may be influenced by specific situations such as the mix between living and deceased donations in a particular tissue establishment (the latter usually being more expensive than the first).

Table 19 Fee determination of musculoskeletal tissues

Country	Legal status of organisation	Determination of fee by	Fee in € charged to local hospitals	
			Cancellous chips 30cc	**Achilles tendons**
Belgium 1	Part of private hospital	National insurance authority		
Belgium 2	Part of university hospital	National insurance authority	340	
Bulgaria	Not for profit shareholder company	Tissue establishment	400	500
France	Part of university hospital	Public body		
Germany 1	Part of university hospital	Not applicable: the grafts are free for all the patients, tissue establishment receive lump sum by social insurance company directly, income is independent from production		
Germany 2*	Not for profit shareholder company	Tissue establishment	350	750
Greece	For profit shareholder company	Public body (not CA)		
Hungary	Independent public foundation	Public body (not CA)		
Italy	Not for profit shareholder company	Competent authority	893	1200
Netherlands	For profit shareholder company	National insurance authority	485	1466
Spain 1	Part of public blood bank	Regional health authority	695	1200
Spain 2	Part of public blood bank	Regional health authority	440	486
UK 1	Part of national health hospital	Tissue establishment		
UK 2	Part of national health hospital	Tissue establishment		
Average fee			**515**	**934**

Source: Survey to musculoskeletal tissue establishments (2014)

*** The not-for profit shareholder company is a legal entity in some EU Member States. Usually the shares are owned by other not for profit institutions such as universities..**

By distributing DBM, tissue establishments are able to reduce the surplus cortical bone stock, while addressing clinical needs, thus generating additional income for their organisations.

Cross-border exchange and import /export of musculoskeletal tissue

Only a small number of musculoskeletal tissue establishments responded to the survey conducted as part of this study and hence the information with respect to donor shortage

and import-export provides a limited view on the economic landscape of musculoskeletal tissues in Europe. Table 20 shows a 25% import from third countries, while two US tissue establishments are responsible for about half of these imports (table 21); it may be expected that the relative share of imports from third countries will increase over time.

Many distributors of orthopaedic instruments and other hardware companies, which have qualified as tissue establishments, do import from different US tissue establishments. Such companies advertise allografts on the websites or in catalogues. This observation was reason for the researchers to look at US imports.

Table 20 Import, export and reported shortages of musculoskeletal tissues

Country	Donor shortage L/D*	Cross-border to EU	Cross-border From EU	Import from third country	Export to third country	Countries
Belgium 1	No answer	No	Yes	No	No	FR
Belgium 2	No	No	No	No	No	
Bulgaria	No	Yes	Yes	No	Yes	NL DE IT EL and Turkey
France	Yes	Yes	No	No	No	Not specified
Germany 1	No	No	No	No	No	
Germany 2	No	Yes	Yes			Not specified
Greece	50/50	Yes?		Yes		ES and US
Hungary	No	Yes	Yes	No	No	Not specified
Italy	No		Yes		Yes	UK DE
Netherlands	200/10	Yes	Yes	No	Yes	UK AT and Turkey
Spain 1	No	No	Yes	No	No	Not specified
Spain 2	No	No	No	No	No	
UK 1	No	No	No	No	No	
UK 2	No	No	No	Yes	No	US

Source: Survey to musculoskeletal tissue establishments (2014)

***L = living donors, D = deceased donors**

All over the European Union musculoskeletal tissue grafts are imported from the US. There are two major reasons for the import of these tissue grafts:

- There is a shortage of tissue donors in the EU, compared to the demand in different EU Member States. EU Tissue establishments, through alliances with US tissue establishments, but also orthopaedic companies registered as tissue establishments, strive to cover the shortage.
- Many tissue establishments in the US have a surplus of tissue grafts. The possibility to export tissues to other countries enables them to reduce their surplus stock while obtaining a better financial coverage of the costs they incurred to recover and process the donations or increase their profits if they work on a 'for-profit' basis.

For the purpose of this study, two US (non-profit) tissue establishments have been willing to provide data with respect to their export to the EU in 2012 and 2013.

Table 21 Export of musculoskeletal tissue from US to EU in units

	US TE 1		US TE 2		Total	
	2012	2013	2012	2013	2012	2013
Bone tissue	4,857	5,572	2,894	2,806*	7,751	8,378
Soft tissue	813	1,070	38	52	851	1,122
DBM	12,156	12,265	1,333	2,318	13,489	14,583
Total	**17,826**	**18,907**	**4,265**	**5,176**	**22,091**	**24,083**

Source: Survey to musculoskeletal tissue establishments (2014)

*** US TE 2 indicated that, because of a change in regulations in Italy, there has been a temporary decrease. In 2014 the level of bone tissue export to the EU was 4,286**

This table reflects the increase (by 9%) of the number of musculoskeletal tissue grafts imported in the EU from 2012 to 2013. Both organisations reported an intention to strive for further growth. The table gives a breakdown of three different categories of tissue grafts:

- Bone. Unfortunately no particular information was received for a more detailed overview of categories (chips, struts, intercalary etc.). The US sources confirmed that more than 50% of the bone tissues were cancellous chips, since this specific graft is mainly used for hip revisions.
- Soft tissue. This includes primarily patella and Achilles tendons. In recent years an increase of tendon grafting has been observed in sports medicine (Leys et al, 2012; Persson et al, 2014).
- DBM (demineralized bone matrix). The result of the research for the report into the exchange of musculoskeletal tissue shows a mixed picture. Looking at the substantial import form the United States, it would be possible to conclude that there are general and specific shortages in the EU. General shortages refer to the number of donors for replacement tissues. Specific shortages refer to 'products' such as DBM, which are in general not produced by European tissue establishments. Clearly, also in the area of distribution of bone tissue grafts, the dependency of the supply from the United States (25% and growing, in relation to the total number of allografts distributed (tables 20 and 21) is noted.

3.1.4 Skin grafts

Clinical application

Skin tissue grafts are mostly used to cover chronic wounds or burn wounds. Skin consists of a thin outer layer called epidermis, and a thick inner layer called dermis. The benefit of a skin graft is that it forms a natural layer (as opposed to bandages) over the exposed tissue of the recipient. The term 'biological bandage' is often applied to skin grafting. Thus, donor skin prevents the recipient from drying out, but skin grafts also protect the patient against the ingress of microbes. Additionally, human donor skin can form a scaffold for the recipient's newly generated autologous skin. Autologous skin is harvested and applied in one procedure and used for limited covering. Large burn wounds are covered with allografts.

In second degree burn wounds a significant reduction in pain can be achieved very soon after grafting of the donor skin. In the first instance the donor skin is adherent and remains in place like a supple scab. In general, a very rapid high-grade epithelialization takes place under the skin grafts, after which the dried-out scab comes loose.

Both in second and in third degree burn wounds, the donor skin can be perforated (meshed) before being grafted. The advantage is that a larger surface of the recipient can be covered. In third degree burn wounds, after operative removal of the necrotic tissue, the wound is, if possible, covered with an autograft. This graft can then be covered with donor skin (so-called sandwich graft). This provides a covering for the areas of the wound left exposed by the distribution of the autograft. Donor skin also promotes rapid epithelialization (Verween et al, 2012).

The standard treatment of burn wounds by applying (donor) skin does not often lead to acceptable functional and cosmetic outcomes and leads to development of scar tissue and skin contractions. By growing skin cells (keratinocytes) in vitro to be applied with a meshed split skin graft, the burn will heal faster with less scarring. Although a well-established process in many tissue establishments, this is now classified as an ATMP with significant cost implications associated with achieving marketing authorisation as a medicine.

In chronic wounds as well as in burn wounds, glycerol-preserved donor skin has a cleansing and granulation-promoting effect on the wound bed. Significant pain reduction is an important side effect. Once the donor skin adheres to the wound bed, the latter is suitable for auto grafting.

Other clinical applications of skin grafting are reconstructive and cosmetic plastic surgery.

Activity level in the EU

In 2012 there were 57 authorised skin tissue establishments within the EU.

Table 22 shows an overview of donation and distribution of skin tissues.

Based on the EUROCET 2013 report, 80% of the distribution would take place in the own Member State. Unfortunately the 2013 EUROCET report has no data with respect to distribution activities from the Netherlands. In an interview the Euro Skin Bank indicated that for distribution in the own Member State about 20-25 donations per annum would be necessary. This means that more than 90% of the donor tissue, equivalent to about 1 500 000 cm^2, from the Netherlands is distributed to other Member States and to third countries. In the same interview it was stated that procured skin from all donations in Bulgaria is processed in the Netherlands and from there distributed by the Euro Skin Bank (Interview 2014).

Table 22 Skin graft donations, distribution, import and export

	Donations		Total Distributed	Distributed in own MS	Cross-border to other MS	Export to third country	Cross-border from other MS	Import from third country
BE	106		198427	198427				
BG	166							
CZ	44		926		1019			
DE	26		35500				2	
FI	32		0					
FR	370		295905					
HR	8		1250					
HU	4		0					
IT	339		845017	845347			330	
LV	0		0					
LT	0		0					

LU	0		0					
NL	495		0		8099	1952		
PL	39		65513	65513				
PT	1		9193	10067			74	
RO	4		500	500				
ES	94		214711	214691	20			
SE	83		0	0				
SK	3		19310	19319				
UK	**0**		1225					1225
Total	**1822**		**1684252**	**1353864**	**9144**	**1952**		**1225**

Source: EUROCET 2012. Please note that total numbers don't add up as not all countries reported.

Procurement, processing and storage of skin

Deceased donor skin grafts are procured after shaving, washing, disinfecting and oiling the skin of the back, side and legs up to 24 hours after death. With an electric dermatome, a layer of 0.2 to 0.8 mm can be removed. Samples should be uniform of thickness and preferably have large dimensions, suitable for treating patients with major burns. Procurement takes place in mortuaries or operating theatres. If musculoskeletal tissue is also donated, it is preferred that skin is procured first.

The retrieved skin is placed in transport medium (e.g. glycerol solution) and transported in refrigerated containers to the tissue establishment for processing. Alternatively, skin can be placed on sterile gauze soaked with saline solution.

Skin from living donors after abdominoplasty operation is procured to obtain full thickness skin grafts for the production of de-epidermilised dermis. The tissue, complete with adipose layer, is stored in sterile containers for transport to the tissue establishment.
The processing of skin takes place in cleanrooms. Every skin tissue establishment uses specific graft processes, according to standard operating procedures and mandatory regulations, and depending whether sterilised or non-sterilised grafts are processed.

Fresh skin grafts and skin for cryopreservation are processed immediately to maintain cell viability (Leung 2009). After receipt, the skin is decontaminated and processed into fresh, glycerol-preserved, cryopreserved or freeze dried allografts. Glycerol preservation, a method in which the skin is preserved in glycerol. As glycerol has virucidal and bactericidal characteristics, the skin can be processed in a laminar flow cabinet (Grade A) placed in a Grade D cleanroom. By using the glycerol method, the skin matrix is kept intact while cells are not viable. With cryopreservation all cells for the donor skin are kept viable. To apply this method of conservation, processing must take place in a Grade A flow cabinet placed in a Grade D clean room. When skin cells are preserved by using cryopreservation, their function is maintained after grafting on the recipient. A disadvantage is that the recipient may undergo an immunological reaction and reject the allogeneic skin. Both glycerol preserved skin and cryopreserved skin are only temporary grafts; the final closure of the wound always takes place with autologous skin.

Freeze dried and glycerol-preserved skin can be stored at room temperature. Glycerol-preserved skin is a non-viable skin-graft that is considered a safe product due to the antibacterial/antiviral properties of high concentrations of glycerol and is less immunogenic than cryopreserved skin. It is used in partial thickness burns and other types of skin loss, or within the sandwich grafting technique, in which meshed human skin allograft is used as an overlay over widely meshed autograft (Vloemans et al, 2002).

Fresh skin has a safety risk, as donor screening and microbiological testing is mostly not completed. Therefore most physicians prefer cryopreserved skin to fresh skin. Also the ease of storage and availability is an advantage of cryopreserved skin. Cryoprotectants such as glycerol or dimethylsulfoxide are used to maintain cell viability during cryopreservation. Despite this procedure, cell viability is negatively affected by cryopreservation in comparison with fresh skin.

Depending on the recipient's wound site, allogenic donor skin can be grafted as "full thickness" as well as "split-thickness". A full thickness grafts consists of the entire epidermis and a dermal component of variable thickness if the entire thickness of the dermis is included (Wax et al, 2015). The interaction of the autologous dermal and epidermal cells ensures a secure secretion of chemokines, growth factors and cytokines into a non- healing wound bed. Wound reactivation and re-epithelialization occurs through the direct secretion and cover of the wound bed (A-skin, Amsterdam). A split-thickness skin graft (STSG) is a skin graft including the epidermis and part of the dermis (Barret-Nerin et al, 2004).

By making openings (meshing) in the graft, the recipient cells are able to "bridge" the gaps toward the allogeneic graft. Thus, the wound site heals by re-epithelialisation from the dermis and surrounding skin and requires dressings.

For many decades, skin banks have also cultured autologous keratinocytes for burned patients. An autologous skin biopsy is taken and cells are cultured during some weeks to form skin sheets. These are often grafted together with allogeneic skin on burn wounds and chronic wounds. They are not rejected and stimulate the wound bed to provide faster healing and definitive coverage of the wound with less scars and contractions.

This method has advantages and disadvantages. The advantages are that, specifically in autologous grafts, the immunological reaction of the recipient is avoided. When used as allograft, cultured skin may function as temporary dressing releasing growth factors that can stimulate wound healing. When skin culturing could be done on a large scale, the necessity to recover skin from deceased donors would disappear. The consequent advantage would be that the extended logistics to maintain a 24/7 donor recovery team and associated costs would become obsolete.

The disadvantage of the autologous skin culture techniques is the time lapse between the start of the culturing process and the final results, which can be at least several days. In urgent situations, such as third degree burn wounds, cultured skin can't bring immediate relief. The second disadvantage is that the laminar flow cabinet (Grade A), in which the culturing (both autologous and allogeneic) takes place, must be placed in a clean room Grade B. The investment and maintenance costs may be 60% higher than when a Grade D background is applied (like for deceased donor skin processing). However, many skin banks anyhow process cryopreserved skin in a grade A/B environment. Also the maintenance costs of a Grade B clean room are considerably higher.

Although a well-established process in many tissue establishments, skin culture techniques are now sometimes classified as an advanced therapy medicinal product (ATMP). The classification of these two products as ATMPS implies significantly higher costs due to investment in obtaining a marketing authorisation as an ATMP (Pirnay et al., 2013).

Cost structure

For the purpose of this study, two skin TEs were investigated in depth: Human Cell and Tissue establishment, Queen Astrid Military Hospital, Brussels, Belgium, and the Euro Skin Bank, part of the Euro Tissue Bank Foundation in Beverwijk, The Netherlands.

Euro Skin Bank is the larger. Annually, 400-500 donors are reported to this foundation, providing about 1 700 000 cm2 of skin. Most of these donors originate from the Netherlands. The Human Cell and Tissue Establishment Queen Astrid Military Hospital reports about 100 donors annually, while its distribution is around 200 000 cm^2.

No specific data were available with respect to the four cost categories: Donation, testing and screening, processing and distribution. Information which was provided during the interviews for this research learned that the costs of virology tests are often shared with the tissue establishments that procure corneas and/or the heart from the same donor. Procurement costs are estimated to be 33%, and processing costs are estimated to be about 50% of the costs (source: Euro Skin Bank).

To enable post mortem donations a well-trained team and accompanying logistics must be available. Each donation generates expenses for logistics, salary costs for procurement personnel, virology testing etc. Specifically at a post mortem skin donation it is important to procure sufficient cm^2 skin to cover those costs by the distribution of allografts after processing; For example the Euro Skin Bank indicated that they strive for 4000 cm^2 per donor to make the donation feasible.
The need for a clean room environment in which establishments usually process takes place under a class A cabinet with a background of class B.

The cryopreservation method is used by some skin tissue establishments, while a glycerol preservation method is used in others. Both methods guarantee a shelf life of several years. However, the investment in hardware for cryo-preservation and to safeguard preservation, the levels of liquid nitrogen must be constantly monitored and kept on a level sufficient to keep the temperature of the tissue grafts at an adequate level.

The culturing of skin requires surgical procurement techniques from the living donor. After a culturing process which takes place under class A clean room conditions, and which may take several weeks, the cultured cells are placed into the wound bed of the recipient. Again, this takes place under class A conditions. Although calculations couldn't be provided, this entire process results in higher costs per cm^2 than other skin grafting methods.

Fee structure

From the interviews for this research, it was reported that the following fees for glycerol preserved skin to the end-user per cm^2 were applicable in 2014: Belgium EUR 1.39; Netherlands EUR 1.20 (when exported, e.g. to Belgium, the fee is adjusted to the local price in Belgium: EUR 1.39).

Cross-border exchange and import /export of musculoskeletal tissue

Since distribution of tissue grafts is done all over Europe, the Euro Skin Bank developed and maintains several donor sites over the continent. Thus, the organisation strives for a balance between national and international activities. In 2012 a total of 1 125 000 cm2 was distributed by the Euro Skin Bank, of which 11% was used nationally, 71% was sent to other Member States and 18% was exported to third countries.

Of all tissues distributed, only 13 units of cultured skin were produced and transplanted (TRIP Annual Report 2012).

Research for this report provided little information about the need for donor skin in the EU Member States. The table below shows the national need in five Member States.

Table 23 Need for donor skin in EU Member States

	Year	cm^2/year	cm^2 per 10^6 inhabitants
Belgium	2011	221,040	0.02
Croatia	2012	295,905	0.06
France	2012	2,960,000	0.04
Netherlands	2012	123,750	0.008
Poland	2012	601,000	0.01

Source: Economic landscape survey NCATC (2015), data over 2012

The number of tissue donors in the Netherlands is more than sufficient to cover the demand (495 in the year 2012, with an estimated yield of 1,980,000 cm^2). The low volumes of distributed skin in the Netherlands is due to the fact that, compared to other Member States, there are relatively few severe burns in that country.

3.1.5 Amniotic membrane

The amniotic membrane or amnion is one of the foetal membranes and is used for various applications in ophthalmic surgery as well as for chronic ulcers, skin burns and other skin wounds. Amnion can be used fresh (Adds et al, 2001) but is mainly cryopreserved or freeze dried and stored (TRIP Annual Report, 2012, Biovigilance;).

Within the EU there were 18 authorised tissue establishments for procurement, processing and distributing amnion, often linked to a cornea tissue establishment.

3.1.6 Pancreatic Islets

Langerhans' islets beta cells can be prepared from donor pancreas. These cells are injected into the liver of a patient suffering from diabetes; the beta cells will synthesise insulin. At this point the procedure is only indicated for patients with type 1 diabetes who have severe complications. In the future, it can be extended to patients with fewer complications.

In order to produce grafts composed of these cells, human donor Langerhans' islets are provided by organ donor centres. Since the recipients are mostly in need of a kidney transplant as well, islet cell donation and transplantation is often considered to be part of the organ transplant network. The processing of grafts, however, is part of the tissue banking framework from a regulatory point of view. After receiving a pancreas in the tissue establishment, grafts with selected size, composition and function are produced. The biological properties of beta cell grafts should be characterized and adjusted to the metabolic and immunological status of the recipient. This type of graft should increase the efficacy of accompanying measures aiming at graft survival and/or metabolic correction (Gaba et al, 2012).

The supply of Langerhans' islets to use for human beta cell grafting is insufficient. To produce a graft which matches the recipient's requirements, at least one organ is needed. Cases of up to 5 organs being used to process one beta cell graft have been reported (Qi et al, 2009).

From the economic landscape survey to NCATC (2015), Poland reported 13 pancreas donations and 10 transplantations of beta cells in the year 2012. In 2012 there were 8 authorized pancreatic islet tissue establishments in the EU.

3.1.7 Other tissues and cells

A variety of tissues and cells can be categorised in this group, including adipose tissue, nerves and hepatocytes. Autologous adipose tissue is sometimes used in plastic and cosmetic surgery, and was identified as a source of pluripotent stem cells (up to now only in experimental therapy (TRIP Annual Report, 2012).

Nerve tissue can be transplanted when nerves are damaged by trauma or resection and to reduce neuropathic pain. Preferably autologous tissue is used but this is not always possible. In those cases an allogeneic nerve graft can be transplanted. Nerve tissue can be radiated, freeze-dried or cryopreserved (Nunley et al, 1996; Houston, 2001).

The grafting of hepatocytes has barely left the stage of clinical experiment (Guha et al, 2000). No hepatocyte implantations were reported in the EU as part of the research survey. The donor tissue for hepatocyte grafts origins from the liver. The liver is recovered in organ donation procedures. In some European centres, the liver is provided to a US-based firm (Cytonet), which processes these livers into hepatocyte grafts.

3.2 ORGANISATION OF THE SECTOR

Tissue establishments are organised in a variety of different legal structures. The table below contains an overview of the total number of tissue establishments per tissue group and a division in public and private establishments for replacement tissues.

Table 24 Number of tissue establishments for replacement tissues

	Number of TEs*	CV*	MSK*	OC*	SKIN*	Amnion*	Pancr. Islets *	Other*	Multi TEs*	All TEs public **	TEs mainly public >75% **	TEs partly public and private*	All TEs private **	Unclear public or private **
DE[15]	154	6	119	24	2	30		41	10			x		
FR	76	14	26	17	10	15		2	16		x			
ES	74	26	38	22	13	1	4	15	29		x			
UK	65	3	45	3	2			53	41			x		
NL	33	1	27	2	1	1	1	2	5		x			
SE	30	2	18	9	3	1	1	8	7	x				
AT	28	1	7	5	1	2		24	17			x		
FI	27	1	22	3	1	1		1			x			
IT	27	5	7	14	5	2	2		7	x				
BE	20	1	15	4	3	4	1	16	7	x				
CZ	20	3	18	5	3	1			5					x
DK	18	1	12	1		1		3	1	x				
PT	11	1	3	6	1				1					x
BG	9		3	3	3									x

[15] DE authorities report 614 sites for MSK, however these do include the procurement sites for chondrocytes

HU	9	2	4	1	2				1		x			
IE	8	2	2	1		1		2	3			x		
PL	8	2	4	5	2			1	6			x		
SK	7	1	3	3	2	1		2	2			x		
HR	6	1	4	1	1				1	x				
SI	6		3	1				5	2			x		
GR	5			5										x
EE	3	3	3	2	1	2			3	x				
LV	3	1	1	1	1	1			1	x				
RO	3		2							x				
CY	2			2									x	
LT	1			1		1			1	x				
LU	0													
MT	0													
Total	**653**	**77**	**386**	**141**	**57**	**35**	**9**	**137**	**166**	**9**	**5**	**7**	**1**	**4**

Sources: *EUROCET128 ** Implementation survey by DG SANTE (2013)

The majority of tissue establishments are (part of) public organisational structures or 'private' foundations that operate on a non-profit basis. Hospital-based tissue banks can be categorised as public or as private, depending on whether they are part of a publicly or privately funded hospital. Supply of tissue by for-profit, shareholder-oriented banks also occurs in Europe, although not on the scale that is practiced in the US.

Initiated by surgeons in need of certain tissues, many tissue establishments are hospital based and associated with the surgical department they supply. The majority (about 75%) of the 653 banks focus on one type of tissue (e.g. skin, bone), or one category of surgeons (e.g. ophthalmologists who need corneas and amnions). Most of the single-tissue banks are hospital-based bone banks where femoral heads are stored. The size of these single-tissue establishments is small (50-250 donations per annum) and the tissue they handle is often only distributed in the own hospital and sometimes to hospitals in the region. The cost for these activities is usually difficult to distinguish from the budget of the hospital in which they are located. Given the similarity of most of the processes, sometimes tissue banks are part of the local or national blood establishments.

Over time, some of these single-tissue establishments have developed into larger independent establishments handling a higher volume of donations. These establishments supply tissue to many hospitals on a supra-regional or national level, and may also exchange or export material internationally. Examples of these are the FBOV (Fondazione Banca degli Occhi del Veneto Onlus - Veneto Eye Bank Foundation) (>2 000 donations a year) and Euro Skin Bank in the Netherlands (>80% of skin distributed internationally).

Public and private tissue establishments

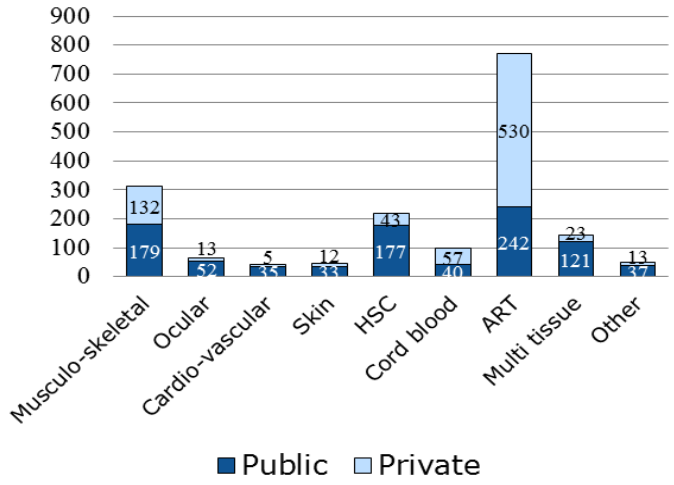
In the common law, a public organisation is an organisation that is directly or indirectly legally related to a governmental body, such as a ministry or a ministerial agency. For tissue establishments, the distinction between public and private tissue establishments is a gross one.

In the survey to tissue establishments as part of this research, tissue establishments indicated that they were either:

- Part of a public (university) hospital
- (Part of) a national health organisation
- For profit shareholder company
- Not for profit shareholder company
- Independent private foundation
- (Part of) a private hospital

From the 27 responding tissue establishments 12 (44%) reported they are part of a university hospital, being a public body, while 5 (19%) belonged to a national health organisation. 10 tissue establishments (37%) indicated that they are a private foundation. The Implementation survey, carried out in 2011, demonstrated that from 461 tissue establishments concentrating on replacement tissue activities, 299 (65%) is considered as a public establishment.

Table 25 Public/Private Status of EU tissue establishments



Source: European Commission Implementation Survey (2013), data 2011

Multi-tissue establishments are in most cases active in the procurement of tissues from deceased donors, and are usually stand-alone, i.e. independent of the surgical units in the hospitals. Given the source of the tissues, some of the multi-tissue establishments are associated with pathology departments. Examples of large multi-tissue establishments include the FBTV (Fondazione Banca dei Tessuti di Treviso) in Treviso, Italy; BST Blood and Tissue bank in Barcelona, Spain; DIZG in Berlin, Germany and the NHSBT Tissue Services in Liverpool, UK.

3.2.1 Associations and foundations of replacement tissue establishments

Given the scattered landscape in Europe with many small establishments that operate locally and a small number of large (multi-tissue) establishments, collaborations are important in this sector. These collaborations find their origin in the limited availability of tissues on the one hand and the regular need for matching/characterisation to find grafts that meet the needs of specific recipients on the other hand. The following sections include an overview of the associations active in the field of replacement tissue banking, the international alliances between tissue establishments in EU Member States and between tissue establishments in the EU and organisations in relevant third countries.

Associations

Two main associations are active in replacement tissue banking. These are the European Eye Bank Association (EEBA) and the European Association of Tissue Banks (EATB). Both associations have been active for over two decades and concentrate their efforts on sharing of information to support endeavours to improve the quality and quantity of tissue donation and tissue banking. The EATB has been actively involved in the development of Good Tissue Practices; a set of GMP (good manufacturing practices) adapted to the specific needs of the different replacement tissue sectors. Both associations hold annual congresses to provide a forum for scientific, ethical and clinical discussions relating to tissue banking and to provide a forum for presentation of research and collaborative working. The associations contribute to formal consultations and seek to actively involve their members in all their activities.

Another organisation, the Foundation of European Tissue Banks (SEGB), was founded in Germany when new national legislation, based on the EU Tissue Directives, was introduced. The aim is to assist tissue establishments in Germany and in Europe with fulfilling legal criteria, by supporting projects focused on the improvement of quality, and to increase the number of tissue donors in Germany and elsewhere in Europe. The Foundation organises meetings focused on specific aspects of tissue banking, mainly of cardiovascular tissue establishments, as well as on the advancement of tissue donation in forensic medicine institutions.

National alliances between tissue establishments

In order to cover the need on a national level, cooperation between tissue establishments is an important tool to ensure allocation and best use of donor tissue, which is available in one tissue establishment, to hospitals in the regional working area of another tissue establishment. Such networks exist in one form or another in Belgium, France, Germany, Italy, Spain, The Netherlands and the UK. In some Member States, such as Italy and the Netherlands, there are regulatory requirements to ensure that tissue grafts originating from national donors are allocated to recipients from that Member State before export is allowed.

In the Netherlands, two large tissue establishments, BISLIFE and the Euro Tissue Bank have agreed to share with other tissue establishments all information with respect to multi-tissue donors. The donation and procurement teams for skin, corneas, cardio-vascular and musculoskeletal tissue are complementary, and procedures are synchronized. Test results for different tissues that are recovered from the same donor, are shared. The evaluation methods of test results and the process to interpret outcomes takes place through consensus between the participating organisations and the tissue establishments, that will carry out the processing of the different procured tissue types. Such shared efforts therefore have a direct cost-reducing impact.

In Germany, there are two active national networks in the field of cornea banking. One consists of a group of Lions Cornea Banks, which exchange tissues on request. This network is, as the name suggests, supported by regional Lions Service Clubs. The Lions have a specific focus on blindness and usually express their support by financial donations that enable the cornea establishments to purchase capital investment goods such as incubators or laminar flow cabinets. The other network consists of a group of cornea establishments that operate under the umbrella of the Deutsches Gesellschaft für Gewebetransplantation (DGfG) (German Society for Tissue Transplantation). This society finances, partly or entirely, mainly cornea establishments, and strives for standardising processing methods and quality management. By optimal allocation of the available tissue graft within the network of 15 tissue establishments, the use of available tissue grafts is optimised for specific patient groups and maximised in order to prevent expiration of grafts in stock.

International alliances between tissue establishments

Mainly for reasons of balancing the supply and demand in different countries, some larger tissue establishments have created alliances to provide tissue to one another, across borders within EU, but also with non-EU countries. These alliances include the following:

BISLIFE (NL) and Musculoskeletal Transplant Foundation (MTF, USA)

The cooperation is based on an agreement that came into effect at the inception of both foundations in 1989. The agreement has been renewed from time to time. Initially, BISLIFE (then BIS Foundation) distributed MTF bone and soft tissue (tendons) whenever BISLIFE couldn't provide tissues from their national donors.

Since 2010, the agreement includes processing of bone tissue from two-thirds of the deceased donors in the Netherlands at MTF's facility in the USA. After processing, the grafts are sent back and are distributed by BISLIFE (until 2010, BISLIFE had a similar processing agreement with Osteotech Inc. in the USA). Since MTF has distributors and marketing experts focused on different European countries, the agreement with BISLIFE limits distribution by BISLIFE to the BENELUX countries.

Euro Tissue Bank (NL) and the Tissue Bank of the University Hospital Brno (CZ)

The Euro Tissue Bank receives donor skin from different sources in Europe. One of these sources is the Tissue Bank of the University Hospital Brno. Donor skin is recovered in the Czech Republic. After medical screening of the donor and negative test results, the skin is processed at the Euro Skin Bank (part of the Euro Tissue Bank) in the Netherlands and distributed to different EU Member States and to third countries whenever the stock assigned for use in European hospitals allows.

Euro Tissue Bank (NL) and Tissue Bank Bulgaria (TBB, BG)

One other source for skin donation is the TBB. Donor skin is recovered in Bulgaria, though tested in the Dutch national blood bank Sanquin. After medical screening of the donor and negative test results, the skin is processed at the Euro Skin Bank and distributed to different EU Member States and to third countries whenever the stock assigned for use in European Hospitals allows.

Euro Tissue Bank (NL) and Banc de Sang I Teixits Barcelona (BST, ES)

As with TBB (above, under 3) donor skin is recovered in Catalunya and processed in Euro Tissue Bank's facility in the Netherlands. After processing, the tissue grafts are distributed to different EU Member States and to third countries whenever the stock assigned for European hospitals allows.

European Cell and Tissue Bank (ECTB, AT) and European Medical Contract Manufacturing (EMCM, NL)

EMCM uses a process, which uses critical CO2 to remove all soft tissue blood and bone marrow bone tissue, reducing viruses or other micro-organisms to the sterility assurance level of log 10^{-6}.

The ECTB sends bone tissue from femoral heads of living donors to EMCM's facility in the Netherlands. After processing, the tissue is sent back to ECTB in Austria. Superfluous tissue, not needed for Austrian recipients, is distributed in other EU Member States. This distribution is always done within the regulatory limits of the respective countries.

Tissue Bank Osteocentre Bulgaria (TBOCBG* 16*, BG) and Deutsche Institut für Zellen und Gewebeersatz (DIZG, DE)

Bone tissue of deceased donors is recovered in Bulgaria and processed at the DIZG in Germany. Tissue grafts are distributed in Germany, while the fulfilment of need for tissue in Bulgaria is guaranteed.

BISLIFE (NL) and Banc de Sanq I Teixits Barcelona (BST, ES)

Since the early 1990s, BISLIFE has functioned as the distributor for cardiovascular tissues of *de Banc de Sang í Teixits in Sant Boi* (near Barcelona). Tissue grafts are imported mainly into the Netherlands and Germany.

In 2015, the relationship was extended to the processing of bone tissue. Donor tissue from the Netherlands is shipped to BST for processing, after which the tissue is returned to BISLIFE for distribution in Europe.

BISLIFE (NL) and DIZG (DE)

Bone tissue of deceased donors is recovered in the Netherlands, one third is shipped to DIZG and, after processing, distributed by DIZG mainly in Germany.

DIZG (DE) and MTF (US)

DIZG is a full subsidiary of MTF through Biocon Corporation, its controlling affiliate. DIZG and MTF exchange (patented) knowledge on processing techniques for processing of tissue including bone and dermis and MTF provides DIZG with base material with the help of US procurement partners.

European Homograft Bank (EHB, BE)

The European Homograft Bank (EHB) is a non-profit association according to the laws of Belgium. The association operates a cardiovascular tissue establishment, and has international members throughout the EU. The members provide donor tissues to the bank. In return they receive processed tissue grafts. The EHB has been instrumental in setting up a cardiovascular tissue establishment in Zagreb (HR) which uses the same methods as the EHB Brussels facility.

University Tissue Bank Leuven (BE) and France

The University Tissue Bank has a regular contact with French tissue banks in which demand and supply are balanced in case there are shortages in either Member State.

Tutogen Medical GmbH (DE) and RTI (USA)

Tutogen Medical GmbH is a subsidiary of RTI (formerly Regeneration Technologies International). The acquisition took place in 2008. It is known that in the past, Tutogen processed donor bone tissues procured in Estonia, Latvia, Czech Republic, Hungary and Slovakia. In 2012 Tutogen terminated import from tissues from deceased donors from Ukraine. Tutogen distributes the final tissues to Europe and exports them to the USA.

Tutogen and TBB (BG)

TBB provides bone tissue to Tutogen. TBB declares that these donations take place according to the legislative rules and regulations of Bulgaria. No other relations are known.

This list includes some well-known alliances in the sector, but is not exhaustive.

[16] Note TBOCBG and TBB are different organisations

3.3 FUTURE PERSPECTIVES IN REPLACEMENT TISSUES

3.3.1 Cardiovascular tissues

Although a few years old, the surveys regarding the use of cardiovascular tissue allografts show no increasing trend in the number of implantations (Foundation of European Tissue Banks, directories of European Cardiovascular Tissue Banks, 2012, 2013). Several meetings of cardiovascular tissue bank experts discussed these trends and their probable causes (consensus meeting 2011). Our recent surveys confirm this finding. The reasons are three:

- The improvement of mechanical (industrially produced) valves and bio-prostheses;
- The limited availability of cardiovascular allografts has lead surgeons to use alternatives;
- The so called Ross operation, in which the own pulmonary valve of the congenital heart disease patient is placed in the aortic position and a pulmonary allograft is placed in the place of the relocated pulmonary graft of the patient, is considered to be extremely difficult. Given the alternatives, residents seem to be less commonly trained to perform the Ross operation. As a result, the use of human valves is reduced.

Alternatives for allograft transplantations are improving, their availability is increasing compared to allografts, and fewer surgeons are trained to apply the complicated transplant procedures; as such it is expected that the number of cardiovascular graft transplants will remain low (1 to 2% of all valve replacements) and even diminish in the coming years. However, there is a continuing demand for human valves for young children to avoid multiple replacement operations as the child grows.

There is a trend to research the possibilities and the long-term effect of decellularisation of homograft valves. The theory is that decellularisation diminishes the immune response of the tissue recipient and would allow the colonisation and growth of host tissue on the graft in vivo. Decellularisation is so far undertaken by a small number of tissue establishments and might be a development that can add to the success of cardiovascular tissue in the future. Long-time results are not yet known but a number of clinical studies are underway and some results are promising (Da Costa et al, 2010).

Cardiovascular tissue can be decellularised and cultured with autologous stem cells to create tissue engineered valves. There is currently no authorised ATMP product of this kind on the market but if one were to be developed and approved it might have a significant impact on the need for cryopreserved heart valves, possibly replacing them entirely at some time in the future (De Jonge, 2013).

In conclusion, it is expected that the use of traditional human cardiovascular tissue allografts will slowly decrease over the next 5 years. Yet the application of homografts will not entirely disappear, especially not for young patients. Research into methods for decellularisation and tissue engineering of both heart valves and vessels may result in grafts with a better recipient compatibility and extended survival as compared to those preserved with traditional methods, and therewith into a new increase of demand.

3.3.2 Ocular tissues

Given the ageing population in the EU, there will be a gradual increase in the demand for corneal tissue. No innovative scientific developments seem to be promising short term alternatives.

What can be observed, however, is the increase of the use of lamellar tissue grafts. These grafting procedures, contrary to the traditional penetrating keratoplasties (PKPs), reduce surgical scarring and the complications of immunological reaction. It is expected that the number of anterior lamellar implants will, because of poor long-term results, be considerably reduced, or almost disappear. At the same time, the posterior lamellar implants are not only replacing the performance of PKPs, they also enable treatment of patients that were not suitable for PKP, and thus increase the demand for cornea donations and grafts.

One side effect for the tissue establishments of these shifts is an increase in costs. The equipment to process a cornea into a lamellar graft, and the instruments used, are still in development. Demands for greater precision using new techniques will require investments at tissue establishments.

A more recent addition to the options to treat corneal damage (especially with limbal deficiencies in cases of burns to the eye), comprises the culturing of limbal stem cells into cell sheets that can be transplanted into the damaged limbal region of the eye. Rama et al. reported long-term corneal regeneration using autologous cultivated limbal stem cells (CLET). They showed that permanent restoration and a renewal of the corneal epithelium were achieved in 76.6% of 107 damaged eyes (Rama et al, 2010). Many centres are providing these cells with good results in the hospital and TE setting (EEBA 2015), while one such technique has been authorized as ATMP in 2015 (Holoclar, see also EMA 2015).

3.3.3 Musculoskeletal tissues

With the increased possibilities presented by alliances between several tissue establishments in the European Union to complement each other's activities and to increase efficiency by making use of investments made, one would expect an increase in the exchange of processed bone grafts within the EU.

These European alliances though, will have to be able to compete with other EU tissue establishments, which have, in their turn, an existing alliance with one or more tissue establishments in the United States. As the latter make use of orthopaedic distributing firms and sales representatives in their working areas, they will certainly remain a very important factor for providing musculoskeletal tissues in the EU.

As the exchange and distribution by the aforementioned organisations increases, a reduction in the number of local or regional bone tissue establishments may be expected, as these cannot cope with the increased needs for investment such as in GMP-level facilities, quality management, software development, training of employees and innovation. Performance under a critical mass of an estimated 150 post-mortem, or 1,000 living (femoral head), donations per year is no longer sustainable[17]. As a result, the number of tissue establishments is likely to decrease.

[17] Internal business plan of BIS Foundation, based on 10 years of procurement, processing and distribution of musculoskeletal allografts, 2004

In the next 5 years, the quantity of exchanged and distributed musculoskeletal tissues is expected to grow. Tissue establishments continue to demonstrate the superiority and safety of allografts over alternatives such as bovine bone products (Amini et al, 2012). While technologies such as, for example, 3D printing of materials which could be equal, or better, than the present tissue grafts, have a long way to go before they can offer an affordable alternative for human tissue allografts, they do not present a viable alternative to tissue grafts in the short term.

Specifically for tissue grafts such as tendons, there is no alternative to human tissue on the horizon.

What will be seen in the next five years is the increase of combinations of allografts and medical devices and pharmaceuticals (such bone tissue impregnated with antibiotics or growth factors).

3.3.4 Skin

In a five-year forward looking assessment of the present techniques, it is expected that skin grafts will remain the first choice for patients with burn wounds and other dermatological diseases which require skin grafting. Yet, there will be a shift toward autologous skin culturing either as an alternative, but mostly in addition to grafting of allografts. In the next 5-10 years, it is likely that grafts of autologous cells will be used to complement meshed allografts by placing cultured autologous grafts in the openings of the allografts. The use of dermis (as a decellularized skin graft), which enables enhanced return of the recipient's epidermis at the wound site, is a trend that is already evident. Further increase in its application is to be expected.

3.4 CONCLUDING REMARKS AND SUMMARY REPLACEMENT TISSUES

- Replacement tissues allow to replace some damaged tissues and therewith their biological functions. The majority of EU tissue establishments focus on four categories of replacement tissues: cardiovascular, musculoskeletal, ocular and skin.

Category	**Cardiovascular**	**Ocular**	**Musculoskeletal**	**Dermatological**
Indications	Congenital, endocarditis, & alternative for mechanical valves	Idiopathic cell loss, cut- & burn-accidents	Bone loss, trauma, cancer, tear & break of tendons	Burns, reconstructive surgery
Tissue types	Heart valves (vascular graft)	Cornea (Sclera)	Bone Demineralised Bone Matrix (DBM) Tendons	Skin grafts
Donors	Deceased	Deceased	Deceased + Living	Deceased
Main costs	Much discard	Much discard, easy expiry	High procurement costs with high yield for DD, end-irradiation reduces processing costs	Easy procurement, some storage cost
Average price/fee	2600€ (950€-	1420€ (250€-	520€ (340€-	1.2-1.4€ per cm2

(min-max) reported by sample of TEs	5250€) for a heart valve	3500€) for a cornea graft	900€) for a 30CC cancellous chip	skin
Tissue establishments	77, small scale, mainly public	141, small scale, mainly public	386, half are private, from local to large international scale	57, mainly local and public, few large international player
Import, export and cross-border exchange	I/+, E/- Informal networks for cross-border exchange	I/+, E/+ Informal networks for import/export	I/ +++, E/ - International partnerships	I/ - E/ - Some international partnerships

- In addition there are 181 tissue establishments authorized to process other tissue grafts like amniotic membrane or pancreatic islets, and 166 to process multiple tissue types.

- Price comparisons for the different types of replacement tissues reveal strong difference between Member States. These differences do not reflect real costs made, but rather are a consequence of different factors including the price-setting process, policy objectives (non-commercialisation, self-sufficiency), the relative high presence of public tissue establishments, limited cost-awareness and intra-EU differences in salaries and purchasing power.

- The absence of a single EU 'market' for tissues and cells is in particular true for the replacement tissue sector and driven by some additional thresholds at national borders:
  - Several Member States have set-up prior authorization schemes for export and (outward) cross-border exchange, in order to ensure local supply and self-sufficiency.
  - Many Member States require additional national requirements on safety and quality including donor screening, testing or processing (in addition to EU legal requirements). These are not always clear for tissue establishments.
  - Some Member States apply national legal frameworks for pharmaceuticals or medical devices on replacement tissues, which can for example lead to the need for prior administrative authorizations to supply tissues to that Member State.
  - Administrative procedures in different Member States are to be addressed in different languages.
  - Fees are set at different levels by different national authorities, often reflecting a more general policy objective (non-commercialisation, self-sufficiency).
  - Some Member States recently changed VAT taxation policies for tissues and cells distributed within their borders, which impacts the fees to be charged.

  All these factors hinder a free distribution of grafts across borders of EU Member States. Also, only few Member States have an overview of the distribution and cross-border exchange of different tissue grafts. More importantly, these thresholds also lead to situations where surpluses in some EU Member States exist in parallel to shortages in other EU Member States. Eventually, clinicians/surgeons cannot access the optimal replacement tissue graft matched to their patients' individual needs.

- Overcoming these thresholds at the border, and supplying tissues to multiple countries, requires dedicated regulatory know-how, which is expensive and usually not available for small-scale, public-funded tissue establishments with limited resources. This prevents many EU tissue establishments from supplying hospitals/clinicians in a larger area and from growing their activities. This puts an important limitation to their development as, for reasons of efficiency a

larger scale of activities might be increasingly needed to obtain economies of scale, and eventually to break-even or remain profitable.

- Over time, a few larger tissue establishments in the EU have built alliances cross borders to overcome these barriers. Several of them are described in the report. These agreements allow for more efficient procurement, processing or distribution.

  In addition, some US-based tissue establishments seem to be able to overcome that barrier as well. They are usually private and well-funded, sometimes even through public listing on the financial markets, and therewith can acquire the resources and know-how to overcome these barriers and supply multiple EU countries. High quantities of surplus musculoskeletal tissues, some corneal grafts and specific sizes of heart valves, are exported to, and distributed into Europe. They often do this by building partnerships with or acquiring major EU-based tissue establishments to do so. This can raise some competitive challenges for the local/smaller-scale establishments. It also brings a need to verify equivalency of safety and quality of the imported substances and to reflect on EU self-sufficiency and dependency on imports.

- Exports out of the EU to third countries seem to be limited. It mainly concerns cornea grafts, which have a limited shelf life and are therefore rather exported than expired, usually during seasonal holiday periods in the EU.

- When it comes to the long term continuity of individual tissue establishments in Europe, there are signs that, given the fact that many of them are small entities, there may be a consolidation or shake-out of tissue establishments in the next five years. It is expected that not all of the small entities will be able to continue processing and supplying a critical mass of tissues large enough to cover the increasing costs of regulatory quality requirements, and many of them may therefore not be able to survive.

- A strengthened collaboration between Member State authorities to facilitate cross-border exchange of tissues within the EU might therefore be a key factor for success for the future of many EU based (replacement) tissue establishments. The fragmented availability of activity data and the need for a common vision on optimal demand and supply for replacement tissues at EU level are priorities to be addressed.

4 HEMATOPOIETIC PROGENITOR CELLS (HPC)

4.1 FIELD DESCRIPTION

4.1.1 An introduction to hematopoietic stem cell transplantation

Since the 1960s, treatment with hematopoietic progenitor cells (HPC), also known as hematopoietic stem cell transplantation (HPCT)[18] has become an important option for patients with congenital or acquired (often malignant) disorders of the hematopoietic system (Gratwohl et al, 2013a). HPC are multi-potent: they have the ability to renew themselves and differentiate into different types of blood cells: red blood cells (erythrocytes), white blood cells (leukocytes) and platelets (thrombocytes). In the continuous process of haematopoiesis, approximately 500 billion blood cells are formed daily. Leukocytes play an important role in the immune system (defending the body against micro-organisms) and have different appearances and functions. In a bone marrow transplant, the blood producing system and the immune system from one individual is transferred into another (Lowsky and Negrin, 2010:390) In general, there is a 0.04% or 1 in 2,500 probability of an individual developing an indication for stem cell transplantation (Kaimal et al, 2009).

Not only is the list of indications for which HPCT is a treatment option rapidly increasing, but the development of less toxic preparative regiments for transplantation (so called reduced-intensity conditioning) has also made it suitable for an increasing number of (in particular, elderly) patients. There are three types of transplants: autologous, syngeneic and allogeneic transplants (National Cancer Institute). In the autologous setting, patients receive their own, previously harvested and cryopreserved stem cells. In syngeneic transplants, an identical twin sibling serves as the donor. In allogeneic transplants, stem cells are donated by the patient's brother, sister or parent (related donor), or a by an unrelated volunteer donor.

Over 75% of autologous transplantations are performed for the treatment of plasma cell disorders (e.g. multiple myeloma) and lympho-proliferative diseases (e.g. Non-Hodgkin lymphoma). The vast majority of allogeneic transplants are performed for the treatment of haematological malignancies, in particular for acute leukaemia (EBMT, 2014).The success of HPCT is dependent, among other factors, on the matching of the Human Leukocyte Antigens (HLA) between recipient and donor. An HLA mismatch (i.e. a difference on one or more HLA-loci between donor and recipient) can induce immune responses in the recipient as well as the donor, which can lead to the rejection of a graft, or a severe reaction in the patient, known as Graft-versus-Host-Disease (GvHD).

The likelihood of finding a full HLA match between donor and recipient is highest between siblings, as they have a 25% chance of inheriting the same HLA genes from their parents. The likelihood of finding an acceptable unrelated donor varies between patients from different ancestries and is highest in patients of north-western European descent (Schmidt et al, 2014). Only 30% of patients who require an HPC allograft have an HLA-matched related (e.g.sibling) donor. The remainder of the patient population is dependent on finding a suitable unrelated donor. Worldwide, 25 million donors are now registered in donor registries and made available through a central database (Bone Marrow Donors Worldwide). In over 50% of all allogeneic HPCTs, the stem cell graft is provided via an unrelated HPC donor registry (World Marrow Donor Association, 2012).

[18]Transplantation with hematopoietic stem cells is in literature also referred to as HSCT.

The probability of finding an HLA-matched unrelated donor is highest from within the same ethnic group. The less ethnically diverse a population is, the more likely it is that a matched donor can be found in the same population. This is particularly true in small, isolated populations that exhibit a strong 'founder effect', since they are less heterogeneous. Since the vast majority of currently registered donors are of north-western European descent, the probability of finding an HLA-matched donor for patients from other than north-western European descent is significantly lower (Van Walraven, 2014; Gragert et al, 2014; Barker, 2010; Navarrete and Contreras, 2009).

Voluntary and unpaid donations are governing principles in accordance with international legislation and regulations. Voluntary donation of hematopoietic progenitor cells thus requires as an imperative that informed consent procedures be established for all stages of the donation process (Rosenmayr et al, 2003). The motivation for HPC donation may vary by gender, age and the method of recruitment, but is mainly altruistic: the prospect of saving lives and showing solidarity with fellow humans (Bart et al, 2014; Lown et al, 2014a).

Donor safety and quality criteria are a key pillar of the EU tissue legislation. For instance, donors who are perceived to be of high risk of contracting HIV and hepatitis are among those excluded from registration and donation. Some countries also exclude donors who have resided in the United Kingdom between 1980 and 1996, due to a potential risk of transmitting Creutzfeldt-Jakob disease.

There has been an impressive increase in the number of procedures performed worldwide, to the current level of over 30,000 autologous and 24,000 allogeneic procedures annually (Khera et al, 2012). The choice for autologous or allogeneic HPC as source depends on the diagnosis. HPCT with autologous stem cells is the treatment option of choice for most lympho-proliferative or plasma cell disorders. In the situation of a relapse of the original disease, or for high-risk malignancies, there is a preference for allogeneic HPC, to induce an allo-immune response in the patient, and thus effect an anti-malignancy action.

Hematopoietic progenitor cells for transplantation are currently collected from

- bone marrow (BM, HPC-M)
- peripheral blood stem cells (PBSC, HPC-A)
- umbilical cord blood (UCB, HPC-CB)

A Transplant Centre (TC) may specify their preference for the source of stem cells in order to optimize clinical outcome, taking into account diagnosis, conditioning regimes and transplantation practice. However, it depends on the donor's choice (at least in the unrelated donor setting) as to whether the stem cells are collected from bone marrow (HPC-M) under general anaesthesia or peripheral blood after administration of growth factors through apheresis (HPC-A). The decision of the TC to use a specific source of stem cells depends on their preference and experience, but may also be based on long-term outcome studies. In general in the paediatric setting, there is a preference to use HPC-M: for related transplants, up to 65% of all products are HPC-M derived, for unrelated transplants up to 54% (Passweg et al, 2014). But for specific metabolic disorders a well-matched cord blood as the stem cell source for children may have equal results as HPC-M of HPC-A (Boelens et al, 2013). Adult recipients more frequently receive an HPC-A product: 81% from related donors and 83% from unrelated donors. Cord blood (HPC-CB) as a stem cell source is more often used in the paediatric setting (20% vs. 6% in adult recipients), in particular for unrelated transplants (Passweg et al, 2014). The number of total nucleated cells (cell count to express the therapeutic dose) in a cord blood unit remains a limitation for its use in adult patients.

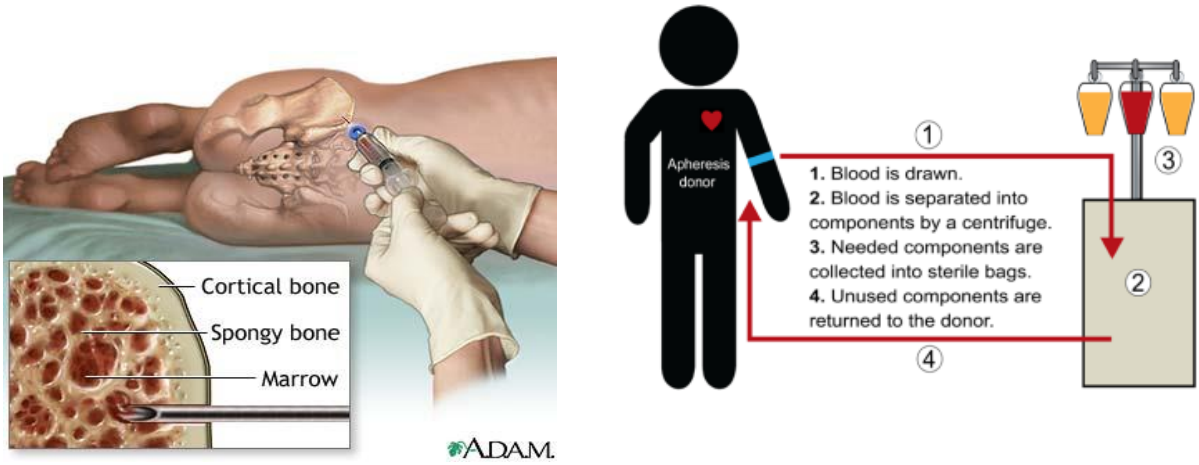
4.1.2 Description of the product groups

This paragraph describes the following hematopoietic progenitor cells: bone marrow, peripheral blood, cord blood, mesenchymal stromal stem cells (MSCs), and donor lymphocytes.

Bone marrow (BM, HPC-M)

Initially, bone marrow was the only source of stem cells for autologous and allogeneic transplantation (Lowsky and Negrin, 2010:382). Bone marrow is the soft, sponge-like tissue found inside bones. It contains fat and immature cells known as hematopoietic progenitor cells (HPC), also called blood forming cells or stem cells. Bone marrow donation is a surgical procedure that takes place in a hospital operating theatre under general anaesthesia (Warwick et al, 2009:212). Bone marrow is generally aspirated from the posterior iliac crests (Eapen et al, 2015). Through multiple punctures in the iliac crest (Figure 1), small samples of marrow (containing blood and HPC) are aspired until an adequate cell dose is harvested. It can be a difficult procedure in child donors (sibling donors), who may require a donor blood transfusion to compensate for the loss of blood (Van Walraven et al, 2012). A maximum of 15-20 ml per kg bodyweight of the donor can be harvested. Complications related to bone marrow harvesting are rare but involve anaesthesia, infection, haemorrhage and transfusion.

Figure 4 Bone Marrow Puncture & Apheresis Chart



Source: Adam (Bone Marrow Puncture) & BMDP (Apheresis Chart)

Peripheral blood (PBSC, HPC-A)

A peripheral blood stem cell transplantation (HPC-AT) consists of HPC collected directly from the bloodstream by a process called apheresis or leukapheresis. The use of HPC-A instead of bone marrow usually results in faster engraftment but also increases the risk of chronic GvHD (Aschan, 2006). Five days before apheresis, the donor starts with daily G-CSF (Granulocyte Colony-Stimulating Factor) injections to increase the number of HPC circulating in the blood stream. These HPC migrate from the bone marrow to the peripheral blood stream. Normally after five days, the yield of HPC in the peripheral blood is sufficient for harvesting through apheresis. In apheresis, the donor's blood is withdrawn to separate the HPC. HPC are collected in a closed circuit in the apheresis

machine and the remainder of the blood is reinfused to the donor (Figure 1). Collected HPC are usually given directly to the patient or can be cryopreserved for use at a later date. The collection procedure typically takes four to six hours (National Cancer Institute). The procedure is considered safe (Pulsipher et al, 2014) and there is currently no evidence for an increase in the development of haematological malignancies after the administration of G-CSF to healthy donors (Shaw et al, 2015).

Umbilical Cord Blood (UCB, HPC-C)

Umbilical cord blood (HPC-CB), collected from the umbilical vessels in the placenta immediately after birth, is a rich source of HPC (Lowsky and Negrin, 2010:394). Since its first successful use in 1988, umbilical cord blood has become an increasingly important source of stem cells (Petrini, 2014). Only 10% of stored HPC-CB units contain enough cells to treat an adult patient; this problem has been overcome by combining two cord blood units for one patient (Barker et al, 2005). Through the transplantation of two cord blood units (also called double cord), CB has become a fully-fledged complement to sourcing HSC from bone marrow through HPC-A donation. More than 20,000 HPC-CB transplantations have been performed worldwide (Petrini, 2014), and approximately 4,000 HPC-CB transplantations are currently performed annually. HPC-CB is used as an alternative source of hematopoietic progenitor cells to treat patients suffering from haematological malignancies, bone marrow failures and inherited metabolic disorders (Navarrete and Contreras, 2009). For patients with rare HLA-phenotypes (as seen in patients from minority ethnic groups or with a mixed ethnic background), or where no acceptable unrelated donor can be identified, HPC-CB has become an important alternative source of stem cells (Petrini, 2014). Cord blood has a number of advantages compared with other stem cell sources. It is rapidly available, has a reduced risk of GvHD, and has less stringent HLA-matching requirements (Guilcher et al, 2014). Further advantages are the relative ease of procurement, without major risks for the (donating) child and mother, the low prevalence of transmissible infectious diseases, and the ability to store fully tested and HLA typed cryopreserved units (Gluckman, 2011). The limitations of HPC-CB include a slower engraftment, increased risk for graft failure and reduced graft-versus-leukaemia effect. Due to the naïve lymphocytes in the CB units, the susceptibility for infections is increased. Also, HPC-CB is an expensive source of stem cells, particularly in the case of double cord blood transplantation. Cheaper alternatives, such as transplantation using HPC from mismatched related donors (haplo-identical approach: See also 4.8), may directly affect the demand for cord blood.

The collection of UCB from full-term deliveries can be performed *in utero* or *ex utero* (Navarrete and Contreras, 2009). The recommended protocol for umbilical cord blood collection, after birth of the infant and before the placenta is delivered, is to clamp the umbilical cord and thoroughly clean and disinfect it to prevent contamination with maternal blood or by infectious agents. The umbilical cord is then punctured under sterile conditions to allow the blood to flow freely and be assisted by gravity into an anti-coagulated sterile collection bag (Butler and Menitove, 2011). In Europe, the collection of UCB can be performed at sites that comply with the regulatory requirements of the EUTCD, i.e. licenced, so-called fixed sites. Occasionally it is still performed in remote non-fixed sites, by providing the appropriate kit and instructions (Navarrete and Contreras, 2009). The latter is mainly applied for private donations.

Testing

The EU legislation on tissues and cells lays down minimum testing requirements for HPC. As with blood donation, donors with a risk or history of HIV, hepatitis C, human T lymphotropic virus type I+II and prion-related diseases are excluded from donation. Some other examples are active hepatitis B, recent malaria and Chagas disease, which are also criteria for exclusion. In affected countries/regions, local infections, like West Nile virus and babesiosis, may also be tested for at later stages, and donors with a history of other potentially chronic infections must be considered on a case-by-case basis (Lown and Shaw, 2013). When a CBU is reserved or selected for transplantation, a number of additional tests are performed at the request of the transplant centres (Navarrete and Contreras, 2009).

Donor lymphocytes

Donor lymphocyte products, commonly DLI (Donor Lymphocyte Infusion), have more recently become known as therapeutic cells (TC-T) (Fehily et al, 2012). An infusion with donor-derived lymphocytes is performed following an HPCT:

- to induce remission in case of relapse after transplantation (graft-versus-tumour effect) (Loren and Porter, 2006)
- to treat a severe viral infection post-transplantation
- as a boost in the situation of poor engraftment

Treatment using TC-T is increasing: approximately 15% of all patients currently receive a TC-T product after an allogeneic HPCT (Passweg et al, 2014). It is possible that the use of donor lymphocyte infusion will increase in the near future due to encouraging results of studies in the area of adoptive T-cell immunotherapy.

New therapies under research

HPCT is a dynamic field. New drug developments and stem cell treatment protocols are rapidly following on from each other and being explored. Besides HLA-matched (related and unrelated) HPC, the use of targeted (autologous) immune cells for cancer treatment is being investigated. Also, new protocols for the application of autologous stem cells outside the field of haematological disorders are emerging. It has been shown that stem cells have the potential to induce cardiac repair and regeneration in both acute and chronic heart disease (Willerson, 2015), and that there is a potential for the treatment of non-malignant gastrointestinal diseases (Al Toma et al, 2014).

However, to the extent that new processes are used that involve substantial manipulation, or lead to non-homologous use, they would be considered Advanced Therapy Medicinal Products. These would therefore not only be subject to the tissues and cell legislation (in connection with the donation, procurement and testing of the cells/tissues) but also to the pharmaceutical legislation. The legal classification and the different legal requirements do however fall outside of the remit of this study.

The extent of involvement, and the final role of allogeneic donors in the future, are unclear and might affect the activities of donor registries. For example, just two decades ago, chronic myeloid leukaemia was only curable by HPCT. Nowadays patients are successfully treated with tyrosine kinase inhibitors (Kindler et al, 2002). This can affect the need for allogenic HPC units. Future considerations and an estimation of the need for hematopoietic stem cells are discussed in the last section of this chapter (4.4).

4.2 ORGANISATION OF THE SECTOR

4.2.1 Organisational structures in the field of HPCT

This section provides an overview of the different organisational structures observed in the field of HPC. International collaboration between groups of non-profit organisations has been a key factor for the development of hematopoietic progenitor cell transplantation. There are several different institutions that participate in the process of HPCT, and there are a number of different ways that the process can be organised. Essentially, the following main parties are involved in the process: the transplant centre (TC), the HPC donor registry (DR), the donor centre (DC), the collection centre (CC), and the cord blood bank (CBB).

The TC is a medical facility where a patient receives a transplant with stem cells from an (un)related donor or UCB. The TC oversees the immediate medical treatment and provides long-term follow up of the patient. The TC defines criteria for an unrelated donor search and may establish a search unit or ask a donor registry (DR) to act as the search unit on its behalf. The TC is responsible for HLA verification testing of the patient and potential donors in an EFI (European Federation of Immunology) or ASHI (American Society for Histocompatibility and Immunogenetics) accredited laboratory and for providing appropriate information to the DR with regards to the donor search and stem cell request (World Marrow Donor Association, 2013). The TC is responsible for the transport of the stem cell product, assigning a (professional) courier, and arranging the pick-up. The European Group for Blood and Marrow Transplantation (EBMT) uses the term 'Transplant Team', for each facility that performs autologous and/or allogeneic stem cell transplantations.

The DR is often a national organisation responsible for donor recruitment, HLA typing and registration that makes available information about donors and/or cord blood units via searchable databases (Bone Marrow Donors Worldwide; European Marrow Donor Information System). Some activities may be carried out by donor centres, under the authority of a DR. Furthermore the DR is responsible for the coordination of the search for hematopoietic progenitor cells from potential donors unrelated to the recipient. This involves the handling of sample and information requests from TCs, and the supervision of donor care management (and follow-up) in case of stem cell donation (World Marrow Donor Association, 2013). The DR can act as the search unit, on behalf of the TC, in performing the unrelated donor searches. The DR acts as an intermediary between the TC and CC. A DR can apply for accreditation from the World Marrow Donor Association. In many European countries there is one national DR providing these services. Donor recruitment can be initiated in several organisations (blood bank, donor centre, recruitment group, or DR). In some countries there is competition between the various recruitment groups. Different models exist for the provision of donors:

- DR manages the donor file and requests; collaborates with donor centres and recruitment groups
- DR recruits potential donors and manages the donor file and requests
- DR manages the donor file and requests; collaborates with donor centres, recruitment groups and cord blood banks
- DR is a cord blood bank.

Donor registries can also play a role in the search process (on behalf of or in conjunction with a transplant centre):

- DR manages each step of the search process
- DR facilitates communication between a transplant centre and other registries
- DR is integrated within a hospital.

The DC is an organisation responsible for donor recruitment, consent procedures, testing, management, and the collection of donors' personal, genetic, and medical details (World Marrow Donor Association, 2013). Several local DCs can act within and under the authority of one national DR.

The CC is a medical facility where HPC collection from (un)related donors actually takes place. This collection might include bone marrow aspiration or apheresis. The CC, or designee, performs the counselling and physical examination (the so-called 'work-up procedure') of a volunteer donor and provides the final approval of suitability for collection ('donor final clearance'). The CC prepares the collected graft for transport to the TC.

In case of a cord blood product, the facility releasing the cord blood unit is the cord blood bank (CBB). This is a facility responsible for donor management and the collection, processing, testing, cryopreservation, storage, listing, reservation, release, and distribution of cord blood units.

International collaboration in HPCT

Transplantation of hematopoietic progenitor cells from unrelated volunteer donors and CBU is made possible through an international collaboration of donor registries and cord blood registries (Petersdorf, 2010). Many international organisations or collaborations therefore play essential roles in the daily organisation of HPCT:

The European Society for Blood and Marrow Transplantation (EBMT)

The European Society for Blood and Marrow Transplantation (EBMT) is the leading, non-profit, scientific society representing 563 transplant centres from 57 countries in and outside Europe. The annual EMBT activity survey, describing the status of HPCT in Europe, has become an instrument used to observe trends and to monitor changes in technology use (Passweg et al, 2013a).

The Joint Accreditation Committee ISCT (International Society for Cellular Therapy) & EBMT (JACIE)

JACIE is a non-profit body established in 1998 for the purposes of assessment and accreditation in the field of hematopoietic progenitor cell transplantation. JACIE actively collaborates with the Foundation for the Accreditation of Cellular Therapy (FACT) to develop and maintain global standards for the provision of quality medical and laboratory practice in cellular therapy. The European Commission supported the JACIE accreditation programme in 2004 under the Public Health Programme (2003-2008).

The World Marrow Donor Association (WMDA)

The World Marrow Donor Association (WMDA) is an international collaborative body of organisations and individuals involved in hematopoietic stem cell donation and transplantation. Every year, the WMDA collects global data on the number of unrelated stem cell products provided by the unrelated HPC donor and cord blood registries. The WMDA has established Standards and an accreditation programme for hematopoietic progenitor cell donor registries to promote the international exchange of high-quality stem cell products while protecting the donor's anonymity, health and well-being. The WMDA annual reports describe the current status of, and observe the trends for, the number and types of HSC products worldwide and monitor the exchange of products between countries (Foeken et al, 2010). To become a member of the WMDA, an organisation must have 500 listed volunteer HPC donors and/or 100 cord blood units. An organisation must have provided at least one stem cell product or cord blood unit internationally or two cell products and/or cord blood units nationally for unrelated transplantation (WMDA Application Form, 2013).

Bone Marrow Donors Worldwide (BMDW)

Bone Marrow Donors Worldwide (BMDW) is a collaborative voluntary and continuing effort to collect the HLA phenotypes and other anonymised relevant data of volunteer HPC donors and cord blood units from HPC donor registries and cord blood banks all over the world. It started as an initiative of the Immuno-biology Working Party of the European Group of Blood and Marrow Transplantation (EBMT). In February 1989 the first edition was distributed, which contained the donor files of eight registries with a total of 155,000 volunteer stem cell donors. It is stated in the BMDW House Rules that participating registries must be able and willing to provide stem cell products to domestic and international patients and adhere to the Standards of the World Marrow Donor Association (Oudshoorn, 2015). Participants currently comprise 75 HPC donor registries from 53 countries, and 50 cord blood banks from 33 countries. In March 2015, the number of donors and cord blood units in the BMDW database was 25,724,143 (25,091,529 donors and 632,614 CBUs). Globally there are currently 917 users from 553 organisations authorised to access the online BMDW services. Participation in BMDW participation is available for a fee, and for any operational unrelated donor/cord blood registry that is willing to provide the required donor files and adhere to the Standards, guidelines and recommendations of the WMDA. The Editorial Board of BMDW consists of one representative from each participating registry. The Bone Marrow Donors Worldwide office is located at Europdonor Foundation in the Netherlands.

European Marrow Donor Information System (EMDIS)

The European Marrow Donor Information System (EMDIS) facilitates the peer-to-peer electronic communication between HPC donor registries and cord blood banks. The scope of operation covers all aspects of an unrelated donor search from the preliminary search to the donor work-up. Technically, EMDIS defines an open specification of a protocol for the electronic communication among registries. Therefore, EMDIS is implemented as an asynchronous peer-to-peer network connecting distributed, heterogeneous databases. Membership of EMDIS is free of charge. The community provides documentation, status information, software tools, support and a project management platform.

Worldwide Network for Blood & Marrow Transplantation (WBMT)

The Worldwide Network for Blood & Marrow Transplantation (WBMT) is a non-profit scientific organization with the mission to promote excellence in hematopoietic progenitor cell transplantation, donation and cellular therapy. The annual global survey is one of the activities of the WBMT. The WBMT is in an official relationship with the World Health Organization (WHO).

Center for International Blood & Marrow Transplant Research (CIBMTR)

The Center for International Blood & Marrow Transplant Research (CIBMTR) collaborates with the global scientific community to advance hematopoietic cell transplantation and cellular therapy research worldwide. CIBMTR is a research program of the National Marrow Donor Program/BeTheMatch and the Medical College of Wisconsin. The CIBMTR facilitates critical research that has led to increased survival and an enriched quality of life for thousands of patients.

International Society for Stem Cell Research (ISSCR)

The International Society for Stem Cell Research (ISSCR) is an independent, non-profit organization established to promote and foster the exchange and dissemination of information and ideas relating to stem cells, to encourage the general field of research involving stem cells and to promote professional and public education in all areas of stem cell research and its application. Members are admitted on the basis of their professional credentials as scientists or clinicians working in the field of stem cell research.

The National Marrow Donor Program (NMDP)/BeTheMatch

The National Marrow Donor Program (NMDP) is a non-profit organization founded in 1986 and based in Minneapolis that operates the BeTheMatch Registry of volunteer HPC donors and umbilical cord blood units in the United States. The BeTheMatch Registry is the world's largest HPC donor registry, listing more than 10.5 million individuals and nearly 185 000 cord blood units. Alongside donors from the USA, BeTheMatch lists donors from so-called affiliated donor centres and registries. As of January 2013, the NMDP had facilitated more than 55 000 transplants worldwide.

DKMS The German Bone Marrow Donor Center

The German Bone Marrow Donor Center (DKMS) is the largest HPC donor centre in the world with almost 4 million registered donors. Over 45 000 DKMS donors have contributed bone marrow or peripheral blood stem cells. DKMS donors currently make up 25% of worldwide registered unrelated bone marrow donors. In recent years, the DKMS have started to establish donor centres outside Germany, both in conjunction with the local registry, and independently in other countries. DKMS have established donor centres in:

- Germany: Deutsche KnochenMarkSpenderdatei; founded in 1991; currently almost 4 million donors registered and over 45 000 donations accomplished
- USA: Delete Blood Cancer; founded in 2004; currently more than 650 000 donors registered and over 1 800 donations accomplished
- Poland: DKMS Polska; founded in 2009; currently more than 700 000 donors with over 2 100 donations accomplished
- United Kingdom: Delete Blood Cancer UK; founded in 2013; currently over 110 000 donors registered
- Negotiations with authorities were reported to start activities in Spain.

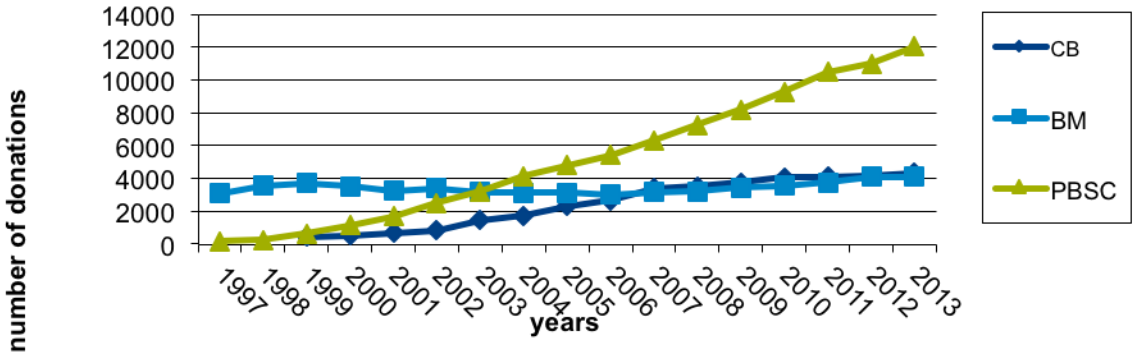
4.2.2 Levels of activity in stem cell transplantation

Transplantation of hematopoietic progenitor cells from unrelated volunteer donors and CBU is made possible through an international collaboration of donor registries and cord blood registries (Petersdorf, 2010). The initiation of an unrelated donor/CB search triggers a worldwide response through a network of communications. The first unrelated donor registries were established in the late 1980s. To date, almost 25 million donors are registered globally, and this inventory is still expanding (BMDW.org). However, there are major differences between the size of the registries and cord blood banks and it is clear that only a few players in the field provide the majority of stem cell products. Overall, the stem cells from less than 0.1% of all global registered donors are collected per year. Only a few EU Member States are able to provide a substantial volume of products for their national patients (2012: Germany 83%, Poland 45% and Portugal 45%, United Kingdom 39%). The availability of sufficient numbers of beds in transplant centres to treat national patients is also a requisite. Registries in Germany and the United States carry out approximately 67% of all collections worldwide (World Marrow Donor Association, Annual Report 2013). At a European level, the major players in the field of stem cell products are Germany, France, Italy and the United Kingdom (World Marrow Donor Association, Annual Report 2012). In 2012, 93% (n=3,722) of all 4,126 HPC-M products were provided by six countries, of which n=1,358 products by European registries (see Table 1 in annex 2 HPC, Provision of HPC-M in 2012). Also, six countries were responsible for 85% (n=9155) of all provided HPC-A products in 2012, of which n=5,408 by Germany and the United Kingdom (see Table 2 in annex 2 HPC, Provision of HPC-A products in 2012).

The exchange of cord blood units is on a much smaller scale. Although the number of HPC-CB units shipped for transplantation increased to 4,150 in 2012 (World Marrow

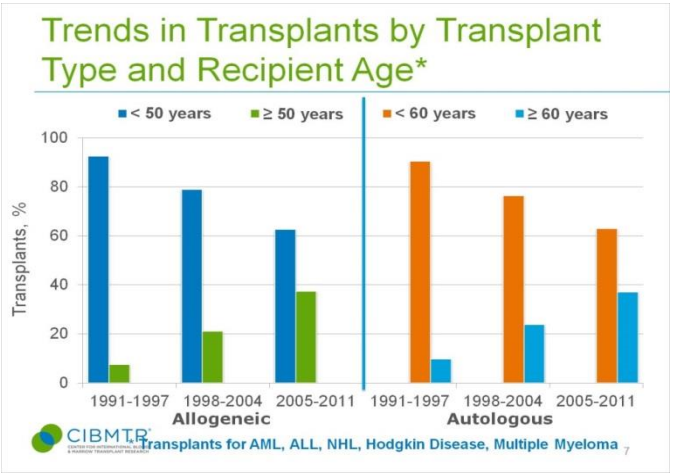
Donor Association, Annual Cord Blood Report 2012) the overall use of cord blood seem to have stabilized (figure 13). European cord blood registries provided a total of 848 cord blood units (20%). However, there is no clear explanation for the lack of growth. One can assume that the price of cord blood products might be influencing their use, and as a result, a pricing discussion is ongoing. An overview of the CB product exchange within and between continents is given in Table 3 in annex 2 HPC (Provision of HPC-CB products in 2012).

Figure 5 Overview of product source provided by unrelated donors



Source: WMDA annual report (2013)

Figure 6 Patient age as a factor of influence over years



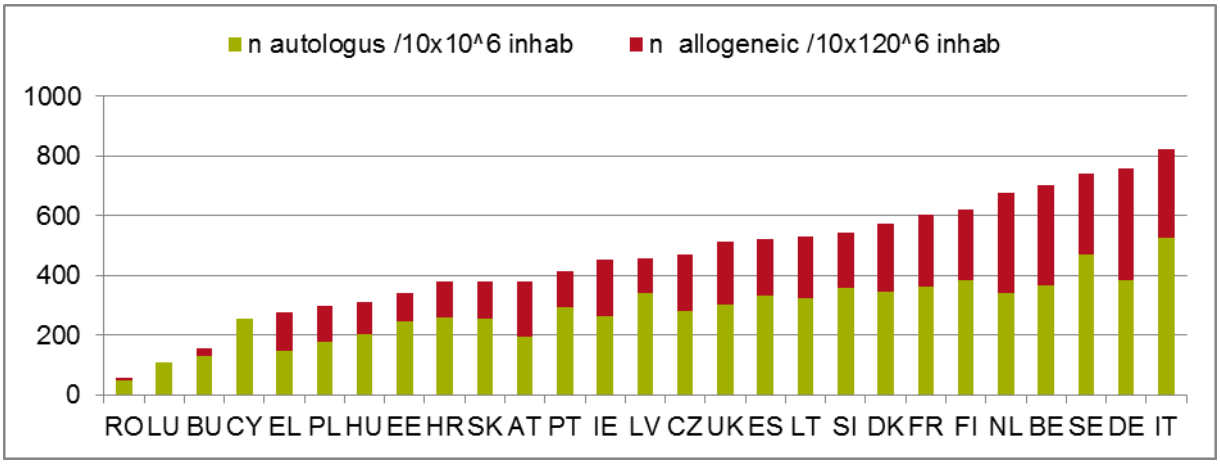
Source: Accessed from National Marrow Donor Program/BeTheMatch (2015). Reprinted with permission.

The number of transplantations has increased significantly over time. The CIBMTR figure demonstrates the change in demographics among transplant recipients. A relative increase in older patients, over age 50, that are being transplanted is seen. This is one of the explanations for the increase in transplantations.

Improvements in supportive care, patient and donor selection, and the use of reduced-intensity conditioning regimens for allogeneic transplants are the major contributors to this trend (CIBMTR).

Age is no longer a strict barrier to offer stem cell transplantation as an option for curative treatment. It was suggested during a meeting with experts to also expose transplantation percentages vs. population in the EU Member States in 2012, to discover trends (see figure below).

Figure 7 Autologous/allogeneic transplantations/10 million inhabitants in EU



Source: WMDA Annual report, 2012

4.2.3 The European donor registries

In 2012 there were 33 donor registries active in 24 Member States. There was more than one registry in Bulgaria, Czech Republic, Cyprus, Denmark, Poland, and the United Kingdom. Efforts to work towards one national registry are encouraged by national legislation in some Member States. In 2012, there was no donor registry in Malta, Latvia, Estonia or Luxemburg. Estonian citizens can register with the Finnish Registry. Efforts are underway to set up the Luxemburg Marrow Donor Program (LMDP) under the governance of the *Stefan Morsch Stiftung*, one of the German donor centres located close to the Luxemburg border. There is an official agreement with the Ministry of Health in Luxemburg and donors will be made searchable through the German Registry ZKRD. Currently, almost 6,500 donors from Luxemburg have been recruited (Morsch, 2015.). Interestingly, Cyprus has a relatively large HPC donor registry (almost 25% of the potential donor population is registered), but there is currently no transplant centre that performs allogeneic transplantations.

With population data provided by Eurostat, it was possible to determine the number of inhabitants aged between 20-60 in each EU Member State in order to obtain an estimate of the number of potential living donors. Only in a very few Member States (n=4), does the number of registered donors surpass 2% of the potential donor population (see table 7 in annex 2 HPC, Percentage of population registered as donor, availability rate and number of donations per EU Member State in 2012). In four Member States (Cyprus, Latvia, Luxemburg, Malta), no HPC transplantation activity was possible in 2012. Patients in need of an HPCT were sent abroad for treatment. Of these four countries, Cyprus is the only one with recruitment activity for unrelated donors through two unrelated donor registries. In Cyprus, the percentage of inhabitants registered as volunteer HPC donors is by far the highest among European Member States (and probably in the world).

The size of the donor inventory and the volume of requests (and thus revenue) seem to correspond with the quality of the registry database but also with its service and response levels. The composition of a large registry takes time and money, and requires more than donor recruitment. The quality of the donor inventory should also be judged by looking at the age, the diversity, and the availability of the donors. Stem cells of older donors as compared to younger donors have been reported as having an adverse impact on overall survival in patients (Ayuk et al, 2013; Servais et al, 2014). Gender compatibility is dependent on the preferences of the transplant centre, but currently more female than male volunteers are registered as donors (World Marrow Donor Association annual report 2012). Diversity as a parameter of registry quality has been discussed above. Donor availability is an important issue that will be discussed separately.

Based on the 2012 annual reports from BMDW, donor registries can be divided into four categories: small (≤ 20,000 donors), medium (>20,000 ≤100,000 donors), large (> 100,000, ≥ 1,000,000 donors) and extra- large sized registries (> 1,000,000 donors). The majority of the European (EU28) EU28 MS registries are small (n=11) or medium-sized (n=13). Extra-large registries are located in the United States, Brazil, China, and Germany. Millions of HPC donors recruited by the DKMS are the underlying reason for the German registry being extra large. Although thousands of patients in Europe and third countries each year benefit from HPC donated by a German (DKMS) donor, it is questionable as to how this affects the small and medium-sized registries in the EU Member States. Decreasing donation rates in these registries are thwarting the chance to overcome the challenges they are facing, such as the ageing of their donor inventory, the complexity of IT systems, and a more complex regulatory framework. In 2011, in order to intensify collaboration, the Group European Medium Sized Registries (GEMS) was established to outline future strategies, such as expansion of the donor pool with young donors, and the revision of HLA-typing strategies (WMDA, 2015). In parallel, also DKMS has expanded activities in other EU Member States and in the USA.

The numbers of registered donors and cord blood units within EU Member States are similar to those in the United States: 7,499,469 donors in EU Member States vs 7,222,570 in the US; and 198,985 CB units in EU Member States vs 209,291 in the US. When the total number of products provided by unrelated donors was compared, HPC-A and HPC-M were provided significantly more often by European donors (see figure below).

The main difference between the European and American situation is that in 2012, in America there were two large registries operating besides the extra-large registry BeTheMatch (former National Marrow Donor Program NMDP). Furthermore, the BeTheMatch registry is heavily sponsored by the US Government. Next to the BeTheMatch registry is the much smaller Gift of Life Registry operating without governmental funding: not only have they been shown to be successful fundraisers, but their vision on the compilation of the registry is also important. By focusing on donors of Jewish descent they have added diversity to the global inventory and filled a gap.

In Europe however, there are 33 registries of which only 9 have more than 100,000 donors and one (DKMS) is extra large (4.8 million donors). This high number of registries, of varying sizes, compete sometimes compete with each other. The EU28 Member States could strive for better collaboration and identify and apply the most effective and efficient approaches.

An overview of registries in EU Member States and their comparative size per category are given in table 4 in annex 2 HPC (Overview growth European HPC Donor Registries).

4.2.4 Cord blood banking

Cord blood banks have been established worldwide for the collection, cryopreservation and storage of UCB for allogeneic hematopoietic stem cell transplantation. Local public cord blood banks are represented by a national donor or cord blood registry. In Spain for example, a single register is established by law, and all Spanish cord blood banks operate under the Jose Carreras Foundation (Querol, 2015, personal communication). The four main types of UCB bank that can currently be distinguished are described below (Petrini, 2014). Given the very low probability that private units will effectively be used to address transplant needs of their private the effectiveness of costly storage by private persons is questionable.

Public non-profit cord blood banks

In European Member States, cord blood banks are formally licensed according to EU Directive 2004/23, and are additionally subject to national regulations. Public cord blood banks can also be accredited for participation in international networks. The cord blood units, collected from voluntary, unpaid and consenting mothers, are stored and owned by the public bank and can be used for the treatment of unrelated patients (Butler and Menitove, 2011). Immediately after collection, UCB is transferred to the cord blood bank and subjected to a series of quality controls and tests (such as total nucleated cell count, infectious disease markers, HLA typing) aimed at characterising the blood and establishing its suitability for storage and therapeutic use. Units of blood that meet the requisites for therapeutic use are submitted to further tests, prior to cryopreservation. The final product is usually stored in a two-compartment bag (Figure 15). A detailed unit report is available upon request through the international registries. International protocols have been established to enhance quality and uniformity in cord blood banking practices (Petrini, 2014). Over 600,000 cord blood units are now stored in over 140 public cord blood banks throughout the world (BMDW; Bart, 2013). The size of a national cord blood bank is crucial: the larger the number of units registered, the more heterogeneous the inventories, and the greater the probability of finding a match between donor and recipient in the given country (Petrini, 2014). The search for unrelated cord blood is usually organised through the same registries that facilitate stem cell transplantation (Guilcher et al, 2014). An overview of the growth of the European Public Cord Blood Registries is given in annex 2 HPC (table 5). Allan et al (2013) concluded that banks with the largest inventories have the lowest ratio of exported units. This may partly be explained by the fact that larger banks are typically older and may have many units with lower cell numbers in their inventory from earlier times. The quality of the HLA typing might also be a limitation for older banks.

Private autologous cord blood banks

Private autologous UCB banks are commercial facilities that promote paid storage of umbilical cord blood for speculative future use by the index child or its relatives (O'Connor et al, 2012; Stewart, 2012). The cord blood unit remains the property of the child under the guardianship of the parents, and is not available for public use; HLA typing is not performed by default. While subject to the same EU legislation, acceptance criteria for storage in private banks may differ from public banks, particularly with regard to the extensive (maternal) donor screening (o.a. infectious disease testing) and the minimal cell count of nucleated cells, that is required for cord blood for public use (Ballen, 2015). Private banks have a financial incentive to accept units that would be considered substandard by public banks. Consequently there is no guarantee about the quality of the stored sample. A major point of criticism related to the private banking of cord blood is that there is no evidence on their medical value, due to the very low likelihood of requiring autologous UCB in later life (Samuel et al, 2008). Estimations have put the number of units stored in private banks as at least six times the volume of public units (Ballen, 2015).

Family cord blood banks (directed donation)

Situations occur where the mother or close relative of a patient, usually a child in (potential) need of stem cells for the treatment of an inborn error or acquired haematological disorder, is pregnant (Petrini, 2012). Cord blood can be collected and stored and tested for histocompatibility with the potential recipient. The total number of family directed UCB units stored is unknown, but it is a very small-scale service in comparison with those in either allogeneic public banks or autologous banks (Petrini, 2014).

Hybrid models for cord blood banks

A hybrid cord blood bank is a private institution in which an umbilical cord blood product is stored for possible public or private use (Guilcher et al, 2014). Parents are required to pay for private storage; however handling fees may be lower than in purely private cord blood banks. Hybrid banking includes several possible models (O'Connor et al, 2012). In the so-called Virgin Model (see Virgin Health Bank) a small amount (the first 5 ml) of cells that might be useful in potential future stem cell therapies, are stored for the exclusive use of the client for 25 years. The remainder of cells are stored in the public inventory for public use. The usability of a split unit with reduced volume and cell count remains unclear. In the Turkish model, 25% of all privately-stored cord blood is donated to the public system. The Spanish model is another option where private stored units can become publicly available: should a stored unit match with a patient in need of a transplantation, the parents are obliged to donate the cord blood and the storage fee is reimbursed. Finally, several German banks offer parents the option of privately storing cord blood which can be made available should it match with a patient in need of a transplantation. However, parents are under no obligation to agree with this donation. Since it is important that the public part of the unit meets the same quality criteria and regulatory standards as apply to public cord blood banks (O'Connor et al, 2012), hybrid banking demonstrate that quality standards can be met under accredited standards (e.g. NetCord-FACT).

Figure 8 Two-compartment cryopreservation of cord blood

Source: Healthbaby website

4.2.5 International cord blood registries and networks

Public cord blood banks collaborate with national registries to share information about stored CB available for transplantation purposes. The search process for unrelated cord blood does not differ substantially from a search for other unrelated donors. When performing the search, donor registries function as a hub, linking TCs, laboratories, CB banks and regulatory agencies.

NetCord

The International NetCord Foundation, established in 1997 is a non-profit organisation currently consisting of 35 umbilical cord blood banks and registries whose members comprise the largest source of high-quality HPC-CB grafts for patients in need of HPCT. Their inventory represents approximately half of the global supply of publicly banked HPC-CB. Besides balancing the global supply and demand for HPC-CB, NetCord actively promotes translational and clinical research and public and professional education. In collaboration with the Foundation for the Accreditation of Cellular Therapy (FACT), NetCord promotes the highest quality of HPC-CB through worldwide Standards and accreditation.

FACT-NetCord

The FACT-NetCord joint venture is the first international body to conduct the same inspection accreditation strategy for all cord blood bank modalities worldwide. FACT-NetCord has established Standards for high quality medical and laboratory practice in cellular therapies. The FACT-NetCord Standards are designed to provide minimum guidelines for cord blood banks, facilities and individuals performing cord blood donor management, collection, processing, testing, cryopreservation, storage, listing, search, reservation, release, and distribution, or providing support services for such procedures (FACT-NetCord Internet 2013). Currently 55 cord blood banks are accredited by FACT-NetCord. An overview of FACT-NetCord accredited cord blood bank is given in annex 2 HPC table 6.

Eurocord

Eurocord is an HPC-CB registry and clinical research group, dedicated to the study of transplantation and innovative stem cell therapies using HPC-CB for malignant and non-malignant diseases. It works in close collaboration with HPC-CB banks and registries worldwide and is affiliated in France to *Université Paris Diderot* and *Assistance Publique des Hôpitaux de Paris* (APHP). Eurocord has collected data on more than 7,000 cord blood transplants from 483 centres, 50 countries and 54 cord blood banks. The results of research contribute to the development of standards and recommendations including the criteria for donor choice, prognostic factors for main outcomes, and protocols for HPC-CB transplantation, and thus to the generation and validation of high quality data for use in clinical research.

Cord Blood Europe

Cord Blood Europe is a non-profit association of family cord blood banks in Europe, founded in 2009, following the transposition of EU Directive 2004/23/EC. Cord Blood Europe aims to promote awareness about the advantages of adult stem cells and encourage the storage of umbilical cord blood for private use. Currently, Crioestaminal (Portugal), Esperite (The Netherlands), PBKM Famicord Group (Poland), StemCare (Denmark) and VITA34 (Germany) are participating in Cord Blood Europe. Cord Blood Europe members have expanded their activities into almost all EU Member States. The main problem for collaboration experienced by Cord Blood Europe members is the lack of interest to collaborate by public cord blood banks and they expect that only a political measure could induce a closer cooperation. Some of the private cord blood banks have systems in place for hybrid banking, although not on a large scale (Cord Blood Europe, 2015). In considering the options for collaboration with the public cord blood registries and the options for hybrid banking, Vita34 reported difficulties in having their units in BMDW, while units from PBKM Famicord have been registered in BMDW through the national Polish registry PolTransplant. The fact that hospitals are starting to charge more money to collect a unit for private storage is a point of concern; it seems that hospitals are now approaching and considering their collection activities on a more commercial basis.

4.2.6 Describing the chain: from donor recruitment to stem cell infusion

This section provides an overview of the process chains from the recruitment of HPC donors and cord blood donors, the donor/cord search, through to the donation and infusion of stem cells. During the whole process, the safety of both donor and recipient is essential and requires appropriate selection and evaluation of donors. A number of accreditation and regulatory bodies - the WMDA, JACIE and FACT-NetCord – have published standards governing the selection, evaluation and management of HPC donors and their recipients (Fehily et al, 2012).

Recruitment of unrelated stem cell donors

Volunteer HPC donors are recruited through donor centres and registries, often in collaboration with blood banks. At this stage, aspirant donors are informed about the registration and tissue typing process and in general, about types of donation (through bone marrow or peripheral blood) (Passweg, 2013b). The minimum age for registration is generally 18 years of age, however, in the United Kingdom, donors can sign up from the age of 16. The age of donor retirement varies per country and is usually between 55-61 years. Globally, 19% of the registered donors are male and younger than 36 years, and only 11% of all donors worldwide are younger than 26 years (WMDA).

Search: selecting a donor

Ideally, as soon as a patient is diagnosed with a condition for which allogeneic HSC transplant is the preferred option of treatment, the search for a compatible HPC donor should be initiated. About 30% of patients used to be able to find an HLA-identical donor within their family. But because families are now generally smaller, more patients are referred for an unrelated donor or cord blood search (Navarette and Contreras, 2009). After a match-run in the worldwide BMDW inventory, preliminary search requests are sent to registries with potential donors. The search results are then studied and the first selection for donors is made.

Verification typing

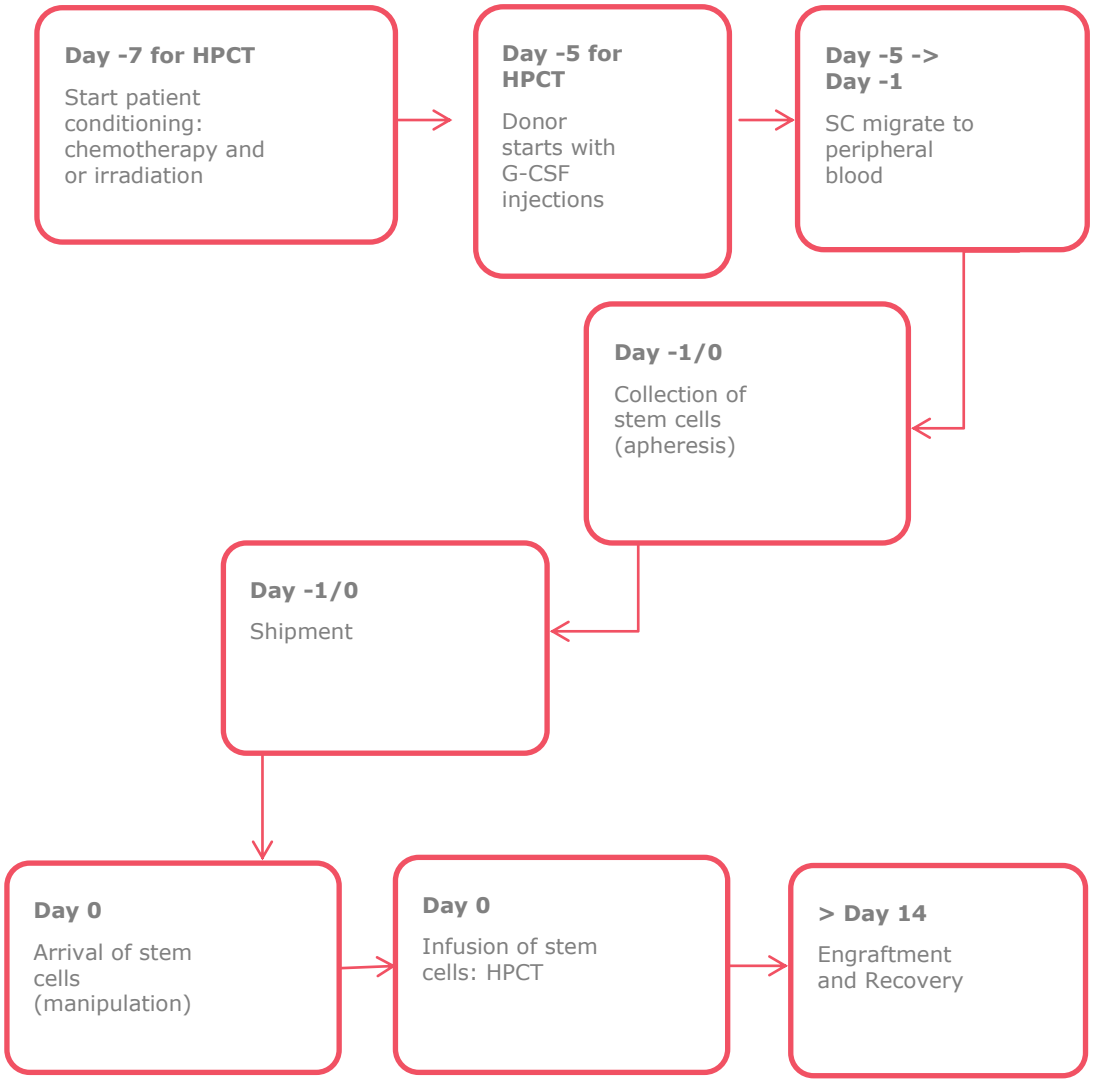
For a successful outcome, it is essential that the tissue typing (human leukocyte antigens - HLA) of the recipient and the donor are identical or close to identical (Lee et al, 2007; Petersdorf, 2008; Boo et al, 2011). To confirm the compatibility of a donor, the TC requests fresh blood samples from potential donors in order to perform a so-called verification typing. The HPC donor registry informs the donor and arranges for the drawing of samples. In addition, the donor health status is evaluated by telephone interview and infectious disease markers (IDM) are tested. The results of verification typing and IDM are studied and taken into account for donor selection.

Product request and donor work-up

Once a donor is identified as being the best match for a given patient, the donor is requested for work-up; an actual request for the collection of stem cells. The proposed date for the transplantation, the preferred source of stem cells (HPC-M or HPC-A), and the number of cells form part of the request as well the date that the donor needs to be cleared for donation (i.e. medical suitability, availability and confirmation of informed consent). This last date is important because it determines the planning of the bone marrow collection or the preparation for the donor by administration of the g-CSF to mobilize the HPC. The conditioning regimen of the patient (the preparative treatment of the patient that is necessary before the transplantation can take place) usually starts 4-5 days prior to the collection of stem cells. The donor also undergoes counselling and medical examination and blood tests before he or she can be cleared for donation.

Finally, the transport of the product needs to be arranged upfront by a professional courier (commercial company) or a designated courier from the transplant centre. The aim is to deliver the cells to the transplant centre for transplantation as soon as possible after collection. A schematic overview of the donation and transplantation process is given in the figure below.

Figure 9 Stem cell transplant process from donation to infusion



Source: figure based on EBMT handbook and clinical experience authors

Donor Care and Safety

Unrelated donors are followed up after HPC donation for a minimum of 10 years, according to WMDA standards.

The WMDA and JACIE have set standards for donor care management, to safeguard both unrelated and family donors. But accreditation is not, per se, proof of safety for the donors: the size of a collection centre is also a dimension for risk. Staff experience is not guaranteed if they do only a small number of collections per year.

While safety of stem cell donors considers mainly the suitability of the donor undergoing the procedure, and whether the donor is an infant or adult, an anonymous person or a relative of the patient, their well-being and interests must always be kept in mind as a duty of care (Van Walraven, 2014). Since the introduction of G-CSF in healthy volunteer individuals, long-term safety has been addressed; serious adverse events were recently analysed in a group of unrelated HPC donors (Pulsipher et al, 2014). It is known that co-morbidities in related donors are more often accepted since 'related donors are willing to take a greater risk' (Buser and Halter, 2013). Internationally there is now a leading opinion that the suitability of the HPC donor is of importance for all parties involved (Lown et al, 2014b). The WBMT has published a consensus paper on the assessment of donor outcome data (Halter et al, 2013. Currently, long-term follow-up and severe events and adverse reactions (SARE) are only registered for unrelated donors. The establishment of a reporting system to cover adverse events of all living HPC donors globally would be a major achievement and there is a substantial need to further investigate and develop this global challenge (Van Walraven, 2014).

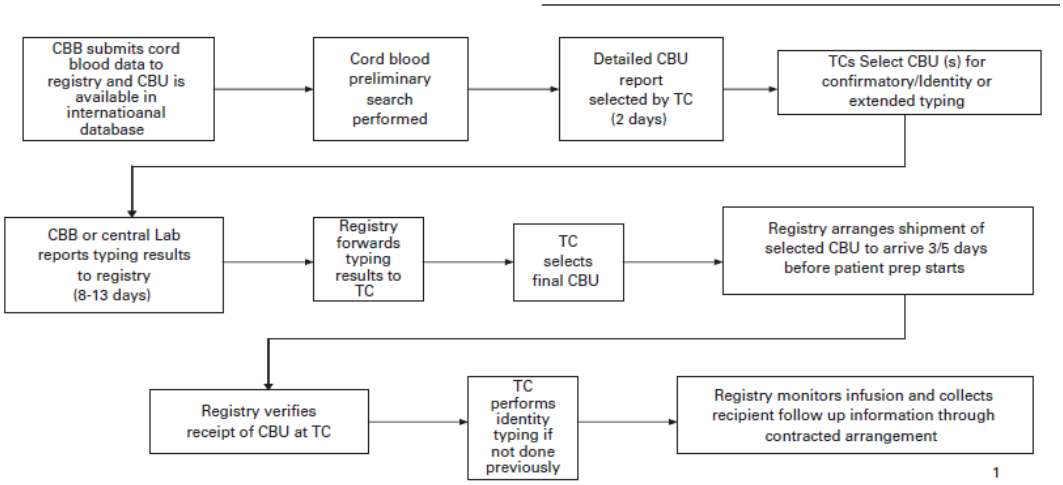
Recruitment of cord blood donors

The donor selection process for public cord blood banks is conducted carefully. Cord blood may not be collected if there are known hereditary diseases specifically involving haematopoiesis in the family or if severe disabilities or diseases have been identified in the donor foetus before birth. Additional exclusion criteria include an infectious disease in the mother, severe pregnancy complications, a premature or complicated delivery, a birth weight of less than 1,500 grams, or if perinatal asphyxia is present in the foetus. These factors negatively impact the quality of collected cord blood (Butler and Menitove, 2011). It is known that only 10-25% of all donated cord blood meet the quality criteria for cryopreservation (Kurtzberg et al, 2010; Lauber et al, 2010). In recruiting cord blood donors (pregnant mothers), it is also important to address those of non-north-western European ethnicity in order to enhance diversity in the cord blood inventory to widen the HLA profile of units banked (Navarrete and Contreras, 2009). Units with high cell counts and from ethnic minorities are requested more often (Lauber et al, 2010).

Cord blood search process

Once the CBUs are HLA-typed and it has been established they meet the safety and quality criteria (e.g. total nucleated cells, infectious disease markers, viability), they can be listed in BMDW for unrelated search activities. A TC can request and receive a Cord Blood Unit Report with detailed information about a specific CBU. This first interaction between the TC and the registry/cord blood bank is called a preliminary search. Based on the information provided, the TC can decide whether to formalise the search and request additional or verification typing data. If it is suitable for the patient, a unit will be ordered and shipped as cargo in a dry shipper (liquid nitrogen dry vapour) (Welte et al, 2010). The treatment centre, or their stem facility unit, should receive the unit before the condition regimen of the patient starts. The figure below shows the different steps of the cord blood search process.

Figure 10 Cord blood search process



Source: Welte (2010)

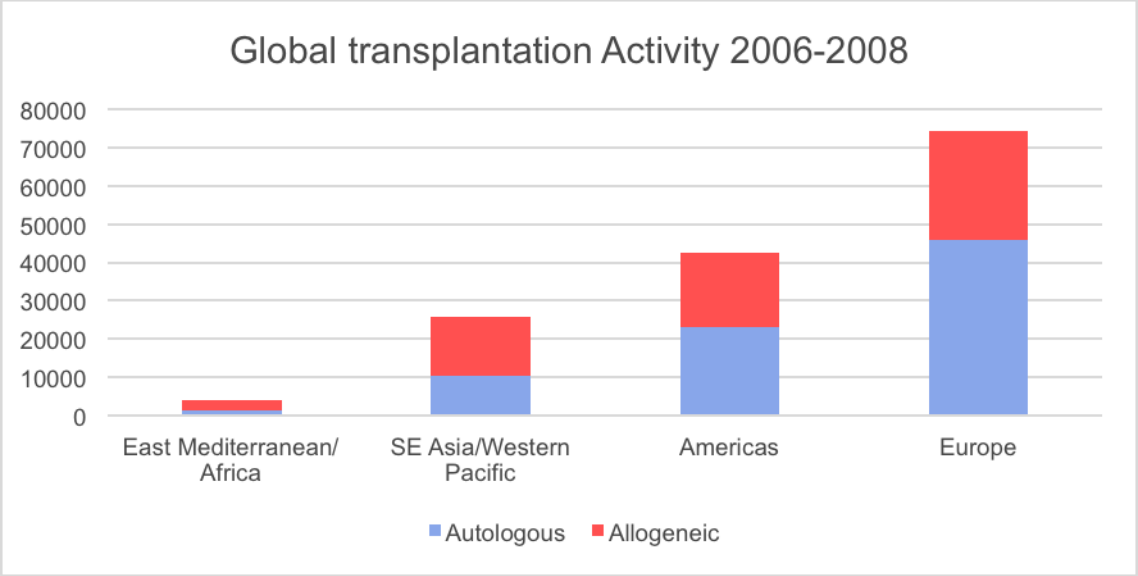
Storage of HPC

Autologous HPC are stored for varying periods of time prior to infusion in either liquid or vapour phase liquid nitrogen or in mechanical freezers (Fehily et al, 2012:71). The storage of allogeneic donor derived HPC is only allowed after permission from the HPC donor registry and the informed consent of the donor. Reasons for a cryopreservation are often unexpected change in remission status of the patient or change in other clinical findings that require additional therapy. It is estimated that several hundred grafts are stored in freezers in Europe, for which donors have been conditioned. The chance is small that these units will ever be infused in a patient. (Rall, 2015, personal communication), because these units are not always registered.

4.2.7 Transplantation activity in EU Member States

Of the EU28 Member States, allogeneic stem cell transplantations are performed in 24 countries: patients from Cyprus, Malta, Lithuania and Luxemburg are referred to a transplant team in another Member State. Transplantation with unrelated donor HPC is currently undertaken in 55 countries and unrelated HPC-CB in 40 countries (Gratwohl, 2015a). There are large regional differences in the use of allogeneic donors that are associated with national income, thus widening the gap between affluent and less affluent countries. Despite a significant increase in HPCT activity worldwide (Gratwohl et al, 2013a) it is assumed that the therapy is still underused as curative treatment, due to various clinical and non-clinical reasons (Yao et al, 2013). Transplantation activity in EU Member States has increased significantly (by 53% over the last decade) and is the highest in the world (see figure below). The annual activity survey from EBMT that analyses the status of HPCT in Europe and affiliated countries has become an instrumental tool for observing trends and to monitor changes in technology use (Passweg et al, 2014). Ten non-European countries also participate in EBMT: Algeria, Kazakhstan, Iran, Israel, Jordan, Lebanon, Nigeria, Saudi Arabia, South Africa and Tunisia.

Figure 11 Global transplantation activity



Source: Gratwohl et al (2013a)

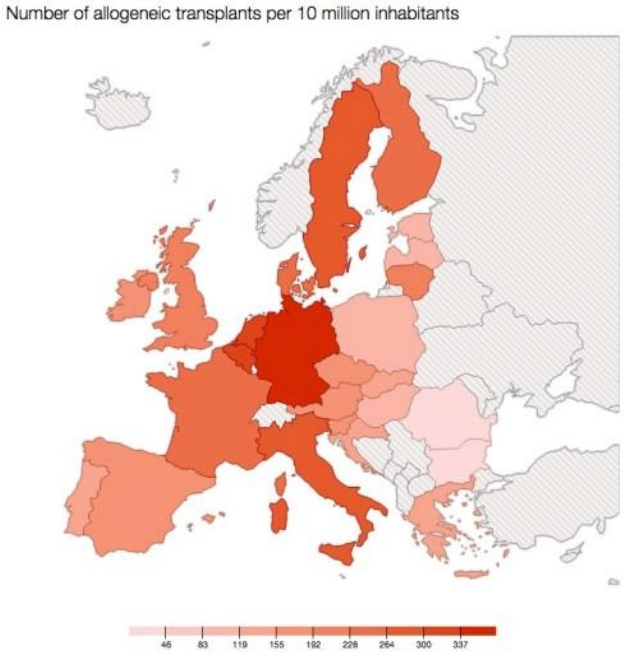
The demand for products provided by unrelated HPC donors has risen threefold over the last decade, and is likely to continue to rise over the next 10 years (Lown and Shaw, 2013). In December 2012, the benchmark of 1 million transplantations was reached, over 40 years since the first successful attempts were undertaken; 50% of these transplantations were performed in the period 2006-2012 (see figure below).

In 2012, unrelated donor/cord blood searches were initiated for approximately 13,000 patients in EU28 Member States. It is unclear if this figure reflects the reality of patients requiring an unrelated donor. of patients without a family donor was initiated, without a clear explanation as to the reasons for the remaining patients being deferred (Labopin et al, 2014). HPCT is a demanding treatment and the age of a patient has previously restricted access to the treatment. The development of reduced-intensity conditioning regimens has cleared the way for HPCT as a potential treatment for an increasing amount of (mainly elderly) patients. A recent prospective study also showed that an unrelated donor search for only 51%

Reasons for not reaching transplantation are various. HPCT might be offered too late during therapy, so clinical deterioration could be the main disturbing factor (Mawad et al, 2013). The reasons explaining the differences in transplantation activity are multifactorial. In the presence nowadays of sufficient sources for HPC for the average donor, access to treatments can also reflect the different medical views on indication for HPCT or different criteria for financial compensation of treatment by health care insurances. The outcome of HPCT in elderly patients for instance is debatable in terms of quality of life, and may lead to different clinical approaches to treatment (Deeg 2015). Also, compensation for treatment by health insurances may be limited to standard care only and may not cover experimental procedures or newly developped therapeutic options or have specific restrictions in general (Sureda et al, 2015). In Greece for instance, patients need to cover the costs of transplantation before treatment starts, which is not feasible for the majority of patients. In France, national HPC products when used in a French patient are not charged. Especially for policy makers it is necessary to perform more in-depth research to get better insight into the different factors that influence the HPC transplantation process from its initial steps, and to understand whether this result in an unequal access to a life-saving therapy to EU citizens.

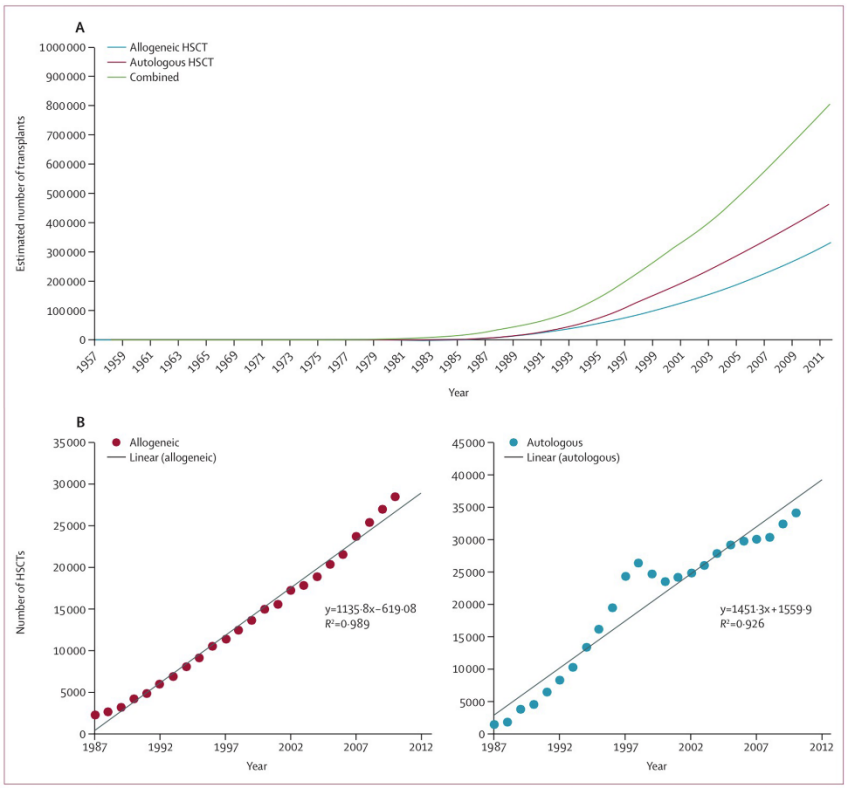
There was not sufficient data in this study to determine how often an unrelated donor or cord blood was identified, and the reason why only 55.9% of patients (n=7,375) reached transplantation (see figure below). The efficiency of the search process is known to be a factor of major importance for patients to reach transplantation (Heemskerk et al, 2005; Craddock et al, 2011; Van Walraven, 2014). The donor registries are aware of this and know that their prompt reaction to a sample request, for example, is not only an advantage for the patient, but will also increase the chance of their donor being requested.

Figure 12 Allogeneic unrelated transplantation activity in EU-28



Source: EUROCET 2012; Economic landscape survey NCATC (2015); WMDA annual report 2012

Figure 13 Trends in autologous and allogeneic HPCT since the start



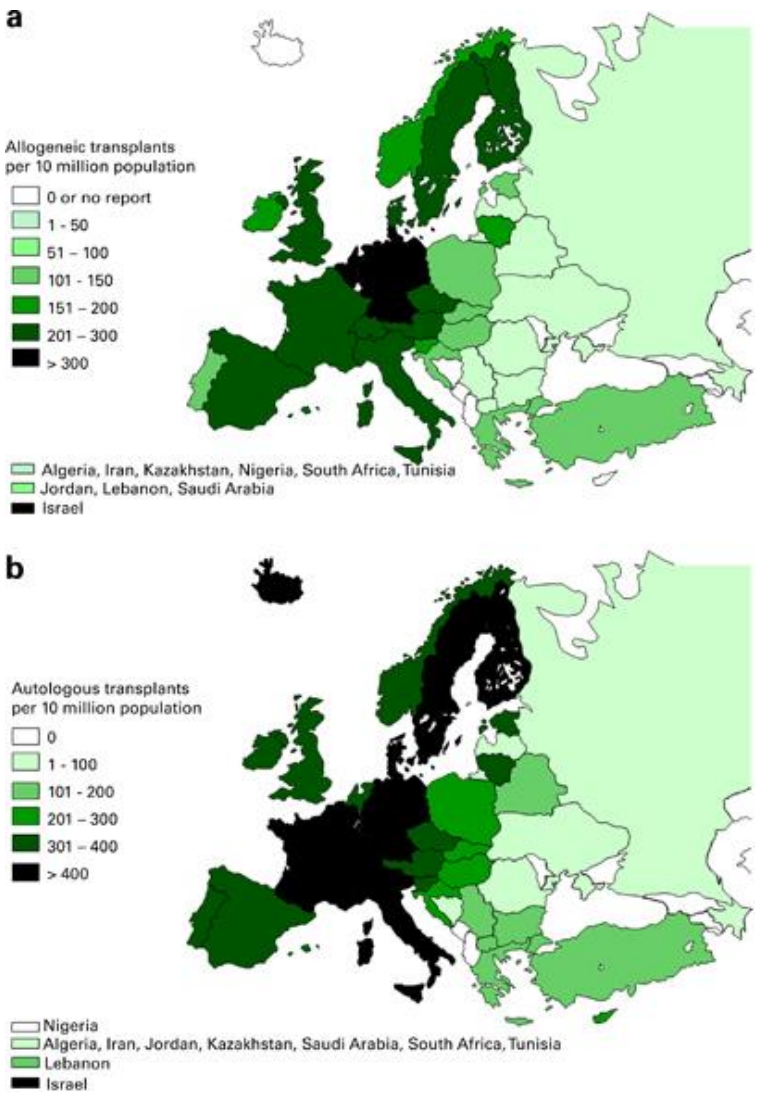
Source: Gratwohl (2015)

The EMBT analyses have shown not only an increase in the annual absolute HPCT numbers and transplant rates, but also a significant increase in the use of unrelated donor derived HPC products. In 2012, according to EBMT survey data, 33,678 patients were involved in 3,818 HPC transplant procedures. Data was received from 661 centres in 48 countries in and around Europe (see annex 2 HPC tables 8-11).

In 2012, a total of 2,501 patients received one or more subsequent grafts (1,186 allogeneic and 2,954 autologous procedures). The number of first HPCT grafts in 2012 was 17,444 (WMDA annual report, 2012). Only 41% of patients worldwide, for whom an unrelated search was initiated, thus reached transplantation.

HPC-A is used in 99% of autologous and 74% of allogeneic transplants, however in the paediatric setting the majority of transplantations is carried out with HPC-M (54%) and HPC-CB (20%). Cord blood as stem cell source was used in 8% of all unrelated procedures and in only 1% of all family transplantations. The highest incidence of cord blood transplants from unrelated donors was seen in France, Spain, Italy, the United Kingdom and the Netherlands. Transplantation rates in European countries are shown in figure 14 below.

Figure 14 Transplant rates in Europe



Source: EUROCET 2012; Economic landscape survey NCATC (2015); WMDA annual report 2012

4.2.8 Managing a Donor registry: key factors to consider

European donor registries are organised in different ways. Some registries are (partially or completely) supported by government; some are independent foundations without any governmental support and dependent on charity and financial donations. Other registries are part of a larger organisation, such as a university, a hospital or a blood bank. Also, the number of donor centres and complexity of the organisations differ per country. Due to economically difficult times, all registries need to seek ways to reduce cost and increase income. There is no standard for determining the success of an HPC donor registry, but in light of needs to make ends financially meet, the following themes were deemed to be important:

- Quality of the donor inventory (high resolution and completeness of HLA typing, male gender, younger age)
- Availability of the donors
- Diversity of the donor inventory (ethnic descent)
- Accessibility and service provided by the HPC donor registry

Donor age and gender

The median age of sibling donors has increased and due to current stricter adherence to eligibility criteria they are more often declared not suitable for donation. Thus the need for unrelated donors and cord blood units has grown over the last years, alongside long term outcome data showing that there is no significant difference in outcome for variant donor sources.

Another strategy is to concentrate recruitment activities on male donors or lowering the age for registration (like the Anthony Nolan Registry in the UK recently initiated), so that donors can be made use of for longer. The lifetime donation probability of an 18-year-old male donor is >10% (Schmidt, 2014). It has even been suggested that a younger unrelated donor could be preferred over an older sibling (Kröger et al, 2013).

Donor availability and eligibility

Donor availability is one of the main success factors of the unrelated donor searches. However, donor registries are often confronted with donors being no longer available or untraceable (Switzer, 2014). Donor attrition can cause a delay during the search process and can thus directly affect the chance of a patient reaching transplantation.

It therefore also has a negative effect for donor registries, both financial and reputational, if many listed donors are not available for verification typing and donation (Lown, 2014a). Maximizing the numbers of donors in common HLA groups does not necessarily improve availability for patients (for example, in 2012, even in the German donor file, 23% of donors were not available at the time of sample request). Within the EU Member States, the median availability of stem cell donors at time of sample request (an early step in the unrelated donor search) was 74% (ranging between 27 and 100% per Member State, Table 7 in annex 2 HPC, Percentage of population registered as donor, availability rate and number of donations per EU MS in 2012).

Concretely, the donor may fail to respond to attempts to contact them by letter, telephone or e-mail or the registry may be unable to trace the donor. Overall in 2012, almost two million (1,819,812 out of 7,574,968) listed European donors were not available. Taking into account the efforts and money invested in their recruitment, registration and laboratory testing, (the minimum cost for initial HLA typing is currently EUR 25-50 per donor, but probably more at the time of recruitment), the amount of unavailable donors represents a (wasted) sum of at least EUR 45,495,300.

It has been suggested that as part of quality control, registries should stay in contact (bonding) with donors after their registration in the donor inventory, which could be essential for preventing donor attrition. It is of the utmost importance to prevent donor attrition and to develop strategies and protocols for preventing the registration of donors that are not fully committed (Hildebrand, 2015, personal communication).

If successfully contacted, approximately 10% of donors need to be deferred at the time of a donation request (Van Walraven et al, 2005). The donor may be unwilling to proceed with testing and possible donation for personal reasons, or may be medically unfit for donation (Van Walraven et al, 2005; Lown and Shaw, 2013). Obesity is by far the most common cause of donor deferral at physical examination pre-donation. The decision to prohibit donations from those with morbid obesity is based on epidemiological studies and anaesthetic risk. Reasons for not being available are various (medically not suitable, personal reasons, unable to contact, no longer interested), but each donor that is not eligible or unavailable is a loss for the registry, and might be a missed chance for a patient to reach transplantation.

Composition, diversity and size of a registry

Despite the steady increase in the global donor inventory, the mainstream of UD/CBU is being registered in the north western European and North American registries, and as a result, patients with another background have no equal access to HPCT, and are often transplanted with less matched UD/CB.

The chance of two randomly selected individuals with the same ethnic background being fully matched is small and estimated to exceed one in 20,000. Unrelated donor registries must therefore recruit in large numbers to create a diverse donor panel required to provide matched unrelated donor for patients who lack an HLA-identical sibling (Lown and Shaw, 2013). There is a need to focus on diversity and selective recruitment and also take regional HLA differences into account in registry planning (Schmidt et al, 2007; Petersdorf 2010; Schmidt et al, 2013). Ideally, the registry should reflect the ethnic composition of its national population – the percentage of diversity should be covered in the donor inventory (Rutt, 2015, personal communication).

A sufficient cell dose is of major importance for transplant outcome, which might explain the preference for male donors, since, due to their body surface they are able to provide quantitatively better grafts (i.e. including more cells) (Wang et al, 2008).

However, determining the optimal size and mix of a donor inventory involves difficult decisions that need to balance competing objectives and requirements (Kollman et al, 2004). There are a number of factors that influence the probability of a donor of being identified and requested to donate. It was shown that completeness and level of HLA typing have a strong impact on probabilities of request (and potential donation) (Schmidt, 2014). Although huge differences exist between the smallest and largest registries, no registry would be good enough to provide a well-matched donor for every one of their national patients. It has for example been estimated that a country such as Germany, would need to register 100 million donors, which is more than the entire German population (Mueller, 2015).

Donor recruitment strategies are changing over time, and this is reflected in a number of policies and strategies:

- Focused recruitment in ethnic minority communities; barriers to recruiting from ethnic minorities include cultural and religious factors, education and awareness, cost and opportunity (Lown et al, 2014).

- Focused recruitment in geographic areas of proven high HLA diversity; improving typing resolution. In 2011, Anthony Nolan completed the Get10K campaign, which successfully recruited 10,000 healthy male donors under the age of 30.
- Focus on altruistic motives, but also prevent for donor attrition (Switzer, 2014).

4.3 ECONOMIC ASPECTS IN HPC

4.3.1 General aspects

Cost of HPC transplantation

The increasing number of treatments using HPC has economic consequences. HPCT is tertiary care and as such involves expensive procedures. As an additional consequence of the economic crisis, transplant centres need to investigate ways to cut costs in their transplantation programs to keep the treatment accessible (Passweg, 2013). Blommestein et al attempted to calculate actual costs for stem cell treatment during the pre-transplant phase (donor search and selection, harvesting of stem cells), to the admission for transplantation until discharge, and during the first year of follow-up (see annex 2 HPC table 12, Average cost for HPCT with autologous donor, sibling donor, unrelated donor and unrelated cord blood in euros) (Blommestein et al, 2012). Although follow-up is continued after the first year, these costs were not taken into consideration.

The main cost drivers are reported to be hospital inpatient days, laboratory costs, and the costs of medication and blood products. These were calculated for a randomly selected group of 191 patients treated in three Dutch transplant centres.

Blommestein et al report that selection and harvesting represents 18% of costs in the allogeneic sibling setting and 12% in the allogeneic unrelated donor setting (Blommestein et al, 2012). Khera et al reported that higher costs are incurred when an HPCT program is being established and that costs and clinical outcomes improve with time and greater institutional experience. The cost of purchasing an unrelated cord blood remains a concern. Broxmeyer and Farag (2013) mentioned that CBB have the potential to price HPC-CB out of competition as a source of stem cells for HPCT.· Double-cord transplantation in particular can significantly affect the costs of a procedure. In countries without a HPC donor registry, BMDW can grant transplant centres access for a fee of an annual €670.

Procedures with unrelated donor/cord blood derived HPC are more costly due to the donor search process, price of products and the greater chance of significant clinical complications that occur after allogeneic HPCT (Warwick and Brubaker (2012). Post-transplantation complications have been reported in multiple studies as being major cost drivers in both autologous and allogeneic settings (Khera et al, 2012).

Remuneration of HPC donors

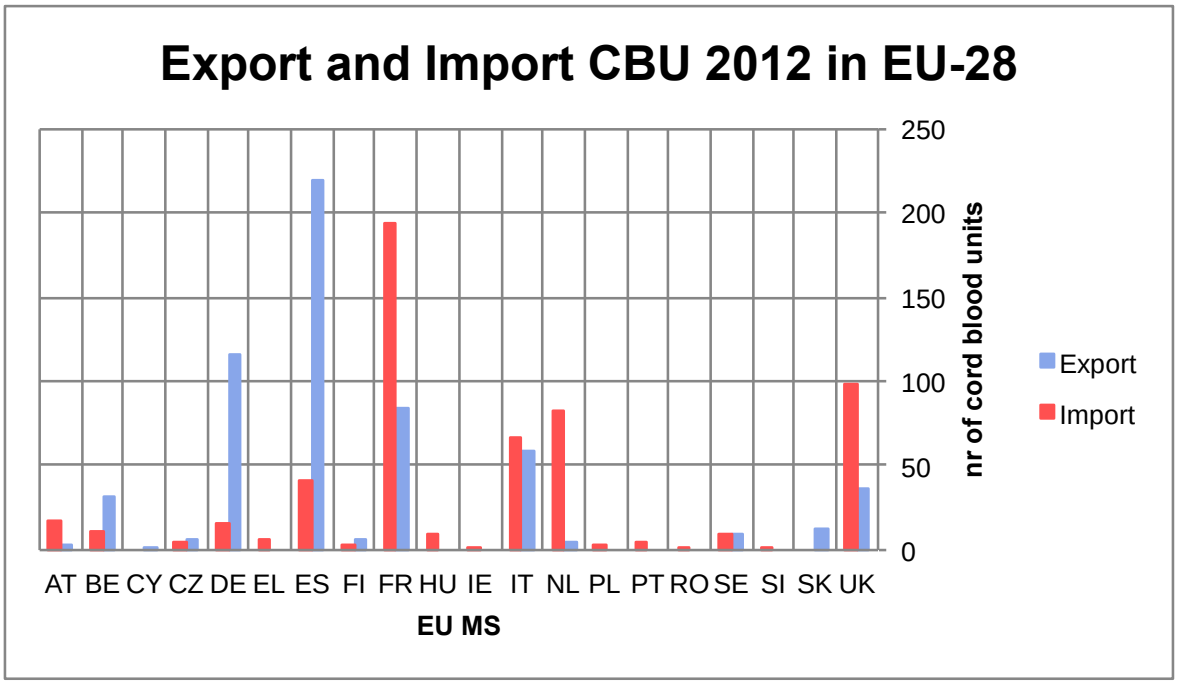
Due to the altruistic character of stem cell donation, the procedure is non-remunerated, i.e. donors are reimbursed for out of pocket expenses such as travel expenses or loss of income. Remuneration of donors has been proposed as a means to incentivise more individuals to join a registry (Boo et al, 2011). However, according to the WHO Guiding Principle 5, cells, tissues and organs should be donated freely, to prevent a human body being turned into a commodity, a product (WHO, 2010). Furthermore, the value of the donation cannot be estimated; it is literally a 'gift of life'. Research in the field of kidney donation has showed that donating a kidney out of affection is a positive experience: 84% of donors would recommend donation. But 79% of donors who sold a kidney out of economic hardship would recommend not donating a kidney (Demme, 2010). According

to Boo et al (2011), a policy where paid donation is allowed would change the registries and the system. It is the opinion of the WMDA that remuneration for HSC donors is therefor undesirable and may be deleterious to the international transplant community of both patients and donors.

Perceived shortage and self-sufficiency

Whether a country is self-sufficient or needs to import units reflects not only the level of local organisation, but also the homogeneity of its population. Many countries in South East Asia are self-sufficient, probably because of the relative homogeneity of their populations (Petrini, 2014). In some countries, for example Belgium, Germany and Spain, export numbers for HPC-CB clearly outnumber import (see figure below).

Figure 15 Export and import of cord blood units



Source: WMDA annual report (2012)

In the Voluntary Unpaid Donation survey (EC) that was consulted as part of this research, EU Member States were asked is they experienced a shortage of tissues and cells. Ten countries (BE, BG, EE, EL, IE, IT, LT, MT, SE, SK) confirmed that there was a shortage of tissues and cells – over 90% of HPC products were derived from non-national donors. The remainder of countries (AT, CZ, DE, DK, ES, FI, FR, HR, HU, LV, NL, PL, PT, RO, SI, UK) did not experience a shortage. Interestingly, patients in all these countries, apart from Germany, are (on average, for over 80%) dependent on non-national HPC products. The only EU Member State that comes close to being self-sufficient is Germany: over 80% of patients are treated with stem cells derived from a national donor.

4.3.2 Economics of stem cell donor registries

In this section, the economics associated with the maintenance of an HPC donor registry and the provision of HPC-donor products are further clarified. The financial aspects of cord blood banking will be discussed separately.

Although hematopoietic stem cells are donated free of remuneration by volunteer donors (Boo et al, 2011), maintaining a donor file and the process from donor recruitment to stem cell collection and follow-up, costs money. The majority of HPC donor registries in the EU are small and medium-sized registries and they are facing hard times in making financial ends meet. Large registries seem to have less financial difficulties.

General cost aspects of stem cell donor registries

Stem cell donor registries are responsible for the maintenance of the national donor file, for collaborating with donor and collections centres, and for the recruitment, care management, stem cell collection, and follow-up of volunteer unpaid stem cell donors.

Due to the wide range of activities, the network of a registry usually consists of transplant centres, laboratories for HLA-typing and infectious disease marker (IDM) testing, blood bank departments, apheresis and marrow collection centres, and stem cell couriers.

The complexity of the tasks and processes require registries to have well-trained staff, information technology resources, and administrative personnel (WMDA Handbook, A Gift for Life, 2013). However, with respect to the ICT systems, the maintenance of registries often includes a doubling of overhead costs.

The costs of maintaining a stem cell HPC donor registry are diverse and consist of expenses for:

- Donor recruitment (including public relations and marketing) and registration
  - Promotion campaigns, promotion material and registration staff
  - HLA sampling and typing
  - Additional laboratory test at recruitment (e.g. infectious disease markers; blood type)
- Information technology – development and maintenance of
  - Website
  - Donor database, including validation
  - Patient database
  - International IT connections (e.g. BMDW, EMDIS, NMDP)
  - National IT connections (HLA laboratories, donor centres, search units, collection centres, transplant centres)
- Maintaining international network
  - Membership fee WMDA
  - Membership fee BMDW
- Quality Assurance
  - Accreditation (WMDA)
- Staff (medical, IT, quality, finance, administration)
  - Education and training
  - Third party insurance
- Housing, equipment, logistics, finance

Costs that are directly related to donor care management (counselling, drawing and shipment of samples, physical examination, and collection of stem cells, follow-up, donor insurance) are invoiced to the requesting organisation and will be discussed later.

Information and communication technology

International collaboration makes registries dependent on ICT solutions, which form a relatively large part of their expenditure (ICT staff). Historically, registries started developing their own software and databases for their local operations, since at that time there was no (commercial) third party to provide an off-the-shelf solution for stem cell donor registries or cord blood banks. In the last few decades, international collaboration, standardisation, regulatory requirements, new matching algorithms and connectivity through the EMDIS network have made maintenance of local systems more expensive. Registries started to seek alternatives to their local systems. Some registries offered to share their locally developed software with other registries, however this resulted in issues with maintenance and support that were no longer sustainable on a non-profit basis (Bakker, 2015).

Recently, the software developed for the Czech Republic Registry in Prague to process the messages communicated with the EMDIS network, has been commercialised. Registries (in particular the smaller and medium-sized registries) with fewer financial resources are looking for ways to cut down expenses, for example replacing their own system with a commercial product and thus reducing the cost of ICT personnel. There is only one commercial ICT solution currently available for small and medium-sized registries, while the large successful registries are still able to maintain and enhance their local systems (that have not only been specified to meet their own needs and requirements, but also set the standard for advanced matching algorithm software).

Several experts in the field expressed concerns that a growing percentage of small and medium-sized registries is dependent on a single commercial software provider with a monopoly. There is a user-group to share experiences and give input for the development of the product, but users have in fact not much of a choice and pay an annual fee for maintenance. Survival of these registries is therefore partly dependent on the survival of the software company.

The costs of donor recruitment

A substantial segment of donor recruitment investment is the cost of HLA-typing at the time of recruitment. The costs of recruitment and procurement differ from country to country and for a long time, were not clear. It was mentioned during the expert meeting in Brussels that it is now known that the costs of procurement in other countries are much higher than in Germany, often as a result of local regulations.

Through information received from registries and competent authorities, it has become clear that there are huge differences in the prices paid for tissue typing. With respect to cost, the volume and resolution level of typing used to be the important factors in the establishment of price. Currently, 10% of all donors registered in BMDW are typed at a high-resolution level for all loci, making them more attractive and likely to be requested. Local HLA laboratories (often hospital or registry based) are often not able to process large batches and charge a considerable amount of money per typed donor. This directly affects and limits the ability of small and medium sized registries to recruit large volumes of donors.

The German Bone Marrow Donor Centre (DKMS) have specified the total registration costs per donor. Every new donor costs the DKMS approximately EUR 50. This price consists of the following: typing (EUR 26.80), medical and other material (EUR 1.49), logistics and communication (EUR 12.48), personnel costs (EUR 5.61) and administration/management (EUR 3.93) (DKMS Annual Report, 2013). Since its early years, when financial funding was scarce, the DKMS has asked each donor for a voluntary contribution towards typing expenses at the point of registration. Donors have shown to be willing to contribute to the costs of their HLA-typing. Although their financial contribution is lower today, it is still an average contribution of EUR 10 per donor (20%

of overall HLA typing costs) (Rall, 2015, personal communication). Other registries in the survey were often not able to breakdown the cost of recruitment, or show cost models.

The fact that DKMS HLA-typing costs are relatively low relates to the fact that they have their own HLA-typing laboratories which process high volumes of samples. In the past decade there have been significant improvements made in the techniques for HLA-typing at high-resolution level. With the introduction of next generation sequencing (NGS), HLA-typing has not only become cheaper, but the typing of further parameters (blood group, CMV, KIR) can easily be done without increasing the costs. Outsourcing the HLA-typing of newly recruited donors could have an impact on local HLA laboratories. A side effect of the improved quality of donors (i.e. typed on high resolution HLA level) is that donor registries receive fewer requests for extensive typing, and thus the income this testing provides. Although the typing of donors in a hospital environment is cost-intensive, it has been noted that hospitals also need to prevent for loss of skills and, despite the costs, should at least proceed with typing of patient, family members and verification typing of donors (Egeland, 2015, personal communication).

The costs of maintaining a donor file

To make their donor inventory digitally available, donor registries need to have access to information technology and highly qualified IT staff for the creation of interfaces that enable a validated donor database to participate in projects such as Bone Marrow Donors Worldwide (BMDW) and the European Marrow Donor Information System (EMDIS); to exchange messages within registries and local software. Smaller registries that cannot afford their own software engineers need to seek out commercial software solutions. For participation in the BMDW project, registries pay an annual fee (approximately ranging €1200 – €13.000), based on the size of their registry (see annex 2, HPC table 13 BMDW fees, actual November 2014). There is an ongoing initiative by BMDW participants to organise the project in a different way and revise the software to develop it into a better tool with better options for exchange of information across the world in the future.

The costs of procurement

Apart from the cost of making the donor file available internationally, donor registries are also facing procurement costs. There is a large variety in the range of costs, and it seems not possible to break down fees to an original cost structure. It is therefore also unclear if a registry could be financially independent through the revenues provided by the products.

The costs of donor procurement comprise:

Blood sample requests for verification typing
- Contacting donor and determining medical suitability
- Drawing of blood samples (including material: needles, tubes etc.)
- Shipment of samples (including appropriate packing material)
- Laboratory tests (infectious disease markers, HLA verification typing, blood group/RhD)
- Reimbursement of donor travel expenses
- Reimbursement to third party for drawing samples (GP or laboratory)
- Handling of results: registration in own system and reporting to TC

Stem cell donation request (Bone Marrow or Peripheral Blood Stem Cells)
- Contacting donor
- Counselling (information on donation request and process) and obtaining informed consent
- Physical examination
- Laboratory tests

- Additional tests (EKG, chest X-ray)
- Consult anaesthesiology
- Reimbursement donor travel expenses

Stem cell collection bone marrow

- Admission costs
- General anaesthetics
- Use of operating room (including staff and material)
- Processing collected bone marrow (TNC, packaging for transport, administration)
- Donor follow up (long term)
- Reimbursement donor travel expenses

Stem cell collection peripheral blood stem cells

- Admission
- G-CSF
- Apheresis (including staff and material)
- Processing collected stem cells (TNC, CD34+, packaging for transport, administration)
- Donor follow up (long-term)
- Reimbursement of donor travel and out-of-pocket expenses

Ideally, all procurement costs are invoiced to the requesting TC. In general de DR in responsible for the invoicing and commissions third parties to perform part of the processes mentioned above like donor counselling, collection of test tubes or shipments. Transport of the HPC product to the TC is usually organised (and paid for) by the TC. Procurement activities are not always performed by the registry itself, but is outsourced to DC like hospitals, blood banks (in case of PBSC collection), or to specialized (private) entities. The charges for these collection activities to the DR may vary substantially.

In general it can be stated that the size and the quality of the registry and DC, is inversely proportional with its expenses. The larger (or qualitatively better) the DR or DC, the lower prices can be achieve for bulk purchases of materials and testing, as was shown by the NMDP and DKMS. The GEMS registries are currently investigating collaboration for (bulk) HLA-typing of newly recruited donors by commercial HLA-typing companies. Financial barriers should no longer restrain a registry in attempting to improve the level of HLA-typing of current and new donors.

Other Financial Obligations

For an HPC donor registry, being a member of the World Marrow Donor Association (WMDA) is important as it indicates their commitment to WMDA Standards. Accreditation by the WMDA strengthens the position of an HPC donor registry and can even play a role in donor choice by a TC. Currently, ten registries in 8 EU Member States are accredited by WMDA. Two non-EU28 registries in Europe (Switzerland, Norway) and nine registries outside Europe are WMDA-accredited (WMDA, 2015).

Membership of the WMDA enables donor registries to stay informed about trends and for their staff to be educated during the WMDA meetings. The WMDA charges a flat fee for membership, based on the size of the registry (the number of registered donors) and from 2015, there is an additional fee based on the number of HPC products they provided in 2013 (€1000 plus an additional €50 euro per product provided in 2014; see annex 2 HPC table 14 WMDA fees, actual May 2015). This measure will have an impact on all registries, but in particular on those that provide high numbers of HPC products.

4.3.3 Economics of Cord Blood Banks

In this section, the economics associated with cord blood banking are explained. Cord blood, collected immediately after birth, can be banked for potential use in the future, both in public and private (for-profit) banks (Santoro, 2009).

Costs

The recruitment of a cord blood donor, a so-called proxy donor since the mother donates on behalf of her new-born child, starts during the pregnancy. Donating cord blood to a public bank is without costs for the donor. For the storage of cord blood in private banks and hybrid banks, prospective parents are charged a fee (EUR 1,500-2,500) to cover the costs of cryopreservation until the child (the actual donor) reaches adulthood. Cord blood from less than 1% of all live births is currently collected for public use, whereas private banks store up to 15% of births; however there is no indication that there is major competition (Hamblin, 2010). Approximately 20% of all requested pregnant women in the Netherlands consent to donate their cord blood to the public bank (van Beckhoven, 2014)

The costs of maintaining a public cord blood bank

The establishment and maintenance of a cord blood bank is comparable, yet also different from, an HPC donor registry. The costs for IT requirements, maintenance of an international network, quality assurance, staff and housing are similar to those of stem cell donor registries. Costs directly related to responding to interest in a specific cord blood unit (additional HLA-typing request, DNA sample request, and information request) are invoiced to the requesting organisation and will be discussed later.

The costs of building up a cord blood inventory are high. It is not a guarantee that donated collected cord blood will fulfil the requirements for the inventory and cryopreservation (Kurtzberg et al, 2005). There is a high discard rate of collected UCB units, as approximately 75-90% of UCB units collected and donated for transplantation purposes fail to meet the very strict criteria for public storage and clinical use and end up as unfavourable for cryopreservation (Petrini, 2014).

In 2009, on study estimated the costs of processing a cord blood at EUR 720.41 per unit (Arrojo et al, 2012). However the costs of units that were received but not met quality criteria, were not taken into consideration. Costs for midwives, technicians, administration and banking staff are included as well as the processing (validation, quality controls: HLA typing, CD34+ count, viability, blood cultures, ABO and Rh, and the required testing for transmissible diseases). Table 17 in annex 2 HPC (Cost of processing umbilical cord units, source Arojo et al 2012) shows that investing in and managing a small cord blood bank (less than 5,000 units) requires a huge amount of money, without the guarantee that it will ever be recovered.

Although initial cord blood matching did not require complete and high resolution typing of HLA, advancing insight is that matching on high resolution HLA improves the outcome of transplantation (Dahi et al, 2014). Newly collected units will therefore more likely be typed on high resolution, effecting a quality backlog in previously stored units, and decreasing the likelihood of them being ever chosen.

The procurement of donated cord blood is thus a very expensive process, and possibly ten times more than the costs of using volunteer HPC donors. Furthermore, the fact that once a unit is stored, there is a smaller chance that it will be released for donation purposes, adds to the costs (Bart, 2010). 90% of the inventory of the New York Blood Centre is still available after 10 years of storage, and thus theoretically available if an HLA identical relative of the donor should be in need of a stem cell transplantation (Guilcher et al, 2014). This might explain the relatively high fees of cord blood units on

the one hand and on the other, explain the struggle for smaller cord blood banks to keep their activity sustainable, since it remains questionable whether they cover the costs (Bart, 2010). In 2009, fees for single cord blood units ranged from $ 20,000–34,000 (EUR17,620-30,130) (Bart, 2010), and today go up to EUR 40,000 per single cord blood unit. For a transplantation where two cord blood units are necessary to infuse a sufficient amount of stem cells, the costs obviously double. The introduction of VAT that may become applicable to cord blood was mentioned as a concern during our research: this would imply that fees potentially will rise, but also that human tissue is a sellable good, which is in contradiction with the WHO guiding principles (World Health Organisation). This concern is further addressed in chapter 2.5

ICT solutions

For the maintenance of the cord blood inventory there are currently more commercial software solutions available. The development of an ICT system for a cord blood bank to use in unrelated cord blood search is comparable to the system of the donor registries. Efforts are ongoing to develop EMDIS Cord, a mirroring system between cord blood registries in different countries, which will make possible the exchange of messages specifically for cord blood banks.

Economics of Family directed, Private and Hybrid cord blood banking

Family directed cord blood banking is the storage of cord blood that can be used for a sibling diagnosed with a disease which can be cured by allogeneic hematopoietic stem cell transplantation or for research that investigates the use of allogeneic or autologous cord blood cells (Gluckman et al, 2011). Services are often offered free of charge for families in need. It is under discussion whether family directed cord blood banking might be cost-effective for children with a likelihood of needing a stem cell transplant (Kaimal et al, 2009. In an analysis by Smythe et al it was shown that 28% of the units collected for a directed donation were HLA compatible, and 4.9% of the units were actually used for donation. Apart from clinical criteria, financial support of the transplant centre was a precondition for cryopreservation (Smythe et al, 2007)).

Autologous cord blood banking, or private banking has grown into a private industry, predominantly used by economically-advantaged families (Gluckman, et al, 2011). This form of cord blood banking sometimes raises ethical concerns since there is no clinical evidence to support the banking of cord blood in a healthy family (Petrini, 2014), and clinical applications are considered speculative (Manegold et al, 2011). The cost of banking is solely covered by families and ranges between EUR 2 000-2 500 for approximately 20 years of storage. It is estimated that the volume of private cord blood samples stored is outnumbering the number of public units, however, the use in transplantation is reported sporadically. Private cord blood banks have grown into major industries; they are often active in more than one country, and have huge inventories (table 18 in annex 2 HPC, Some major private cord blood banks active in the EU MS) compared to public banks (table 5 in annex 2 HPC, Overview growth European Public Cord Blood Registries). In the EU 28 Member States there are approximately 123 non-public cord blood banks active, and it is known that a number of them are listed on the stock market, however precise figures on actual market value are unknown. Apart from the storage of cord blood, private banks also offer paid-for cryopreservation of stem cells from dental pulp, adipose/lipo or fat tissue and stem cells from adult bone marrow and blood (see also http://parentsguidecordblood.org).

Contrary to the public banks, private cord blood banks are paid immediately for their service rather than having to wait for the income until the units are selected for treatment for a specific patient.

A combination of public and private banking, the so-called hybrid model, is still rare. This is partly due to the differences in ethical, regulatory and quality issues between the public and the commercial activities, and as such creating hurdles for the establishment of hybrid banks. A Swiss study showed that parents who donated to a public bank were most likely to do this again in a future pregnancy and not particularly interested in private storage (Manegold et al, 2011). The Spanish model, where parents have the obligation to release a unit if it matches a patient has not been very successful: to date only 112 units are stored in Spain in this way (Querol, 2015, personal communication) Although private banks are considering hybrid solutions, this may only apply for future parents: according to the German legislation, the stored units belong to the child (Opitz, Cord Blood Europe, 2015).

A hybrid banking model could be constructed so that parents' investments are reimbursed when a unit is sold for donation. However the chance that a product will be used is small, given the number of units that are released worldwide annually. The major benefits would be for patients in need of HPCT for whom no acceptable donor or cord blood unit is available in the current inventory.

In Europe there are over 120 cord blood banks active in private or family-directed cryopreservation of cord blood. Globally, it is estimated that the number of private stored cord blood samples (approximately 4,03 million units) is at ~six times more than the world wide public inventory (730.000 units) (Ballen, 2015).

4.3.4 Income for stem cell donor registries and cord blood banks

Reimbursement for delivered units of HPC

The provision of stem cell products is the main source of income for HPC Donor Registries. The product fees should effectively include all cumulative costs of donor care management, stem cell collection and handling until the point where the stem cell product is handed to the designated courier, and include costs for (long term) donor follow up (WMDA Handbook: A Gift for Life, 2013).

Registries contacted for this report were reluctant or not able to provide us with a detailed breakdown of their product fees. Product fees differ per registry/country and are dependent, among other factors, on the registry policies, local regulations, local currency, and fluctuations in the exchange rate. Ideally, a certain proportion of fees should be reserved for the recruitment and initial HLA-typing of new donors, however this is not the situation in most countries. More frequent HPC product requests would translate into more means for recruitment. The fast growth of the DKMS, the large German DC is exemplary and is discussed in more depth in section 4.7.5.

The fees are paid for HPC units delivered, and differ between countries and hospitals, as does the overall cost of HPCT. Based upon a literature review, it was estimated that the costs of the first year of allogeneic HPC treatment ranges from $ 84,000-204,000 (EUR 84,000-180,000). Example of fees for the organisation and collection of stem cell products fees include:

- South African donor: ZAR 95,000 (± EUR 6,800)
- German donor: EUR 13,500 – 14,500
- British donor: GBP 20,000 (± EUR 25,500)
- American donor: $ 32,500 (EUR 26,100)

From the transplant centre's point of view, a national product would probably be the best option. The chance of finding a donor is highest from within the same population; a graft collected in the same country is available for infusion faster with more moderate transport expenses. Fees charged to national TC are sometimes lower than to TC's in other countries. Dutch TCs indicated a preference for donors from European origin: it was indicated that German (DKMS) donors are favourable (due to runtime, fee, and availability); if no acceptable donor can be identified, the search for an unrelated donor can be extended to the USA or cord blood as a stem cell source would be considered (Cornelissen, 2014).

Apart from product fees for HPC units procured and delivered, donor registries charge transplant centres also for tests and activities already performed if there is a postponement or cancellation of procurement prior to collection, to cover these costs made. This fee varies, depending on the timing of the cancellation. Donor registries within the European Union were contacted for this report and asked to provide a schedule of their search fees (typing, samples and shipment), and product fees. The actual date of the received pricelists range from 2009-2014. Product fees in the EU MS range from €11,000 to approximately €20,000. An overview of the fee schedules is given in annex 2 HPC table 15 (Fee schedules actual November 2014).

During a meeting with experts in the field of HPC in Leiden (March 3rd and April 7th, 2015), HPC financing in terms of income and expenditure was discussed. Not all registries are willing to share their fee list. There were concerns that fee schedules could be misinterpreted when compared without further background information. Information that would have enabled a fee breakdown for HPC-collection (collection costs, hospital cost, laboratory cost etc.) was not provided by any of the registries.

Additional revenues come from subsequent donations (e.g. donor lymphocytes) for treatment for relapse or viral infections post-transplantation. Some registries offer the organisation of (paid for) stem cells transport. Fees for transport are mainly dependent on the length of the journey, although for destinations within Europe, fixed prices are usually charged. Registries also offer services for performing the unrelated donor search. Thorough knowledge of HLA (tissue typing) and the worldwide network make an efficient search possible. A shorter timespan in identifying an acceptable donor increases the chance of a patient reaching transplantation (Heemskerk et al, 2005; Van Walraven, 2014).

Since the majority of HPC donations in Europe are provided by one extra-large scale organisation, the income of small, medium, and even large size European registries is at risk, due to decreasing numbers for donation and distribution. Given that the costs are usually incurred a long time before the income is received, donor registries have to carefully manage their liquidity and cash situation. Those organisations therefore also need to reflect on other sources of income, such as from charitable organisations.Other sources of income: services and funding

According to the WMDA handbook, finding sufficient financial resources is typically the biggest obstacle for the establishment or expansion of a stem cell HPC donor registry (WMDA, 2013). Recruitment activities cost money and are not directly reimbursed, and less than 0.1% of registered donors actually donate per year (see table 4 in annex 2 HPC, Overview Growth European HPC Door Registries). It also needs to be taken into account that income of a potential donation comes often years after costs for donor recruitment are made. This can lead to liquidity or cash problems for registries, in particular when they are smaller and have a higher variability in annual requests to procure and deliver HPC units.

The costs of recruitment are not well known, but the overall costs need to contribute to the maintenance of the registry. If recruitment is to be (partially) financed from product

fees, an increase in fees is unavoidable, in particular in small registries. Activities in the area of donor sample procurement are recharged to the requesting hospitals and should ideally not add to the costs of the registry. Governmental funding for donor registries is not very common, registries sometimes seek extra funding from insurance companies, charity, donations. Examples of sources of financial funding are given in table 16 (annex 2 HPC), real figures are unknown.

Registries also seek alternative ways for funding and often use social media to draw attention to:

- Charity activities (sponsored sport such as marathons)
- Company-sponsored donor recruitment drives

Donors are asked to pay for their HLA typing.

4.3.5 HPC distribution beteen, import to and export from EU Member States

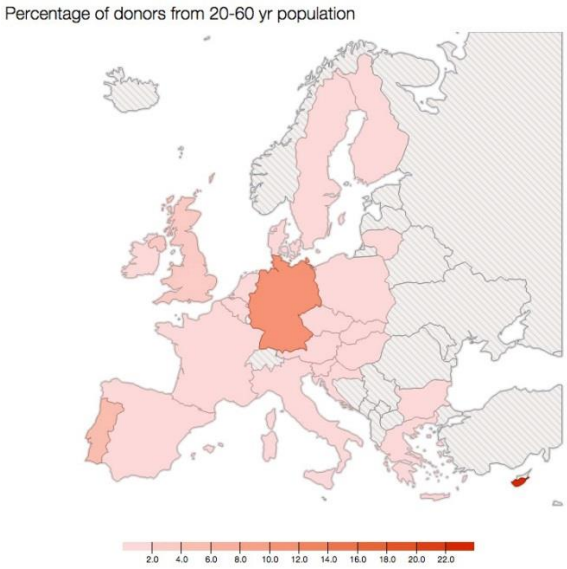
Data collection, results and discussion

For this report, questionnaires were sent to the NCATC in each of the EU28 Member States, to gain insight into the exchange (volumes and cost) of donor-derived stem cells (e.g. bone marrow and peripheral blood stem cells), and cord blood units. Additional information provided by the WMDA was used to compile an overview of the export and import of HPC. Results were summarised in fact sheets per country. The most important and distinctive facts for each country were merged and analysed to give insight into activities in the EU28 Member States. The following paragraphs provide more detail on the main topics covered.

Donor facts and figures

Whereas family donors can donate stem cells for virtually their whole life, unrelated donors are only allowed to donate from the age of 18 years until 55-60 years. The number of inhabitants in EU28 Member States that are aged from 20-60 is 280,983,456. Only 2.7% (n=7,481,619) are registered as stem cell donors. There are major differences in donor density between countries (Figure 12). Cyprus is the hotspot with almost 25% of its inhabitants aged between 20-60 registered as donors. This is particularly remarkable, since there is no centre performing allogeneic HPC transplantations on Cyprus. The major HPC donor registry of Europe is in Germany, with a registration rate of 10%.

Figure 16 HPC donor density in EU28 Member States



Source: EUROCET 2012; Economic landscape survey NCATC (2015); WMDA annual report 2012

4.3.6 Origin of HPC products

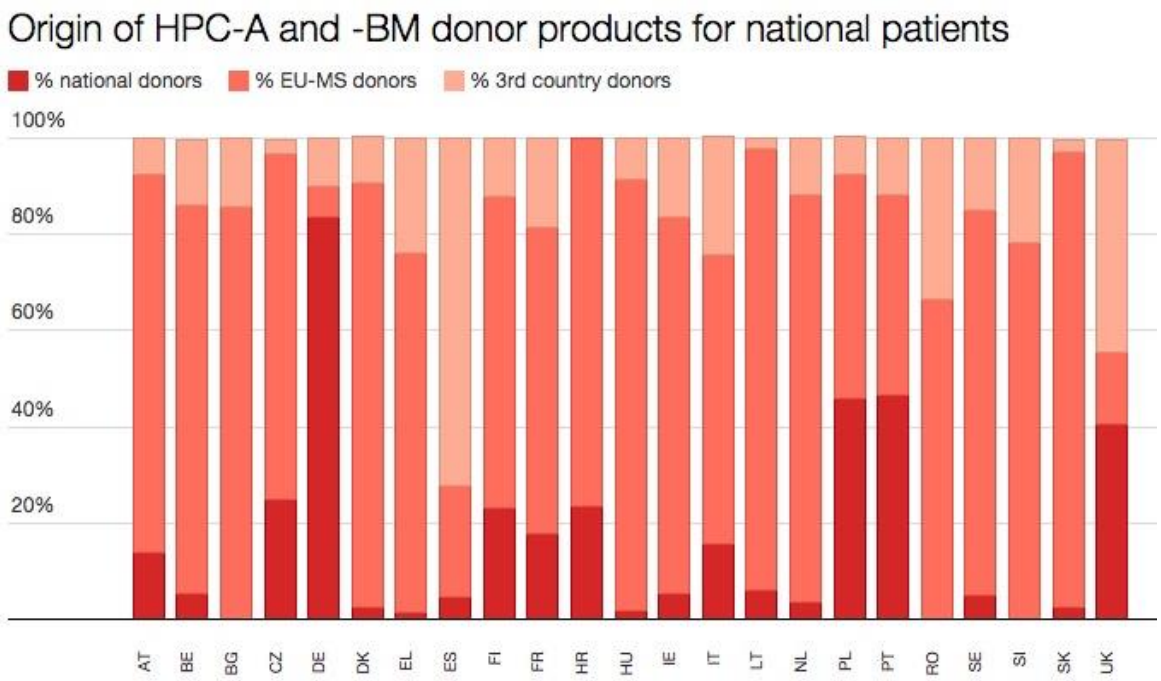
In 2012, almost 7,500 patients in EU Member States received an allogeneic HPC graft. The majority of grafts (72.3%) were HPC-A products. Patients were transplanted with a product derived from a

- National donor (39.9%)
  5.9% of all grafts, as HPC-M transplantations (n=441)
  31.1% of all grafts, as HPC-A transplantations (n=2,316)
  2.9% of all grafts, as HPC-CB transplantations (n=216)
- Donor from another EU Member State (43.9%)
  8.8% of all grafts, as HPC-M transplantations (n=656)
  31.5% of all grafts, as HPC-A transplantations (n=2,352)
  3.6% of all grafts, as HPC-CB transplantations (n=267)
- Donor from outside EU Member States (16.2%)
  - 2.8% of all grafts, as HPC-M transplantations (n=210)
  - 9.7% of all grafts, as HPC-A transplantations (n=722)
  - 3.7% of all grafts, as HPC-CB transplantations (n=275)

Germany is the only EU Member State that is close to self-sufficient in terms of national products for national patients. Only 14% originated from a non-national donor (7% EU Member State donor, 6% third country donors and 1% cord bloods). Runners up included Poland (47.7% national products), Portugal (37.3% national products) and the UK (34.5% national products).

The fact that over 80% of patients in Germany received a transplant using a national product distorts the picture for the other EU Member States. Without the figures for Germany, 17.1% of EU Member State patients received a graft derived from a national donor source, and on average, over 65% of transplantations were performed with a product from EU Member State origin (see figure 17).

Figure 17 Origin of HPC products



Source: EUROCET 2012; Economic landscape survey NCATC (2015); WMDA annual report 2012

Cross-border exchange of HPC, leading role of DE/DKMS

More than 33 HPC products cross a border every day, however there is only one country/continent (Germany/Europe) with much more export than import; a direct effect of the activities of the DKMS donor centre. Germany is the only country in the world with much more export than import. In 2014, not only in Europe, but also globally, almost half of HPC products originated from Germany. The majority of donors in the German Registry are recruited through the DKMS donor centre, which operates independently, but is under the governance of the German Registry with regards to making donors searchable.

The DKMS, the largest donor centre in the world, started as a private initiative in 1991, initially with a 4-year financial support program from the government. After losing this support, they decided to ask each new donor to voluntary pay EUR 50 for HLA typing, which up to 70% of them did. In this way they were able to grow their donor inventory. The difference with other HPC donor organisations is probably the fact that the management of the DKMS has always been more business-like, pursuing their aim (helping blood cancer patients who are at risk of dying all over the world) and focusing on the long-term fulfilment of their vision to conquering blood cancer (DKMS). Activities of the DKMS have been extended to other countries, in particular Poland and the UK. Efforts to start activities in Spain have led to a lot of local media attention and have been limited. These steps have led them to a position where DKMS procures more donor products than any other donor centre in the world.

Several experts in the field however start to be concerned on the global dependency on this one extra-large registry. Concerns relate to the governance, transparency and accountability of DKMS activities. Any registry and donor centre need to make internal

strategic choices. However, choices made by DKMS, can have a strong (positive or negative) impact on public health systems.

Social media

The use of social media by donor registries and donor centres to enhance awareness for stem cell donation is flourishing and is even showing a touch of competition between organisations. It seems that every self-respecting DR or DC is active on Facebook. And here also, larger organisations that have more 'likes' are able to reach out to a larger public.

This triggers some interesting debates with regards to the WHO Guiding Principles 5 and 11 (WHO)[19], which emphasise that all donation practices are defined explicitly and executed in a transparent fashion, ensuring personal anonymity of donors and recipients. Notably, despite regulations on confidentiality in stem cell donation, most organisations do not hesitate to use detailed information, including full names, and even pictures of patients (often children) and donors during the collection process, to promote their activities, or call for donors. And donors do not hesitate to post a picture of their Donor Identification Card with name and DID on the internet, showing their pride. No doubt further debates will come on this.

4.4 FUTURE PERSPECTIVES IN HPC

4.4.1 Consolidation of European Registries?

With the dominance of a single registry in the EU Member States, with increasing competition and with the need for cost-efficiency, the option of a consolidated European Registry has been mentioned by several consulted experts as important and something that should be seriously considered and investigated.

The economic landscape has changed and, unlike in the past, there is now competition between registries as they rely on providing donors to recover their costs. In the Nordic region, collaboration has already been sought between the registries, however, it is perhaps for political reasons that there is no single registry (Engeland, 2015). Some experts mention that a central European Registry could be established following the example of the Eurotransplant Registry for solid organ donation. In the current situation, the majority of stem cell products in Europe are provided by one registry (in Germany), and from that point of view one could consider that there is already a 'European registry' (see figure below).

[19]World Health Organization guiding principles on human cell, tissue and organ transplantation. http://www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf

Figure 18 the 2012 export flows HPC

The figure shows the export flows between Germany, other EU MS and third countries for HPC donor products (left graph) and HPC-CB (right graph). The ratio (on the arrow) is the number of products going from A to B, for every product going in the other direction.

Further maximizing the numbers of donors in the common (European) HLA groups will not improve their chances of finding a match. The likelihood of being selected from a registry to give a donation is already rather small: annually, stem cells are collected from only 0.07% of all registered donors for the treatment of approximately 13 000 patients.

The question remains: what is the additional benefit for all other European registries if their donors are added to the German registry? For the current donor inventory there would not be much difference, since the 'quality' (age, gender, level of HLA typing) remains the same. The European registries would become more dependent of the German registry. Furthermore, a centralised database with detailed personal information of donors and recipients (including names, addresses, DNA profiles) would raise a serious data security concern and should not be underestimated.

Alternatively, advantages can come from negotiating for cheaper HLA typing (bulk typing can be purchased for a better price) and perhaps centralisation of ICT solutions (reduction of staff and hardware) and quality control, and overhead. The GEMS registries have recently negotiated for a good HLA typing offer by commercial companies.

4.4.2 The future of cord blood banking

Comparable to donor registries, smaller cord blood banks will suffer most from the decline in the number of transplantations using cord blood.

A hybrid cord blood bank is a private institution in which an umbilical cord blood product is stored for possible public and/or private use (Guilcher et al, 2014). The different new modalities that are being tested out (Turkish model, German model, Spanish model) are explained in section 4.2.6. Since it is important that the public part of the unit meets the same quality criteria and regulatory standards as apply to public cord blood banks (O'Connor et al, 2012), hybrid banking allows to demonstrate that quality standards are met under accredited standards (e.g. NetCord-FACT).

The development of hybrid banking, and in particular the involvement of private banks in this area, is a topic of interest and discussion. Hybrid banking could also allow to combine efforts to support all banking activities and make public banks more cost effective, e.g., by outsourcing some public activities to private actors.

However there are some concerns as quality and safety standards can differ for public and private banking (while both being subject to EU legislation), which need to be overcome.

4.4.3 Future applications of stem cell products

Over the last decades, the use of allogeneic hematopoietic progenitor cells has become a treatment option of choice for patients with defined congenital or acquired disorders of the hematopoietic system. However, during the WMDA Spring meeting in 2015 in Istanbul, concern was expressed about two seemingly opposite trends. On the one hand, there has been a decrease in utilisation of unrelated donor and cord blood unit transplantation in areas where the use of transplant has been well established (Boo, 2015, personal communication).

The reason for this trend needs to be investigated; it could be the renewed interest in (less costly) haplo-identical HPCT or a result of fewer economic resources being available to organise relatively expensive HPCT. On the other hand, the establishment of new registries, particularly in emerging countries, seem to indicate that there are still many patients who would benefit from this therapy in all parts of the world. Clinical practice of HPCT is subject to changes that can directly affect the activities of unrelated donor and cord blood registries, both positively and negatively.

It needs to be noted that some of the therapies mentioned in this section might be legally be considered not only to be subject of tissue and cell legislation, but also of the pharmaceutical legislation for Advanced Therapy Medicinal Products (ATMPs). Such classification decisions fall outside the remit of this report. The economic opportunities and challenges from the developments in the ATMP sector are further addressed in chapter 6.

An increasing use of haplo-identical HPCT?

There is a renewed interest in transplantation with stem cells derived from related haplo-identical (i.e. only half HLA-matched) donors. It has been reported that treatment with high dose Cyclophosphamide given early after HPCT to reduce the incidence of GvHD and graft rejection, results in (for leukaemia, at least) outcomes comparable with HLA-identical or matched unrelated donors (Raiola et al, 2014).

If these results lead to a more permanent change of practice, it will initially most likely affect the cord blood banks, with more expensive products. If no matched unrelated donor is available, the choice of the TC would be to proceed with haplo-identical transplantation, rather than cord blood, since the (high) cost of cord blood grafts are subject to discussion. These haplo-identical donors can be found (relatively) more frequently within the family of the patient in need of a transplantation. However, when prospective studies show similar results on overall survival and disease free survival with (relatively cheap) haplo-identical grafts, a change of policy will also affect the activities of the donor registries as well.

Despite overlapping aspects in the procedures for HPC collection, dynamics of care management for family donors differ from unrelated donors. The needs for family donors have only recently been explicitly addressed (Van Walraven et al, 2010). Facilitation of family donor care management is still not optimal, but with an expected intensification of the use of family donors, it is important to address this issue. Family donors have the right to be protected and, as for living organ donation, free voluntary and unpaid donation is to be ensured. However an adequate compensation is necessary. Systems should be in place to determine medical suitability and register any serious adverse

events or complication resulting from the donation procedure (Halter, 2013). If transplantation with family donors increases due to these developments, the settings for collection and donor care will shift further toward the hospitals. Despite legal requirements for reporting of product related Serious adverse reactions and events, the surveillance of donor complications is different. In particular follow-up and registration of donor reactions of family donors is less organized compared to volunteer allogenic donors.

Donor registries, experienced in donor care for allogenic donors, could play a role in the care management (including consent procedures and collection) of family donors. The WHO has addressed the need for protecting the health and welfare of living donors including appropriate long-term follow up (Noel, 2011). Interestingly, a comparable discussion is being held in the field of living kidney donors, where governmental support is considered essential to set up a national system for life-long donor follow-up, a legal requirement put on the EU Member States through EU legislation (Directive 2010/53/EU) (Mandelbrot et al, 2009; Ommen et al, 2011). For small and medium-sized registries, it can be an opportunity to compensate for the loss of allogeneic donor activities by contributing to the family donor care with their expertise in the management of these processes.

Mesenchymal Stromal Cells (MSC)

In addition to hematopoietic progenitor cells, bone marrow comprises a population of marrow stromal cells or MSCs. MSCs have multi-lineage differentiation capacity and are capable to generate progenitors including fibroblasts, osteoblasts, chondrocytes and adipocytes (Ball 2008; Warwick 2012). MSCs are isolated from bone marrow but are also present in a variety of other tissues, including adipose tissue, muscle and connective tissue and foetal liver, bone marrow and blood (Lowsky, 2010). The properties of MSCs make them suitable for immune modulation in the treatment of autoimmune disorders, and are potentially also able to repair tissue. It was shown that multiple infusions of MSC are effective for the treatment of refractory graft-versus-host-disease (Ball, 2013). Graft versus Host Disease (GvHD) is the situation where the donor (graft) cells recognize the recipient (host) as unknown and start to attack the recipient's body. If the disease is not responsive to regular treatment (corticosteroids), this may be fatal for the recipient. The commercial product Prochymal is being evaluated in phase 3 trials for several indications (including GvHD e and Crohn's disease) and is designated by the FDA as both an Orphan Drug and Fast Track product (Osiris.com). Professionals in the field expect that, if a treatment like MSC for GvHD is developed in a hospital setting and considered standard of care after closure of a clinical trial, administration might be continued locally, e.g., under hospital exemption regulation (Slaper-Cortenbach, 2015).

Chimeric antigen receptors (CARs) and tumour-infiltrating lymphocytes (TILs)

Novel therapies to treat cancer patients are sought in (autologous) so-called tumour-infiltrating lymphocytes (TILs) and chimeric antigen receptors (CARs). The basis are the patient's own cells. Tumour infiltrating lymphocytes interact most closely with the tumour cells (they are frequently found in tumours) (Boon, 1997) and are more likely to accurately reflect tumour host interactions than peripheral blood lymphocytes. The development and application of TILs is potentially possible in a wide range of oncological diagnoses, such as refractory breast cancer (Salgado, 2015). However, methods are still experimental and only when clinical validity and utility are demonstrated, might TILs be used as biomarkers in research and clinical trial settings. These complex cellular products for personalised medicine are to be manufactured in good manufacturing practices (GMP) facilities.

Cord blood ex-vivo expansion

Although the number of transplantations with HPC-CB has showed a decrease, expansion of cord blood treatment has shown some success. In a clinical multicentre phase III trial,

patients received ex-vivo expanded cord blood cells. Early results showed a median engraftment time of 8 days (usually 21 days for cord blood). Patients suffered fewer infections and less GvHD due to the fast engraftment. A specific unit with an acceptable match grade is worked-up for a given patient through ex-vivo expansion of HPC-CB, which is still very costly (Querol, 2015, personal communication).

This development will probably not lead to a huge increase in the use of HPC-CB for transplantation, but has given opportunities for cases where no donor and only a CB-unit with marginal or not enough cells is available. On the other hand expansion techniques are also focusing on the culturing of specific cell lines for immunotherapy such as natural killer cells, dendritic cells and T-cells (Cany, 2015).

Other new therapies

The use of targeted (autologous) T-cell therapy is currently under investigation, and if results can be confirmed in larger randomised controlled trials this may ultimately lead to a decrease of the proportion of HPCTs. There is accumulating evidence of the role of HPCT in non-haematological disorders such as autoimmune diseases and some clinical interest is shown in the therapeutic effects of (autologous) HPC in the treatment of solid organs (Sureda et al, 2015)

The development of clinical protocols for additional treatment of relapse, viral reactivations and immunotherapy, often require multiple donations of multiple stem cell products. The majority of these current developments is undertaken in clinical trials.

4.5 CONCLUDING REMARKS AND SUMMARY HPC

- Transplantation with hematopoietic progenitor cells (HPC) has become a standard of care procedure for the treatment of haematological malignancies, immune-deficiencies, and metabolic diseases. Stem cells, donated by either unrelated or family donors or collected from the patient, can be obtained from bone marrow (HPC-BM, under general anaesthesia) or peripheral blood (HPC-A, after administration of hematopoietic growth factors). Umbilical cord blood (HPC-CB) donated to public banks is a third stem cell resource.

- Since genetic markers for tissue typing and matching (Human Leukocyte Antigen, HLA) are inherited from both parents, approximately one third of patients only will find a matching HLA identical donor within their family. The remainder are dependent on finding an acceptable match in the global inventory of voluntary unpaid donors. The chance to find an HLA-identical donor depends on the genetic background of the patient, and varies from 1 in 12 000 to 1 in 50 000.

- Worldwide, currently over 25 million donors and cord blood units are registered with unrelated donor registries, the majority from north western European and north American origin. As a direct result, the access to hematopoietic stem cell transplantation (HPCT) is unequally divided among patients. The main limiting, non-clinical, factor for patients with a non-Caucasian background for not receiving an HPC transplantation, is the lack of donors from ethnic groups that are in a minority in Western countries. Further maximizing the numbers of donors in the common (European) HLA groups will not improve their chances of finding a match. The likelihood of being selected from a registry to give a donation is already rather small: annually, stem cells are collected from only 0.07% of all registered donors for the treatment of approximately 13 000 patients.

- In 2012 there were 33 donor registries active in 24 EU Member States, with a total of 7 499 769 registered donors. The registries are classified as small (< 20 000 donors, n=11) or medium sized (20 000-100 000 donors, n=13), large (>100 000, n=8) or very large (>1 million, n=1). All registries are searchable through Bone Marrow Donors Worldwide, an online search tool, established in 1989, that was designed to simplify international search activities. The main investments in maintaining a donor registry are the recruitment of new donors (including HLA-typing and registration), as well as the costs of an ICT infrastructure. The availability of internationally-compatible ICT systems and software are crucial for the search of suitable HPC donors or products. The ongoing development of a protocol to exchange information between registries in which over 30 registries worldwide participate, has showed the importance of Information and Communication Technology (ICT), and international collaboration.

- In Europe, 33 donor registries were active in 2012 but approximately 80% of all European patients in need of a HPCT received a product donated by a German donor. The German Registry (ZKRD), and in particular their donor centre DKMS, registered over 4 million donors and not only dominate the European field in terms of stem cell provision, but also internationally: 30% of patients outside the EU Member States were also transplanted with a HPC donation of German origin. In terms of self-sufficiency, over 80% of German patients receive products from their fellow citizens, followed by Poland (45%), Portugal (45%) and the United Kingdom (39%).

- The overall probability of obtaining an eventual HPC transplant depends on a couple of factors, which also define the success of donor registries and cord blood units:

    - Finding a matching donor within the family of the patient. The probability of finding such match is expected to increase significantly with the uptake of new techniques like haplo-identical donations.
    - Finding a matching HLA-profile of an unrelated donor within one of the globally accessible registries.
    - The availability of the candidate donor at moment of a possible request. Availability ratios in the EU vary between 27-100% (on average 74%). Donor registries therefore need to organize regular binding to keep in touch with their candidate donors.
    - The medical screening of the candidate donor to donate HPC on request in order to ensure donation does not harm donor or recipient.
    - The access to transplant programs and sufficient resources. The overall cost of an allogenic HPC transplantation varies from EUR 50,000 (family related HPC) to EUR 250,000 (use of unrelated cord blood unit(s)).

- The costs for donor registries are mainly driven by recruitment activities, HLA typing, IT (database costs) and binding activities to keep donor coordinates up to date. Procurement costs (and eventually transplant costs) are made only when a donation is requested for a specific patient. The costs for cord blood banks relate mainly to collection and storage, and need to take account of a very high discard rate of collected units which are of insufficient quality to store. Many of the public registries and banks have no clear view of their costs, so it is unclear whether costs are effectively covered by the fees.

- Provision of stem cell products is the main source of income for Donor Registries; hospitals or insurance companies are charged between EUR 12 000 and EUR 25 000 per HPC donor product. It remains unclear to what extent this fee covers the total cost of managing a donor registry, since insight from the registries in the breakdown of the real expenses is often not published. However, it is often assumed that it does not fully cover the cost of initial investments and registry maintenance. The costs of donor care management and collection might differ

between registries and is also dependent on the scale of activities carried out. Since the majority of HPC donations in Europe are provided by one extra-large scale organisation, the income of small, medium, and even large size European registries is at risk, due to decreasing numbers for donation and distribution.

- Increasing interest and success of using haplo-identical donors (using HPC from non-matched relatives) is reducing the need and demand for unrelated/allogenic HPC grafts from registries and cord-blood banks. Economic and practical factors, like HPC transplantation with related donors is faster and costs less, may also play a role. If the clinical outcome of transplantation with HPC of haplo-identical donors is equal to full matched donors, it is expected to substantially reduce the demand for unrelated donors. This trend adds further pressure on the more expensive cord blood banks and registries.

- Given that the costs are usually incurred a long time before the income is received, donor registries have to carefully manage their liquidity and cash situation. Those organisations therefore also need to reflect on other sources of income, such as from charitable organisations. Without the necessary financial income, registries report that they struggle to improve the quality of their services with just the funding from units distributed, and that they need to seek additional financial support from local government, insurance companies and, gifts, subsidies or charitable funds. Sometimes donors are asked to contribute financially to help cover the cost of registration and HLA typing.

- Cord blood as a source of stem cells is used for specific indications (e.g. in the paediatric setting) or when no suitable adult donor is available. These are often patients from an ethnic minority background, or mixed ethnic background or patients with rare or uncommon HLA typing. Since for the use of HPC-CB, match grade criteria are less strict, it is often possible to identify an HPC-CB for a patient lacking an unrelated or family donor. After donation to a public bank, cord blood units are processed and cryopreserved and are almost immediately available for treatment. In 2012, worldwide over 640 000 cord blood units were stored in public banks, of these 196 997 cord blood units were registered in 23 Cord Blood Registries in 18 EU Member States.

- The establishment of a cord blood bank requires large initial investment. They are often funded by public bodies like blood banks or governments. Cord blood Registries, often representing the interests of more than one cord blood bank, have large infrastructural maintenance costs, and face an additional financial burden, since only 10-15% of the donated material is compliant with the strict quality criteria. In general, cord blood units containing high numbers of total nucleated cells (TNC) are more sought after, since the success of transplantation with HPC-CB depends largely on this indicator. Currently, more than half the global stock of cord blood units are low-cell-count products, which is cost ineffective. Cord blood units are more expensive than adult donor derived HPC, and can sometimes double the price (EUR 15 000-40 000), but still the income of public cord blood banks does not balance with the overall costs. Given that the costs are, again, usually incurred a long time before the income is realised, issues of liquidity and cash flow become more challenging.

- Cord Blood Registries contribute to patient care in particular by providing HPC-CB to patients lacking an unrelated or family donor. Since the probability to deliver a rare HLA typed unit from an adult registry is relatively low, collecting these rare/unique products fulfils a medical need. It is however very expensive, at least from a perspective standalone of the Registry.

- There is an opportunity to look for different opportunities for cost effectiveness. For example, costs for ICT equipment and staff are a heavy burden for small and

medium sized registries, but it is usually not an option to work without ICT personnel. Intensifying collaboration in this area could reduce costs, and be of direct benefit for the smaller and medium sized registries.

- The HPC donor registries and cord blood bank are a public provision, and since it is based upon HLA selection it prevents it from exploiting a normal business model. In the current situation there is a very strong dependency on German donors, and the majority of EU Member States are not self-sufficient in terms of providing national HPC products to their own patients. This has raised some concerns on governance and public accountability of this non-public registry on which a large number of EU patients and healthcare systems are dependent. Furthermore, collaboration between HPC Donor Registries could enhance the efficiency and quality of services, which will be an advantage for patients and take away the need to compete between Donor Registries.

- Besides donating their child's cord blood to a public Cord Blood Bank, in many European countries parents are offered the opportunity to store it in a private Cord Blood bank, as a means for potential lifesaving treatment in the future. These services are offered by commercial enterprises that are charging the parents upfront for the costs of storage (approximately EUR 2 000–EUR 2 500 for processing and storage for 20 years). Contrary to the public banks, private cord blood banks are paid immediately for their service rather than having to wait for the income until the units are selected for treatment for a specific patient. A combination of public and private banking, the so-called hybrid model, is still rare. This is partly due to the differences in ethical, regulatory and quality issues between the public and the commercial activities, and as such creating hurdles for the establishment of hybrid banks. In Europe there are over 120 cord blood banks active in private or family-directed cryopreservation of cord blood. It is estimated that the number of private stored cord blood is at least five times more than the world wide public inventory. To the contrary, the number of distributed grafts is far less.

5 ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)

5.1 FIELD DESCRIPTION

This chapter provides an introduction to the field of reproductive medicine, including types of technologies and treatments, the main drivers for demand, an analysis of the size and organisation of the ART sector, and finally the main actors and international playing field.

5.1.1 Reproductive technologies and treatments

Assisted reproductive technology (ART) is an important part of infertility treatment in EU countries. Often the clinical definition of infertility is used in this context: Infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse." (WHO-ICMART glossary).[20] Some countries use alternative definitions, such as the UK, where infertility is defined as 'failing to get pregnant after two years of regular unprotected sex' (NICE, HFEA 2014). Discussions about the disease status of infertility (especially in relation to reimbursement of ART treatment) are ongoing. Still, infertility is the second most common reason for women in their reproductive years (aged 20-45) to see their general practitioner, after pregnancy. Most ART treatments take place in women between the ages of 30 and 39.

According to the European professional society for reproductive medicine ESHRE, the current prevalence of infertility is estimated to be around 9% worldwide for women aged 20-44, with about one in six couples experiencing infertility problems of some sort at least once during their reproductive years (ESHRE fact sheet 2014). Recent figures indicate that 20-30% of infertility cases can be explained by physiological causes in men, some 20-35% by physiological causes in women. In 25-40% of the cases a problem in both partners is the main reason for infertility, while in 10-20% no cause can be found (ESHRE 2014).

ART, sometimes also called MAR (Medically Assisted Reproduction) refers to all treatments that include in vitro handling of human reproductive cells (gametes) and embryos to establish a pregnancy. This includes, but is not limited to, in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI), intra-uterine insemination (IUI), and cryopreservation of gametes and/or embryos. The box below provides a short overview of current methods that are used to achieve pregnancy by (partially) artificial means.

Estimates for total treatment markets for infertility differ per continent and per marketing report. Some predict a growth in the global infertility industry of up to $ 24.63 billion in 2020, from an estimated value of $ 16.3 billion in 2013 (OBRC 2013). In terms of the segments of infertility treatment, by far the largest share is IVF (73.26%), followed by surgical (10.23%), drug and hormonal (7.28%), IUI (4.88%) and others (4.35%) (OBRC 2013). But while IVF would be the largest market segment, male infertility treatment is the fastest growing (with CAGR of 7.3%, compared to 6.1% for overall infertility treatment market). According to figures from professional society ESHRE, ICSI is now the most common treatment option available, but it's difficult to relate the treatment figures and outcome (or success) rates with market estimates.

[20] See the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009 and ESHRE. See: http://www.eshre.eu/Guidelines-and-Legal/ART-glossary.aspx and http://www.who.int/reproductivehealth/publications/infertility/art_terminology2/en/

Box: ART treatments[21]

In vitro fertilisation (IVF)

Fertilisation of an egg by sperm in a laboratory dish.

Intracytoplasmic Sperm Injection (ICSI)

The process by which an egg is fertilised by injecting a single sperm into the egg.

Intra-Uterine Insemination (IUI)

The insemination of washed semen directly into the uterus. The sperm can originate from the partner (IUI-H for Husband) or from a donor (IUI-D).

Embryo Donation (ED)

The transfer of an embryo resulting from gametes (spermatozoa and oocytes) that did not originate from the recipient and her partner. The embryo is defined as the product up to eight weeks after fertilisation (later it is called a foetus).

Frozen Embryo Transfer (FET)

The procedure in which one or more embryos are placed in the uterus or fallopian tube.

Egg donation (ED)

Egg (oocyte) donation is the process by which a woman donates eggs for purposes of assisted reproduction (typically involving IVF) or for biomedical research. The eggs can be fertilised in the laboratory or unfertilised eggs may be frozen and stored for later use via fast-freezing cryopreservation methods.

In the ART context, partner donation is the donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship; while non-partner donation means that the donor is another person apart from the couple (2004/23/EC).

5.1.2 Driving factors influencing the use of infertility treatments

Several factors play a role in the increased demand for reproductive treatments over the last few decades. Technological innovation has brought a large range of treatment options to the clinic, making infertility or subfertility treatable conditions.

- The introduction of hormonal therapies was followed by improved insemination techniques, and then the introduction of IVF in 1978; still one of the biggest ever breakthroughs in reproductive medicine. It is now estimated that more than 5 million IVF babies have been born worldwide. Via IVF, women with blocked tubes could be treated, which was the original medical indication for fertilisation in the

[21] Definitions are from the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009

lab. Over the years, IVF has become the preferred treatment option for a range of (unexplained) infertility causes, although clinical evidence for these additional indications is largely lacking (Repping, 2015).

- No much later, surrogacy became an option for women who were not able to carry or deliver a child themselves. Today, most surrogacy arrangements are gestational (as opposed to traditional), which means that the pregnant woman is not genetically related to the child. The pregnancy follows after IVF treatment with gametes from the intended parents. Today many of these intended parents include same sex couples.

- The next major breakthrough came in 1991 with ICSI, where fertilisation takes place by injecting a single sperm into the egg. This method overcomes male infertility problems (which more recently were also joined by surgical retrieval techniques to extract sperm directly from the testis, such as TESA and MESA). ICSI is currently the single most performed reproductive technological treatment.

  Today, in every school class in Western Europe there is at least one child born as a result of IVF treatment. In addition to the increased availability of artificial reproductive treatment, demand in the population for these treatments has also become more articulate.

- Several lifestyle factors have b dered as causes for reduced fertility, such as stress, body weight, smoki y transmitted infections, alcohol consumption and substance abuse.

- Age is another common cause of infertility. In Europe, the average age of motherhood has risen significantly over the last decades, and postponement of child bearing is also considered a dominant driver, especially for treatment with donor eggs, in the near future.

- Improved freezing techniques for gametes and reproductive tissue have provided an opportunity to store material for future use for patients undergoing medical treatment (mainly cancer treatment) that may affect their ability to have children. It has also led to novel business models for fertility banking. Female fertility preservation has become especially popular, where (single) women can store their own eggs for future use. In the US, several multinational companies have offered female employees an 'egg freezing package' should they wish to postpone family building, which in turn has caused some media attention and public debate.

- Another popular model that increases access to ART, especially in the UK and US, is egg sharing. This is a specific arrangement by which a woman undergoing IVF makes some of her eggs available for another woman's treatment, or for research, in return for free treatment or significantly reduced treatment costs. Egg sharing has also been mentioned 'half price IVF'.

- The desire for genetically related children has also increased in several groups in society, most notably gay and lesbians. Social 'acceptability' factors may also play a role in increased diversity in family building. Gay marriage has become legal in more Western countries, but the traditional adoption markets are not always accessible to same sex couples, or to solo parents. Single households are more prevalent than a few decades ago, and with individualisation of society, norms and values about the stereotypical or ideal family have changed. More children grow up in non-traditional households. These alternative variations on parenthood, especially same sex adoption schemes and surrogacy arrangements,

have also spurred debate in several countries about legal and biological parenthood.

- The possibilities for pregnancy and parenthood have become both more global and more commercial, with international clinics and (online) brokers offering a diverse range of reproductive treatments and 'one-stop-baby shops' (Geesink & Steegers, 2011). Increased awareness about the possibilities of infertility treatment, lower cost treatment options across the globe and alternative arrangements have democratised the fertility spectrum. The internet and low cost carriers have brought fertility destinations closer to home and made them more accessible to a larger group of patients and consumers that are willing to travel and willing to pay.

- Many governments have decided to reimburse/fund (part) of the costs of ART treatments. While these levels of reimbursement/funding can vary significantly between countries, overall they do help to reduce thresholds for citizens to access relatively costly ART therapies, and therewith increase demand. Governments in several countries also regulate conditions for access to ART therapies, which can reduce demand or drive cross-border activities (see section 5.12.3)

5.1.3 ART establishments in the EU

The way that fertility treatments are organised in EU Member States differs significantly. Some countries offer ART mostly in hospitals, some in private clinics, and others through a combination of organisational and licensing arrangements. In table 26 are the number of tissue establishments per Member State licenced for ART with oocyte, sperm and embryo (source: EUROCET128).

Countries with the largest number of facilities in the EU are: Spain (394 ART clinics), Italy (196 tissue establishments in ART), Germany (182 tissue establishments in ART), France (188 tissue establishments in ART)[22], and the UK (82 licenses to tissue establishments for oocyte, 119 for sperm, 82 for embryo, and 2 for other activities). As these are also the countries with the highest number of women of fertile age this might just reflect the size of population.

Spain, Denmark and Belgium have a relatively high number of clinics relative to the number of females in the reproductive age band (see table 26 and Figures 19 and 20).

Looking at general trends Czech Republic, Slovakia, Bulgaria and Portugal have the highest growth in number of IVF clinics between 2005 and 2010, comparing the total number of clinics as provided by ESHRE. It should be noted though that ESHRE counts IVF clinics and not tissue establishments in ART, as does EUROCET128. The latter can also include establishments only licenced for sperm related activity.

Data do not cover the size of the clinics, however; a high amount of clinics does not necessarily mean a high amount of activity. In section 5.2 the organisational landscape is further described along the lines of the main suppliers of gametes and legal structure of tissue establishments (public/private).

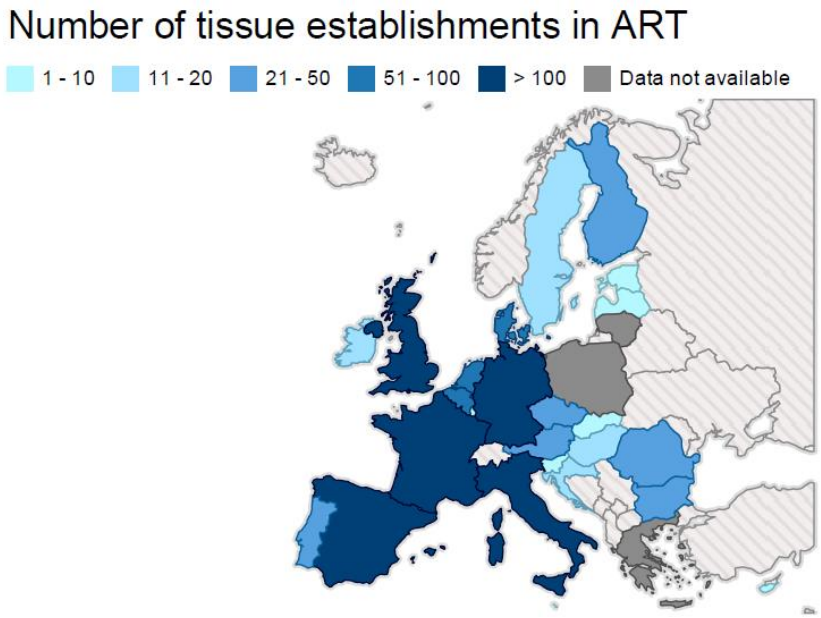
[22] Source: Eurocet128. Please note these numbers cannot be added into a grand total as tissue establishments can be licenced for more than one gamete.

Table 26 Total number of TE in ART and number of IVF clinics

Country	2005 total number of IVF clinics (ESHRE)^^	2010 total number of IVF clinics (ESHRE)^	TE in ART EUROCET 128 (2014)	Total establishments per 1.000.000 women in reproductive age (between 15 and 45) 2012
AT	NA	29	29	16,7
BE	18	18	60	27,3
BG	15	21	32	22
CY	NA	NA	9	42,4
CZ	22	32	39	17,6
DE	118	124	180	11,6
DK	21	20	64*	58,3
EE	NA	NA	5*	18,5
EL	49	50	Not on list	NA
ES	184	160	394*	44,1
FI	18	18	23*	22,6
FR	102	107	188	15,1
HR	7	NA	12	14,2
HU	11	12	13	6,2
IE	7	7	12*	11,6
IT	194	202	196	16,9
LT	3	4	Not on list	NA
LU	NA	NA	1	8,7
LV	NA	NA	6	14,2
MT	NA	NA	2*	23,5
NL	13	13	78	23,5
PL	37	38	Not on list	NA
PT	20	25	27*	12,4
RO	NA	13	23*	5,3
SE	15	16	15	8
SI	3	3	3	7,3
SK	NA	NA	8	6,6
UK	72	72	>100**	NA

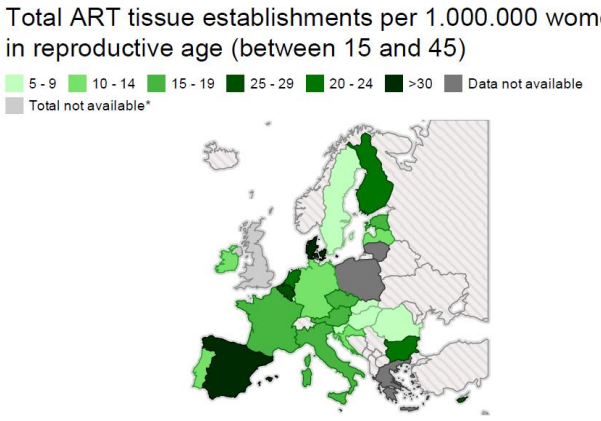
Sources: EUROCET128 unless stated otherwise. *CA verified data **list does not distinguish licence UK: 119 Sperm, 82 Oocyte, 82 Embryo. ^ Nyboe Andersen et al. (2009) ^^Kupka et al. (2014). Please note that ESHRE does not provide any definition of IVF clinic and that in several occasions numbers are not equal to numbers of tissue establishments (TE).

Figure 19 Number of tissue establishments in ART



Source: EUROCET128 provided by DG SANTE, verified by Member States (2015)

Figure 20 Total ART tissue establishments per 1 million women of reproductive age (15-45)



Source: EUROCET128 provided by DG SANTE

* For the United Kingdom the number of ART tissue establishments relative to the number of women in the reproductive age could not be calculated as the total number of tissue establishments cannot be inferred.

5.1.4 Professional societies in reproductive health

The European Society of Human Reproduction and Embryology (ESHRE) is an international, scientific non-profit society for reproductive medicine, registered in Belgium. The main activities of ESHRE are promoting research and spreading the results of research regarding human reproduction and embryology among the general public, scientists, physicians, patient organisations, politicians and other decision-makers throughout Europe. On a practical level, ESHRE aims to promote improvements in the field of medical practice, both in the lab and in the clinic, by organising training, education and advanced medical training activities, by setting up and maintaining databases and by applying methods that promote the safety and quality of clinical and laboratory procedures (Bylaws, 2009).

One of the activities of ESHRE is the European IVF Monitoring Program (EIM). This program was established to collect, process and publish regional data for Europe on direct clinical results and side effects, follow-up children's well-being and also the availability and structure of services in the different countries. This is done by the IVF Monitoring (EIM) Consortium, a group of representatives of national registries on ART collecting data. The results on ART in Europe generated from the European registers are annually published in the official ESHRE journal *Human Reproduction.*

Outside Europe, the main organisation for reproductive medicine is the US counterpart ASRM, the American Society for Reproductive Medicine, which also issues guidelines.

5.1.5 Fertility monitoring

Every year the European IVF Monitoring Program (EIM) from ESHRE collects clinical outcome data (success rates) of reproductive treatments. Around 1.5 million ART cycles are performed each year worldwide, with an estimated 350,000 babies born. The latest figures, published in 2014 but dating from the year 2011, indicate that Europe is leading with 588,629 treatment cycles reported from 33 European countries (around half of all reported ART cycles worldwide). In 2011, France (85,433 cycles), Germany (67,596), Italy (63,777), Russia (56,253), Spain (66,120) and the UK (59,807) were Europe's most active countries. In the Nordic countries, Sweden is leading with 18,510 cycles, followed by Denmark (14,578). Worldwide, the most active countries are Japan and the US. Relatively speaking, in terms of cycles per million population, the Nordic countries and Belgium (but also Iceland and Slovenia) have the highest ART availability, with over 3% of all babies born via reproductive technologies in many of these countries.

Of all reproductive technologies, ICSI is the most common treatment, accounting for around two-thirds of all treatments worldwide, while conventional IVF accounts for around one-third (ESHRE facsheet, 2014).

These monitoring data, which are absolute figures based on number of cycles, need to be understood in the context of population size and, more importantly, the number of women in the fertile age range, to prove meaningful for a comparative analysis of markets and activities.

5.1.6 Fertility drugs and producers

In addition to the tissue establishments in ART, the commercial developers and industrial players provide clinics and patients with the medication, tools and services needed for healthcare professionals to organize and offer fertility treatments.

In terms of the companies manufacturing and supplying (hormonal) infertility drugs, the market is fragmented but both generic drug makers and originator companies providing

specific hormonal treatment are active in the global market. Merck Sereno is the biggest global player, with a share of 40% of the overall infertility market; their product Gonal-F is the most widely used drug for infertility treatment, with recorded sales of $ 700 million in 2013 (compared to $ 297 million for other infertility drugs). Ferring Pharmaceuticals is the second largest player with an estimated market share of 24% and revenues of $ 600 million in 2013. The remainder of the market includes several smaller players, such as Auxilium (12%) and others (17%) (market figures from OBRC, 2013).

From this overview it can be concluded that a few large multinational corporations dominate the market (e.g. Merck Sereno leading, followed by Ferring Pharmaceuticals).

Furthermore, one specific market trend notes that these companies offer packages of pharmaceuticals (hormone therapy) with accompanying equipment, disposables, testing and training of professionals, therewith facilitating the set-up and running of IVF clinics

BOX: Main fertility drugs

Follitropin alpha

Follitropin alpha is used as a fertility medication by women who have not been able to become pregnant as a result of problems with ovulation. Brand names are Gonal-F (manufactured by EMD/MERCK SERONO) and Cinnal-f (manufactured by CinnaGen). Follitropin alpha belongs to the class of medications called gonadotropins. It is a synthetic version of the naturally-occurring follicle stimulating hormone (FSH), a hormone produced by the pituitary gland that helps egg development in the ovaries. Follitropin alpha works by helping to stimulate the development of eggs in the ovaries. It is also used by women having IVF in fertility clinics. It is usually given in combination with a medication called human chorionic gonadotropin (HCG), which causes ovulation to occur by mimicking a natural hormone called luteinizing hormone (LH).

Follistim AQ (follitropin beta)

Follistim AQ (follicle stimulating hormone) is a synthetic hormone that occurs naturally in the body, similar to follitropin alpha. Brand names are Follistim (manufactured by Organon) and Puregon (also manufactured by Organon). This hormone regulates ovulation and the growth and development of eggs in a woman's ovaries. Follistim AQ is used to treat infertility in women who cannot ovulate and do not have primary ovarian failure. Follistim AQ is also used to stimulate sperm production in men. Follistim AQ is often used together with another medication called human chorionic gonadotropin (HCG).

Human Chorionic Gonadotropin (HCG)

Human chorionic gonadotropin (HCG) is a hormone that supports the normal development of an egg in a woman's ovary, and stimulates the release of the egg during ovulation. HCG is an injection used to cause ovulation and to treat infertility in women, and to increase sperm count in men. Brand names are: Novarel (manufactured by Ferring Pharmaceuticals), Ovidrel (manufactured by EMD SERONO), Pregnyl (manufactured by Organon) and Profasi (manufactured by EMD/MERCK SERONO).

Testosterone topical

Testosterone topical contains testosterone, a naturally occurring male hormone. It works by replacing or supplementing the testosterone that is naturally made in the body. It is used to treat conditions in men that result from a lack of natural testosterone. Brand names include AndroGel (manufactured by ABBVIE); Androderm (manufactured by ACTAVIS LABS UT INC); Axiron (manufactured by Eli Lilly), Fortesta (manufactured by ENDO PHARMS), Testim (manufactured by ENDO PHARMS, former Auxilium Pharmaceuticals, Inc.) and Vogelxo (manufactured by Upsher-Smith).

Source: http://www.drugs.com

5.1.7 Brokers

Intermediary organisations (or brokers) have emerged to bring together intended parents and clinics, sometimes to facilitate travel to other Member States (e.g. to Spain or Czech Republic) or third countries (e.g. the US, Northern Cyprus), and offering additional services such as travel and insurance. Relatively new business models include fertility banks (especially egg banks for female fertility preservation, also referred to as 'social freezing') and clinics offering reduced price IVF or egg sharing arrangements (which are especially popular in the UK and the US).

5.2 ORGANISATION OF THE ART SECTOR

5.2.1 Methodological considerations in ART

As also discussed in the introduction chapter, fragmentation of data is particularly problematic for the ART sector. Main data sources such as from ESHRE and EUROCET cover different types of data on assisted reproduction (on outcomes and success rates rather than tissue and cell types for example, or not discriminating between partner and non-partner donation),[23] over different years, in different Member States (but not covering import or export or cross-border distribution) and some covering (part of the) IVF clinics while others count tissue establishments. Overall, reporting rates for ART are improving over the last few years, especially to the EUROCET database, but are still poor or partial, so data are both limited and difficult to collate and compare as they cover different variables.

As a general reflection, data on gamete donors, ART treatment with non-partner donations and flows of gametes are incomplete. There are various factors hindering collecting a complete database on ART: often data on volumes and flows between Member States are not collected at national level by the National Competent Authorities for Tissues and Cells, or large variability exists in the way these data are collected (for example some Member States make a disctinction between IVF and ICSI, others do not, and the same goes for partner and non-partner donation activities). Existing templates are sometimes difficult to fill out.

In order to get better insights into the economic structure and organisation of the clinics, and to complement the existing datasets as discussed above, an extensive internet search has been performed of 180 ART clinics in EU Member States. The sampling strategy is described in chapter 1. It is important to note here that the focus of the internet search was on considering the internationalisation of the markets for tissues and cells for assisted reproductive technologies, which is why the internet search was narrowed down to fertility clinics that addressed clients from abroad. The internet search

[23] For example, ESHRE does not collect data on the number of those donating sperm, oocytes and/or embryos in each Member State; data collection is motivated by getting insight into clinical results and side-effects. Furthermore, ESHRE data do not cover the volume of donations or donated sperm (straws), oocyte or embryos or the flow of gametes between Member States or import from or export to countries outside the EU. With regard to the number of treatments (e.g. cycles or aspiration cycles) for IUI, a distinction is made between IUI with partner donation and that with non-partner donation. For IVF, ICSI and FET, no distinction is made between treatment using partner donation or treatment with non-partner donated sperm or oocytes. The limited coverage of non-partner donation practises makes ESHRE data less relevant for the purpose of this study.

is thus not meant to be representative for ART activities (such as number and size of clinics) within a Member States but to get additional information on the movements between Member States and cross-border reproductive care.

5.2.2 Main suppliers for non-partner gamete donation

Member States indicated the main suppliers of gametes and embryos for non-partner donation, if they are public or private national tissue establishments and whether the main suppliers of gametes are from other Member States or from third countries (source: VUD survey by DG SANTE). These data have been used to build on the landscape of the main organisations. Below is the analysis on the main players in the EU, focusing on size and type of organisation.

In most Member States the main suppliers of gametes and embryos for fertility treatment with non-partner donation (excluding cross-border reproductive care) are national tissue establishments (see figure 21). Cyprus, Portugal, Finland and Romania rely on both national tissue establishments and establishments from other Member States for the supply of gametes and embryos for fertility treatment with non-partner donation. Ireland is the only Member State to rely largely on other Member States and on third countries for supply of gametes. In addition to Ireland, the UK is the only Member State reporting third countries as a main supplier of gametes and embryos, besides national establishments and establishments from other Member States.

The description of main suppliers of gametes for fertility treatments with non-partner donation (excluding cross-border care) are below. These are based on data from the VUDTC survey by DG SANTE, in order to make an additional typology of this organisational activity, which is only part of the activities in the entire ART-sector, as cross-border care is not included (see figure 21).

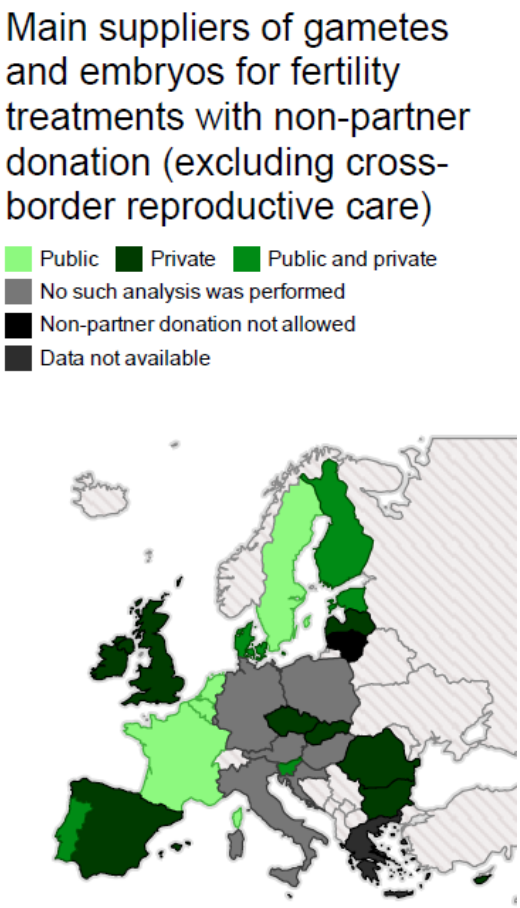
Figure 21 Main suppliers of gametes and embryos non-partner donation

Source: VUDTC survey[24]

It should be noted that the distinction between public and private institutions is not an absolute categorisation but an indication of the playing field. Private tissue establishments are the main suppliers of gametes and embryos for fertility treatments with non-partner donation in the majority of the Member States (see figure 22). Only France, Belgium and Sweden have only public tissue establishments as main suppliers.

[24] Please note this includes only those gametes used in tissue establishments in the Member States and excludes cross-border reproductive care (where citizens travel abroad to access ART treatments)

Figure 22 Main suppliers of gametes and embryos; public, private status



Source: VUDTC survey

5.2.3 Organisation of the sector: Sperm donation and banking (including economic aspects)

Introduction: the emergence of for-profit sperm banking

Sperm banking only developed into a for-profit business after the emergence of technological innovations, such as cryopreservation and artificial insemination techniques, developing alongside advances in logistics and transport, quality insurance and control, preservation and storage facilities. In the post-war period, considerable knowledge was derived from livestock breeding techniques, including bovine artificial insemination, moving across from animal to human reproductive science. The scaling up of insemination volumes and distribution across geographical areas became a reality, working towards more industrial types of reproduction (Cooper & Waldby 2014: 40; Gaudilliere 2007; Clarke 2007).

The first for-profit human sperm banks emerged in the United States in the late 1960s, most notably in California. Following the model used in animal reproduction, the banking of human sperm used liquid nitrogen cryogenics to better preserve the potency and viability of human semen (which was considered frailer using freezing and thawing, compared to animal material). With the advent of HIV/AIDS in the 1980s, the demand

for frozen sperm increased. Material was kept in quarantine for 6 months in order to test the donor for HIV. Thus cryopreservation contributed to quality control and safety regulations, but it also allowed sperm banks to improve and control their distribution and storage, and to build a stock of semen samples for both future use and for distribution to other parts of the country, or internationally. The clinician, that used to be the key intermediary between the provider and recipient of the fresh semen, was now left out of the equation.

In terms of regulation and market activity, different systems for the for-profit banking of sperm emerged in the US as opposed to European nations. In the US, semen was classified as renewable tissue (just like blood and oocytes back in the 1980s) and as such, was not subject to the Organ Transplant Act's prohibition on the sale of solid organs. In other words - and in contrast to European countries - both semen and oocytes could be sold on the market in the US, which further prompted producers to pursue commercial routes into procurement of the material.

In European, on the other hand, donor insemination was allowed in most countries (and the least restricted form of assisted conception in general) but payment of donors was prohibited according to most jurisdictions. Fertility compensation for oocyte or sperm donors was allowed, but payment considered against the widely accepted notion of voluntary unpaid donation in Europe.

Main players in sperm banking (EU and US)

The largest sperm bank in the US, which also caters for the European market, is the California Cryobank (CCB), which has been in business since 1977. According to medical director Cappy Rothman, the bank emerged from an ideology that everyone has a right to children (interview 2010, IG). Currently it holds some 474 donors on file and delivers to most countries in the world. In the last 3 years, CCB has shipped vials to the following countries in Europe: Belgium, Cyprus, Czech Republic, Denmark, Germany, Greece, Ireland, Romania, Russia and Switzerland. It also used to export to Spain, but not so much recently (data from June 2014, ESHRE meeting). The most popular destinations outside the US and Europe include Singapore and the Middle East (including Israel). Other global destinations include Australia, Central and South America and the Caribbean.

In Europe, the largest provider of donor sperm is Cryos, based in Denmark, which has been active since 1987. This company is described in more detail below.

Selection of key players in sperm banking

For the purpose of this study, key players in sperm banking are included based on size, volume (number of donors on file and number of samples) and import/export activity in Europe. These include EU-based organisations and non-EU players (which are all based in the US). The table provides geographic location (country of registration) and the language on the website as an indication of the target audiences of the banks. It also provides the volumes (number of donors and number of samples) as an indication of size. As the Spermbank International in Czech Republic and the European sperm bank in Denmark explicitly state on their websites to offer sperm to other European Member States a brief description of these spermbanks is included in this chapter. More elaborate case study information is provided on Cryos International sperm bank in Denmark because of the dominant position of this specific player (in boxes throughout this chapter).

Table 27 Key players in sperm banking

Member State	Spermbank	Languages on website	# donors in stock	# Samples (per donor)
Czech Republic	Spermbank International	English, Czech	31	Varies: 'under 10' or 'over 10'
Denmark	Cryos International	English, Spanish, French, German, Dutch, Danish, Swedish, Norwegian, Greek, Polish, Bulgarian, Romanian, Finnish, Czech, Russian, Portuguese, Hungarian, Croatian	448	1 to >50
Denmark	European sperm bank (ESB)	English, German	258	0 to 150
Germany	Berliner Samenbank – Berlin Sperm Bank	German, English	NA	NA
Germany	Erlanger Samenbank	German	NA	NA
Greece	Cryogonia	Greek, English	NA	NA
United Kingdom	London Sperm Bank	English	NA	NA
United Kingdom	Birmingham Sperm Bank	English	NA	NA

Source: Internet fertility search Rathenau Instituut (2014)

While Cryos is by far the most dominant actor in the EU market, these banks are used as a reference point for the description of the donation chain in ART, from procurement and donor selection to clinical outcome. What follows below is a further analysis of the donor selection process, screening, matching, compensation and other steps in the donation process.

Case study: Cryos international (DK)

Cryos claims to be the world's biggest sperm bank, holding 170 litres of sperm, a total of 130,000 sperm samples, from 448 donors currently on file, with a donor waiting list of 600 males. It has accounted for over 30,000 births in total (some 2,000 babies a year) and exports to more than 70 countries (Manzoor, 2012; Schou, 2013). It is the core supplier for the European market, followed by the European Spermbank, which is also from Denmark (the 'sperm capital of the world', according to popular media aka 'the Viking invasion'). The main shipping destinations for Cryos include the UK, Ireland, the Netherlands, Belgium, Germany, but also Pakistan and other non-EU destinations. In addition to the Danish branches, and in order to collect more diverse (non-Danish)

sperm, Cryos aims to open banks in Spain, South Africa and India (Manzoor, 2012).[25] The following figure contains data reported by Cryos director Ole Schou on the development of the firm (see figure below).

Figure 23 Development of Cryos sperm bank (DK)

Year	Development	Staff (m²)	Pregnancies
1981	The Sperm Dream	-	-
1983-86	The Sperm Study	-	-
1987	Start Cryos in Aarhus, Denmark (deposit only)	1 (9)	-
1990	First donor	1 (9)	-
1991	First pregnancy	2 (9)	55
1993	Supply to clinics in 19 countries (B2B only)	3 (43)	534
1998	3 departments in Denmark. >200 donors	6 (397)	3,159
2006	Supply to clinics in 50+ countries (Guinness Book)	12 (551)	10,636
2007	Department in New York (B2C only)	19 (706)	12,172
2009	Start B2C from Denmark. >300 donors	32 (1723)	16,186
2013	Supply to private/clinics in 75+ countries. >400 donors (Estimate: only 2/3 of pregnancies are reported)	41 (1723)	22,708 (~35,000)

Source: Cryos presentation Ole Schou (2013)

The European spermbank, also in Denmark, is less than half the size of Cryos International with 258 donors in stock and 0 to 150 samples per donor. Shipping of donor sperm can take place to European and non-European countries; no restrictions in shipping destinations for the semen are stated on the website. Contrary to Cryos, the European spermbank does not deliver directly to individuals but only to clinics. The Spermbank international in Czech Republic is considerably smaller with 31 donors in stock. This spermbank does not deliver directly to individuals either but only to clinics. Clinics in or outside the European Union can contact the spermbank for arranging sperm delivery. Three clinics outside the Czech Republic are mentioned as having active collaboration with the spermbank: two in Denmark (Vitanova and Sellmer Klinik) and one in Macedonia (Pzu Plodnost Hospital). The spermbank does not treat lesbian couples or single women. Single women can however contact the spermbank to undergo treatment with Czech donor sperm in another country, as is stated on the website: 'We offer a private consultancy for women without partner. Single women can undergo a treatment with our semen samples outside Czech Republic' (source: internet search Rathenau Instituut 2014)

Donor recruitment

Sperm donation has been advertised as effortless, quick, without medical risk and not without pleasure. Banks emphasize the altruistic nature of the donation, such as helping

[25] See for a more elaborate profile of Cryos: http://www.theguardian.com/society/2012/nov/02/worlds-biggest-sperm-bank-denmark

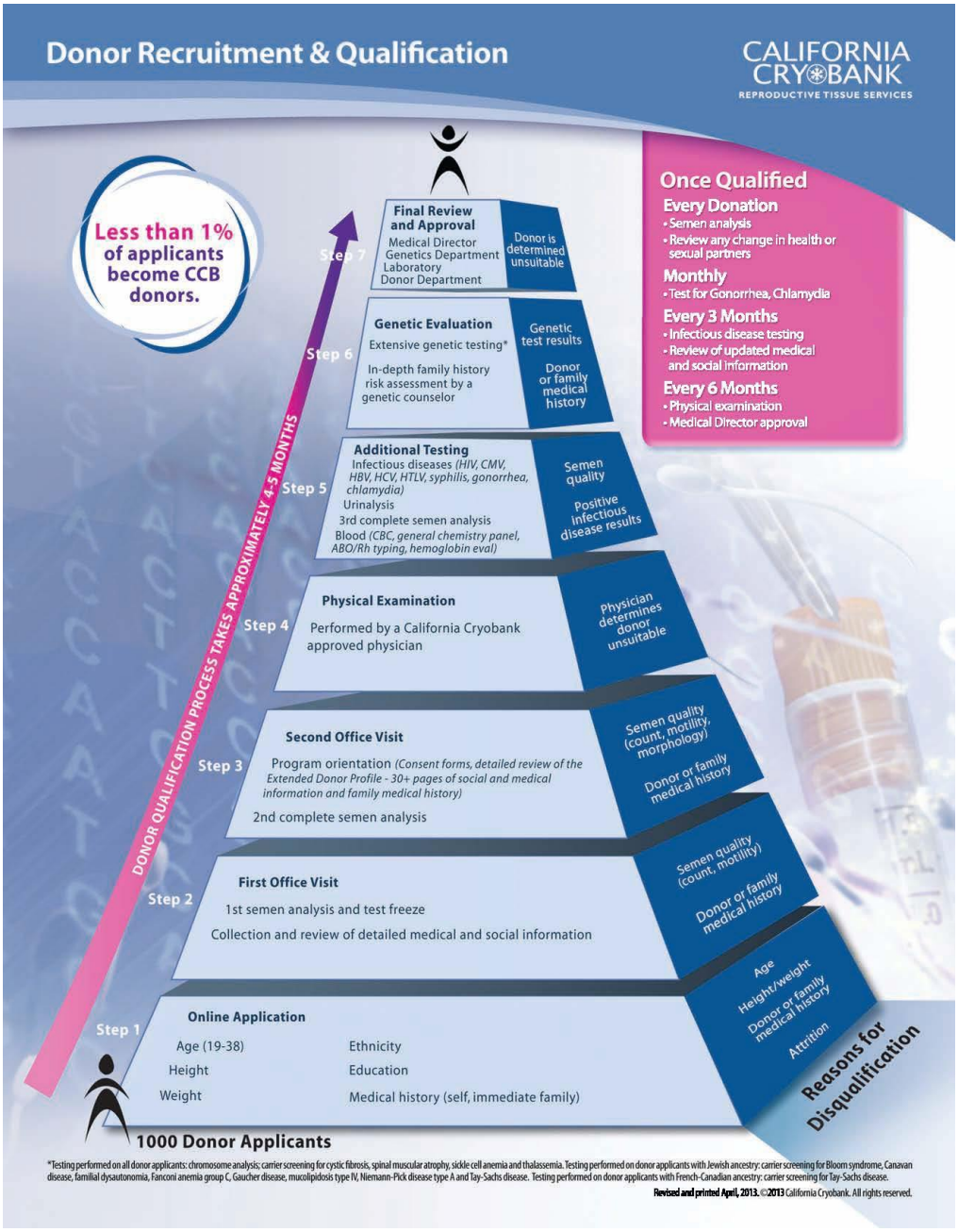
family building or emphasising the right to offspring for all members of society, including lesbian, gay or single clients. Recruitment of donors is generally targeted at young, bright and healthy males, who are willing to enrol and make a longer-term commitment to the bank. Especially this commitment to keep donating over the years is an important driver for success in sperm banking. Sperm banks have prerequisites when it comes to basic characteristics such as height (at least 5'9'' tall, about 1.80 meter), age (usually between 18 and 38 years old, at some banks up to 45), medical condition (in good health), level of education (a bachelors or advanced degree or currently attending a four-year university course) and healthy lifestyle.

Donor selection and screening process

In both the US and EU, the selection process for donors is considered strict, with a range of social and medical criteria that prospective donors should meet. For example, Cryos in Denmark accepts about 10% of prospective donors (the main reason for non-inclusion being 'a bad freezer'). Several banks refer to FDA guidelines and the EU Directive for Tissues and Cells as a mark for quality and safety testing. The degree of testing for especially infectious and hereditary disease varies between banks and across continents, also depending on US, EU or national legal requirements and also based on the biological background of prospective donors. US sperm bank CCB has developed a donor recruitment pyramid that explains the selection process step-by-step and also includes reasons for disqualification (see figure 24). The full donor qualification process takes about 4-5 months.

Screening at most banks is a combination of health and safety checks that are legally required (under Directive 2004/23/EC and national legislation), and social parameters for marketing and sales purposes. Screening includes medical and psychological check-ups and usually involve additional educational and IQ testing. Donor applicants have to provide blood and urine samples, which are typically screened for HIV, hepatitis, sexually transmitted diseases and drug use. Prospective donors might also undergo physical examination and have to meet particular requirements for height, weight, age, ethnicity and sometimes appearance, in addition to self-reported information on religion, education, personal history and so on. Medical and family histories are also checked. The major commercial sperm banks perform genetic testing on donors, and advertise the free genetic screening and consultation as a perk for prospective donors. These tests are usually performed at a later stage in the selection process after physical examination, semen quality testing and disease testing.

Figure 24 Donor recruitment pyramid CCB (US)



Source: CCB Donor Pyramid on website

Case example: Cryos International (DK)

Below is an example of the way in which Cryos (DK) provides screening information on its company website:

"Donors are selected and screened in accordance with applicable national and international rules as well as the internal politics applicable at Cryos at the time of donation. The selection criteria comprise a wide range of aspects in terms of age, risk behaviour and medical history of the donor candidate and his family three generations back as well as of his own children, if any. During the medical examination, the donor candidate will complete a comprehensive medical questionnaire and participate in an interview with set questions aimed at rejecting candidates with a risk behaviour and symptoms of disease. Furthermore, candidates with a family history of serious hereditary mental and physical diseases are also rejected." (Cryos 2014 website)

Donors at Cryos are screened for the following infectious diseases: HIV-1 and -2, HTLV-I and –II, hepatitis B (HBsAg & Anti – HBc), hepatitis C (anti-HCV-Ab), chlamydia, syphilis, gonorrhea, cytomegalovirus (CMV), malaria and trpanosoma cruzi. Hereditary diseases that donors are tested for include karyotype (46XY), sickle cell anemia, familial Mediterranean fever, Gaucher's disease, thalassemia, cystic fibrosis, Tay-Sachs disease, Canavan's disease, familial dysautonomia, congenital adrenal hyperplasia, and carnitine transporter deficiency.

While sperm banks screen extensively for hereditary and infectious disease risk, not all banks cover the same testing methods and screening criteria. Some banks focus on specific genetic conditions of specific donor subpopulations, such as Irish donors (cystic fibrosis) and Jewish donors (several hereditary diseases) or offer specific or advanced testing methods, such as NAT testing (by PCR).

Most demanded donor profile: Bright, healthy and preferably non-anonymous

In Europe, students or higher education donors are welcomed,[26] but contrary to the US not all EU countries' legislation allow donor selection beyond phenotypical characteristics (such as hair, skin and eye colour, height and weight) which is reflected in the availability and compensation of donors across continents. In Europe and the US, the search for non-anonymous donors has intensified, where donor children can get to know the donor at a certain age (e.g. basic information at age 12, and full contact at age 16 or 18).

The EU branch of Cryos in Denmark recruits only national donors; the donor recruitment website is aimed at Danish donors (and is only in the Danish language) while donor profiles, for future clients, are international.[27] Also the European Sperm Bank's recruitment is aimed at Danish donors. Both Cryos and the European Sperm Bank do

[26] In comparison, the Spermbank international in the Czech Republic recuits donors on their English language website. Healthy males between 18 and 38 with at least secondary education are asked to apply. On individual basis also donors between 38-40 and students older than 18 may be accepted, as listed on the website.

[27] Below is an excerpt from the Cryos International website (translated from Danish): 'We are looking for physically and mentally normal, healthy men of all races and nationalities. You can choose to be an anonymous or non-anonymous donor. Age 18-45 years. Non-anonymous donors under 25 years only by special doctor's approval. We are looking for all types of sperm donors taller than 170 cm, but especially non-anonymous. That is where the child can get access to the identity of a donor when they are 18 years old. We are also seeking sperm donors of different ethnic background than Danish - such as donors of African, Asian, Turkish or other Middle Eastern origin. Even if you do not belong to any of the above groups, you may submit an online sperm donor application. Then you will be registered on a waiting list and we will contact you as soon as we need you." Source: Cryos DK website

receive sperm from their US franchise branches though for the EU market. The age range is slightly broader than elsewhere (from 18-45 years) and non-anonymous donors from African, Asian, Turkish or other Middle Eastern origin are particularly invited to apply.

In addition to medical and lifestyle considerations, the motivation of the donor is also queried during the selection process, and an estimation made of the likelihood that the donor will stay loyal to the bank for prolonged time, e.g. to stay within the program for years rather than months in order to compensate for the cost of the screening and selection process (Almeling 2011, Mohr 2015).

Once an applicant is deemed suitable, which is usually only after several months for safety testing purposes, a contract between donor and sperm bank is signed in which the donor commits to (typically) 12 or 18 months of semen production. The donor provides one or two units each week (and a maximum of three with most banks) and commits to a healthy life style, including safe sex but also periods of abstinence in order to maintain high sperm count. Donors are expected to disclose information that may have a negative effect on sperm quality, such as sexual activity, drug use, illness or medication. In return, sperm donors receive a flat rate of, typically, $100 per useful ejaculate in the US. In Europe prices are more variable, with an average of DDK 300 and a maximum amount of DDK 500 (about EUR 67). Section 5.9 provides more details on donor compensation schemes for both semen and oocytes.

Processing and storing sperm

Donor sperm samples are usually washed by the sperm banks to extract the sperm which is then frozen and stored for future use in liquid nitrogen tanks. These tanks are to be filled regularly and require continuous monitoring.

One sample typically contains between 1-20 straws, each of which holds between 0,4-1.0 ml of sperm. While there is some discussion on upper limits of sperm storage, success cases have been reported with sperm stored for over 20 years. Also laboratory techniques have improved in order to select and enrich motile and functional spermatozoa from the ejaluculate; from washing procedures to migration, filtration and centrifugation for ART treatments (see also WHO 2014, Henkel 2013). Of these techniques, the conventional 'swim-up' method is considered simple, cheap and not requiring highly specialised skills or equipment (Henkel, 2013). Other techniques may require equipment only commercially available (like tubes for migration of the sperm).

The semen must be processed in a separate laboratory, with a separate room with a laminar air flow. According to the EU Tissue and Cell Directive, sperm processing should take place in Grade B air. This may imply additional cost factors to consider for the maintenance and daily operations of clean room facilities, as also discussed in chapter 3 on replacement tissues.

As much ART activities concern partner donation, discard rates are relatively low. Stored gametes and embryos have very long expiry periods, and therefore few are lost. However in case of successful pregnancies, remaining (rest) gametes or embryos might be stored for a very long period.

Home insemination and direct to consumer sales

Until recently, sperm banks only delivered samples to clinics for insemination by a health professional, and not to individual consumers for self-insemination. Our investigation demonstrates that this is still the case for most sperm banks. For example, the European Sperm Bank (ESB) in Denmark allows individual consumers to order samples online, but only for insemination in a registered clinic. The bank does not deliver to home addresses in order to secure registration in donor registries (following legal requirements of Member States).

Cryos International, the other main bank from Denmark, does however deliver directly to consumers without intervention by a clinic or health professional. Indeed, the last few years have seen an increase in delivery to home addresses for self-insemination by women. The development of cheaper and smaller transport and shipping devices for optimal quality of distributed sperm may add to further ease of home insemination. This home insemination brings emerging direct-to-consumer delivery (and marketing) rather than delivery to clinics. Almost 50% of sperm orders from Cryos are for home insemination according to national company representatives (2014).

Some concerns have been raised relating to regulatory oversight, lack of follow-up data on clinical outcome and pregnancy rates, and potentially limited traceability. Some countries have donor registries that require the clinician to administrate the donor's identity for future reference by the donor's offspring; e.g. the Netherlands only allows non-anonymous donation via a donor registry for gamete donation (see section on donor anonymity for an overview per Member State). Others argue that registration of pregnancies directly by consumers ordering on the company's website is more reliable than reporting via clinics that inseminate the semen. Cryos claims that home insemination is not against the law, as donor registries only apply to clinicians that inseminate the sperm, and this is not applicable for home insemination.[28] Many other online guides or instruction manuals on DIY or home insemination are available.[29] The fact that shipments of sperm often goes to other EU or third countries, complicates this situation.

Cost structure of a sperm bank

A cost structure estimate could be provided based on recent calculation of costs for donors in Sweden.

Table 28 Cost divisions in a sperm bank

	No distribution	Incl distribution
Donor recruitment	16%	14%
Testing, donors (viral screening, medical and social screening)	21%	17%
Processing (sperm collection, and processing) and storage	63%	54%
Distribution	0%	15%
Total	**100% (*100*)**	**100% (*100*)**

[28] Cryos has developed a special information page with an instruction manual for home insemination:

> "Single women or same sex couples may not be allowed treatment, there may be requirements concerning specific tests or special documents or a ban against treatment using Anonymous donors, or against treatment using Non-anonymous donors or other bans and requirements. As far as Cryos is aware, such legislation only applies to treatment by doctors and other healthcare professionals. In other words, home insemination is not covered by any of the above legislative restrictions and must therefore be deemed legal." (Cryos, 2014 website: http://dk.cryosinternational.com/donor-sperm/home-insemination)

[29] See for example http://www.free-sperm-donations.com/order_self_insemination_kit.htm

It needs to be noted that, in an ordinary IVF clinic, third party donor gametes are very seldom distributed to other clinics. If they are distributed (within the country), the sum is here estimated to 15% of the total cost. Percentages above are calculated without and with distribution costs.

Costs for application are not included in this assessment.

Volumes sperm

When analysing the donation and treatment practices in different EU Member States, a large variation can be observed between countries with respect to the number of sperm donors and the number of treatments with donor sperm. For this report, the source used for the analysis was the 2012 data from EUROCET, or if data was not available, from 2011, as this database distinguishes between partner and non-partner donation. Data on flows of sperm from the Implementation survey was used if available. Furthermore, National Competent Authorities for Tissues and Cells were asked to verify or add data. As indicators for the volume of activity in sperm donation related activity, a combination of the following numbers were used:

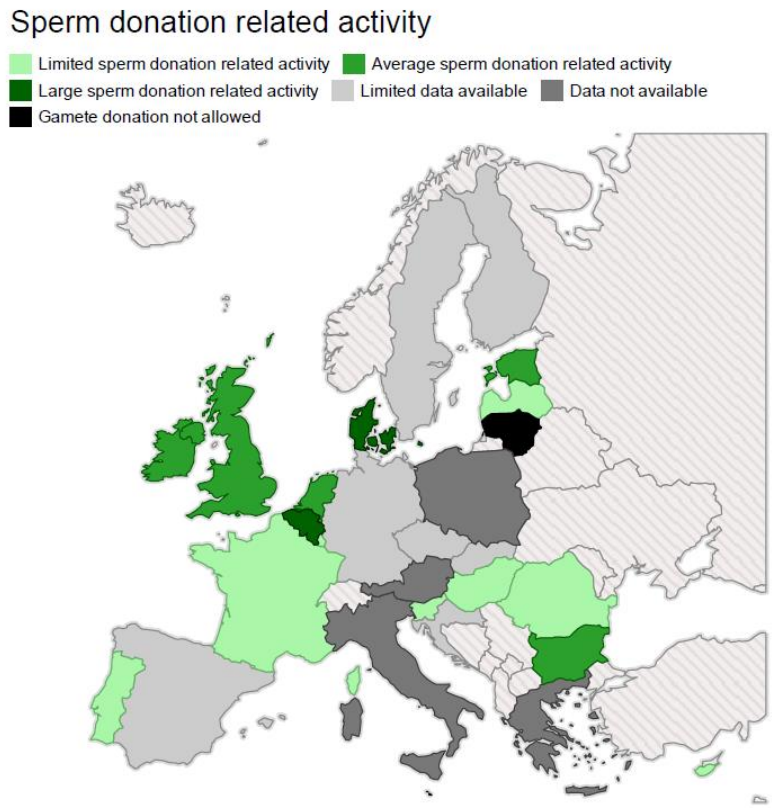
- The number of donors, donations and donated sperm within each Member State;
- The number of received sperm from other Member States, and imported sperm from third countries;
- The number of distributed or exported sperm;
- The number of treatments with donated sperm: IUI with non-partner donation and IVF and ICSI with non-partner donation. We have added up IVF and ICSI with non-partner donation as distinguishing between these types of treatment does not add to our analysis.

For this analysis a rather broad definition of sperm-related activity was therefore used, as it includes also the number of received and imported sperm and the number of treatments with donor sperm. Data compiled in this way gives an indication of which countries are relatively more active, have average activity or have limited activity relative to the number of women in the fertile age. Do however note that the reasons for being classified as having more/average/limited activity can vary. Data are for the year 2012 where available, or from 2011 when 2012 data were not available.

To give an indication of volume Member States were categorized into large activity, average activity and low activity based on these indicators relative to the number of women in the fertile age (following the Eurostat fertility definition of women between 15 and 45 years). The year of reference is 2012 where available.[30]

[30] The most recent data available for EUROCET is for the year 2012, but not for all Member States these 2012 data are available. In those cases we used EUROCET 2011 data or data provided to us by the national Competent Authorities through the competent authority survey (Rathenau Instituut 2014). All data has been double checked by the Competent Authorities of responding Member States in 2015 and if updated data were available we have used these in our final analysis. Furthermore in the EUROCET database numbers on cross-border distribution and import and export are provided in as far as they are available. There are many limitations to be considered when using these data sources (see introduction paragraph).

Figure 25 Sperm donation related activity Europe



Source: EUROCET 2011, 2012; Economic landscape survey NCATC (2015), data from 2011

Integrating the findings on the number of donors, donations or donated sperm straws with the number of received and imported sperm straws provides the following classification:

Denmark and Belgium have **relatively large sperm donation** related activity. Denmark has by far the highest amount of donated sperm, both in absolute terms (42,223 donated units) as in relative terms (3,845 units per woman in reproductive age).[31] Belgium reported the highest number of sperm straws received from other Member States.[32]

Bulgaria[33], Ireland[34], the Netherlands[35], Estonia[36] and the UK[37] have **average sperm donation** related activity relative to the number of women in the reproductive age. The

[31] Denmark has by far the highest amount of donated sperm, both in absolute terms (42,223 donated units) as in relative terms (3,845 units per woman in reproductive age). Denmark furthermore has the highest amount of imported sperm from third countries (3,000 units); no sperm is received from other Member States. The amount of sperm distributed to other Member States (45,224) and exported to third countries (2,662) is higher than the amount donated by sperm donors in Denmark. Also, in terms of treatments with donor sperm, Denmark has considerable activity. Looking at IUI with donor sperm, Denmark has the most cycles started, for example 2.6 times the number of cycles of the UK in absolute terms (Denmark: 10,612; UK: 4,015) which is considerably higher when the number of cycles per woman in reproductive age is compared (Denmark: 0.966; UK: 0.03).

[32] Even though Belgium can be considered as having a shortage in sperm, it is classified as having high sperm-related activity. Belgium has an average number of sperm donations (1,447 donations) but reported the highest number of sperm straws received from other Member States (9,056 straws). The number of treatments with donor sperm is not available. No sperm is exported and only a limited amount of sperm is distributed to other Member States (37 straws).

[33] Bulgaria has two thirds of the number of donations compared to Belgium (Bulgaria: 932; Belgium: 1,447). Relative to the number of women in reproductive age however, the number of donations is similar (for Bulgaria:

Netherlands has a relatively high number of donations compared to other Member States of which data are available.[38] Bulgaria and Estonia might not have high number of donors, donations or treatments in absolute terms, but have average activity relative to the number of women in the reproductive age. The UK and Ireland are using relatively much imported sperm compared to other Member States of which data are available.

Countries with **limited sperm donation** related activity are Hungary, Cyprus, Latvia, Luxembourg[39], Portugal, Romania, France[40] and Slovenia. France has the lowest number

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0.063 sperm straws per woman in reproductive age and for Belgium: 0.066). Bulgaria however receives far less sperm compared to Belgium (Bulgaria: 287 straws; Belgium 9,056 straws) and is therefore classified as average.

[34] Ireland does not facilitate non-partner donation from Irish sperm donors due to its small population and absence of an overarching (ethical) ART framework. Legislation is however under development and is expected to be implemented within 3-5 years. Ireland is classified as having average activity since Ireland receives a considerable amount of sperm from Denmark (1,270 straws) and imports some sperm from the USA (25 straws). The number of treatment cycles with donated sperm relative to the number of women in reproductive age (IUI, IVF & ICSI) is similar to the UK, Bulgaria and Estonia.

[35] In the Netherlands the absolute and relative number of sperm donations is highest after Denmark (compared to other Member States for which these figures are available). The number of sperm donors is unknown. As in the Netherlands the number of children that can be born from one donor is the highest in Europe (25 children per donor), the number of donors might be considerably lower. Furthermore, the number of couples treated with IUI with donor sperm and number of cycles started with donor sperm relative to the number of women in reproductive age is highest after Denmark and slightly higher compared to Bulgaria, UK, Ireland and Estonia. It should be noted this data is not available for Belgium. However the number of couples having IVF or ICSI treatment with donor sperm or the number of cycles started for IVF & ICSI for donor sperm relative to the number of women in reproductive age, is lower in the Netherlands compared to Estonia, Bulgaria, UK, and Ireland (for Belgium and Denmark this data is not available).

[36] Estonia has limited sperm donors in absolute terms (53 donors). The number of donations (596 for Estonia) relative to the number of donors is higher than for other Member States for which these figures are available. This could indicate donors in Estonia donate more frequently compared to other Member States for which this data is available (Bulgaria, Cyprus, France, Latvia and Slovenia). Relative to the number of women in reproductive age, the number of donations in Estonia is the largest compared to Member States for which this data is available (Belgium, Bulgaria, Cyprus, France, Hungary, Latvia, Netherlands, Slovenia and Slovakia). Furthermore, although in absolute terms the number of couples treated with donor sperm for IUI (74) or IVF and ICSI (141) is not considerably high, in relative numbers Estonia has an average number of couples treated with donor sperm.

[37] For the UK, no data on donors, donations and the number of sperm donations is available (only the number of donors recruited each year is available, not the total number of donors on the website of HFEA) but sperm received from other Member States (1,003 straws) and from third countries (1,104) is considerable. In absolute terms, the UK has the highest number of IUI cycles started with donated sperm (4,015) from Member States reporting and the second highest number of couples treated with IVF and ICSI with donor sperm (1,917). However the UK is classified as average since relative to the number of women in reproductive age the number of IUI, IVF and ICSI treatments is not considerably high and comparable to Bulgaria, Ireland and Estonia, for example.

[38] Having non-anonymous donation as a legal context, the number of donations would have been expected to be lower. However only the number of donations is known, not the number of donors; since the Netherlands has the largest number of children that can be conceived from one donor (25), the ration of donations per donor might also be relatively high, explaining the relative large number of donations.

[39] Luxembourg had no sperm donors, donations or donated sperm in 2012 and did not receive or import sperm.

[40] France has a considerable number of sperm donors (235) but relative to the number of women in the reproductive age have the lowest rank (0.002). This is also the image that arises from the figures in the annual report of the Agency the la Biomedicine, as can be seen on their website www.agence-biomedecine.fr (French National Competent Authority for tissues and cells).

of sperm donors compared to women in the reproductive age, followed by Cyprus, Hungary, Latvia, Slovenia, Portugal and Romania. Luxembourg has no sperm donors at all. In these countries also the numbers of received and imported sperm are low (Cyprus, Latvia and Romania) to zero (Luxembourg, Hungary and Slovenia) or unknown (France). Portugal does not import sperm, but sperm received from other Member States is unknown. Consequently numbers of ART treatments with donor sperm are very low.[41]

Countries with **no sperm donation** related activity: in Malta and Lithuania, gamete donation is prohibited. In Italy, gamete donation was prohibited at the time of data collection but the legal situation changed in 2015.

For Czech Republic, Germany, Finland, Croatia, Slovakia, Spain and Sweden the picture remains unclear due to limited data. Available data suggest average activity for Czech Republic and Germany (based on numbers of received and imported sperm), average activity for Finland (based on the number of IUI treatments with donor sperm) and average to high activity for Spain (based on the number of IUI and IVF& ICSI treatments with donor sperm).[42]

Furthermore available data suggests limited to average activity for Sweden (based on the number of donors and on the number of couples receiving IUI treatment with donor sperm), limited activity for Slovakia (based on the number of donations) and for Croatia (based on numbers of received and imported sperm).[43]

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[41] Cyprus, Hungary, Latvia, Slovenia, Portugal and Romania rank lowest in terms of donors, donations or donated sperm relative to the number of women in reproductive age. Hungary and Slovenia also do not receive sperm from other Member States or import sperm from third countries. Cyprus, Latvia and Romania receive some sperm from other Member States but this is less than other Member States who receive sperm (40 straws for Cyprus, 177 straws for Latvia and 166 straws for Romania). Portugal does not import sperm but the number received from other Member States is unknown. For France, both the number of imported and received sperm is unknown.

France, Latvia, Luxembourg, Portugal, Romania and Cyprus rank lowest in terms of IUI treatment with donor sperm relative to the number of women in reproductive age (e.g. couples treated, cycles started or aspiration cycles). Luxembourg had no donations nor received nor imported sperm in 2012. Treatments with donated sperm might be done with cryopreserved sperm donated in previous years. For Slovenia and Hungary this data is unavailable.

France, Hungary, Latvia, Portugal, Romania and Slovenia rank lowest in terms of IVF & ICSI treatment with donor sperm relative to the number of women in reproductive age (e.g. couples treated, cycles started or aspiration cycles). Cyprus ranks slightly higher.

[42] For Czech Republic, Germany, Finland, Croatia and Spain the number of donors, donations or donated sperm is not available. For Czech Republic, Germany and Croatia, numbers of imported and received sperm are available. These suggest average sperm donation related activity for Czech Republic (598 received and imported sperm straws) and Germany (1,007 received and imported sperm straws) and limited activity for Croatia (no imported or received sperm straws). For Czech Republic, data on IVF and ICSI treatment with donated sperm suggests average activity (737 cycles started). For Germany and Croatia, no data on treatments with donor sperm is available. For Spain and Finland, the numbers of received or imported sperm are not available but data on the number of treatments is available. For Spain this suggests average activity for IVF & ICSI with donor sperm (3,812 couples treated) and average to high activity for IUI with donor sperm (7,035 aspiration cycles) in both absolute terms and as relative to the number of women in reproductive age. For Finland IUI treatment with donor sperm (1,049 cycles started) also suggests average to high activity relative to women in reproductive age. IVF & ICSI data is not available.

[43] For Sweden and Slovakia, data on the number of donors, donations or donated sperm is available (647 donors for Sweden and 121 donations for Slovakia). For Sweden this suggests average activity, for Slovakia this suggests limited activity. For Sweden, the number of couples receiving IUI treatment with donor sperm is known (133 couples), suggesting limited activity relative to the number of women in reproductive age (0.01).

For Austria, Greece and Poland, no data is available on numbers of donors/donations or treatments with donor sperm.

Further details on the situation per country are provided in annex 3/B1 on ART.

The volumes of donated sperm and number of treatments are tightly knit to a couple of factors, which need to be taken into account for understanding the extent of activities per country:

- The regulation of ART treatment: countries which do not allow sperm donation obviously have limited volumes of donated sperm;
- Access to treatments in terms of who has access (for instance age restrictions, marital status, sexual orientation)
- Reimbursement of treatment (phase, amount or extent of reimbursement)
- Regulation of anonymous or non-anonymous donation.

For some countries, the figures covering the number of donors and/or number of treatments with donor sperm are not available but data on access and reimbursement are. A relatively restrictive access and reimbursement policy can be an indicator of limited donation activity and limited activity in treatment with donor material and vice versa, as discussed later on in this chapter.

Cross-border distribution, import and export of sperm

Very limited data is available to indicate flows of gametes between Member States and to or from third countries. We have used absolute numbers as indicated in EUROCET 2012, added with EUROCET 2011 and verified by the Member States.[44]

A few Member States do not have any cross-border exchange, import or export of sperm: Croatia, Hungary, Luxembourg, Portugal and Slovenia.

Countries that depend for a large part on sperm **received** from other Member States (relative to donations in their own Member State) are Belgium, Bulgaria, Cyprus, Estonia, Latvia and Romania. Ireland depends fully on other Member States and on third countries.

The Czech Republic, Germany, Finland and the UK also receive a considerable amount of sperm straws from other Member States but the number of donors in those individual Member States are not known and therefore the relation between donation in the individual country and received sperm cannot be stated.

[44] 15 Member States report data on received sperm (10 receive sperm from other Member States and 5 do not); 15 Member States report data on imported sperm (5 import sperm and 10 do not). 16 Member States report on distributing sperm (8 distribute sperm and 8 do not); 18 Member States report on exporting sperm (5 export sperm and 13 do not). It should be noted that the Czech Republic and Germany make no distinction between imported, and received sperm or between exported and distributed sperm. In the EUROCET database, no distinction is made between which countries gametes are received or imported from or distributed or exported to. In the survey of National Competent Authorities for Tissues and Cells for this report, Member States were asked to specify the countries from which they received or distributed gametes. No additional information was provided. Most Member States that responded to the survey indicated these data are not collected at the national level. In the implementation survey by DG SANTE, some Member States have specified countries for cross-border distribution, import and export. Member States were asked to verify these data in the country factsheets.

The Member State of origin is reported by only a few respondents but some Member States reported that all of the sperm they received from cross-border exchange came from Denmark. This is the case for Bulgaria, Estonia, Finland and Ireland.

Only very few countries report importing sperm from third countries; this is the case for Ireland (25 sperm straws from the USA), the UK (1,104 sperm straws from Australia, USA and Uruguay) and Denmark (3,000 sperm straws origin not specified, a.o. from the US). For Germany and the Czech Republic, the picture remains unclear as no distinction is made between cross-border exchange, import and export.

For Austria, Spain, France, Poland, the Netherlands, Sweden and Slovak Republic, the number of sperm straws received from other Member States and imported from third countries is unknown.

Few countries report **distributing** sperm to other Member States. Denmark distributes a large quantity of sperm to other Member States (45,224). Other countries that do report distribution of sperm report only small numbers; these countries are Belgium (37), Cyprus (27), the Netherlands (157), Sweden (12) and the UK (42).

Ireland also exports sperm (776) but this is sperm for partner donation in clinics outside the European Union, as part of an oocyte donation programme between an Irish clinic and an Ukranian clinic. Germany reports a considerable volume of distributed and/or exported sperm straws (325) but no distinction is made between cross-border distribution and export.

All of these countries also receive sperm from other Member States or third countries besides distributing sperm.

This poses the question for what reasons sperm is distributed considering shortages in an individual Member State. The Czech Republic reported small numbers of distributed or exported sperm (5 straws) but also has a commercial sperm bank with large numbers of donors in stock, offering shipment of sperm to other Member States. Data on distributing countries can also be inferred from information on received sperm. Data concerning received sperm by other Member States indicated that other Member States distribute sperm. Belgium reported receiving sperm from Italy and Spain alongside Denmark, Germany and the Netherlands. Only very few countries report exporting sperm to third countries; this is only the case for the UK (47 straws to Australia, USA and Uzbekistan) and Denmark (2,662, destination not specified). Germany and the Czech Republic make no distinction between cross-border distribution and export.

For Austria, Estonia, Finland, Spain, France, Poland and Slovak Republic, the number of sperm straws distributed to other Member States and export to third countries is unknown. For Finland, the number of sperm straws distributed to other Member States is unknown but export to third countries is 0.

From these data the **key messages** are the following:

- Denmark and Belgium have high numbers of sperm related activity relative to the number of women of fertile age.
- There is considerable cross-border exchange of sperm within Member States, with many states reporting to receive sperm but few countries reporting to distribute sperm.
- Denmark is the most important distributer of sperm in the EU, but other Member States also distribute sperm.
- Import and export of sperm is very limited for reporting countries. Except for Denmark, which imports and exports considerable quantities of sperm. Only

Ireland and the UK report importing sperm from the US. This raises questions as to the importance of US sperm banks for the EU market, and whether or not these banks are facing competition from the commercial Danish sperm banks, and whether import has dropped. Another option is that non-reporting countries are importing sperm from US sperm banks. For example, it is known that both the European Sperm Bank and Cryos International in Denmark import sperm from their franchise branches in the US and sell this on the EU market. Also both banks sell their sperm directly from their US affiliation within Europe.

- A disclaimer on the data is necessary, as information is limited. Data are either unavailable for a significant number of Member States, or incomplete, and data on cross-border distribution, import and export are hardly specified per country, making it impossible to map flows of gametes.

Cost and compensation of sperm donation

Some variety exists in compensation schemes for sperm donors between banks, but most notably, between the EU and third countries, including the US. In legal terms, different concepts are used as well. This section takes the EUTCD Directive for quality and safety as guiding framework. In this Directive, article 12 states:

Article 12: Principles governing tissue and cell donation

- Member States shall endeavour to ensure voluntary and unpaid donations of tissues and cells.
- Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation. In that case, Member States define the conditions under which compensation may be granted. (2004/23/EC:12)[45]

Thus, according to the EU Directive, only making good the expenses and inconvenience are covered by the compensation. The opposite occurs in the US where donors receive payment and benefits, which means that the amount available for compensation covers more than just expenses (such as loss of income or travel costs). This also relates to the US legislation in which semen was classified as renewable tissue (just like blood) which was not subject to prohibition on sale, and which spurred for-profit banking and commercial enterprises in this clinical domain. In this section the term compensation is used in the context of the Directive, while payment refers to (usually larger) monetary amounts that are not proportionate to making good the expenses. Benefits often take the format of movie tickets or food vouchers.

Sperm donor compensation

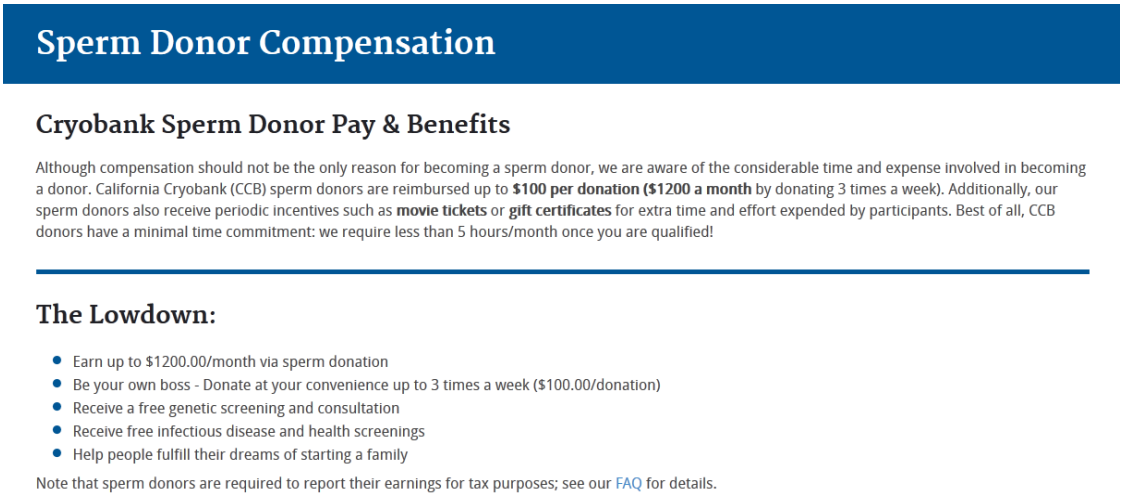
This section compares the US sperm banks to those in the EU. The rationale for this comparison is that US banks have been 'in business' for a while, with an increasingly commercial model, while until recently, most EU banks were public sector (oriented).

In the US, banks advertise that donors may benefit up to $1,200 per month, which translates into three qualified donations per week. On average, $100 is paid per unit of quality sperm. Donors with extended profiles (who reveal more personal information) and

[45] Recital 18 of the Directive underlines the voluntary unpaid character of donation: "As a matter of principle, tissue and cell application programmes should be founded on the philosophy of voluntary and unpaid donation, anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient. Member States are urged to take steps to encourage a strong public and nonprofit sector involvement in the provision of tissue and cell application services and the related research and development." (2004/23/EC: 18)

non-anonymous donors can get bonuses. Donors are paid by check or cash, and are often anonymous, but the donor still has to pay tax on this amount. In addition to monetary payment, donors can get in-kind benefits such as movie tickets and gift certificates. No payment is made for units below the required levels of potency or volume. Cryobank describes its donor benefits as follows:

Figure 26 Donor benefits Cryobank (US)



Sperm Donor Compensation

Cryobank Sperm Donor Pay & Benefits

Although compensation should not be the only reason for becoming a sperm donor, we are aware of the considerable time and expense involved in becoming a donor. California Cryobank (CCB) sperm donors are reimbursed up to **$100 per donation ($1200 a month** by donating 3 times a week). Additionally, our sperm donors also receive periodic incentives such as **movie tickets** or **gift certificates** for extra time and effort expended by participants. Best of all, CCB donors have a minimal time commitment: we require less than 5 hours/month once you are qualified!

The Lowdown:

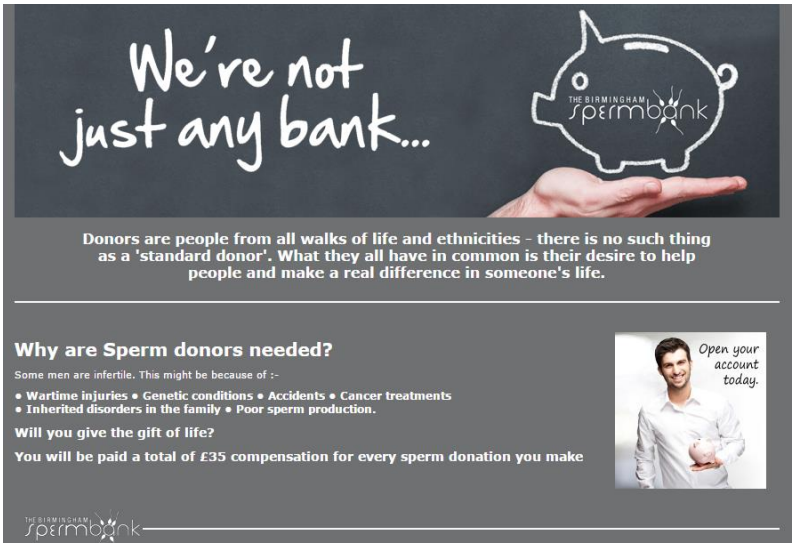
- Earn up to $1200.00/month via sperm donation
- Be your own boss - Donate at your convenience up to 3 times a week ($100.00/donation)
- Receive a free genetic screening and consultation
- Receive free infectious disease and health screenings
- Help people fulfill their dreams of starting a family

Note that sperm donors are required to report their earnings for tax purposes; see our FAQ for details.

Source: California Cryobank website

A bank that recently opened its doors in the EU is the Birmingham Sperm Bank, which advertises a GBP35 compensation for every donation.

Figure 27 Donor benefits Birmingham Sperm Bank (UK)



Source: Birmingham Sperm Bank website

Donors do not receive direct payment after donation, but after qualification of the use, and sometimes in different instalments. Cryos in the US makes 40% of the payment when a batch is closed (e.g. when a minimum of 10 approved samples have been obtained) and 60% when the sperm samples are released from quarantine (e.g. after quarantine for six months, and after medical examination and normal test results). Compensation is paid by check and anonymous.

Cryos states that sperm donors are paid for their services, with financial compensation for the time and trouble: "We call it compensation, as it is intended as a form of compensation. In principle, the amount you are paid is seen as an inconvenience and transport allowance. As such, it is not payment for use of your sperm." (Cryos website 2014).

In Europe, Cryos compensates its donors from €30 up to €70 (DKK 300-500) per donation, depending on the level of information the donors are willing to share with clients and potential offspring. Anonymous donors with only basic information are on the lower threshold, while non-anonymous donors with complete family history and shared information can get up to € 70 per unit. Most donors receive €30 though. Interestingly, as research has shown, increasing the amount of compensation paid to donors does not lead to a larger donor pool suggesting there is an upper limit (which in Denmark was set at between DKK 300-500) for optimal donor recruitment and compensation. For Cryos the average number of donations per donors is unknown and therefor an indication of average compensation cannot be provided. A minimum of 10 donations is however required, which leads to a minimum compensation of €300 to €700. For other European sperm banks this calculation is as follows:

The Berliner Samenbank in Germany offers €105 per sample and states on the website 'candidates are expected to donate regularly, roughly every 14 days for at least one year'. This comes to a monthly amount of €227,50 on average and €2730 per year.

The Erlanger Samenbank, also in Germany, also offers €105 per sample to be provided in a cycle of 6 donations in six months, thus offering an amount of €630 for six months. After a cycle of six donations a new cycle can be started, thus donors can receive up to €1260 annually.

In the UK the London sperm bank and the Birmingham sperm bank both offer £35 (approximately €48) per visit to the clinic. The London sperm bank website states: 'You will be asked to donate once or twice a week for a period of three to six months.' This indicates donors can receive up to €192 per month and about €1152 annually (in six months). The Birmingham sperm bank states on the website: 'Regular appointments can be made for you to make donations, this normally involves making around 10 to 15 visits'. This indicates an average annual amount of €720.

Spermbank International in Czech Republic offers 1500 CZK (about €55) per donation. Donors are expected to donate at least once a week for at least six months. The minimum annual amount for donors is therefor €1430 although by donating for longer than 6 months and more than once a week a donor can receive €5720 annually. Cyogonia in Greece and the European sperm bank in Denmark do not list the amount compensated to donors on their website.

Moreover, the success of donor recruitment in sperm banking is more about logistics of donation, for example in publishing the high level of donations actually being used for achieving pregnancies. Finally, the fact that prices differ between anonymous and non-anonymous donors underlines the fact that price is not relative to the cost of sperm banking, as cost is comparable for both types of donors, but that price is relative to the demand for specific types of donors (Stine Willum Adrian 2015; see also Sebastian Mohr 2015). In terms of business models, the professionalisation and development in logistics that are economically feasible is another driver in sperm banking. One could argue that the 'success' of the Danish banks is that they are able to have donors donating for a longer period, since they can cover not only the Danish market (where the current limits only enable 12 families with children), but are able to sell globally. Furthermore, the sperm banks are dedicated exclusively to sperm banking (so no egg banking or other additional in-house reproductive services) and to the care of their donors (advisory panel 2015).

Table 28 further down in this chapter gives an overview of the compensation schemes and amounts for sperm donors compared to egg donors per Member State (see paragraph 5.10).

Donor profiles

After donation, sperm samples are divided into different vials, frozen and stored and only after sufficient supply will the banks start marketing the units to potential clients – ideally with enough samples in stock to continue marketing until long after the donor has acquitted his obligations (Cooper and Waldby, 2014).

Potential clients generally need to register via the sperm bank's website in order to access donor samples and profiles. From here they can choose anonymous or known donors, with basic or extended profiles. The prices of these different types of samples vary. The more information provided, the higher the price for donor sperm, with non-anonymous sperm being more expensive (availability depending on national legalislation).

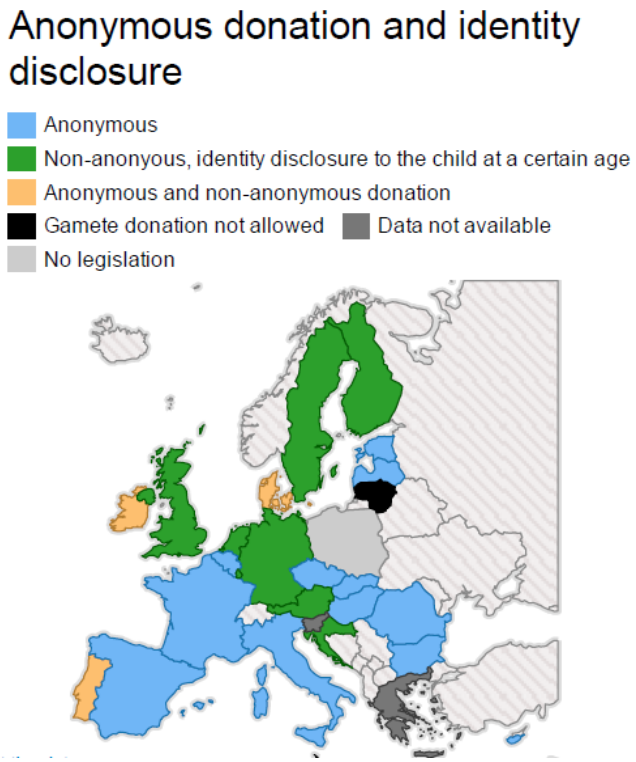
After donor selection, samples can be shipped for home insemination or delivered to fertility clinics. The main categories of anonymous versus non-anonymous donation are explained below, and of basic versus extended profiles.

Anonymous or non-anonymous donation

The identity of anonymous sperm donors always remains confidential, while with non-anonymous donors children can learn the identity of the donor at the age of 18 (in certain countries, the age is lower e.g. it is 16 in the Netherlands and 14 in Austria) which means that sperm donors have to agree to meet their prospective children. For reference, the map below provides the legal framework on anonymous or non-anonymous donation of gametes, including sperm. All clinics in the internet search matched the legal framework of the respective Member State.

In the majority of countries in the European Union, sperm donation is anonymous and disclosure of the identity of the donor to the child is not allowed. In Austria, Finland, Croatia, Luxembourg, the Netherlands, Sweden and the United Kingdom donation is non-anonymous. This means the donor is anonymous to the intended parents but the child has the right to know the identity of the donor when it reaches a certain age. In Denmark and Portugal the disclosure of the identity of the donor to the child is allowed, but a donation can be both anonymous and non-anonymous. The identity of the donor is only disclosed in the case of the donor giving consent. Anonymous and non-anonymous donation is also available in Ireland and Poland but this is due to lack of legislation on ART related to non-partner donation in general (Poland), or specifically on (non-) anonymous donation (Ireland). In those countries both anonymous and non-anonymous donation are offered. It should be noted that donor identity disclosure in those countries is to the child and not to the prospective parents. In Ireland new legislation is being drafted which will remove the use of anonymous donors.

Figure 28 Anonymous donation and identity disclosure ART



Source: Implementation survey by DG SANTE; VUDTC survey by DG SANTE; Internet fertility search Rathenau Instituut (2014)

Some countries with strict anonymity of donors do however allow selection of donors based on phenotypical characteristics (such as height, weight, eye/hair/skin colour) for instance Belgium and Estonia. An extended profile fits into both an anonymous and non-anonymous legal framework. These extended profiles might include more detailed but non-identifiable information in the context of a non-anonymous framework. For instance Cryos and the European Sperm Bank offer 'extended profiles' of non-anonymous donors including, for example, voice recordings of the donors. But extended profiles are also available in Member States with an anonymous donation legal framework, for example the 'International Spermbank' in the Czech Republic.

The difference between anonymous donors or non-anonymous donors is important for several reasons.

- Firstly, non-anonymous donation is related to lower numbers of potential donors, as donors might be less likely to donate if this implies the possibility of having to deal with offspring at some point in the future. The National Competent Authorities for Tissues and Cells in the Netherlands and in Austria state suggest scarcity of sperm donors could be due to the fact that the identity (name) might be disclosed to the child at a certain age.

- Secondly, the wish for intended parents to conceive from an anonymous donor while non-anonymous donation is the legal framework in their own Member State or vice versa, might be a driver for cross-border fertility care. The Competent Authority for Tissues and Cells in the Netherlands states that the difference between the legal framework in the Netherlands (non-anonymous donation) and in Belgium (anonymous donation) can be a driver for cross-border reproductive care between these countries (both ways). This issue will be further discussed later on.

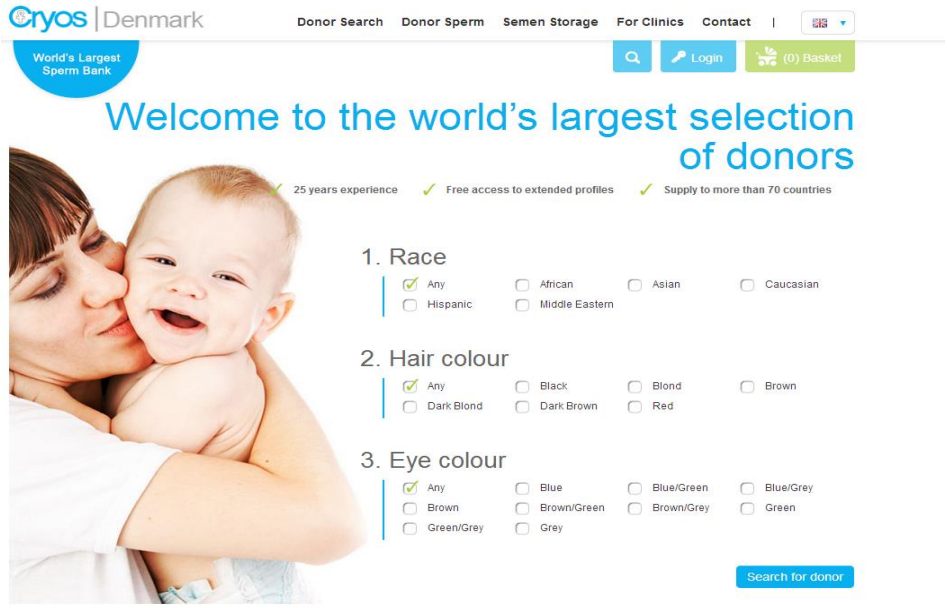
- Finally, the more recent developments in home insemination might challenge the legal framework of particular Member States offering anonymous sperm to intended parents, were the legal framework give children the right to know their biological parents. Due to the specifics of these legal frameworks, some operators consider that this practice does not imply illegal activity (see Cryos statement home insemination, 2015).

Denmark is one of the few countries in the European Union where both anonymous and non-anonymous sperm is offered and that has commercial sperm banks. From a business perspective, the choice of anonymity and non-anonymity is also based on economic factors as it is much cheaper to use anonymous donation for the intended parents. In the end, this creates issues for the mothers and maybe also the children, who might want to change the status of anonymity.

The two largest Danish sperm banks offer extended profiles of their donors. The examples of Cryos and the European Sperm Bank are examined more fully in this report. Extended profiles can also be offered from anonymous donors, such as from the International Spermbank in Czech Republic where disclosure of the donor identity is not allowed by law.

Cryos offers basic profiles and extended profiles, from anonymous (e.g. the identity must be kept secret forever) and non-anonymous donors (e.g. the identity can be released to children when they are 16 or 18 years of age). According to Ole Schou from Cryos in Denmark, different target groups select different donor profiles. Heterosexual couples tend to choose anonymous donors with a basic profile, whereas lesbian couples and single women select non-anonymous donors with an extended profile.

Figure 29 Donor selection Cryos (DK)



Source: Cryos website (2014)

Donors can be selected on the following criteria:[46]

- Eye colour: (Blue, blue/green, blue/grey, brown, brown/green, brown/grey, green, green/grey, grey),
- Hair colour (black, blond, brown, dark blond, dark brown, red)
- Race (African, Asian, Caucasian, Hispanic, Middle Eastern)
- Ethnicity (Afghan, American, Australian, Bosniak, Brazilian, Bulgarian, Chinese, Danish, English, Filipino, French, German, Guatemalan, Indian, Inuit, Iranian, Iraqi, Israeli, Italian, Japanese, Korean, Lebanese, Lithuanian, Malaysian, Norwegian, Peruvian, Polish, Portuguese, Romanian, Russian, Scandinavian, Spanish, Swedish, Swiss, Tamil, Turkish, Ukrainian, Vietnamese)
- Anonymity (Anonymous, non-anonymous)
- Standard (indicates which national legal requirements the semen is released according to, options: AUS, DK07, DK97, EU, FI, NL, NO, NYS, UK, USA)
- Height cm/ft (in cm: <150, 150-159, 160-169, 170-179, 180-189, 190-199, 200-209) (the height is also indicated in ft)
- Weight kg/lbs (in kg: <50, 50-59, 60-69, 70-79, 80-89, 90-99, 100-109, 110-119, >120)
- ICI/IUI (Search unprepared ICI-unwashed, or prepared units IUI-ready)
- Blood type (0-, 0+, A-, A+, B-, B+, AB-, AB+)
- Profile (Basic, Extended)
- Motility (Motility (MOT) indicates the number of motile spermatozoa per ml after thawing. Options: MOT10, MOT20, MOT30, MOT40, MOT50, MOT50+)
- Units available (<50, 50-99, >100)

[46] Source: Cryos Donor search http://dk.cryosinternational.com/donor-search/

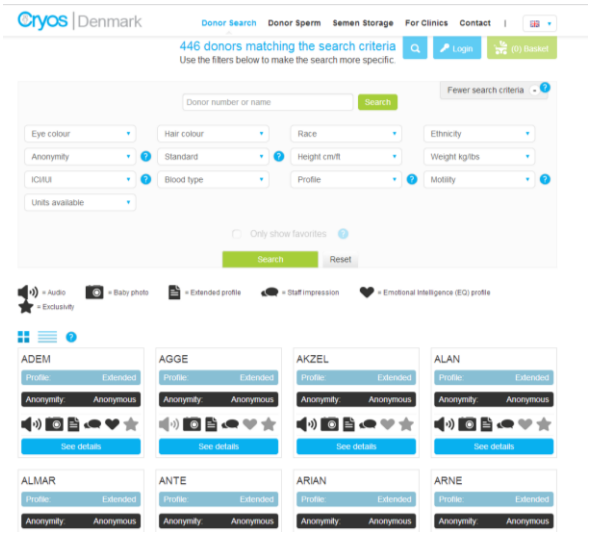
Basic and extended profile

Sperm donors with a basic profile are registered under a number like 456, 8756, 11250, etc. Basic profiles only provide information on race, ethnicity, eye colour, hair colour, height, weight, blood type and usually profession/education.

Sperm donors with an extended profile are registered under a fictitious name such as ERIK, IB, PER, OLUF, SVEND, etc. The extended profiles consist of up to 8-10 pages of personal information on the sperm donor's background, education, family background, interests, hobbies, etc. The following additional information may apply: staff impression, childhood photos of the sperm donor, a handwritten greeting, a sound recording of the sperm donor's voice, EQ profile, etc.

To get an idea of what donors are like, clients can listen to an audio fragment of the donor speaking to the future intended parents. A baby photo is attached (adult photos of the donors less so for privacy considerations), and an extended profile, staff impression of the donor, and emotional intelligence (EQ) profile are available at Cryos. When clicking on a specific donor (under a fictitious name) an extended profile is shown. It is here where semen can be ordered.

Figure 30 Extended profile Cryos (DK)

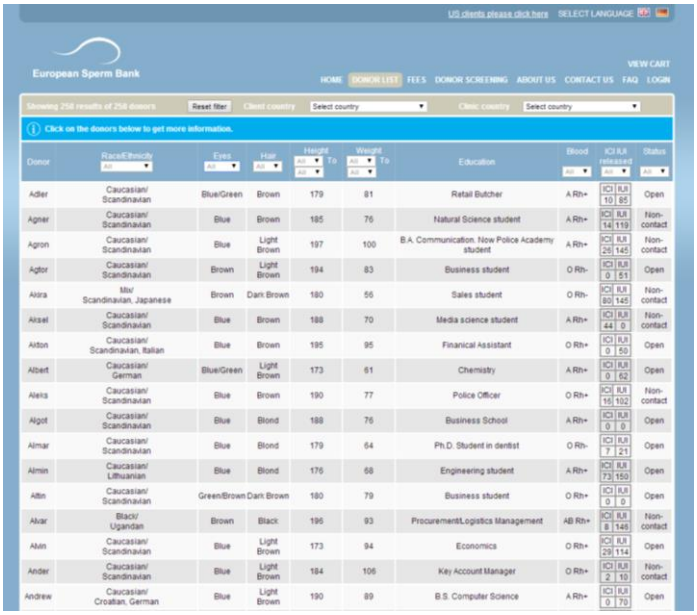


Source: Cryos (2014)

The European Sperm Bank (ESB), the second largest EU bank, has website information on donors in English and German only (where the two versions don't seem to differ from each other) with basic profile information on race/ethnicity (Caucasian, non-Caucasian), eyes (blue, brown, green, hazel), hair (red, brown, light brown, dark brown, blond, black), height (from 150 – 200, to 150 – 200), weight (from 60 – 110, to 60 – 110), education, blood (RH-, RH+), ICI/IUI released and status (non-contact, open).[47]

47 Source: ESB http://www.europeanspermbank.com/spermdonor/sperm_donor.php

Figure 31 Donor information European Sperm Bank (DK)

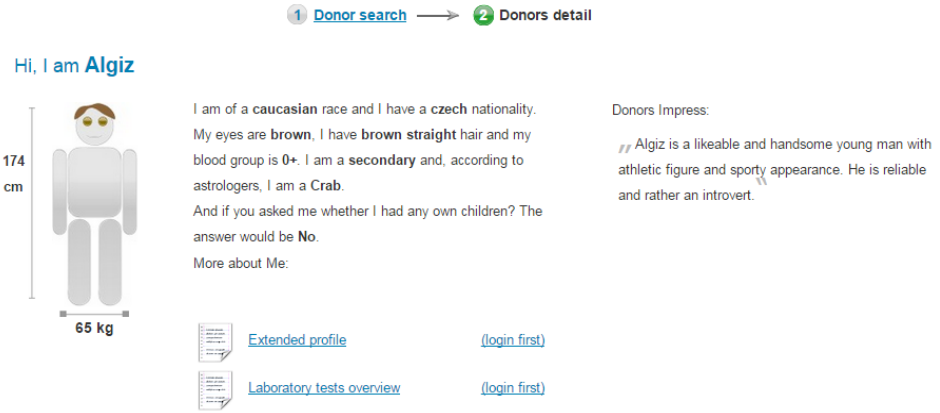


Source: ESB website (2014)

ESB also offers extended profiles and additional services, such as baby photos, an audio interview with the donor, an extended donor profile (which includes general information, educational/occupational background, personal characteristics, fertility history, three-four generations of family medical history, interests, hobbies and future plans and dreams), staff impressions of the donor and a personality test of the donor (the Keirsey Temperament Sorter (KTS), a self-assessed personality questionnaire). This is a model that is common in sperm banks in the US.

Spermbank international in the Czech Republic also offers an online catalogue of donors. Donors can be selected on factors such as degree of education, physique, religion, ethnicity, skin tone, hobbies, psychological profile, family history, future plans and more. After login, extended profiles and laboratory test overviews are available. These extended profiles are still anonymous as non-anonymous donation is prohibited in the Czech Republic.

Figure 32 Donor information Spermbank International (CZ)



Source: Spermbank International CZ website (2014)

Special and exclusive donors

Banks have different ways of marketing their donors. For example, new donors in a bank are advertised with special features on the company's websites. Exclusive donors are also offered, for clients who don't want other offspring from the same donor; in effect they buy the exclusive right to one donor and claim the full existing and future stock. For example Cryos in Denmark offers exclusive rights to new donors for €12.000.

Other banks advertise selection criteria such as preferred star sign, religion, area of study etc. US bank Fairfax offers videos for face matching between clients and donors; California Cryobank offers celebrity look-a-like sperm, where clients can select sperm from a dropdown list of actors, athletes or other celebrities.

Figure 33 Look-a-like sperm (US)

Source: California Cryobank CCB website (2014)

Finally, in the US a novel selection and donor matching system has entered the market for sperm banking, called Genepeeks. This company offers sperm bank partners pre-screening of all their donors to identify high-risk matches based on genetic signature.

In terms of demand and supply, though, it is not necessarily the tall athletes with high grades in physics that are most popular and most pricey. The need for special donors also reflects certain cultural taboos; sperm from particular ethnic groups or religion (such as Asian or 'Muslim' sperm) is in demand because of a supply shortage and a growing market in South East Asian countries for donor semen. Furthermore, with changing legislation on donor anonymity, open donors and non-anonymous donors of all ethnic origin are also sought after.

In addition to phenotypical characteristics, a range of choice is offered in the cultural or communication skills of donors, empathic behaviour, sports, being good at maths or creative arts etc. Similarly, all kinds of social, entrepreneurial, physical, intellectual, educational and even lifestyle characteristics are attributed to gamete donors. Typically though, the donor traits often being advertised are non-heritable; a practice which has led commentators to refer to a popular misunderstanding of genetics (Daniels and Golden 2004) or at least that reflects certain desires and fantasies in the search for sperm donors (Waldby 2002).

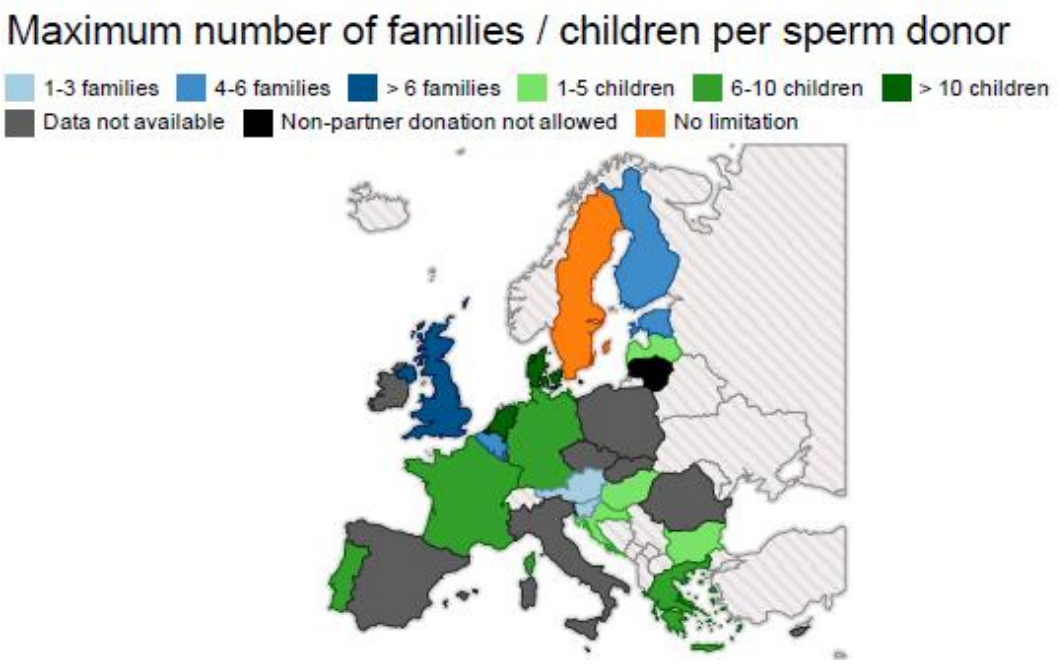
From an economic perspective it should be stressed once again that cost and price in sperm banking are totally different parameters, where for example price is related to demand (for non-anonymous donors with extended profiles) and not to the cost for recruitment, testing or managing the sperm bank.

Limitations to the number of offspring per donor

Most European Member States have set limits to the maximum number of offspring that can be born from one sperm donor within the country, in order to avoid future risk of consanguinety. Such limitations are however also of economic importance for sperm banks, as they will define how much samples they can distribute and charge from one donor (and one donor recruitment procedure).

Countries vary in how they set the limits for offspring from one donor. Limits can be counted in terms of maximum number of children per donor, or maximum number of families (or women) receiving sperm from one donor. The maximum number of children is mostly counted in terms of children born but in some exceptions in terms of pregnancies (for instance in Germany). Number of children born does not generally include the donor's own children, except in some cases (for instance in Bulgaria). These legal limits vary in different European Member States and limits range from 3-25 children and 2-10 families. Irish clinics run voluntary registers aiming to limit the families to 3 per donor (new legislation will make this mandatory).

Figure 34 Maximum number of families/children per sperm donor



Source: VUDTC survey by DG SANTE; Janssens et al. (2011)

The rationale behind setting a limit on the number of offspring from one donor is to protect the (potential) offspring, and minimise the chances for unintentional consanguineous relationships between children from the same donor. This risk is calculated in different countries using different models resulting in different limits and reflecting variation in culture (Janssens, Nap and Bancsi, 2011).

These limits were mostly set under a legal framework of anonymous donation, while some countries have since adjusted this framework to non-anonymous donation. It is now a matter of debate as to whether this change in legal framework also implies increasing the maximum number of offspring. In a non-anonymous system, children are more likely to know they are the offspring of donor semen and know the identity of the donor, thus decreasing the chances for unintentional consanguineous relationships between children from the same donor. Increasing the maximum number of children per donor could be a strategy to address shortage. The perceived burden of potentially being contacted by offspring by donors, which could increase with raising the number of

children per donor, could result in less willingness to donate, although this is still under debate (Janssens, Nap and Bancsi, 2011). In some countries, such as the UK, donor consent is asked when setting the number of children that can be conceived from the sperm of a donor; it is part of the professional guidelines. This can set another limit to the maximum number of children born, especially in cases were donated sperm is distributed to other countries. In other countries such as Denmark, this is not common practice (advisory panel meeting, 2015). The increased use of donor sperm by lesbian couples or single women furthermore makes it more likely children are aware of being conceived with donor sperm, while other developments such as the availability of genetic testing both decrease the chance for unintentional consanguinity (Janssens et al 2015).

The limitations on the number of offspring of the donor are all set within the Member State. This means that sperm from one donor that is distributed to several Member States can be used for the inception of more offspring; the maxima of different Member States can thus be cumulated. This also is of concern for intended parents traveling to other Member States to receive donor sperm. This internationalisation is not regulated in terms of number of children. In an effort to establish recommendations on the maximum number of offspring per donor for use on an international scale, a working group of multidisciplinary professionals from different European countries was established in 2012. This working group concluded a maximum of 100 families was justifiable. This figure was debated,[48] as a balance is required between access to gametes, ethical considerations and business operation. Important to note here is that the economics of the sperm bank are a consideration for not setting the numbers too low. As the cost of recruitment of donors is high this has to be balanced by the revenues. Sperm banks that operate internationally have a larger return on investments from their donor compared to sperm banks that operate locally as the sperm can be distributed to more intended parents (Janssens et al, 2015). These limitations also increase importance of a good reporting back on eventual successful pregnancies to the sperm banks.

Fees charged for delivering donor sperm

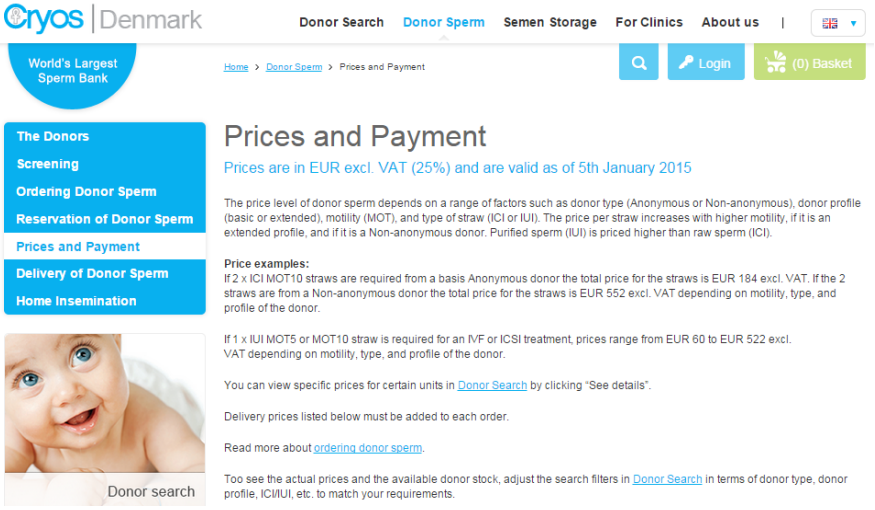
Different fees are charged for donor type (anonymous and non-anonymous samples) and for donor profile (basic or extended). Many banks discriminate between the degree of processing of the sperm and the type of straw. Other factors that influence the fee are motility of the sperm (an indicator for quality, and eventual probability of a pregnancy).

Fees for different sperm banks in Europe vary from € 76 per straw offered by a sperm bank in the Czech Republic to € 400 by a sperm bank in Germany. In addition, fees vary according to delivery options and transport means (such as dry ice or nitrogen tanks), for destinations (within the country/continent or outside) and delivery times.

Cryos international lists all prices on their website and explains the differentiation in pricing as follows.

[48] This figure was debated, and the psycho-social professionals in the group could only support a lower number. The limit is not the result of scientific evidence or calculation but of weighting the different arguments and different interests of different stakeholders. In Janssens et al (2015) this is expressed as: "When the number of offspring per donor is set low, there are likely to be problems of accessibility to donor gametes for users, while the operation of the sperm bank will become uneconomical. Causing insufficient supply may also be considered unethical, alien to social justice. Allowing more children reduces the strengths of these considerations; however, psychosocial worries increase for donors and their families, and maybe also for the donor offspring. At much higher numbers of donor offspring (around 200) medical-genetic doubts arise, as may ethical doubts, depending on the point of view taken (i.e. should a donor child be considered to have a bond with his donor or not)." (Janssens et al, 2015).

Figure 35 Delivery prices Cryos (ex VAT) (DK)

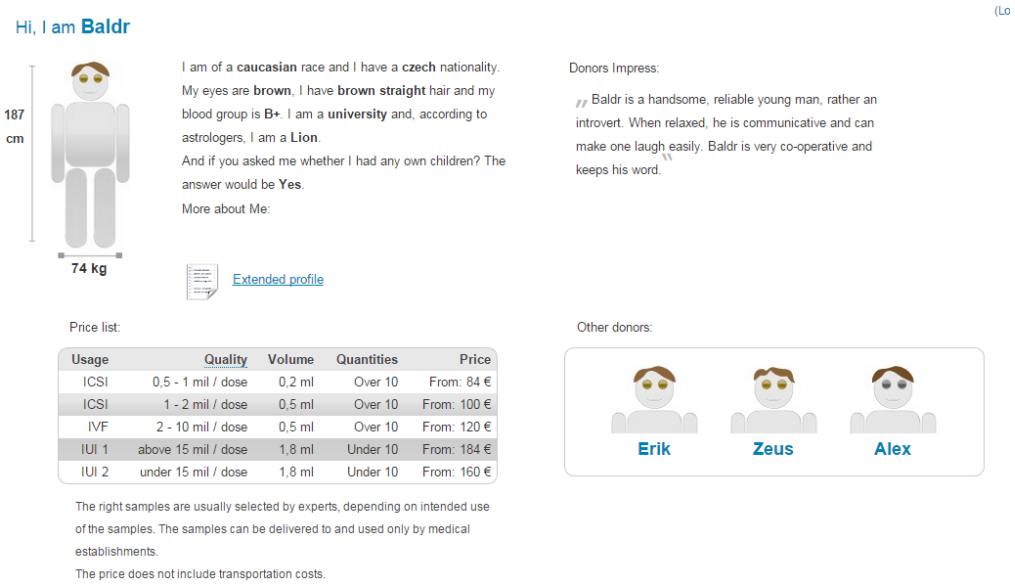


Delivery prices

Service	Price
Pick up* (dry ice)	EUR 39
Pick up and return* (nitrogen tank)	EUR 45
Denmark** (dry ice)	EUR 55
Denmark** (nitrogen tank) r/t	EUR 79
Europe (dry ice)	EUR 169
Europe (nitrogen tank) r/t	EUR 219
Rest of the world (nitrogen tank) r/t	EUR 349

Source: Cryos website (2015)

Figure 36 Prices International sperm bank (CZ)



Source: International Spermbank CZ website (2014)

Several banks also offer to store sperm samples for future use (to have more children from the same donor), which has a separate cost structure. Fees for storage for one year range from €117 from Cryos International, to €360 by a sperm bank in Germany. Annex 2 (see 8.3) on ART lists fees and fee ranges for all banks. Most banks accept all major credit cards and payments can also be made via bank transfer or in cash. During the ordering process, clients are also reminded to consider future purchase of sperm, to make sure the donor is not sold out in the middle of treatment or in order to reserve straws for genetic siblings. Refunds can also be given after reservation of straws for future use (for example Cryos guarantees to repurchase at 75% refund of the original straw price).

5.2.4 Organisation of the sector: eggs and embryos (including economic aspects)

The emergence of egg banking

In contrast to sperm banking as a business, the market for (donor) egg cells is more varied and diverse, and the differences between Europe and other parts of the world more prominent. Oocyte markets are made up of intermediary organisations (brokers), online matching agencies, fertility clinics, law firms, reproductive travel agencies, support industries, national funding and social security agencies, not to mention both donors and intended parents that are willing to travel for optimal (or value for money) treatment with donor eggs. Furthermore, more creative business models have emerged, such as half-price IVF or discount treatments in return for egg donation, egg sharing schemes, bring-your-own-donor, pay-it-forward and other reimbursement and payment variations for donors and clients.

Also, and in contrast to sperm banking, egg donation and procurement is always part of a (rather invasive) medical intervention which means that direct-to-consumer marketing for home use (without clinical oversight) is uncommon. Still there are several parallels

between sperm and egg banking, and in the recruitment of donors, which are described in more detail below.

While sperm banking has been in existence for many decades, the large-scale emergence and commercialisation of female gametes is of more recent origin. In part this has to do with the origin of the material. Semen is biologically speaking, more easily accessible than oocytes, without the need for extensive and invasive medical intervention. It regenerates itself and each ejaculate provides, in theory, sufficient material to fertilise an oocyte and produce a conception. Sperm is also produced in excess of what is needed for reproduction by a single man, it can be stored and accumulated and more easily transferred (Cooper and Waldby 2014). In short: quantity is not the issue, but quality. Oocytes on the other hand, are not normally produced in excess (e.g. without hormone stimulation), they cannot be accessed without biomedical intervention and procurement involves more medical risk.

Techniques for procurement, of both human semen and oocytes, date back to livestock breeding. In the post-war period, scientists experimented with hormonal treatment, multiple embryo transfers, embryo freezing, superovulation and ovulation induction in sheep and cows. In the 1960s, experiments with ovarian stimulation in humans started, but the first IVF births in 1979 and 1980 were performed during the woman's natural cycle (also because it proved difficult to schedule oocyte recovery in the hospital). Hormonal stimulation cycles were improved in the following decade, which meant that the number of oocytes to harvest increased and the procedure and timing could be better controlled. It became possible to produce multiple oocytes, for the fertilisation of more than one embryo, which could then be frozen for future use – by the woman herself for a future IVF cycle or via donation for other women. From the 1980s onwards, older women were also now able to become pregnant with donor oocytes via an IVF procedure.

Because of the split between conception and pregnancy, a new range of reproductive opportunities emerged followed by all kinds of regulatory activity to cover the complexity of embryo handling and research, distribution of gametes across the globe and new kinds of family building. Legislation emerged in several countries, such as the Human Fertilisation and Embryology Act in the UK (1990) and the Embryo Protection Act in Germany (1990) that set restrictions on the handling of embryos and the management of gametes. European regulations for gametes were predominantly based on the principle of voluntary unpaid donation, although some level of compensation was allowed. In the US, on the contrary, the market for human oocytes was largely unregulated and more commercialised. Because of the conservative anti-abortion climate of the Reagan and Bush administrations, reproductive science mostly developed through private funds creating a regulatory vacuum for entrepreneurial experimentation in fertility outsourcing, free of formal state control. All kinds of reproductive services emerged, from IVF to surrogacy, artificial insemination for singles and lesbians, to embryo adoption, and for special egg donors of Jewish origin or with Ivy league degrees (Cooper and Waldby 2014; Clarke 1998; Franklin 2013; Jasanoff 2005).

The US market for oocytes was initially not so much modelled on the sperm banking business, but originated in the surrogacy agency world, where women were contracted for their reproductive services (such as traditional surrogacy during the time when the woman carrying the child was still using her own genetic material, rather than donor eggs that are now more commonly used in gestational surrogacy). These surrogacy agencies were mostly legal firms, not clinics, working in family law and looking for alternatives to adoption. Thus in the 1980s, there was already an agency model in place for the recruitment and screening of women for reproductive services in exchange for fees, making it easier for these agencies to extend their area of activities to oocyte donors and matching supply and demand. Even when IVF clinics started to run their own donor recruitment programmes, the agency model was used. Whereas sperm banks mostly recruited their donors from campuses and based on anonymity, for egg donation

the maternal and altruistic values of the donor were considered more important, and also a personal relationship between the donor and purchaser of the material. Egg donors were recruited via local communities, and were often young women who already had children of their own and were willing to help out another couple wanting to have a baby (Spar 2006; Almeling 2011).

In the 1990s this model started to change, as demand in the gamete market increased and consumer preferences started to diversify. Fertility clinics, mostly from California, hired private agencies for the recruitment of donors, and niche markets emerged for donors with particular looks or qualifications. As such, the sperm model started to gain ground, as (also for oocyte donation) recruitment started to cluster around university campuses in search of elite donors.

Global players in fertility and egg banking

In the US, there are specialised companies that exclusively focus on egg donation such as Egg Donation Inc, Egg Donor America or Gifted Journeys. These companies are usually brokers or intermediary organisations that perform donor selection and matching, but have agreements with clinics for the medical procedures for egg procurement, testing and implantation.

In Europe, egg donation tends to be part of a broader fertility service package offered by an ART establishment, which includes many other sorts of fertility treatment. While separate donor egg banks do exist, these are usually part of a fertility clinic or chain. Brokers that are specialised in just the matching between supply and demand are less common in Europe. As described in the previous section, the market for egg donors in the US followed a slightly different tradition than in Europe, which may explain the different business models.

In Europe, IVI clinics in Spain is one of the leading organisations, although Europeans in search of donor eggs also travel to the US, which has a more established infrastructure for commercial egg donation. Increasingly, they travel to Russia and the Ukraine (and in some instances Israel and Cyprus) which offer cheaper treatments and gametes than in the US and Europe. India is mostly in demand for surrogacy (in combination with donor eggs) and is left out of this analysis.

Donor recruitment

Oocyte agencies target particular populations for donation and as potential vendors, take care of the screening process and create an 'inventory' of characteristics of donors in order to better match them with intended parents. Giving 'the gift of life' is commonly used as a phrase to recruit oocyte donors online or via university campuses.

Donor profile

Oocyte donors are chosen based on phenotypical and clinical characteristics: age, body mass index (as indication of how well the body responds to hormonal stimulation) and family health history, followed by appearance, such as height, beauty, race, hair and eye colour and slimness. Also education level is an asset, with the high SAT scores and elite schools as well documented values of gamete donors (Almeling 2011; Spar 2006, 2007; Geesink and Steegers 2011). These values are all listed in a database by the recruitment agency in order for intended parents to search for desired characteristics.

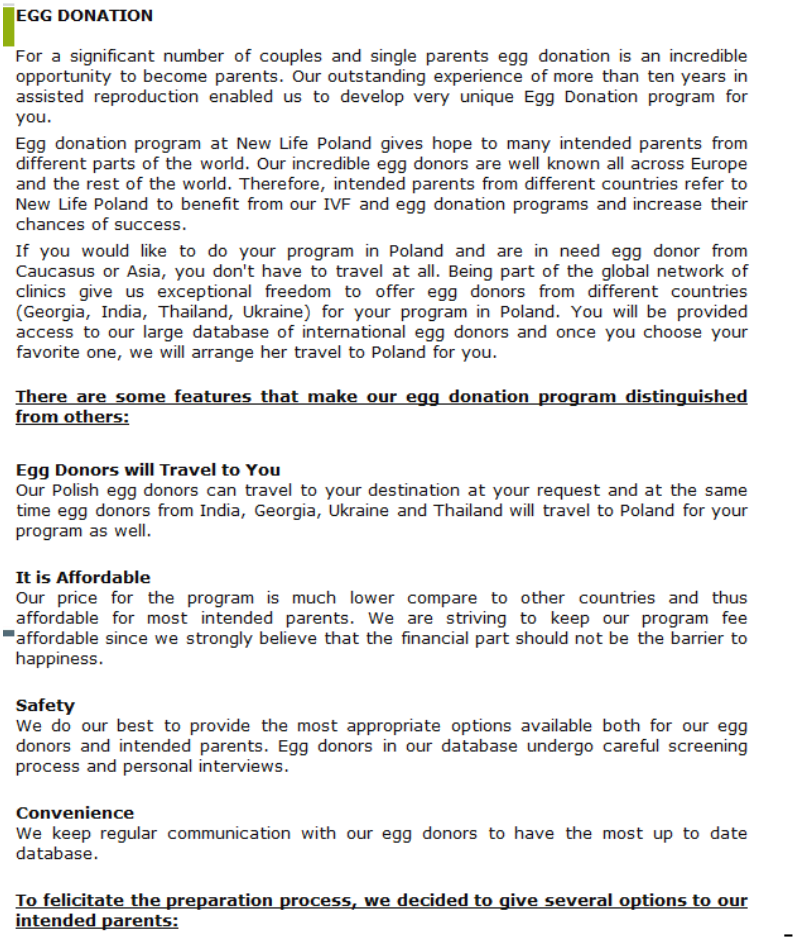
Popular donor profile: Bright, healthy and white but not blond

Contrary to popular belief, it is not blond donors that are most in demand (they are plentiful in California and Europe), but Asian and Jewish donors that are in short supply. Several critics have reported oocyte markets witnessing preference for lighter skin tones (Whittaker and Speier 2010; Leem and Park 2008). This would explain the popularity of

donors from Central European countries including Ukraine, Russia, Czech Republic and Romania travelling to Western Europe, or intended parents travelling towards Central European countries for egg donation. Similar reproductive movements are seen in Latin American countries with preference towards the brighter skin toned donors of Ecuador. Overall though, clients seek donors with similar phenotypes as themselves, in order to match appearance, and also agencies report only slight trading up in skintone.

Also, it is not uncommon for donors to travel to the country of residence of the intended parents - a service offered by the Polish clinic (see below) - or vice versa, for donors from other countries (such as India, Ukraine, Georgia and Thailand) to travel to Poland on request.

Figure 37 Travelling donors and clients (PL)



EGG DONATION

For a significant number of couples and single parents egg donation is an incredible opportunity to become parents. Our outstanding experience of more than ten years in assisted reproduction enabled us to develop very unique Egg Donation program for you.

Egg donation program at New Life Poland gives hope to many intended parents from different parts of the world. Our incredible egg donors are well known all across Europe and the rest of the world. Therefore, intended parents from different countries refer to New Life Poland to benefit from our IVF and egg donation programs and increase their chances of success.

If you would like to do your program in Poland and are in need egg donor from Caucasus or Asia, you don't have to travel at all. Being part of the global network of clinics give us exceptional freedom to offer egg donors from different countries (Georgia, India, Thailand, Ukraine) for your program in Poland. You will be provided access to our large database of international egg donors and once you choose your favorite one, we will arrange her travel to Poland for you.

There are some features that make our egg donation program distinguished from others:

Egg Donors will Travel to You
Our Polish egg donors can travel to your destination at your request and at the same time egg donors from India, Georgia, Ukraine and Thailand will travel to Poland for your program as well.

It is Affordable
Our price for the program is much lower compare to other countries and thus affordable for most intended parents. We are striving to keep our program fee affordable since we strongly believe that the financial part should not be the barrier to happiness.

Safety
We do our best to provide the most appropriate options available both for our egg donors and intended parents. Egg donors in our database undergo careful screening process and personal interviews.

Convenience
We keep regular communication with our egg donors to have the most up to date database.

To felicitate the preparation process, we decided to give several options to our intended parents:

Source: New Life Poland website

Donor screening

In terms of screening criteria, prospective donors are screened from a medical perspective (physical examination, cultures, blood test, blood type, infectious diseases such as HIV, Hepatitis B and C, gonorrhoea and chlamydia), meeting requirements laid down in Directive 2004/23/EC as well as additional national requirements; they get a psychological intake (motivation for donation, lifestyle); and sometimes they are screened for hereditary diseases (for example, cystic fibrosis or blood disorders).

Processing and storing oocytes

Oocytes are retrieved after several weeks of hormone injections to stimulate the ripening of multiple oocytes and to induce final maturation. Via surgical procedure the oocytes are retrieved from the female body (usually under sedation) and then frozen. The preferred method according to professional guidelines is flash-freezing or vitrification, which prevents the formation of ice crystals and gives higher success rates in pregnancies (compared to slower freezing methods). The costs of the freezing procedure for future preservation vary, e.g. in the US between about $5,000 and $12,000 (without fertility medication and also excluding embryo transfer), while storage can vary between about $100 and over $1000. In the EU prices vary as well, with rates between about 4.000 and 6.000 not uncommon in European countries (usually cheaper in destinations including Cyprus, Bulgaria and Czech Republic). The full pricing table can be found in ART annex A8.

These are the costs for oocyte cryopreservation for women wanting to preserve their fertility to have children in the future, for example because they don't have a partner or for personal or medical reasons (such as chemotherapy or radiotherapy in cancer). Costs for processing and storing from the professional point of view are less widely published. These would include facilities, cleanroom and equipment.

Cost structure of an oocyte bank

A cost structure estimate could be provided based on recent calculation of costs for donors in Sweden.

Table 2999 Cost divisions in an oocyte bank

	No distribution	Incl distribution
Donor recruitment	9%	8%
Testing, donors (viral screening, medical and social screening)	11%	10%
Processing (oocyte collection including drugs, and processing) and storage	80%	74%
Distribution	0%	8%
Total	**100% (*100*)**	**100% (*100*)**

It needs to be noted that, in an ordinary IVF clinic, third party donor gametes are very seldom distributed to other clinics. If they are distributed (within the country), the sum is here estimated to 15% of the total cost. Percentages above are calculated without and with distribution costs.

Costs for application are not included in this assessment.

Volumes of egg and embryo donation

Looking at the donation and treatment practices in different European Member States, a large variation can be observed between countries with respect to the number of oocyte donors and the number of treatments with donor oocytes. As with sperm donation, the source for analysis was the 2012 data from EUROCET or if not available, data from 2011 as this database distinguishes between partner and non-partner donation. Furthermore we asked National Competent Authorities for Tissues and Cells to verify or add data. The

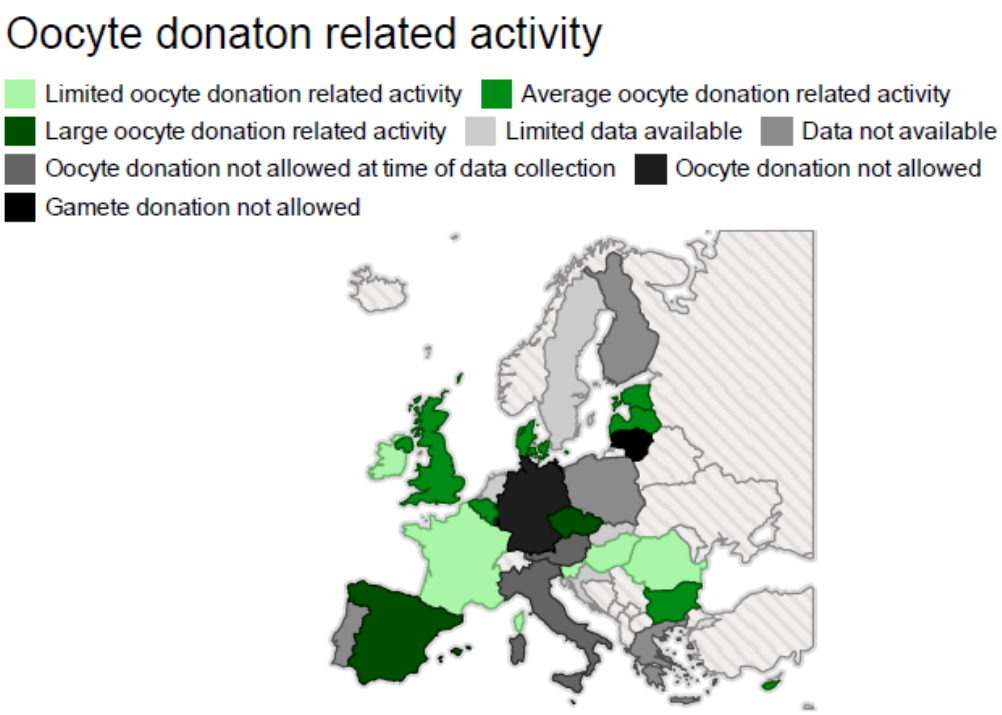
availability of data is however limited. In the VUD survey by DG SANTE, only a few Member States reported having a national register for oocyte donors: Only Slovenia, Bulgaria, Hungary, Portugal, Finland and the UK. The reasons for not having a registry included: it is the responsibility of the clinics to do follow-up; oocyte donation is performed mostly in private clinics, and there are legal provisions on protecting personal data. As indicators for the volume of activity in oocyte donation related activity the following were used:

- The number of donors, donations and donated oocytes within each Member State;
- The number of received oocytes from other Member States and imported oocytes from third countries;
- The number of distributed or exported oocytes; and
- The number of treatments with donated oocytes: IVF & ICSI with non-partner oocyte donation. IVF and ICSI were combined with non-partner donation as the distinction between these types of treatments did not add to the analysis.

A rather broad definition of oocyte related activity was used for this analysis as it also includes the number of received and imported oocytes and the number of treatments with donor oocytes. This compiled data gives an indication of which countries are relatively more active, have average activity, or have limited activity relative to the number of women in the fertile age. Do however note that the reasons for being classified as having more/average/limited activity can vary. Data are for the year 2012 where available, or from 2011 when 2012 data were not available.

The map below gives an overview of the number of donors/donated oocytes/donations relative to the fertile population; received and imported oocytes; and the number of treatments/cycles.

Figure 38 Oocyte donation related activity



Source: EUROCET 2011, 2012; Economic landscape survey NCATC (2015), data from 2011

This leads to the following classification of ART activity within EU Member States:

The Czech Republic and Spain have **relatively large oocyte donation** related activity. Spain has the largest number of donated oocytes, but relative to women in the fertile age, the Czech Republic has the highest volume of donated oocytes. Both countries have the highest numbers of cycles initiated with donor oocytes.[49]

Belgium, Bulgaria, Cyprus, Denmark, Estonia, Latvia and the United Kingdom have **relatively average oocyte donation** related activity. In therms of absolute number of oocyte donors and number of IVF and ICSI cycles started with donor oocytes, the UK follows Spain and the Czech Republic. However, the UK is classified as having average activity as relative to the number of women in reproductive age the activity of the UK is classified much lower.[50] In terms of the number of donors, donations and donated oocyte relative to the number of women in the reproductive age, Cyprus and Latvia have the largest activity after Spain and Czech Republic.[51]

Hungary, Ireland, Romania, Slovenia and France have **relatively limited oocyte donation** related activity. Slovenia, Hungary and Romania have the smallest number of donors, and donated oocytes; for Ireland this information is unknown. France has a

[49] In absolute numbers, Spain has the largest number of donated oocytes (123,447 for Spain and 37,621 for Czech Republic) but relative to women in the fertile age, the Czech Republic has the highest volume of donated oocytes (1.2 donated oocyte per woman in reproductive age for Spain and 1.7 for Czech Republic). Spain might also import or receive oocytes from other Member States, but these data are not available. The Czech Republic does not import oocytes. IVF and ICSI with donated oocytes was used as an indicator for the number of treatments with donor oocytes. Again, Spain has the largest number of cycles started in absolute numbers, followed by Czech Republic (11,155 for Spain and 3,820 for Czech Republic) but relative to the number of women in reproductive age, Czech Republic has more activity (0.07 of cycles started per woman in reproductive age for Spain and 0.11 for Czech Republic). As stated before, Spain has the largest number of fertility clinics in the EU with a total of 438 clinics and 44,1 clinics per 1.000.000 women in the fertile age. Spain is regionally organised when it comes to oversight of fertility clinics.

[50] In terms of absolute numbers of donors, donations and donated oocytes, the UK follows Spain and Czech Republic (6,457 donors for Spain, 1,485 for UK). In terms of absolute numbers of IVF and ICSI cycles started with donor oocytes, the UK again follows Spain and the Czech Republic. The number of oocytes received from other Member States is not available for the United Kingdom. This is also the image that arises from the information on the website of the HFEA (the National Competent Authority for tissues and cells for ART in the UK). However, the UK is classified as having average activity because of relative activity based on the limited treatment offered, in combination with low donation rates and limited donations. Thus, relative to the number of women in the reproductive age, the UK has smaller numbers of donors, donations or donated oocytes compared to other Member States with average activity: Belgium, Bulgaria, Cyprus, Estonia and Latvia (and large activity: Spain and Czech Republic). The number of received oocytes is also an indicator of activity of a country. For instance, if a country has limited numbers of oocyte donors, but receives oocytes from other Member States and has a large number of IVF and ICSI cycles with donor oocytes, this Member State still has a large activity. For the UK, the number of received oocytes from other Member States is unknown. However the relative number of IVF and ICSI cycles with donated oocytes in the UK is smaller when compared to Bulgaria, Cyprus, Estonia and Latvia (and Spain and Czech Republic). For Belgium the number of IVF and ICSI cycles started with donor oocytes is not available.

[51] Also in terms of number of IVF and ICSI cycles with donor oocytes relative to the number of women in the reproductive age, Cyprus and Latvia follow Spain and Czech Republic. In absolute numbers, oocyte donation related activity in Cyprus and Latvia is only a fraction of that of Spain considering Spain has a much larger population of women in the reproductive age (see for example the absolute number of oocyte donors: 6,457 for Spain, 147 for Cyprus and 239 for Latvia). Bulgaria, Belgium and Estonia have the largest number of donors, donations or donated oocyte relative to the number of women in the reproductive age after Cyprus and Latvia (and Spain and Czech Republic). Bulgaria and Estonia have the largest number of IVF and ICSI cycles with donated oocytes relative to the number of women in reproductive age after Cyprus and Latvia (and Spain and Czech Republic). For Belgium these numbers are not available. Denmark closely follows the UK on the number of oocyte donors, donations and donated oocytes and number of IVF and ICSI cycles with donor oocytes relative to the number of women in reproductive age.

considerable number of oocyte donors in absolute terms but relative to the number of women in the fertile age this activity is very limited. For Ireland the number of donors and donated oocytes is low (6) and limited to specific situations (e.g., between siblings, friends), however an oocyte donation programme is in place with a clinic in Ukraine. Slovenia, Ireland, Romania and France also have relatively limited number of IVF and ICSI cycles started with donor oocytes. For Hungary these data are not available. But since Hungary has limited numbers of donors, and also does not receive oocytes, consequently the number of cycles with donor oocytes is limited.[52]

Countries with **no oocyte donation** related activity. In Malta and Lithuania, gamete donation (both sperm and oocyte) is prohibited. Gamete donation in Italy and oocyte donation in Austria were prohibited at the time of data collection. In Germany and Luxembourg, oocyte donation is not allowed while sperm donation is.

For Croatia, the Netherlands, Sweden and Slovak Republic, the picture remains unclear due to limited data. Available data suggests average activity for the Netherlands, limited to average activity for Sweden and limited activity for Slovak Republic (based on the number of donors or donations). For Croatia no information on number of donors or treatments is available.[53] For Greece, Finland and Poland no data is available on numbers of donors/donations or treatments with donated oocytes.

Further details on the situation per country are provided in annex 3, which includes country specific activities in ART.

Cross-border distribution, import and export of oocytes

Very limited data are available for assessing the flows of gametes between Member States and to or from third countries. The data used in this section are absolute numbers as indicated in EUROCET 2012, with added data from EUROCET 2011 and verified by the Member States.[54]

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[52] Slovenia, Hungary and Romania have the smallest number of donors, donations and donated oocytes both in absolute and relative terms. For France the absolute number of oocyte donors is highest after Spain, Czech Republic, United Kingdom and Belgium (422 donors and 3,879 donated oocytes). But in relative terms, France has very limited numbers of oocyte donors and donated oocytes. For Ireland the number of oocyte donors, donations and donated oocyte is unknown. Slovenia, Hungary, Ireland and Romania do not receive oocytes from other Member States or from third countries. For Ireland and France these data are not available. Slovenia, Romania and France have very limited number of IVF and ICSI started cycles with donor oocyte relative to the number of women in the fertile age. For Hungary this data is not available. For France this is also the image that arises from the figures in the annual report of the Agency the la Biomedecine, as can be seen on their website www.agence-biomedecine.fr (French National Competent Authority for tissues and cells).

[53] For Croatia, no oocytes are received from other Member States or imported from third countries. But since both the number of donors, donations and donated oocytes as the number of IVF and ICSI treatments with donor oocyte is unknown it is not possible to classify the size of the oocyte donation related activity. For the Netherlands, Sweden and Slovakia, the number of donors, donations or donated oocytes is known (612 donations for the Netherlands, 211 donors for Sweden and 66 donations for Slovakia). Since both the numbers of received and imported oocyte and the number of IVF and ICSI treatments with donated oocytes is unknown, it is not possible to classify the size of the donation related activity. Comparing only the number of donors/donations or donated oocyte relative to the number of women in reproductive age, the Netherlands and Sweden have average oocyte donation related activity, and Slovak Republic has limited donation related activity.

[54] Data on the number of received oocytes from other Member States are available for 11 Member States (1 receives oocytes, 10 do not); on distributed oocytes to other Member States for 13 Member States (1 distributes oocytes, 12 do not); on imported oocytes for 13 Member States (1 imports oocyte, 12 do not); and exported oocytes for 14 Member States (none export oocytes). In the EUROCET database no distinction is made however as to from which countries gametes are received or imported from or distributed or exported to. In the survey to the Competent Authorities for Tissues and Cells, Member States were asked to specify to and from which countries they received or distributed gametes. This has provided no additional information. Most

Belgium, Bulgaria, Cyprus, Croatia, Czech Republic, Denmark, Hungary, Latvia, Romania, and Slovenia do not report any cross-border exchange, import or export for oocytes.

Sweden does not distribute or export oocytes, but the number of oocytes received from other Member States or imported from third countries is unknown. Portugal does not import or export oocytes but the number of oocytes distributed to other Member States or received from other Member States is unknown.

Only very few countries report **receiving** oocytes from other Member States and/or importing oocytes from third countries; this is only the case for the UK (297 oocytes imported in 2011 as indicated in the Implementation Survey, data on number of oocytes received from other Member States is unknown). Ireland reports that it largely relies on an oocyte donation program with an Ukranian clinic, exporting sperm and importing the consequent embryos. Belgium receives oocytes from the Netherlands but this is mostly oocytes that are being transported from tissue establishments in the Netherlands to be inseminated. The zygotes or embryos are then transported back to Dutch fertility clinics for implantation or cryopreservation.

For Estonia, Greece, Spain, Netherlands, Poland, and Sweden, the number of oocytes received from other Member States or imported from third countries is unknown.

Only the Netherlands reported **distributing** oocytes to other Member States (745) but this is mostly oocytes that are being transported from tissue establishments in the Netherlands to fertility clinics in other Member States, to be inseminated. The zygotes or embryos then are transported back to Dutch fertility clinics for implantation or cryopreservation.

Export of oocytes to third countries is not reported by any Member State. For Estonia, Greece, Spain, Finland, France, Poland and the Slovak Republic, the number of oocytes distributed to other Member States and export to third countries is unknown. Portugal does not export oocytes but the number of oocytes distributed to other Member States is unknown.

For Estonia, France and Portugal, the number of donations in their own Member State is not particularly high, indicating distribution and export of oocytes might not be significant.

For Spain, the number of donated oocytes is considerable (123,447) but so is the number of fertility treatments with donated oocytes (11,155 ICSI & IVF) indicating there might not be considerable cross-border distribution or export of oocytes. For Finland and Poland, the number of donations in their own Member State is also unknown.

As with sperm donation, the volumes of donated oocytes and number of treatments are tightly knit to a couple of factors, which need to be taken into account for understanding the extent of activities per country:

Member States that responded to the survey indicated this data is not collected at the national level. In the implementation survey by DG SANTE, some Member States specified countries for cross-border distribution import and export. Member States were asked to verify these data in order to use them in our description of cross-border distribution, import and export.

- The regulation of ART treatment: countries which do not allow oocyte donation obviously have limited volumes of donated oocytes;
- Access to treatments in terms of who has access (for instance age restrictions, marital status, sexual orientation);
- Reimbursement of treatment (phase, amount or extent of reimbursement).

For some countries, figures relating to the number of donors and/or number of treatments with donor oocytes are not available but data on access and reimbursement are. A relatively restrictive access and reimbursement policy can be an indicator of limited donation activity and limited activity in treatment with donor material and vice versa. These interrelations are discussed later on in this chapter.

This analysis leads to the following **key messages**:

- Czech Republic and Spain have high numbers of oocyte related activity relative to the number of women in the fertile age.
- There is hardly any cross-border exchange of oocytes between Member States for reporting countries.
- There is hardly any import and export of oocytes or it is very limited for reporting countries.
- Possibly it is more feasible for patients and/or oocyte donors to travel than for oocytes to be distributed, or imported.
- Information is limited as data are unavailable for a significant number of Member States. For other Member States, data are incomplete and cross-border distribution, import and export is barely specified per country, making it impossible to map flows of gametes.

Embryo donation

This section contains volume data on embryo donation per Member State. There are large variations between Member States in the number of embryo donors and donated embryos and donation.

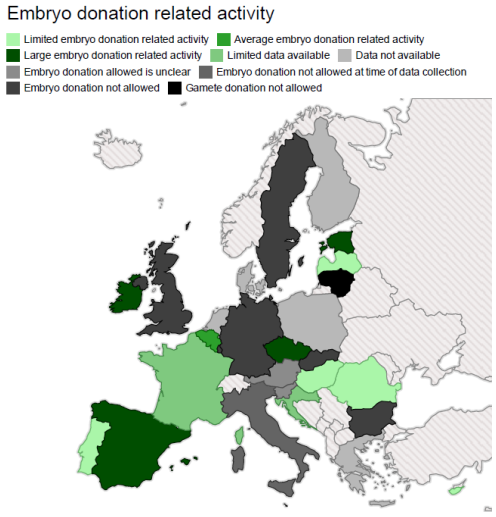
As with the sections covering sperm and oocyte donation, the source for the analysis is data from EUROCET as this database distinguishes between partner and non-partner donation. Indicators for the volume of activity in embryo donation related activity were:

- The number of donors and donated embryo within each Member State;
- The number of received embryo from other Member States and imported embryo from third countries;
- The number of distributed or exported embryos

A rather broad definition of embryo related activity was used for this analysis as it also includes the number of received and imported embryos. When compiled, this data gives an indication of which countries are relatively more active, have average activity or have limited activity relative to the number of women in the fertile age. Do however note that the reasons for being classified as having more/average/limited activity can vary. Data are based on the year 2012 where available, or from 2011 when 2012 data were not available.

The map below gives an overview of the number of donors and donated embryos relative to the fertile population; received and imported embryos.

Figure 39 Embryo donation related activity



Source: EUROCET 2011, 2012; Economic landscape survey NCATC (2015), data from 2011

The analysis leads to the following classifications:

Czech Republic, Estonia, Spain and Ireland have **relatively large embryo donation** related activity. Czech Republic and Spain have the highest number of donated embryos in both absolute and relative terms. Estonia has limited embryo donation in absolute terms, but a high number compared to the number of women in reproductive age. Ireland is classified as having large embryo related activity as it has the highest volume of received or imported embryos. [55]

Belgium and the UK have a relatively average embryo donation related activity. While activities in Belgium are mainly with nationally donated embryos, activities in UK are often based on embryos received from other Member States or third countries besides donations in the own Member State.[56]

[55] Czech Republic and Spain have the highest number of donated embryos. Czech Republic has the highest number of donated embryos both in absolute terms (1,341) as relative to the number of women in reproductive age (0.061). Spain has slightly fewer donated embryos in absolute terms (1,233), however considerably fewer relative to the number of women in reproductive age (0.012). The Czech Republic furthermore received 7 embryos from other Member States and imports no embryos. For Spain these data are unknown. In absolute terms, few embryos are donated in Estonia (103). Estonia is classified as having large embryo donation related activity however as there are more donated embryos than Spain relative to the number of women in reproductive age (0.038). The numbers of received and imported embryos are unknown. Ireland has limited or no embryo donation in its own Member State. Ireland is classified as having large embryo related activity however as it has the highest volume of received or imported embryos.

[56] Belgium follows Spain in the number of embryos donated relative to the number of women in reproductive age (230 donated, 0.01 relative to women in reproductive age). No embryos are received from other Member States or imported from third countries. The UK has considerable embryo donation in absolute terms (315) but very limited if seen relative to the number of women in reproductive age (0.002). The UK is classified as average as embryos are received from other Member States and also imported from third countries although the exact number is unknown.

Bulgaria, Cyprus, Hungary, Latvia, Romania and Portugal have **relatively limited embryo donation** related activity both in terms of absolute numbers of donated embryos, or embryo donors as relative to the number of women in reproductive age.[57]

Countries with **no embryo donation** related activity. In Malta and Lithuania, gamete (both sperm and oocyte) donation is prohibited. In Italy, gamete donation was prohibited at the time of data collection. In Germany and Luxembourg, oocyte and embryo donation is not allowed while sperm donation is. In Denmark, Sweden and Slovak Republic, embryo donation is not allowed, but oocyte and sperm donation are allowed. For Slovenia and Austria it is unclear if embryo donation is allowed but no embryo donation related activity is reported.

For France, Croatia, Finland and the Netherlands, the picture remains unclear due to limited data. Available data suggests limited activity for France (based on number of donated embryos relative tho the number of women in the fertile age). For the Netherlands, Croatia and Finland the number of donated embryos is unknown.[58]

For Greece and Poland, no data is available on the numbers of donors/donations or treatments with donated embryos.

Cross-border distribution, import and export of embryos

Belgium, Bulgaria, Cyprus, Croatia, Hungary, Portugal and Slovenia do not report any cross-border exchange, import or export for embryos.

Only a few countries reported receiving embryos from other Member States and/or import from third countries. Ireland imports a significant volume of embryos: some from Czech Republic (18, in 2011), but mostly from the Ukraine (2015). Czech Republic reports few received embryos from other Member States.

For Estonia, Spain, Finland, France, the Netherlands, Poland and the UK, the number of embryos received from other Member States and imported from third countries is unknown. For Greece, 106,329 imported embryos are reported to EUROCET (year data: 2011) but this figure could not be verified by the National Competent Authority for tissues and cells in this particular Member State.

Few countries report distributing embryos to other Member States and/or exporting embryo to third countries; this is the case for Czech Republic, Latvia, the Netherlands, Romania and the UK. Although for the UK, export of embryos was only reported to the Implementation survey, not to EUROCET. The Czech Republic exports a significant amount of embryos to third countries.

For Estonia, France, Greece, Spain, Finland and Poland, the number of embryos distributed to other Member States and exported to third countries is unknown.

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[57] Bulgaria, Cyprus, Hungary, Latvia, Romania and Portugal have relatively limited embryo donation related activity both in terms of absolute number of donated embryos (22 for Bulgaria; 7 for Cyprus; 6 for Hungary; 13 for Latvia), or embryo donors (7 for Portugal) as relative to the number of women in reproductive age (0.002 for Bulgaria; 0.003 for Cyprus; 0 for Hungary; 0.003 for Latvia). Romania had 79 embryo donors in 2012 but relative to the number of women in reproductive age, this is very limited (0.002).

[58] For France the number of donated embryos is known. In absolute terms, there is a considerable number of embryos donated (332) but relative to the number of women in the fertile age, the number of donated embryos is very limited (0.003). For France, the number of received or imported embryos is unknown, making it difficult to classify the activity. For the Netherlands, Croatia and Finland, the number of donated embryos is unknown. Croatia does not import or receive embryos. For the Netherlands and Finland, this is unknown.

This leads to the following **key messages**:

- Czech Republic, Spain, Estonia and Ireland have high number of embryo related activity relative to the number of women in the fertile age, each within its specific context.
- There is hardly any cross-border exchange of embryos between Member States for reporting countries.
- There is hardly any import and export of embryos for reporting countries, except for Ireland, which had a large import of embryos from the Ukraine. As explained by the National Competent Authority for Tissues and Cells, this can be traced back to an oocyte donation programme between Irish and Ukrainian clinics (exporting sperm, and importing consequent embryos). The Czech Republic also had a large export to third countries.
- Information is limited as data are unavailable for a significant number of Member States; for other Member States data are incomplete and cross-border distribution, import and export is barely specified per country, making it impossible to map flows of gametes.

Cost and compensation of egg donation

In the EU, the EUTCD Directive for quality and safety prescribes the voluntary unpaid donation (VUD) character of gametes. Globally, different legal terms are used for compensation and payment schemes. According to the EU Directive, only making good the expenses and inconvenience are covered by the compensation. The opposite occurs in the US where donors receive payment and benefits, which means that the amount available for compensation covers more than just expenses. As also discussed in relation to sperm donation, payment is a more appropriate term to use than compensation in this US context.

Donor compensation and payment procedures

In Europe, most Member States allow compensation for egg donors (Art 12.1 of EU Directive on Tissues and Cells), but the amount is determined solely at national level. Compensation for egg donation ranges from €900 (Spain, the Netherlands), to GBP 750 in the UK, to 0 (zero) in several Member States where compensation (or treatment with donor gametes) is completely prohibited. Most websites and donor recruitment agencies don't advertise promising huge amounts for egg donation though, and it is difficult to get exact compensation rates without being enrolled in a programme or being already involved in treatment. The internet fertility search (Rathenau Instituut, 2014) indicates that also in Europe it is exception rather than standard practice to list the amounts of compensation received for donors on the websites of clinics where compensation to egg donors is offered.

In the US, by comparison, two professional societies have developed guidelines for self-regulation of the sector: the American Society of Reproductive Medicine (ASRM), and the Society for Assisted Reproductive Technology. According to their guidelines, the upper limit for egg donor remuneration is $10.000, however amounts up to $80.000 have been reported (Geesink and Steegers 2011).

Compared to the US, which pioneered the 'market' for oocyte products, the reproductive 'marketplace' in Europe is much more complex, with a wide array of regulatory restrictions per country, different reimbursement rules for (part of the) fertility treatments, a variety of different access restrictions to reproductive care, and a mix of public and private clinics offering donor material and fertility services.

Some EU countries have strict prohibitions on all kinds of oocyte donation (Austria, Germany, and until recently, Italy). Others have modest compensation schemes for direct expenses (Estonia); some countries compensate for loss of wages (such as the UK before the change of law in 2011); other countries also compensate for inconvenience and/or time (Spain, Czech Republic, recently also the Netherlands). It has to be noted that several third countries (e.g. Russia, Ukraine), which may be sources of egg donors for the EU, don't have any regulations at all covering donor compensation (see for figures also table 28 later in this section).

EU Member States are bound by the EU Directive for Tissues and Cells (EUTCD), and most have signed up to the Oviedo Convention, which forbids payment for the exchange of human tissues but permits compensation which is strictly limited to making good the expenses and inconveniences related to the donation (EUTCD 2004, article 12.1). According to some experts, this Directive prevents an oocyte 'market' from fully developing as it has in the US, but does in effect – according to some critics - create a compensation market where purchasers from the North and West travel to the South and East of Europe to purchase donor eggs (Cooper and Waldby 2014).

In the last few years, several regulations on donor compensation have been interpreted differently by EU Member States. The UK authority HFEA issued a public consultation on donor compensation before amending the 1990 Act allowing donor compensation of a fixed sum of GBP750 per cycle for egg donors and GBP35 per clinic visit for sperm donors. In the Netherlands, it was only in 2013 that compensation for egg donation (of around €900) was introduced, while Italy more recently (May 2014) lifted the ban on the use of donor gametes for reproduction in general.

Figure 40 Donor compensation in Europe

Source: Website HFEA consultation donor compensation (2014)

Donor preparation

The treatment cycle of hormonal stimulation for (commercial) egg donation follows a similar trajectory as for regular IVF. Oocyte donation involves hormonal and clinical intervention, where the biological rhythm and natural cycle of the donor is changed in order to produce a sufficient supply of oocytes. This process must be tightly regulated and scheduled in order to match the receiving party although recent technological advances in oocyte vitrification imply more 'off the shelf' availability of oocytes rather than having to rely on fresh supply. For ovarian stimulation, the donor has to comply

with a drug regimen of usually two weeks of daily hormone injections to suppress the natural biological activity (controlled via blood tests and ultrasound), followed by the administration of follicle-stimulating hormone (FSH) to stimulate production and maturation of multiple oocytes. Some concerns have been raised over the degree of hormonal stimulation deemed necessary for commercial egg donors, compared to women undergoing regular IVF treatment, as the safety of the procedure or the comfort of the donor might be put at risk in the desire to yield as many oocytes as possible from a single cycle. Increase in medication dosages and higher risk of ovarian hyperstimulation have been reported (Almeling 2011). After about two weeks of hormonal stimulation, the oocytes can be 'released' via surgical procedure under sedation (egg retrieval).

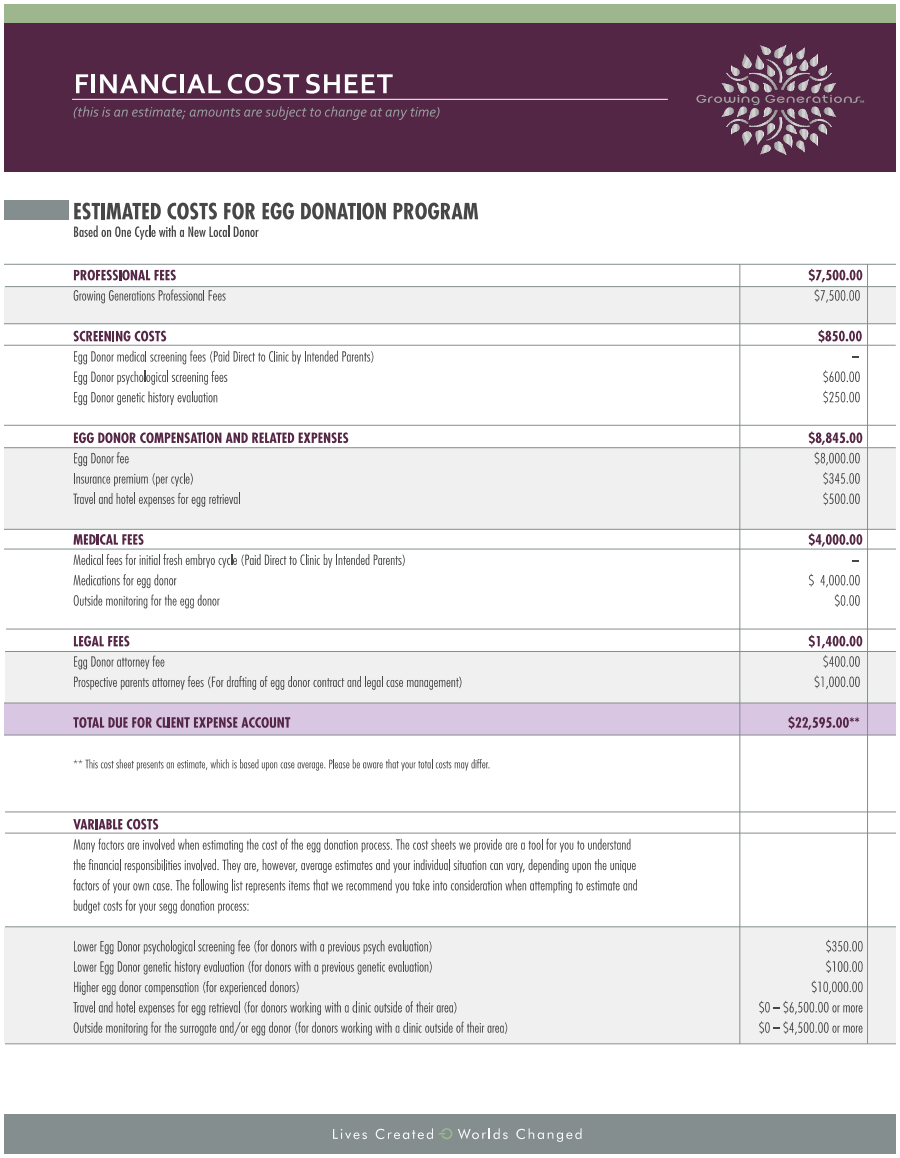
In the US, it is also reported that the donor needs to sign up for a healthy lifestyle, including abstinence from sexual contact, smoking, illicit drug use and unprescribed medication. Most agencies provide medical insurance for the donor.

Prices and procedures

In the US, the overall costs for egg donation for vendors can vary between agencies and, more widely, between continents. The following cost table is from one of the largest family building brokers in the US, Growing Generations, reflecting the upper end of the market (see figure 41).

Pricing of oocytes, embryo and treatments with donor oocytes and embryo are discussed in more detail in paragraph 5.11. An indication of prices is given based on the internet search of 180 fertility clinics. However it is very difficult, if not impossible, to compare prices listed on the websites of fertility clinics, as it varies greatly as to what these prices cover. Prices for oocytes and embryo are generally not stated as separate entities but only as part of a fertility treatment. The fees for treatments vary greatly in terms of what is covered. This variability includes factors such as what part of the treatment is included in the price, the quality and qualifications of donated oocytes and quantity of oocytes or number of treatments covered in the price.

Figure 41 Cost table egg donation (US)



FINANCIAL COST SHEET

(this is an estimate; amounts are subject to change at any time)

Growing Generations

ESTIMATED COSTS FOR EGG DONATION PROGRAM

Based on One Cycle with a New Local Donor

PROFESSIONAL FEES	**$7,500.00**
Growing Generations Professional Fees	$7,500.00
SCREENING COSTS	**$850.00**
Egg Donor medical screening fees (Paid Direct to Clinic by Intended Parents)	–
Egg Donor psychological screening fees	$600.00
Egg Donor genetic history evaluation	$250.00
EGG DONOR COMPENSATION AND RELATED EXPENSES	**$8,845.00**
Egg Donor fee	$8,000.00
Insurance premium (per cycle)	$345.00
Travel and hotel expenses for egg retrieval	$500.00
MEDICAL FEES	**$4,000.00**
Medical fees for initial fresh embryo cycle (Paid Direct to Clinic by Intended Parents)	–
Medications for egg donor	$ 4,000.00
Outside monitoring for the egg donor	$0.00
LEGAL FEES	**$1,400.00**
Egg Donor attorney fee	$400.00
Prospective parents attorney fees (For drafting of egg donor contract and legal case management)	$1,000.00
TOTAL DUE FOR CLIENT EXPENSE ACCOUNT	**$22,595.00****

** This cost sheet presents an estimate, which is based upon case average. Please be aware that your total costs may differ.

VARIABLE COSTS

Many factors are involved when estimating the cost of the egg donation process. The cost sheets we provide are a tool for you to understand the financial responsibilities involved. They are, however, average estimates and your individual situation can vary, depending upon the unique factors of your own case. The following list represents items that we recommend you take into consideration when attempting to estimate and budget costs for your segg donation process:

Lower Egg Donor psychological screening fee (for donors with a previous psych evaluation)	$350.00
Lower Egg Donor genetic history evaluation (for donors with a previous genetic evaluation)	$100.00
Higher egg donor compensation (for experienced donors)	$10,000.00
Travel and hotel expenses for egg retrieval (for donors working with a clinic outside of their area)	$0 – $6,500.00 or more
Outside monitoring for the surrogate and/or egg donor (for donors working with a clinic outside of their area)	$0 – $4,500.00 or more

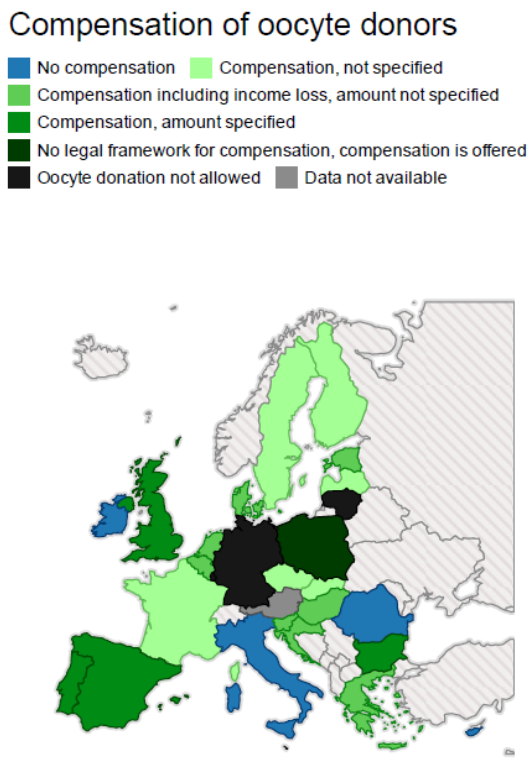
Lives Created ○ Worlds Changed

Source: Website Growing Generations (2014)

Compensation of sperm and oocyte donors in relation to legal system

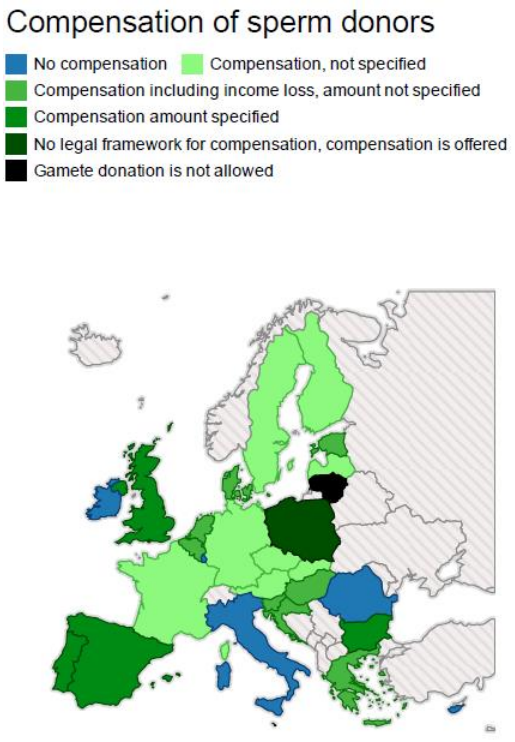
This section covers compensation schemes for all gamete donors who may receive compensation for the donation of sperm and oocyte. For information on compensation to donors, responses from National Competent Authorities for Tissues and Cells to the VUDTC survey were studied and cross-referenced with data from the internet fertility search. The websites of clinics were examined to see if compensation was offered, what kinds of expenses were covered, and the amount of the compensation. The maps below provide an overview of compensation to sperm donors and of compensation to oocyte donors (see figures below).

Figure 42 Compensation of oocyte donors



Source: VUDTC survey DG SANTE

Figure 43 Compensation of sperm donors



Source: VUDTC survey DG SANTE

In Cyprus, Ireland, Luxembourg, Italy and Romania, no compensation to sperm donors or oocyte donors is offered (in Luxembourg oocyte donation is not allowed). No sperm donation is allowed in Ireland (legislation is under review), while oocyte donation is minimal and mainly within the context of a programme with an Ukranian clinic. In these countries, the number of sperm donors and oocyte donors are limited.

In Italy, new legislation has been drafted on non-partner donation. This new legislation might include compensation to donors. Romania is the only Member State where ART treatment is not reimbursed. In this context, non-reimbursement of donors is to be expected. In these Member States, none of the clinics included in the sample in the internet fertility search offered compensation to donors.

In Poland, there is no legislation for compensating donors of sperm and oocyte. In the internet fertility search however, one clinic that was part of the sample in Poland did offer compensation to sperm donors (PLN 200, about €50), and two clinics offered compensation to oocyte donors (PLN 4,000 PLN, about €990). Figures were also given if the oocyte donor was willing to travel to another country to do the donation ($1000 and $1500, about €920 and €1380).

Other Member States have legal provisions that allow for compensation, with many Member States limiting it to the inconveniences and expenses related to donation. These expenses can cover travel costs to and from the place of the donation, for example, medical expenses related to the donation in case they are not covered by health insurance and loss of income due to making the donation. In Spain and Portugal, there can be compensation for inconveniences related to the donation. The amount of money in countries that compensate donors for loss of income and/or other inconveniences related to the donation might be higher than in countries where only travel expenses or medical expenses are covered. For some Member States it is not made explicit in the VUDTC survey what type of expenses (e.g. travel, medical or income loss) are compensated. On the map, these countries are labelled 'compensation not specified', which indicates that it is not known what type of expenses are compensated for, while this may be made specific in the respective laws or regulations of those Member States. For some Member States, for example Sweden, which expenses are compensated for is not established at a national level but on a more local level and may therefore vary within the individual Member State.

In Estonia the legal provisions for donor compensation explicitly allow for payment to donors; they may be offered an amount of money that is not necessarily related to making good expenses related to the donation. This may be a political decision related to decreasing population (according to the National Competent Authority for tissues and cells in Estonia). In Estonia no maximum limit for payment is set, but the legal provisions state that living donors shall be paid benefits for temporary incapacity for work. In Bulgaria a maximum amount for compensation is set. For sperm donors the maximum amount is €200 (and the average compensation given to donors is around €50). For oocyte donors, the maximum amount is €1,500 (average compensation is around €1,000).

Spain, Portugal, and the UK have explicitly set (maximum) amounts for the compensation of expenses made in relation to the donation of sperm and oocyte. In Spain, sperm donors may receive € 100 per donor and oocyte donors € 900. This maximum amount and the conditions under which compensation may be ensured, is periodically defined by the Ministry of Health, Social Services and Equity, based on a mandatory report by the National Commission on ARTs, the advisory board of this Ministry. In the UK, sperm donors may be compensated up to GBP 35 per clinic visit (about €49). Oocyte donors may be compensated up to GBP 750 per cycle of donation (about €1,047). This amount is set by the National Competent Authority for Tissues and Cells in the UK. In Portugal, the maximum amount of compensation to sperm donors is

one-tenth of the social support index of each course of donation, which comes to €41.92. The maximum amount for oocyte donation is 1.5 times the social support index, which comes to €628.83. The internet fertility search gave a further indication of the amounts of compensation in the Czech Republic, Denmark, Germany and the Netherlands (see table 28 below for an overview of amounts compensated). In other Member States, the amounts compensated were not listed on the websites of the clinics included in the sample.

Table 30 Compensation for sperm and oocyte donors

Member State	Compensation to sperm donors	Compensation to oocyte donors
Bulgaria	€ 200 (maximum of payment set)*	€ 1500 (maximum set)*
Czech Republic	CZK 10,000 CZK (about € 364) per 10 donations; € 40 per single donation (two clinics in the internet fertility search sample)	CZK 15,000 (about € 546) per donation; € 60-100 per donation (two clinics in the internet fertility search).
Germany	€ 105 per sample (two sperm banks in the internet fertility search sample). One sperm bank expects donors to donate regularly (roughly every 14 days for at least a year). The other sperm bank has a maximum compensation per donor of € 630.	
Denmark	€ 67 per sample (one sperm bank in the internet fertility search sample). At this sperm bank, a minimum of 10 samples is required. A bonus can be given to sperm donors particularly sought after (for instance, specific ethnicity). Non-anonymous sperm donors with extended profile get 10% extra.	
The Netherlands		€ 900 (one clinic in the internet fertility search sample)
Poland	PLN 200 (about € 50) (one clinic in the internet fertility search sample)	PLN 4,000 PLN (about € 990); $ 1,000 (about € 920) or $ 1500 (about € 1380) if the oocyte donor was willing to travel to another country to do the donation. (Two clinics in the internet fertility search sample).
Portugal	€ 41.92 for each course of donation (maximum of compensation set)*	€ 628.83 (maximum of compensation set)*
United Kingdom	GBP 35 (about € 49) per clinic visit (maximum of compensation set)*	GBP 750 (about € 1,047) per cycle of donation (maximum of compensation set)*

Source: Internet fertility search Rathenau Instituut (2014) unless stated otherwise. *Maximum compensation set at national level.

For sperm donation, the highest (maximum) amount is given to donors in Bulgaria. This is followed by Germany and Denmark. For oocyte donation, the highest (maximum) amount is also given to donors in Bulgaria, followed by Poland (when donors are willing to travel for their donation) and the UK. The amount of compensation given to oocyte donors is higher than the amount given to sperm donors, but sperm donors can (and are required to) donate more often.

5.2.5 Pricing of ART treatments in the EU

This section discusses pricing procedures and practices of ART treatment, also in relation to legal obligations in Member States. It is argued that a wide variation in pricing mechanisms exists and discusses the factors influencing this variability.

Pricing of gametes and pricing of treatments

Pricing of sperm, oocyte and embryo is mostly set as part of a fertility treatment. Oocytes and embryos are not priced separately; a price is set for the whole fertility treatment including the non-partner oocyte or embryo. Sperm is priced separately from the treatment by sperm banks, and by some clinics in some European Member States, but mostly prices are for treatments including donor sperm.

In some Member States, the price for fertility treatment is centrally determined by the public insurance institution or by the National Competent Authority for Tissues and Cells. This is the case in Belgium and Croatia, for example.

In other Member States, the price of fertility treatment is determined by the tissue establishments (hospitals or clinics), which typically leads to a larger variability of prices between clinics. This is the case in Bulgaria, Denmark, Ireland and Luxembourg.

In Member States where both public and private institutions operate, the process of determining the price can be different between public and private institutions, whereby prices in private institutions are set by the tissue establishments themselves while the prices in public institutions are centrally determined by a public body.

Where price setting is undertaken by the tissue establishment, it is often seen to be set in function of the reimbursement of the patient or of the clinic providing the treatment, by the health insurance institution. For example in Sweden, the price of the treatment is set by the clinic/hospital in agreement with their 'country council'. The 'country council' reimburses the hospital for their costs in providing the different treatments. Prices for treatments in the private sector are set by the clinic in agreement with the health insurance that partly reimburses intended parents for their treatment in this private sector.

Changing legal requirements and pricing of treatments

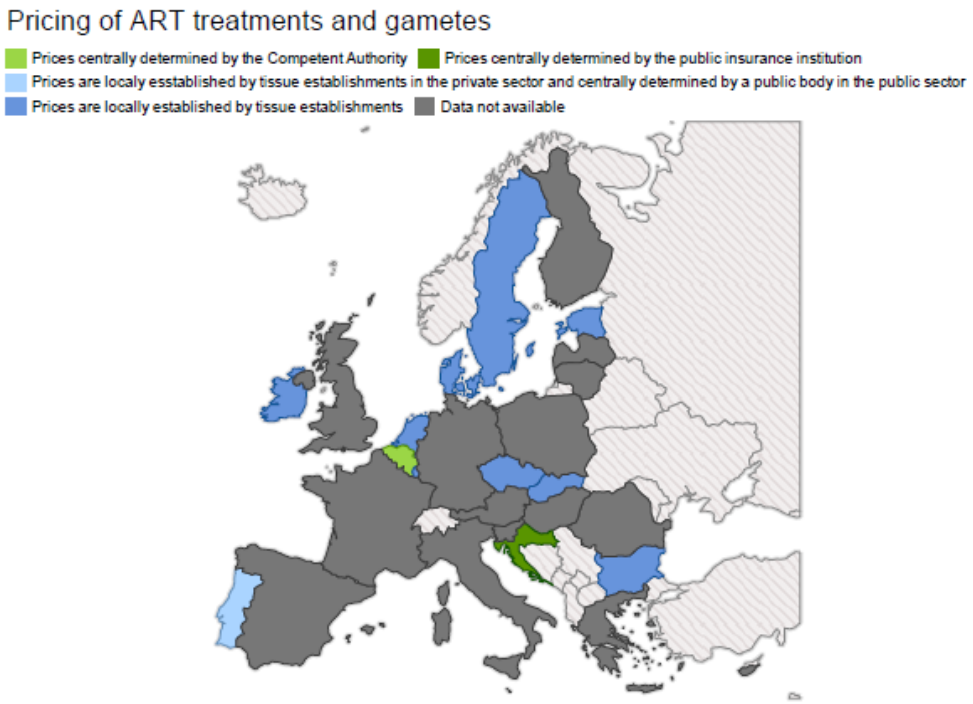
Changing legal requirements such as mandatory testing in donor screening or new coding requirements can impact the cost of treatment and thus have implications for the financial situation of the tissue establishments.

In countries with flexible pricing, where pricing is determined by the tissue establishment, prices of treatments can be adjusted more easily to these changing costs compared to countries with fixed pricing, where prices are centrally determined by a public body. If costs increase due to changing legal requirements, but prices cannot adapt consequently, clinics face a financial loss. This does depend of course, on how regularly costs are reviewed by the public body that determines the price and if those prices are adjusted to changing costs. In countries where tissue establishments can determine the price of the treatments themselves, pricing is more flexible and can be adjusted more easily to rising costs for treatment.

However, also in countries with flexible pricing, reimbursement to the clinics for the cost of the treatment or reimbursement to the intended parents for (part of) the treatment might still be centrally determined. Changing legal requirements in those cases can be

factored into the price of treatments charged to intended parents, but if reimbursement to the clinic or to the intended parents is not adjusted, this implies greater out-of-pocket expenses for the intended parents, possibly creating barriers for access.

Figure 44 Pricing of ART treatment and gametes in the EU



Source: Economic landscape survey NCATC (2015), data from 2011

Fees for treatments

For an indication of treatment prices, figures were collected from websites of a sample of clinics within each Member State. This was part of the internet fertility search of 180 fertility clinics and complementary to information collected in the survey to National Competent Authorities for Tissues and Cells, which also provided information on the pricing system described previously. Prices for treatments are very hard to compare within each Member State and even harder to compare between Member States since there is a great variability of what the prices for treatments actually cover. The overview of price-ranges per Member State should therefore be interpreted with caution (for a complete overview of prices per clinic see ART tables A9 in the annex). The paragraphs under the table indicate the factors that may account for the variability in prices. Firstly, variability exists as to what part of the treatment is included in the price. Secondly, the quality and qualifications of donated sperm can be a factor in the price. Thirdly, also the quality and qualifications of donated oocytes can be a factor in the price. Fourthly, the quantity of donated material or the number of treatments that are covered by the price can vary. Finally, some clinics list prices that are adjusted to what is being reimbursed to intended parents. This is described in more detail underneath the next table.

Table 31 ART treatment prices

	Ranges of fees in €										
Member State	IUI part-ner	IUI non-partner	IVF part-ner	IVF non-partn er	ICSI partner	ICSI non-part-ner	FET part-ner	FET non-partner	Oocyte donation	Sperm donation	Embryo donation
AT	440-495	1320	853,99-	NA	945,51-	NA	NA	NA	NA	NA	NA

n=6/6			3590		3890*						
BE n=5/12	125-300	125	0-3800	500	0-3800	500	NA	NA	NA	150	NA
BG n=7/7	179*-256*	281*	210*-2900*	NA	320*-1534*	NA	NA	NA	NA	306*	NA
CY n=1/8	NA	NA	NA	NA	NA	NA	NA	NA	3,838.37*	628,07*	NA
CZ n=7/7	110-140	200-350	1040-2200	4980-9900	400-1950	NA	220-1500	1140-1800	3500-6100	150-240	1000-2200
DE n=5/10	59,82-1000	NA	523,42-3000	NA	705,06-5200	NA	NA	NA	NA	NA	NA
DK n=12/12	0-509,21*	201,04*-924,69*	2278,36*-3015,2*	3115,71*-3340	2948,28*-3600	3600	670,09*-1072,15*	NA	3484,33*-6031,22*	174,21*-379	1072,15*
EE n=1/3	NA	NA	NA	NA	NA	390	1650-5100	1650-5100	NA	260	NA
EL n=7/15	200-3000	836-840	1500-3747	NA	300-3953	1455	700-4800	NA	3600-6245	250-500	3780,61*
ES n=11/13	750-1195	1000-1500	1650-6950	5500	3700-6950	NA	1200-1620	NA	5500-25000	NA	3585-6000
FI n=3/3	366,50-687	707-783	1815-2784	2470-5707	2353-3461	NA	712-1102	NA	5000-7400	737	NA
FR n=0/4	Prices are not listed on any of the websites										
HR n=1/3	263,08*	NA	591,95-1052,36*	NA	591,95-1314,81*	NA	328,70*	NA	NA	NA	NA
HU n=2/5	440	NA	1520-9000	NA	1840-1960	NA	800	NA	NA	NA	NA
IE n=5/5	400-950	NA	3750-4600	5150	4250-5000	5470	990-1250	NA	8000-9500	NA	NA
IT n=3/5	375-700	NA	2373-3900	8743	2373-3900	NA	375-900	NA	7000-8743	NA	NA
LT n=3/5	145-600	NA	1304-3050	NA	435-2900	NA	NA	NA	NA	NA	NA
LU n=0/1	Prices are not listed on any of the websites										
LV n=5/5	150-1500	300-2300	950-2080	1100-2450	1250-6000	1708-6300	300-1800	NA	3690-8250	150-370	8600
MT n=0/1	Prices are not listed on any of the websites										
NL n=4/10	724,83-750	724,83-1924,82	1100-2050	NA	1100-2306,90	NA	286,62-959,24	NA	2400	213	425
PL n=11/11	100-650	220-1250	875-3248	1625,10*-4000	875-2200	1625,10*	250-500	NA	4000-8000	150-490	4502,13*
PT n=1/2	680	970	2950	2950-3240	3900	3900-4190	900	NA	5950	290	NA
RO n=2/5	200-245	NA	1514-2550	NA	293-400	NA	400	NA	NA	NA	NA
SE n=5/5	693,86*-1067,51*	1601,32*	2188,47*3629,79*	4483,74*	3416,08*-3629,79*	NA	1387,82*	NA	7472,90*	NA	NA

SI n=0	No English language websites found.										
SK n=2/2	100	NA	1300-1990	NA	1300	NA	500	NA	4450	200	1450
UK n=11/11	347,86-1801,71*	1213,81*	1773,76-5008,26*	6984,63-7930,76*	1321,79-5922,03*	NA	709,63-1669,72*	3756,87*	2393,19-10713,72*	417, 42-3548,09*	4382,93-4994,75*

* Exchange rate 22-04-2015; for an overview of prices in national currency see annex ART A9

Source: Internet fertility search Rathenau Instituut (2014)

It is very difficult, if not impossible, to compare prices listed in the table as it varies greatly as to what these prices cover.[59]

Firstly, variability exists as to what part of the treatment is included in the price. Pre-treatment consultation and medical check-up, medications that are part of the treatment, hormone stimulation, lab costs, the cost for transfers of the embryo for IVF & ICSI and follow-up visits, are in some cases included in the price, while in other cases the prices listed are without. Often, it is not made explicit what part of the treatment is actually covered by the price listed by the clinics and what are additional costs. For example, the Austrian clinics in our sample list prices without medications, while most clinics in other Member States include medications in their price. In Bulgaria, some clinics have different prices listed for IVF and ICSI with hormone stimulation or without hormone stimulation. In Germany, various prices are listed for IUI with or without hormone injections. In some clinics in Finland, 2 or 3 follow-up visits are included in the price, while in other clinics in other Member States it is not clear if follow-up visits are included. Furthermore, some clinics include 'extra' procedures in their prices. For example, in some clinics in Spain, Pre-implantation Genetic Screening (PGS) of the donated gametes is part of the treatment price, but in the Czech Republic, PGS is included in the price at some clinics, while in most other clinics it is not. Furthermore there is variability as to what part of the treatment process is part of the price. Some clinics have one location where gametes are procured and stored but more locations where treatments are offered. Treatments in clinics where gametes are not stored are then more costly as cost for the transportation is added to the price. Also some clinics list prices for fertility treatment excluding the cost for medications for the donor, or costs for screening of the donor.

Secondly, the quality and qualifications of donated sperm can be a factor in the price. In the Czech Republic, for example, some clinics offer lower prices for treatments with non-partner sperm donation with lower quality sperm. The price of treatments with non-partner gamete donation can vary based on the anonymity or non-anonymity of the sperm. In some clinics in Denmark, IUI, IVF and ICSI with non-anonymous donor sperm is more expensive compared to these treatments with anonymous donor sperm.

[59] The following is an example of how this can lead to misleading conclusions. The table gives an overview of available prices of all the clinics that are part of the sample. So for instance, only two clinics in Belgium list prices for both IVF partner and IVF non-partner donation. The other clinics only list prices for IVF partner donation. For the clinics that list both partner and non-partner donation prices for both are the same; €500,-. However this is the price listed, but which is influenced by other factors (for instance the price is adjusted to compensation). Some of the other Belgian clinics list lower and higher prices for IVF with partner donation, ranging from €0,- up to €3800,-. To compare €3800,-for IVF with partner donation with €500,- for IVF with non-partner donation is to compare prices from two different clinics that have very different ways of presenting the price of the treatments. So this example shows it would be incorrect to conclude from the table in Belgium IVF with partner donated sperm is more expensive than IVF with non-partner donation. The same would be the case for Greece and Romania. Here the range of prices for ICSI with partner donation starts with a lower number than IVF with partner donation but to compare these and conclude ICSI is cheaper than IVF in Greece and Romania would be false as this is comparing two different clinics that present their prices differently as not all clinics list prices for all treatments.

Furthermore treatments with donor sperm from donors with an extended profile (for instance including an audiotape of the donor's voice) are more expensive.

Thirdly, also the quality and qualifications of donated oocytes can be a factor in the price. Prices for treatments with donor oocyte might be cheaper with frozen oocytes than for using fresh oocytes. Shared donor for oocytes vs exclusive donor for oocytes or from a known donor, are the extreme options on the spectrum.

Fourthly, the quantity of donated material or the number of treatments that are covered by the price can vary. In Greece, different prices exist for treatments with one donated oocyte or embryo or with two donated oocytes or embryos, the latter being a 'reduced price'. In Romania in some clinics, IVF with partner donation is cheaper if a limited number of oocytes is retrieved. Furthermore, the number of sperm straws included in the price for IUI with non-partner donation can vary between clinics and is often not explicitly stated. Also the number of treatment cycles included in the price can vary. For instance in some clinics in Sweden, prices are for a package of three IVF/ICSI cycles or treatments while in other clinics in other countries prices are for one cycle/treatment.

Finally, some clinics list prices that are adjusted to what is being reimbursed to intended parents. Some clinics list prices for both reimbursed and non-reimbursed treatments while for other clinics this is not made explicit. Some clinics in the Netherlands for instance, list different prices for non-reimbursed and for reimbursed patients. Furthermore, in some clinics prices vary per age category of the woman, as reimbursement is also related to age. In Sweden, prices for IVF and ICSI for women under 39 are lower than for women between the age of 39 and 41. In Austria, treatment is also less expensive for women aged under 36 than for those aged 36-40.

Access and reimbursement to ART

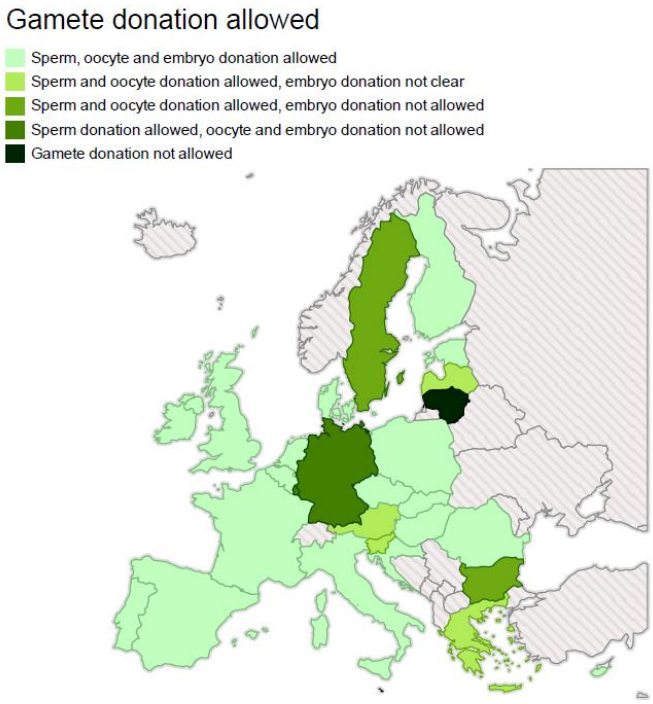
Countries within the EU vary on which gametes can be donated, which treatments are allowed and who has access to those treatments related to age, sexual orientation or marital status, for example. Furthermore, in relation to these restrictions there are differences regarding which treatments are reimbursed, how many treatments are reimbursed (e.g. how many IVF cycles) and who is reimbursed (depending on infertility diagnosis, age restrictions, sexual orientation and marital status). These factors are related to volumes of activity in each Member State and to cross-border reproductive care. The Economic Landscape survey sent to National Competent Authorities for tissues and cells that formed part of the research for this report and the check on country factsheets verified by the National Competent Authorities for tissues and cells, are the data sources for the following analysis. For cross-referencing, criteria information from the internet fertility search has been used to see if clinics offer treatments that are not allowed, and to provide information on treatments offered by clinics in those cases where there is missing data from the NCATC survey. As discussed in Chapter 1, this survey did not reach full coverage of all EU Member States due to non-response.

Access to non-partner donation

Countries within the EU vary as to whether non-partner donation is allowed in general and if sperm donation, oocyte donation and/or embryo donation are allowed more specifically (see figure 45 below).

In most EU Member States, donation of sperm, oocyte and embryo are allowed. In Italy gamete and embryo donation are allowed since April 2014, but these have not yet been regulated by law.

Figure 45 Gamete donation



Source: Economic landscape survey NCATC (2015), data from 2011

Countries with restrictive access to gametes are Malta and Lithuania where non-partner donation (sperm, oocyte and embryo) is not allowed. In Luxembourg and Germany, sperm donation is allowed but oocyte and embryo donation are not allowed. In Sweden, sperm and oocyte donation are allowed, but embryo donation is not allowed. In Austria, sperm and oocyte donation (oocyte donation since February 2015) are allowed but embryo donation is not specifically allowed. In Latvia, Denmark and Slovenia sperm and oocyte donation are allowed but data is unavailable for embryo donation.

For Greece and Slovenia, data from the National Competent Authorities for Tissues and Cells is not available but the internet fertility search showed that Greece offers non-partner donation with sperm, oocyte and embryo. Slovenia was not included in the internet search as no clinics with English language websites were located.

Access and reimbursement for ART treatments

Besides restrictions to the donation of gametes in some Member States, access to certain treatments is also restricted. In this section we focus on 'common' treatments IUI, IVF, ICSI and FET. If donation of gametes is not allowed, then treatment with these donated gametes is also not allowed. In most EU Member States, IUI, ICSI, IVF and FET with both partner and non-partner donation are allowed. In some Member States FET is not allowed. In Malta, FET with partner donation is not allowed, in Luxembourg FET with non-partner donation is not allowed while other treatments are allowed. For Greece and Germany and Slovenia, no data was available on the access to treatment. Based on the internet fertility search, it was established that Greece offered all treatments with partner and non-partner donation. In Germany, IUI, ICSI, IVF and FET with partner donation is offered, while FET with non-partner donation is not offered. Slovenia was not included in the internet search as no clinics with English language websites were found. It should be noted that the internet fertility search merely gives an indication of treatments offered in the Member State and the sample could have been biased as only English language websites and clinics having a website were included in the search.

Not all available treatments are reimbursed. In Romania for instance, IUI, IVF, ICSI and IVF with partner and non-partner donation are all allowed but none of these treatments are reimbursed. In Bulgaria, IUI and FET are allowed, but not reimbursed, while IVF and ICSI are reimbursed. In Poland, IUI, ICSI, IVF and FET with partner donation are reimbursed while those same treatments with non-partner donation are not reimbursed. In Italy reimbursement varies from region to region.

In all Member States where treatments are being reimbursed, this reimbursement is limited. Some Member States set limits in terms of a percentage of the treatment being reimbursed. In Austria 70% of IUI treatment is reimbursed, and in Ireland 21% (as tax refund which can be claimed for medical expenses). Other countries reimburse only part of the treatment, for instance in Malta, medications are not reimbursed. Most Member States set limits to the number of cycles reimbursed ranging from one cycle for IUI or ICSI, IVF and FET in Latvia, to six cycles in Belgium. Most Member States reimburse 3-4 cycles of treatment.

Table 2 Treatment reimbursement levels of ART treatments

Country	Reimbursement IUI	Reimbursement IVF, ICSI and FET
Austria	70% of the treatment	4 cycles
Belgium	6 cycles	6 cycles (including IUI cycles)
Bulgaria	Not reimbursed	3 cycles for IVF & ICSI, FET is not reimbursed
Cyprus	Data not available	Data not available
Czech Republic	4 cycles	4 cycles (including IUI cycles)
Germany	Data not available	Data not available
Denmark	Data not available	Data not available
Estonia	Number of cycles is limited, exact figure unknown	Number of cycles is limited, exact figure unknown
Greece	Data not available	Data not available
Spain	Number of cycles is limited, exact figure unknown	Number of cycles is limited, exact figure unknown
Finland	3-4 cycles in public sector / 3-5 cycles in private sector (out-of-pocket maximum of insurance for treatment in private sector is about the cost of the first cycle)	3-4 cycles in public sector / 3-5 cycles in private sector (out-of-pocket maximum of insurance for treatment in private sector is about the cost of the first cycle)
France	3 cycles*	3 cycles*
Croatia	4 cycles	6 cycles for IVF (for ICSI and FET data not available
Hungary	Data not available	Data not available
Ireland	21% (tax refund)	21% (tax refund)
Italy	Data not available, public reimbursement is different from region to region	Data not available, public reimbursement is different from region to region
Lithuania	Data not available	Data not available
Luxembourg	Data not available	Data not available
Latvia	1 cycle	1 cycle
Malta	Partly reimbursed, medications are not reimbursed	Partly reimbursed, 3 cycles (for IVF and ICSI, FET is not allowed) medications are not reimbursed
Netherlands	Number of cycles is limited, exact figure unknown	3 cycles
Poland	Number of cycles is limited, exact figure unknown	Number of cycles is limited, exact figure unknown

Portugal	3 cycles	3 cycles
Romania	No reimbursement	No reimbursement
Sweden	Number of cycles is limited, exact figure unknown	Number of cycles is limited, exact figure unknown
Slovenia	Data not available	Data not available
Slovakia	Data not available	Data not available
United Kingdom	Data not available, individual NHS Clinical Commissioning Groups (CCGs) or health boards decide who qualifies for NHS provision	Data not available, individual NHS Clinical Commissioning Groups (CCGs) or health boards decide who qualifies for NHS provision

Source: Economic landscape survey NCATC (2015), data from 2011; Response to country factsheets by NCATC * www.agence-biomedecine.fr

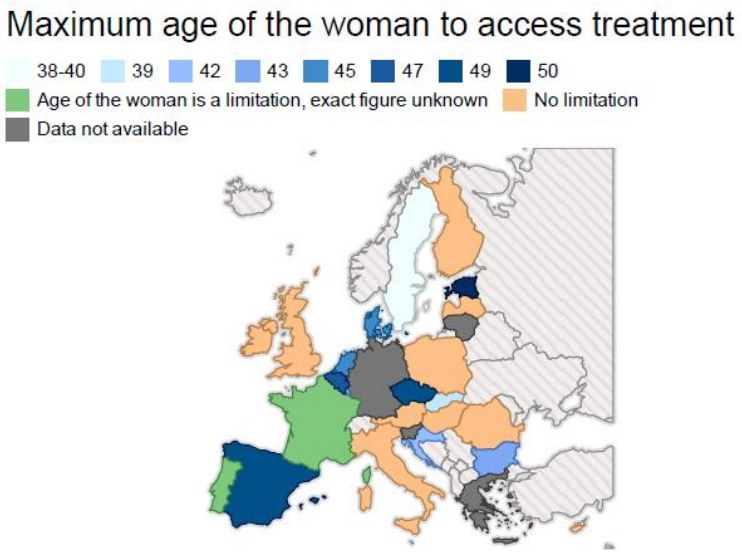
The number of cycles reimbursed is important in terms of demand; where more cycles are reimbursed, more demand for treatments can be expected. Furthermore when limited numbers of cycles are reimbursed this has implications for cross-border fertility care. Not being reimbursed for treatment might be a motivation for looking for (better priced) treatment abroad.

Limitations to access and reimbursement

Besides general limitations to access and reimbursement of ART treatments and of gamete donation, certain specific treatment limits are set to specific population parameters: the age of the woman, for example, or same-sex couples or single women, as discussed in the next paragraph.

Many Member States set no restriction on the **maximum age of the woman** for access to treatments. But while age restrictions are not set by law, individual clinics might set their own limits based on professional standards. Other Member States have legal restrictions ranging from 39 years in Slovakia to 49-50 years in Czech Republic, Spain, and Estonia (see Figure below). Other Member States have set 'procreation age' as a limitation for access to fertility treatment, as is the case in France. Restrictions on age can be a motivation for cross-border fertility care while countries that have set a relatively high age for access or have set no age limit, might attract intended parents from countries where age limits are set.

Figure 46 Maximum age of the woman to access treatment



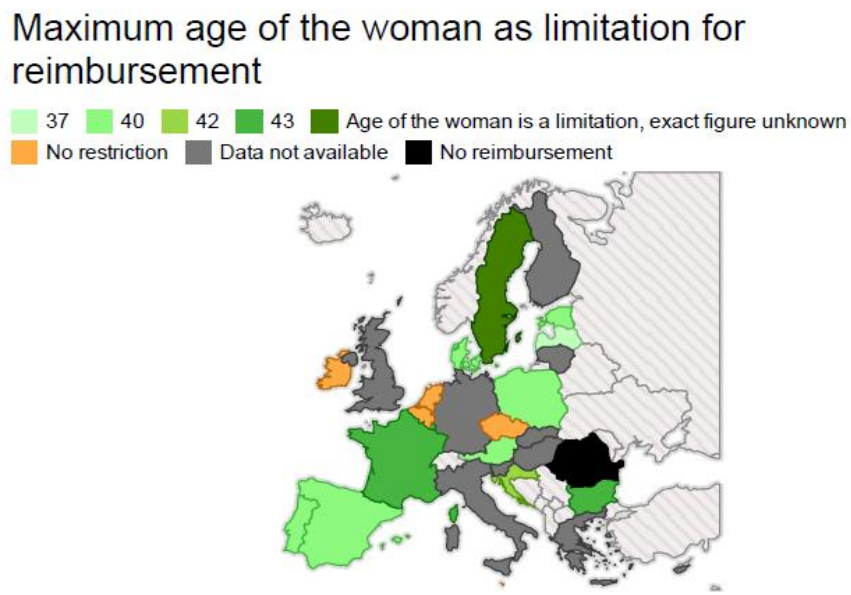
Source: Economic landscape survey NCATC (2015), data from 2011; Response to country factsheets by NCATC * www.agence-biomedecine.fr

Clinics might set their own access criteria related to the maximum age of a woman for accessing treatment based on clinical guidelines, for example. This could mean that although there is no limitation for access to treatment for women of a certain age from a legal perspective, older women might not be treated by any of the clinics in a Member State due to the access criteria set by these clinics. Having said this, a relatively high, or no age limit at all policy might attract intended parents from other Member States for fertility treatments. In Belgium, the Czech Republic, Estonia and Spain, the age limit of a women seeking treatment is set relatively high (>48). Furthermore, in Austria, Cyprus, Finland, Hungary, Ireland, Italy, Latvia, Poland, Romania and in the UK, no legal age limit is set for women to access treatments.

It should also be noted that oocyte or embryo donation might be the only feasible treatment option for older women. If oocyte and embryo donation is not allowed in a Member State, this might leave very limited feasible treatment options for older women even though no access criteria on age have been set. In all Member States with a relatively high age limit or with no restriction on age for women, oocyte donation is allowed. But in Austria and Italy, oocyte donation has only become available in recent years (2015 for Austria and 2014 for Italy) and legislation is still being drafted. In Member States where age limits for women to access treatments are set relatively low, this might be a reason for older women to travel to other Member States with fewer age restrictions for fertility treatments. In Sweden and Slovakia, the maximum age for women to access fertility treatments is <41.

Some Member States have set a **maximum age of the woman for reimbursement**. This age limit ranges from 37 in Latvia to 43 in Bulgaria, France and Luxembourg. Most common is setting the age limit for reimbursement to 40. Some countries have set no age limit for reimbursement but have set an age limit for access. This then naturally becomes a limit for reimbursement. Austria has set an age limit to the man (50) as well as to the woman (40) (see figure below). Belgium has set 47 as the age limit for access (although the procurement and request for insemination/implantation has to be done before the age of 45), and this is also the case for the Czech Republic where there is no restriction for reimbursement but maximum age for access is 49 and for Malta is 42.

Figure 47 Maximum age of the woman as limitation for reimbursement



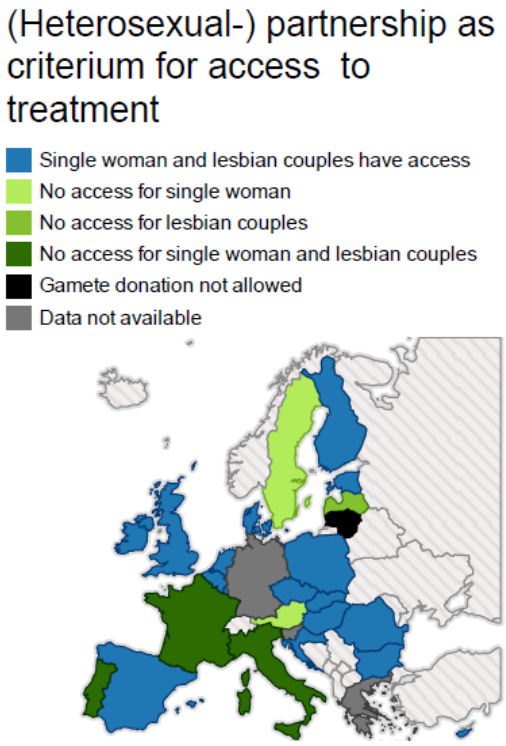
Source: Economic landscape survey NCATC (2015), data from 2011; Response to country factsheets by NCATC * www.agence-biomedecine.fr

Besides these limitations to reimbursement that have been centrally set in some Member States, it might also depend on the insurance scheme if limitations such as age criteria are set for reimbursement. For instance, in the UK there are no restrictions for access to treatments, but individual NHS Clinical Commissioning Groups (CCGs) or health boards decide who qualifies for NHS provision. In Romania there is no restriction to access based on the age of the woman but also no reimbursement for ART treatments at all, meaning all women – regardless of age - pay for their treatment themselves either through a private insurance scheme or out-of-pocket. Ireland has set no age limit to access to treatment and also no age limit to reimbursement; here the relatively low reimbursement to treatment ratio in general (21% for IUI, ICSI, IVF and FET) means both younger and older women pay a significant amount of treatment out-of-pocket or through a private insurance scheme.

A low age for reimbursement (alongside a low age for access) can be a driver for cross-border fertility care, even where there is no age limit for access to treatment or the limit for access is higher than the limit for reimbursement. Latvia has the lowest age for reimbursement (37). In Austria, Estonia, Spain, the Netherlands, Poland and Portugal, the age of reimbursement is 40. All these Member States have set a higher age or no age limit, for access to treatment. If treatment is not reimbursed in their own Member State, intended parents might be more prone to look for treatment abroad for reasons such as better quality of treatment, higher success rates, shorter waiting lists or treatment that is relatively better priced.

Besides the age of the woman seeking treatment, **sexual orientation and single status** also restrict access to treatments in some Member States. (See figure below for an overview.) It should be noted that this study does not look into surrogacy, which is why access to ART treatment for male same-sex couples is beyond the scope of this study.

Figure 48 Heterosexual partnership as a condition for access to treatment

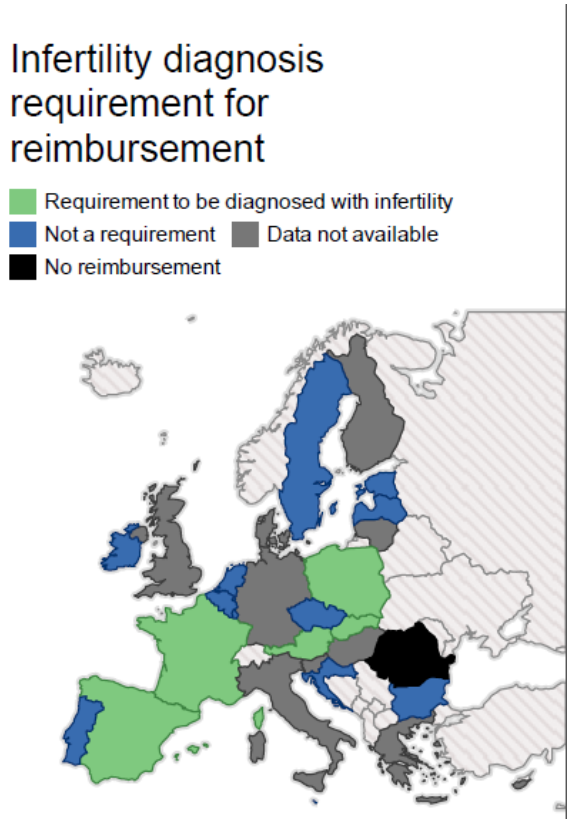


Source: Economic landscape survey NCATC (2015), data from 2011; Response to country factsheets by NCATC * www.agence-biomedecine.fr

None of the Member States lists 'marriage' as a criterion for access. Partnership is, however, a criterion in France, Italy, Portugal and Sweden. In those countries single women do not have access to ART treatment. Bulgaria restricts direct use of sperm for IUI treatments outside a partnership: women are thus not allowed to bring a sperm donor for direct donation if this is someone other than their partne. A partnership is however not restricted to a heterosexual relationship. In Sweden, lesbian couples do have access to treatments while in Italy, France and Portugal lesbian couples do not. In Latvia, lesbian couples do not have access to treatment but partnership is not required so single women do have access. In Malta and Lithuania, gamete donation is prohibited, excluding both single women and lesbian couples from ART treatment. Restrictions for single women or lesbian couples could be a driver for cross-border fertility care.

Sexual orientation and marital status can also be criteria for reimbursement. In some Member States this is implicitly stated by making infertility by diagnosis a criteria for reimbursement (see figure 49). Single women and lesbian couples are not eligible for having such an infertility diagnosis, given that the reason for not being able to conceive is the absence of a male partner.

Figure 49 Infertility diagnosis requirement for reimbursement



Source: Economic landscape survey NCATC (2015), data from 2011; Response to country factsheets by NCATC * www.agence-biomedecine.fr

In Austria, Spain, Poland and Slovenia, single women and lesbian couples do have access to treatment but reimbursement is based on infertility by diagnosis. This could be a driver for cross-border care as if treatment is not reimbursed in the own Member State since intended parents might be more prone to look for treatment abroad.

5.3 FUTURE PERSPECTIVES IN ART

Several factors are expected to increase the demand for reproductive therapies and services significantly in the coming years.

5.3.1 Increasing demand for fertility treatments

First of all, it is important to note that both social and clinical-scientific factors play a role in the increased demand for reproductive treatments over the last few decades.

In terms of medical technological trends, innovations in freezing technology has led to safer and more efficient techniques to retrieve, store, defrost and implant reproductive tissues and cells and embryos, with higher success rates (especially compared to fresh gametes).

While still experimental, recent progress has been made in the formation of artificial gametes, i.e. gametes generated by manipulation of their progenitors or of somatic cells. This has stirred scientific and societal debate about their use in medically assisted reproduction. Artificial gametes could potentially help infertile men and women but also post-menopausal women and gay couples conceive genetically related children (Hendriks et al 2015).

Overall, technological innovation has brought a large range of treatment options to the clinic, making infertility or subfertility treatable conditions. Alongside improved IVF, ICSI and IUI treatment options, also new economic activities and opportunities emerged. For example, companies have emerged offering 'one-stop-baby-shops' or package deals mostly catering for singles and gays in search for a genetically related child, for example including surrogacy. Today, most surrogacy arrangements are gestational (as opposed to traditional), which means that the woman carrying is not genetically related to the child. The pregnancy follows after IVF treatment with gametes from the intended parents. Today many of these intended parents are same sex couples.

In addition to increased availability of artificial reproductive treatment, the demand in the population for these treatments has become more articulate. Several lifestyle factors have been considered to cause reduced fertility, such as stress, body weight, smoking, sexually transmitted infections, alcohol consumption and substance abuse. Age is another common cause of infertility. In Europe, the average age of motherhood has risen significantly over the last decades, and postponement of child bearing is also considered a dominant driver for especially treatment with donor eggs in the near future.

5.3.2 Changes in fertility treatment offers and services

Improved freezing techniques for gametes and reproductive tissue have provided an opportunity to store material for future use for patients undergoing medical treatment (mainly cancer treatment) that may affect their ability to have children. It has also led to novel business models for fertility banking. Female fertility preservation has become particularly popular, where (single) women can store their own eggs for future use. In the US, several multinational companies have offered their female employees a paid 'egg freezing package' to postpone family building, which in turn has provoked media attention and public debate.

Another popular business model, especially in the UK and US, is egg sharing. This is a specific arrangement by which a woman undergoing IVF makes some of her eggs available for another woman's treatment, or for research, in return for free treatment or

significantly reduced treatment costs. Egg sharing has also been marketed as 'half price IVF'.

The delivery of sperm directly to consumers for application/insemination at home is also on the rise, with estimations from the largest sperm bank in Denmark now delivering over half of all straws directly to consumers, rather than via clinics. This has provoked some debate on regulatory oversight, especially in countries with registries for non-anonymous donors.

But in addition to the increased availability of technological means to establish a pregnancy or to preserve fertility, lifestyle factors, the increased age of women, also the desire for genetically-related children has increased demand from several groups in society, most notably LGBTs. Social 'acceptability' factors may play a role in increased diversity in family building. Every school class in Western Europe has, on average, one child born after IVF treatment. Gay marriage has become legal in more western countries, while the traditional adoption markets are not always accessible to same sex couples, or to solo parents. Single households are more prevalent than a few decades ago, and with the individualisation of society, the norms and values about the stereotypical or ideal family have changed. More children grow up in non-traditional households. These alternative variations of parenthood, especially same sex adoption schemes and surrogacy arrangements, have also spurred debate in several countries about legal and biological parenthood.

Finally, the possibilities for pregnancy and parenthood have become both more global and more commercial, with international clinics and (online) brokers offering a diverse range of reproductive treatments and 'one-stop-baby shops' (Geesink and Steegers, 2011). Increased awareness about the possibilities of infertility treatment, lower cost treatment options across the globe and alternative arrangements have democratized the fertility spectrum. Internet and low cost carriers have brought fertility destinations closer to home and easier accessible to a larger group of patients and consumers that are willing to travel and willing to pay.

5.4 CONCLUDING REMARKS AND SUMMARY ART

- ART refers to all treatments that include in vitro handling of human reproductive cells (gametes) and embryos to establish a pregnancy. This includes, but is not limited to, in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI), intra-uterine insemination (IUI), and cryopreservation of gametes and/or embryos. These treatments are performed with reproductive cells from a man and a woman in an intimate physical relationship (partner donation), or with gametes or embryos from another person apart from the couple (non-partner donation). A couple of establishments are focusing on collection, banking and distribution of sperm and egg cells (so-called sperm and egg banks).

- The total number of tissue establishments dedicated to ART in the EU-28 is unclear; ranging from 772 (of which 69% private and 31% public) according to the EC implementation survey (2011), to 1519 in EUROCET128 (2013). The largest countries have the highest absolute numbers. However Spain, Denmark and Belgium have a relatively high number of clinics compared to the number of females in the reproductive age (however, a high amount of clinics does not necessarily mean a high amount of activity).

- These TE's are supplied by a few large multinational pharmaceutical corporations, in particular to supply hormone therapies to stimulate female patients undergoing an IVF cycle. Merck Sereno is leading this market with 40% share, followed by Ferring Pharmaceuticals. There is a trend that these companies also offer packages combining pharmaceuticals (hormone therapy) with accompanying equipment, disposables, testing and training of professionals, hence supporting the entire set-up and operations of an ART tissue establishment.

- Furthermore, some intermediary organizations (or brokers) have emerged in the sector to bring together intended parents and clinics, sometimes facilitating travel across borders (Spain or third countries like the US or Northern Cyprus), and offering additional services such as travel and insurance. Additional innovative models exist to facilitate uptake of fertility services like egg sharing (donating part of the collected egg cells in return for a rebate on the costs of the IVF cycle) or social fertility preservation (freezing egg cells for use at a later, more convenient time).

- More than 550,000 IVF cycles were initiated in the year 2011. According to the European professional society for reproductive medicine (ESHRE), one in six couples experience infertility problems of some sort at least once during their reproductive years. The increasing demand for ART is driven by age and lifestyle factors (including stress, obesity, smoking, substance abuse). Also new technological possibilities, like storing gametes for future use, and the desire for genetically related children amongst gay and lesbian couples, are further drivers for growth in the ART sector.

- Access to ART is strongly related to national legislations, which are less or more strict in factors like maximum age (relatively high in EE, ES and CR), family composition (e.g. taken into account in IT, LV, PT and SE) or the possibility to use donated gametes (strict in AT, DE, LU and until recently IT). Reimbursement is another important factor that defines access and is less or more strictly stipulated in national laws (e.g., with 6 reimbursed IVF cycles BE has a relatively large reimbursement). Reported fees vary from €210 to €9900 per IVF cycle, but it differs widely what is covered as part of the procedure.

- These national differences are drivers for cross-border ART services. Women and couples of Member States with stricter access and/or reimbursement criteria travel to ART establishments abroad. CR, EE and ES seem to be countries attracting foreign citizens for ART treatment in facilities that announce their activities online in multiple languages.

- Within the EU, DK is the leading country for sperm collection, banking, distribution and sale. The two largest EU sperm banks (Cryos and European Sperm Bank) are both located in DK and ship sperm to multiple other EU Member States. BE is an important destination for sperm. Only IE and UK report import of sperm from the US, while it is however also possible that part of the sperm distributed by DK banks is collected outside the EU.

- The selection of donors contains an extensive selection for medical criteria (in line with Directive 2004/23/EC) as well as for social criteria. Once accepted, sperm donors are requested to make several donations within a few months. DK sperm banks compensate donors with € 30-70 per donation. The more personal information the donor is willing to share with candidate recipients, the closer this amount is to the higher end. Higher compensations are however not thought to increase the overall donor pool.

- Tissue establishments in ES and CZ are the most active in collecting donor egg cells. However these egg cells are hardly distributed across borders. Rather egg cell donors as well as recipients are travelling to these countries to make donations or undergo ART treatments with donated egg cells.

- Egg cell banks in ES and CZ announce their search for donors in multiple languages, which indicates they are attracting donors from different countries. Several clinics recruit oocyte donor online in PL, offering compensation for travelling to other countries. Egg cell donation is an invasive and long process requiring multiple injections with stimulating hormones and eventually a (minimally invasive) surgery to pick-up the egg cells. Reported compensations are around € 900. Another approach to obtain donated egg cells is the so-called 'egg-sharing' scheme applied in the UK, where women get a significant reduction in the fee for their own IVF treatment if they agree to donate part of the collected egg cells to another woman (or to research).

- Embryo donation is mainly reported in CZ, EE, and ES. Embryos are however hardly shipped across borders but, as for egg cells, it is rather recipients that travel to these countries to undergo ART treatments with donated embryos. IE has organized an oocyte donation program in collaboration with a non-EU country, to which sperm is exported and from which consequent embryos are reimported.

- Overall fees/prices paid for donated gametes are usually not set in function of the cost of collection and storage, but are rather set in function of the demand for specific donor profiles.

6 FORWARD LOOK: NOVEL THERAPIES

6.1 INTRODUCTION

The growing importance of human tissue and cells in medical therapies started in the seventies of the 20th century and continues to foster innovation, bringing new and improved therapies. For many decades the tissue and cell transplantation sector developed in parallel with the organ transplantation field, its progress being stimulated by the new advances in microsurgery, immunology (e.g. HLA system, immunomodulation, immunosuppression) and cryopreservation. Moreover, some scientific discoveries have also introduced a new type of tissue and cells products based on tissue engineering, gene therapy or somatic cell therapy (Advanced Therapy Medicinal Products or ATMPs). This chapter aims to provide insights into the innovations and developments that can be expected in the coming years. The first section reiterates the main trends per therapeutic segment (replacement tissues, HPC, ART), as described in the previous chapters. The next section explains the possible impact on the tissue and cell sector resulting from developments in related fields including ATMPs. A final section describes some key horizontal factors that may impact on the economic development of the tissue and cells sector across the board.

6.2 EMERGING INNOVATIONS AND TRENDS IN THE TRADITIONAL TISSUES AND CELL SECTORS

This first section briefly explains the main trends for each of the therapeutic segments covered in the three previous chapters. While it reiterates the main innovations described in these chapters, it also explains the expected growth trends for each of the segments. The trends mentioned are a general reflection at EU level, and differences in national legislations and organisations can create significant variability between Member States.

6.2.1 Replacement tissues

In replacement tissues, growth trends vary per type of tissue, each one being subject to different factors. Overall, the use of ophthalmologic grafts is expected to increase due to higher needs of our ageing population, while the use of bone grafts is expected to grow due to an increased commercialisation, evidenced by the entry of private operators. The growth trends in use of skin and cardiovascular grafts are less clear due to different, partly opposing, factors.

- A continuous increase is expected for ophthalmological grafts due to the ageing of the population. Within the sector there is however a shift towards increased transplantation of lamellar tissue grafts (and less of transplants of full corneas). This requires some additional processing in the tissue establishment, previously undertaken by the surgeon in the operating theatre, and hence might also bring an increase of processing activities for the tissue establishments. The increasing use of limbal cells for regeneration might drive further eye bank activities, either as supplier of starting materials and/or as processing entity.

- Also for musculoskeletal grafts, demand is expected to continue growing, (in particular) due to commercial promotion of these tissues by larger (international) tissue establishments towards the orthopedic, neurosurgical and dental care providers. This uptake is further supported by the development of new applications where bone-grafts are provided in combinations with medical devices, biologicals and/or pharmaceuticals.

- For skin banking the future growth trends are less clear. While skin allografts remain the first choice of treatment, the combination with autologous skin culturing is expected to develop further. However, such autologous skin cultures are more demanding in terms of processing facilities and require investments in additional quality, safety and efficacy requirements, which may not be within the possibilities of every skin tissue establishment. This might then increase their reliance on services from third parties or these activities have to be handed over to other actors like manufacturers of ATMPs.

- Also overall growth in the cardiovascular tissue sector is less clear. Given the limited availability of human cardiovascular tissue and the developments of good alternatives like medical devices, the use of human grafts will remain low, and will focus on a number of specific indications, like for pediatric patients. On the other hand, the application of decellullarization techniques might broaden the indication for use and thus increase the demand for human heart valves again, if their benefits are indeed confirmed by further clinical results and processing costs are acceptable.

- The use of other tissue types, like amniotic membrane and pancreatic islets, is still relatively limited but might increase significantly if research lead to further clinical progress. Also the use of other tissues and cells, like nerve cells, might pick up as new clinical applications are investigated and the clinical outcome is confirmed.

6.2.2 Hematopoietic progenitor cells (HPC)

The use of allogeneic hematopoietic progenitor cells (HPC) has become the treatment of choice for patients with disorders of the hematopoietic system, in particular with blood cancers like multiple myeloma or leukaemia. In December 2012, the benchmark of 1 million HPC transplantations was reached, over 40 years since the first successful attempts were undertaken; 50% of these transplantations were performed in the period 2006-2012. The annual transplantation number of allogeneic HPC in Europe has increased from 5,000 in 1998 to 15,000 in 2013 (Passweg et al, 2015). The rise in use of HPC is likely to continue over the next 10 years (Lown and Shaw, 2013), however subject to some trends. Some of these new developments might be considered medicinal products:

- There is an increased interest in haplo-identical HSC transplants, using mainly family-related donors. This is a cheaper approach that seems to allow for similar clinical outcomes compared to using HLA-identical or matched unrelated donors. If this technique is confirmed by further clinical studies, the demand for unrelated allogeneic HPC is expected to go down significantly. This would in first place reduce demand for (more expensive) cord blood units, but might in the long-term also reduce the need for registries.

- HPC, and cells found in HPC grafts, are increasingly subject of research for the development of new therapies like MSC for treating Graft versus Host diseases, tumor-infiltrating lymphocytes (TIL) and chimeric antigen receptors (CAR) for personalized therapies and dendritic cells for solid tumor. As explained in section 6.3, the uptake of these therapies, if based on allogeneic HPC, can have a significant impact on the therapeutic landscape and demand for specific grafts.

- The impact of cord-blood ex-vivo expansion is expected to remain low. While it allows working-up a specific unit of HPC-CB (with an acceptable match grade to the recipient) through ex-vivo expansion techniques, the techniques are very costly and will therefore probably not lead to a huge increase in the use of HPC-CB for transplantation. Though the technique provides a medical alternative where

no bone marrow donor and only a CB-unit with marginal or inadequate number of cells is available.

6.2.3 Assisted reproductive technologies (ART)

The forecast for assisted reproductive technologies (ART) is based on medical, social, technological and commercial parameters. The combination of these factors is expected to further increase the demand for IVF therapies in the coming years:

- Medical infertility rates continue to increase, with a current estimate of 9% amongst couples in Europe. Many underlying lifestyle factors are becoming only more important: stress, body weight, smoking, sexually transmitted infections, alcohol consumption and substance abuse.

- In Europe, the average age of motherhood is rising significantly over the last decades, and postponement of child bearing is also considered a dominant driver for IVF, especially for treatment with donor eggs. This trend is partly facilitated by IVF itself which allows for female fertility preservation for (single) women who can store their own eggs and postpone their eventual use.

- The increased acceptance of new family compositions, like single-mothers and gay/lesbian couples, where IVF allows for these groups to have children.

- The increasing commercialization of the sector also brings increasing uptake of new business models like direct-to-consumer delivery of sperm, online brokerage services and access to cross-border treatments. Obviously the development of these activities will depend on the regulatory actions of the Member States' authorities, who are becoming increasingly concerned on the impact of these developments on safety and quality.

- The uptake of the IVF sector is further facilitated by many governments who foresee (more or less) reimbursement to citizens undergoing IVF treatments.

Overall, growth is expected in each of the three segments of the tissue and cell landscape over the coming years, but to a varying degree.

6.3 OPPORTUNITIES AND CHALLENGES FOR THE TISSUE AND CELL SECTOR

The development of the tissue and cells sector might also be affected by the development of neighbouring sectors like the development of the ATMP and medical device industry. This section examines these potential impacts. It sets out opportunities and challenges brought by these new fields. The terms ATMP and medical devices used throughout this section should be understood in accordance with the respective definitions in the EU legislation.[60,61]

[60] REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

6.3.1 Impact

Availability of human tissues and cells as source materials for neighbouring sectors

Due to the success of tissue and cell transplantation procedures and the improvements in, post-transplant outcome, the demand for human tissues/cells has increased all over the world during the past decades (Newsletter Transplant published by Council of Europe/EDQM[62]). However, the unavailability of suitable tissues/cells for transplantation (due to limited resources and lack of donors) has resulted in shortages in some countries. In this relative scarcity, a potential competitive demand for human tissues /cells by the (ATMP) manufacturing industry raises concerns on scarcity among tissue bankers, healthcare professionals, competent authorities and eventually patients. The concern became apparent for the first time in the US in 2004, when the competition for starting material became evident for Alloderm™ (Lifecell inc.), a skin derivate from human cadaveric skin. The commercial success was not only creating scarcity for traditional tissue banks, in the end this scarcity of the base material was also considered a potential threat for shareholders of Lifecell (Birger 2006)[63].

However with the currently developed ATMP therapies these concerns are limited, because over the last ten years the development of the ATMP sector has focused mainly on **autologous cell products** (Cuende et al., 2014)[64]. This trend seems to be confirmed by the TERMIS-EU project, which looks at a broader set of databases and describes the activities of five established scientific organizations in Europe in the area of cellular and engineered tissue therapies (Martin et al, 2015). Participating in this survey were 313 research teams active in cell and tissue therapy (26 European, 7 EBMT affiliated countries). According to this survey, 2157 patients were treated with cellular or engineered tissue therapies in 2012. Of these patients, the majority was treated with autologous cells (69%). The percentage of treatments using autologous versus allogeneic cells increased from 36% in 2008 to 69% in 2012, with the actual number of patients treated with autologous cells more than doubling in this period (from 664 to 1485

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[61] COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices

[62] https://www.edqm.eu/en/organ-transplantation-reports-73.html

[63] http://archive.fortune.com/magazines/fortune/fortune_archive/2006/09/04/8384735/index.htm

[64] In the EU, 4 of the 5 ATMPs *with central marketing authorisation* are for autologous use: MACI (matrix-induced autologous chondrocyte implantation, intended for the repair of cartilage defects - Genzyme/Sanofi), ChondroCelect (autologous chondrocyte implantation intended for the repair of symptomatic single defects in the cartilage of the femoral condyle - TiGenix), Provenge (autologous treatment for prostate cancer - Dendreon) and Holoclar (autologous stem-cell treatment used for the testament of moderate to severe limbal stem-cell deficiency - Chiesi Farmaceutici S.p.A.). In the US, three autologous cell therapies have been approved: Carticel (autologous chondrocytes for cartilage repair - Genzyme/Sanofi), Provenge and LaViv (an autologous fibroblast product for filling wrinkles - Fibrocell). In South Korea, two autologous programmes have received approval in the past few years, an autologous bone marrow–derived cell therapy for myocardial infarction (HeartiCellgram -AMI; PharmiCell Co. Ltd) and an adipose tissue–derived cell therapy for anal fistulas (Cupistem; Anterogen).

patients). If this trend were to continue, concerns on scarcity and limited availability of human tissues and cells for transplantation might be less funded.

When just focusing on the commercial operators/companies, data show however that these seem more interested in developing cell products for **allogeneic** use (Foley and Whitaker, 2012; Maciulaitis et al, 2012; Hourd et al, 2014). While for a number of years large conventional pharmaceutical companies seemed reluctant to invest in the ATMP sector, recent reports show that this is beginning to change. According to the 2014 Annual Report of the Alliance of Regenerative Medicine,[65] a US-based multi-stakeholder advocacy organization in the field of regenerative medicine, 91 companies in the world (of the 247 biologics companies covered by the report) were involved in stem cell and progenitor cell-based therapeutics, some of them considered medicinal products, with 9 marketed products and 289 ongoing clinical trials of which 65% referred to new allogeneic products. More recently, several companies announced significant investments in the development of allogeneic ATMPs, especially in the field of immunotherapy with new tumour-specific antigen targeting products against for instance B-cell leukaemia, lymphoma and even solid tumours. When these therapies become successful, eventually using allogeneic cells, increase in demand of human base material can be expected and some traditional therapies like stem cell transplantation might be replaced with these new therapeutic approaches and products.

Product innovations: replacement or supplement to existing tissue and cell therapies?

Until recently, the best or only therapeutic solution for some diseases was human tissue and cell transplantation. However, recent advances in medical research and development show that in the future some of these traditional therapies may be replaced by interventions based on product innovations, in- and outside the legal framework of EU Directive 2004/23 for Tissue and Cells. This could have a significant impact on the tissue and cell sector, especially in fields where alternative treatments become available.

A good example is the field of heart valve replacement. Currently, patients with severe valvular heart disease typically receive either mechanical or biologic valves and only in specific indications human heart valves. Mechanical and biological valves however have limitations because they may cause haemorrhage and thromboembolism, and require anticoagulants. Human valves on the other hand are prone to fibrosis, calcification, and degeneration in the end. To overcome these issues several research projects are working on bioengineering new heart valves by seeding human cells (e.g. mesenchymal stem cells, fibroblasts, and umbilical blood stem cells) on appropriate scaffolds (Rippel et al, 2012; Mack, 2014). Although there is still a long way to go, tissue-engineered heart valves have the capability in the future to effectively replace the current heart valve transplantation procedures without having the limitations of medical devices. An alternative, and simpler technology, to address the side effects of the current implants, is decellularisation of human allografts. This technique applied a.o. by tissue establishments, removes the existing immunogenic cells of the heart valves, which can then be implanted and serve as human in-vivo scaffolds for the patient's own endothelial cells, without causing direct immunological response by the host. Although in the latter example human heart valves are still needed, experiments with decellularized pigs valves are already on their way (Luo et al, 2014).

[65] http://alliancerm.org/sites/default/files/ARM%20Annual%20Report%202014-28pgs.pdf

Another example is the development of artificially-grown skin for major burn patients. In 2013, Garzon et al. succeeded for the first time to grow artificial skin from stem cells derived from the umbilical cord. Other cell types may be used. Again, these new forms of treatment could change the concepts for burn care.

In conclusion, while numerous research is going on in the world to develop new tissue and cell based therapeutic interventions (not only in the direction of advanced therapies) it is difficult to predict with precision the impact on the traditional tissue and cells sector. If however breakthroughs will be significant, complete replacement over time of some traditional transplant therapies can be expected, in some specific segments. Essential is that these developments bring significant advantages for patients, in terms of therapeutic benefit, quality and safety, in order to become approved by relevant authorities and reimbursed by the national healthcare schemes.

Limited central overview on product development in tissue and cell area

Assessment of the impact of neighbouring sectors on the tissue and cell field is hampered by the facts that many developments take place on a local level and that seize and volume of these activities are not always clear. In a recent paper (MedNous, 2015) three causes explaining the difficulties in quantifying the ATMPs produced outside the central marketing authorisation scheme were quoted:

- lack of reporting systems to capture all cell-based manufacturing activity
- national regulations allowing doctors to produce cell-based products in the context of a prescription for an individual patient under their responsibility (the so-called 'named patient basis' exemption).
- different approaches in implementing the Hospital Exemption (HE) clause (e.g. under the specials scheme which is a national derogation of Directive 2001/83/EC in the UK).

Regarding the HE, there are few data on the number and type of ATMPs authorised under the HE across EU. This can be explained by the diversity of approaches taken by the Member States when implementing the HE. There are various interpretations of the situation or circumstances in which it applies, of the definition of "non-routine basis", and of the entities allowed to have such a license or differences in application of the GMP requirements (Cuende et al, 2014). Some information can be deduced from the information in the Pharmaceutical Committee survey[66] (2011 data, with only 6 Member States reporting having ATMPs approved under the HE) and the Commission Report on advanced therapy medicinal products (2014)[67] in which 60 derogations from the obligation to obtain a marketing authorisation prior to the marketing of advanced therapies had been granted up to April 2012 by the Member States (both under the HE and under other provisions of the Directive 2001/83/EC, notably Article 5). Member States have reported 31 ATMPs as being legally on the EU market prior to the entry into force of the ATMP Regulation. Although this figure must be viewed with caution, it is known that some of these products have been processed by tissue establishments before ATMP legislation came into place (Pirnay et al, 2012). Unclear is to what extent these products still continue to be used locally in the absence of a marketing authorisation under derogations granted by Member States (the hospital exemption or otherwise). Local production may also have been discontinued because of the national regulatory

[66] http://ec.europa.eu/health/files/advtherapies/2013_05_pc_atmp/07_2_pc_atmp_2013.pdf

[67] http://ec.europa.eu/health/files/advtherapies/2014_atmp/atmp_en.pdf

approaches on classification of these products, their authorisation and reimbursement at national level.

The lack of data on the implementation of the HE was also highlighted by the AGORA[68] survey on regulatory differences for the ATMP sector, which involved 55 facilities from 13 European countries. According to these 2013 data covering 1174 patients admitted for an ATMP therapy (in the 41 facilities that shared production data), 55% were treated under either HE or named patient use (the remaining 45% were treated in the context of clinical trials). Based on the replies from these facilities, the AGORA consortium concluded that there is no strong support for central classification before requesting approval for HE or clinical trials, with most of the respondents considering that HE harmonization is preferable above central classification. They also concluded that there is a strong support for the creation of registries for ATMPs given authorisation under the HE clause.

The absence of comprehensive data on the number of ATMPs developed and applied under the other jurisdiction hinders any precise forecast of its impact on the tissue and cell sector and on the involvement of tissue establishments in this area. If most of these therapies continue to be autologous as is currently the case, their impact might be only minor, unless existing treatments with allogeneic grafts are thus replaced. If however, the predicted development of the allogeneic segment by the commercial sector will prevail, the impact could be significant. Tissue establishments could become the prime suppliers of the required base material, but their position as providers of classical allografts may reduce whenever the added value of novel products like ATMPs, medical devices and other cell and tissue innovations will be of more therapeutic use and therefore replace the original allografts.

6.3.2 Opportunities: developing and manufacturing ATMPs

Some procurement organisations and/or tissue establishments are already operating as **suppliers of tissues and/or cells for ATMP manufacturers**. In a recent survey performed by the European Commission on the implementation of the EU Tissue and Cell Directives, it was shown that 332 procurement organisations (7% of all EU procurement organisations; 2011 data) were carrying out procurement of tissues/cells for ATMP manufacturing. This collaboration may be triggered by the current legal requirements (i.e. Article 3 in the ATMP Regulation) but it could also represent a mutually beneficial situation where tissue establishments contribute with their expertise in procuring tissue/cells from appropriate allogeneic donors, providing safe and high-quality material for the ATMP manufacturers.

Due to the nature of their activities, tissue establishments are in a good position to become otherwise involved in the ATMP manufacturing process, not only because they have access to starting materials and competence in donor selection, consent and procurement of donations, but mostly because some have already the appropriate infrastructure in place (e.g. GMP facilities) and expertise to pursue such an endeavour. Especially when these establishments are already licensed as GMP productions site, the production of new cell therapies can come with a limited incremental cost

[68] AGORA = acronym of an FP7 sponsored project "ATMP GMP Open-access Research Alliance", a follow-up of the Academic GMP project; http://agora-gmp.org/

This is best seen in tissue establishments that are associated with academia and academic hospitals. Much of the product developments regarding ATMP originate in universities and affiliated hospital settings, where GMP licensed tissue establishments play a supporting role in the processing of the products for therapeutic use, for instance in clinical trials. When however the ATMP product development shows clinical potential, universities may embark on a more commercial route to develop and produce ATMPs (including a strong patent and licensing policy) by establishing independent spin-off SMEs (Etzkowitz 2003). Examples of these spin-offs in the field of regenerative medicine are TiGenix - founded in 2000 as a spin-off from the University Leuven and the University Gent, producing ChondroCelect; and Holostem Terapie Avanzate srl – a spin-off company of the University of Modena and Reggio Emilia which manufactures Holoclar with the participation of the Chiesi Group. Founding of these enterprises is essential to obtain sufficient external funding for development, a task which public tissue banks can never undertake, given that they often have a not for profit status.

In the last decade, several EU tissue establishments also developed **cell culture facilities**, departments specialised in isolating and expanding cells for further research and/or human application:

- Tissue Services, which are part of UK NHS Blood and Transplant - is not only a tissue bank but also include a tissue development laboratory for cell culture and tissue engineering, and a GMP Technology Transfer Centre completes the chain from novel idea to novel tissue graft[69].
- The Rizzoli Musculoskeletal Tissue Bank in Italy is part of a larger structure – the PROMETEO (Products for Regenerative Medicine and Tissue Engineering in Orthopedics) laboratory,[70] which aims to manufacture products based on regenerative medicine and tissue engineering in orthopaedics. Approved by the Italian Competent Drug Agency AIFA, the centre is working on identifying and developing alternative sources of mesenchymal stem cells (MSC) and new biomaterials for use in combination with MSCs for musculoskeletal regeneration and it takes part in clinical trials by developing and providing cell therapy products.
- Blood and Tissue Bank of Catalunia (Banc de Sang i Teixits), which is the public organisation of the Health Department that not only functions as blood bank, cord blood bank and tissue bank, but also incorporates a cell therapy unit ("Joseph Carreras Cell Factory") which performs ex vivo expansion and production of progenitor cells[71].

Most of these public tissue/blood establishments remain non-commercial, also as a result of their legal setting (Pirnay et al., 2012). However, also some of these public tissue establishments have launched commercial entities. One example is PDC line Pharma, founded in April 2014 in Grenoble (France) as a spin-off of a blood bank (EFS) which is a clinical-stage biotech company that develops a new class of therapeutic cancer vaccines based on a line of plasmacytoid dendritic cells,[72] which are generally considered to be an ATMP.

These examples show that tissue establishments may become involved, not only in the procurement, but also in **developing and processing of tissue and cells for (clinical trials of) ATMPs, in particular where authorised locally under the HE** or other

[69] http://www.nhsbt.nhs.uk/tissueservices/aboutus/whowhereweare/

[70] http://www.ior.it/en/area-stampa/news/prometeo-lab-and-cell-factory-two-realities-operating-innovation

[71] http://www.mediterraneumrc.org/pls/portal30/docs/PAGE/CANCRE/CCM/ISSUES/CCMYOTH/YOUTH_EX_BLOOD_DONATION/TAB16279466/BLOOD%20BANK_PRESENTATION.PDF

[72] http://pdc-line-pharma.com/about-us/

derogations from the medicinal products legislation. This may be seen as an opportunity (e.g. with the possibility of enlarging activities in the future or for further development), but also as a challenge (see section 6.3.3).

6.3.3 Challenges

One important challenge concerns **availability of tissue or cell products, that were developed decades ago** and supplied to hundreds of patients on a regular basis by tissue establishments, and that became medicinal products after the entry into force of the ATMP Regulation, and therefore now require a central marketing authorisation. Entering the market with these ATMPs requires organisational structures (logistics, marketing and sales, production) that differ in many aspects of traditional tissue and cell establishments.
While the majority of tissue establishments may not be interested in entering the more complex field of developing ATMPs, or may not be capable of investing in the infrastructures and technical skills required to develop and ATMP and to apply for a marketing authorisation, it remains possible to play a role in the non-routine use of these products. In some countries such products received authorisation for non-routine use under the HE (or other derogations in the Directive 2001/83/EC), while in other situations therapies might need to be discontinued because of non-implementation or different interpretation of the hospital exemption. For instance, keratinocytes produced by the keratinocyte bank of the Queen Astrid Military Hospital in Brussels since 1987 have been used as auto- and allografts in more than 1 000 patients, primarily to accelerate the healing of severe burns (De Corte et al, 2012; Pirnay et al, 2012). In 2010 the Committee for Advanced Therapies (CAT) of EMA recommended to classify keratinocytes as ATMPs, following which the national authority forced the hospital to become fully compliant with the ATMP regulation. This would imply a significant increase in production costs for the hospital, a clinical trial of a product already in routine consolidated use and the request for a marketing authorisation. As a consequence higher costs would lead to higher prices to be charged for the same product, without any additional benefit for the patients. The professionals in the tissue bank argued that, as a public cell and tissue bank, they are not necessarily interested 'putting their product on the market' and thus in obtaining a centralized marketing authorization or intellectual property. They also highlighted that the numerous inspections by the competent authorities in the past 25 years had never revealed any safety or quality concerns. As a consequence, the availability of the keratinocyte therapy to the severely burnt patients in the burn wound centres may be threatened, unless they can be approved locally, e.g., to continue under the HE. Similar cases could include therapies with chondrocytes (for the treatment of cartilage defects) or amniotic membrane (for treating ocular defects) which are supplied in several Member States under the HE or as tissues for transplantation in the case of amniotic membrane.

What is considered a challenge for tissue banks working under the HE can be perceived as lack of a level playing field by ATMP manufacturers (Brévignon-Dodin et al, 2009; Van Wilder, 2012). In a recent article, TiGenix NV, which manufactures ChondroCelect, considers that hospitals should not be allowed "regardless of whether they are public or private, whether they are a company or a hospital, to produce a cartilage product that has not gone through the same regulatory hurdle as, in this case, ChondroCelect, because that is creating an uneven competitive environment". It should be mentioned

that ChondroCelect, has so far only obtained (conditional) agreements for reimbursement in 3 EU Member States (BE, NL and ES, the 3 countries where it has facilities),[73] six years after obtaining marketing authorisation. The draft guidance by NICE in the UK (2014)[74] recommends that these therapies (ChondroCelect as well as MACI, another ATMP), priced around €20,000 per treatment, are used only in research, as more evidence is needed on how well it works in the long-term and its cost-effectiveness. The difficulties that are illustrated in this example to obtain return on investment for developing centrally authorized ATMPs, emphasize the benefits of maintaining the status of HE for ATMP products and discourage many tissue establishments involved in this field, to strive for full market authorisation. In a time of financial pressure/constraints for many healthcare systems in the EU, the high costs of some new ATMPs may represent a serious issue which should be taken into account and discussed in advance by manufacturers and regulators.

Last but not least, one of the challenges identified by some professionals in the tissue banking sector is the **legal framework and legal uncertainty** for tissue and cell therapy development in the future. Legal uncertainty is an important factor hampering investment and developments in these sectors.
Some critics underline the complexity of the EU and national legal frameworks, emphasising that the regulatory burden of cell-based therapeutic products (including ATMPs) should be related to the risk it may pose to the health and safety of recipients (Närhi and Nordström, 2014). In order to address this complexity and offer guidance to researchers some organisations and authorities have developed toolkits (e.g. Cell Therapy Regulatory Toolkit devised by the London Regenerative Medicine Network/LRMN; see Culme-Seymour et al, 2015; see also the ATMP toolbox developed by the EU-funded project AGORA). Some put in place mechanisms providing early advice to ATMP manufacturers (e.g. the 'One stop shop' regulatory advice service for regenerative medicine established jointly by four regulatory agencies in the UK: HFEA, HTA, MHRA and HRA)[75]. Also the Committee of Advanced Therapies (CAT) in EMA offers the possibility for advice.

A related and important concern in the tissue and cell sector relates to the classification of products at the borderline between tissues and cells, medicinal products and medical devices. According to Article 17 in the ATMP Regulation, the Committee of Advanced Therapies (CAT) in EMA was given the task to provide (upon request from developers) scientific recommendations on whether a product falls within the definition of an ATMP. However CAT opinions are not legally binding and the final decision on classifying borderline products is within the responsibility of relevant national competent authorities, which may lead to situations with the same product having different status across the EU. National authorities also address similar questions of interpretation in expert meetings of NCATC, not necessarily with similar conclusions as the CAT.

Whilst recognizing the scientific expertise of CAT, some professionals in the tissue and cell banking sector also expressed concerns that the current system does not involve or does not require adequate consultation of experts/authorities from other related areas such as medical devices, blood, tissues and cells, with decisions taking into account primarily the legislation, expertise and concerns of the medicinal products sector.

[73] Tigenix Annual Report 2014, p43 (http://www.tigenix.com/public/uploads/files/2015/shareholders_meeting/20150420/2015-tigenix-annual-report-2014-en.pdf)

[74] https://www.nice.org.uk/news/press-and-media/nice-consults-on-research-recommendation-for-knee-cartilage-treatment

[75] https://www.hta.gov.uk/policies/regulatory-advice-service-regenerative-medicine

This situation triggered concerns especially among professionals in tissue establishments not interested in applying for central marketing authorisation or in commercialisation of their processes, but in continuing their small scale/local activities under appropriate authorisation, and thus ensuring the treatment of patients in need. They questioned how a decrease in number and in variety of conventional grafts with well-established medical use (which would have to be discontinued in the case of a similar product being given central marketing authorisation) would serve the general public/patients when sophisticated but expensive products will be accessible to a limited part of the population (Pirnay et al, 2010, 2012). Furthermore, in the case of a new preparation process which includes a technique not listed in Annex I of the ATMP Regulation (i.e. the list of non-substantial manipulations), tissue establishments don't have the certainty that their new preparation process, even though approved by the competent authorities for tissues and cells will not be considered an ATMP by CAT. The situation is further complicated by the fact that NCATCs cannot submit requests to CAT for a classification opinion. There are also concerns regarding this classification mechanism expressed by ATMP manufacturers which are however not included here, since they are available through other sources (e.g. Summary of the responses to the public consultation on the application of Regulation (EC) No 1394/2007 on advanced therapy medicinal products).[76]

The complexity of the current legal and economic landscape does not allow for a precise forecast for the tissue and cell sector which is, in many respects, caught between two worlds; a traditional one which is – except for ART – characterized by smaller scale public sector operators and a new one, which is based on private/commercial operators. The consolidation of large private tissue establishments could lead to challenges for small-scale/local (often not-for-profit in the EU) operators and the development of large-scale central tissue banks (de Kort and Verhagen, 2008). A challenge for both authorities and tissue and cell banks is how to handle the area of potential tension between the presence of the for-profit players in this filed and the voluntary non-remunerated donations that allow for the base material for this sector. Another challenge could be how less profitable parts of the sector are maintained if more profitable parts are taken over by the private sector.

Despite these challenges, it is clear that the human tissues and cells sector has an important part to play in the development of regenerative medicine, either by providing the human material or by engaging in research and manufacture of ATMPs together with industry.

6.4 FACTORS WITH IMPACT ON FUTURE DEVELOPMENTS IN THE TISSUE AND CELL SECTOR

This final section highlights some general trends and horizontal issues that need to be considered for the future development of the entire tissue and cells sector. These cross-cutting factors are usually linked to medical, social, ethical or political developments that influence demand and/or supply, and consequently, on the future economic landscape.

6.4.1 Economic factors: entry of the private sector and the drive for efficiency

While the procurement and supply of tissue and cell for transplantation were initially developed and offered within the public sector (e.g. hospitals, universities and blood services), an increasing involvement of the private sector is observed in recent years. Most often, this growing involvement is commercial by nature and driven by the potential

[76] http://ec.europa.eu/health/files/advtherapies/2013_05_pc_atmp/2013_04_03_pc_summary.pdf

for profit. These commercial activities could significantly impact the future landscape. The following factors have facilitated increasing commercialisation:

- Cheap and easy global communication, in combination with simplified transport possibilities for biological materials, have allowed for the development of direct-to-consumer activities. Most notable activities are private cord blood banking for family use and direct sperm distribution for home application. Competent Authorities reported that in 2011 60% of cord blood banks were private (Implementation Survey), and about half of the sperm distributed by Cryos, the leading and private sperm bank in Europe, is reported to be sent directly for home insemination (see chapter 5). While profitable, future growth of these activities might face regulatory obstacles due to concerns expressed regarding vigilance of quality and safety in the case of sperm[77] or regarding the information provided to the public, particularly regarding clinical justification, in the case of cord blood.[78]
- Particularly in the field of bone banking, large scale processing in an industrial set-up can bring economies of scale and significant economic advantages. In this context, there has been a change whereby, Competent Authorities reported over 40% of 2011 tissue establishments processing bone to be privately owned (Implementation Survey). The largest of them are run in a very similar way to companies in the plasma derivative sector and pharmaceutical sector. Some are listed on the public stock market or owned by publicly listed companies[79] and hence they are expected to engage in profit maximizing efforts (including increased marketing and sales activities). While these companies are mainly US based, they have increasing sales activities and impact in Europe, many having subsidiaries established in EU Member States with marketing and sales teams promoting the tissues they sell.
- Changes in societal structure do impact demand in a couple of sectors, e.g., because tissue and cells are needed for an ageing population, or because the use of IVF is more accepted and needed in view of trends like delaying childbirth or non-traditional family models. Governments follow these changes with decisions to reimburse these therapies, which helps guarantee income. Competent Authorities reported 70% of ART establishment in the EU to be private in 2011 (Implementation Survey) and this trend is likely to increase.

The rising importance of private players introduces a certain degree of competition between private and public sectors. This can be well observed in the supply of bone grafts by international companies, with direct marketing and sales approaches to orthopaedic surgeons and dentists. Consequently the activity level of many smaller local bone banks risks dropping to sub-critical levels insufficient to recover costs.

As a consequence, public sector tissue establishments are likely to focus in future more on those segments and/or activities which are less interesting from a commercial perspective, but still important from a public health perspective. The supply of cardiovascular or cornea grafts seem to be such segments, even if some private actors can be observed.

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[77] http://ec.europa.eu/health/blood_tissues_organs/docs/ev_20150603_sr_en.pdf

[78] https://www.edqm.eu/sites/default/files/parents_guide_to_umbilical_cord_blood_banking_organ_transplantation_2015.pdf

[79] http://www.rtix.com, http://www.wsj.com/articles/SB10001424052748704554104575435330553595548

This does and will also require further attention to organise the public sector activities in a more cost-efficient way, very much in the way the private sector is organised. Several examples of initiatives to increase cost-efficiency can already be observed today:

- Sharing costs for donation and testing has been the rationale for agreements between actors, typically if their activities are complementary, like in NL between BISLIFE (bone) and Euro Tissue Bank (skin) (mentioned in chapter 3). Cost sharing is also the reason beyond the joint negotiations for cheaper HLA testing by the Group of European Medium Sized Bone Marrow Registries (GEMS)
- Concentration of processing of significant volumes in one facility or tissue establishment: this has been the driver for many cooperation agreements described in chapter 3, where all procured tissues/cells are brought together from different countries for processing in one establishment
- These first two drivers for efficiency can also go a step further and lead to the consolidation of tissue establishments and the set-up of multi-tissue banks. The set-up in 2005 in the UK of NHS Blood and Transplant aimed for such rationalization and centralization of tissue banking into one tissue establishment (Liverpool), complemented by four eye and five heart valve banks (Gaum et al, 2012). Another consolidation trend was seen in France. During the period when EU regulation was being developed, the number of tissue banks reduced from 226 in 1993 to 43 authorized banks in 2004, reflecting the closure of a large number of small banks run within surgical departments, where it was not possible or cost-effective to raise standards adequately to ensure compliance with the new requirements.[80]
- Exchange agreements to optimise the use of (often short-lived) tissue grafts, in particular where a good match between graft and recipient is important: these agreements come in multiple formats, from ad-hoc informal contacts between professionals to established networks involving multiple tissue banks and clinics like the Deutsche Gesellschaft für Gewebetransplantation gGmbH.[81]

With increasing overall economic scrutiny in the healthcare sector, the public actors in many countries will need to adopt more of such measures to increase efficiency and ensure a sustainable supply of tissue grafts. This will be a challenge in a number of countries, but it also brings about new opportunities for the public establishments that embrace the challenge. From a public health perspective it is of course important that efficiency gains do not lead to discontinuation of activities and supply of grafts that are important for small patient groups, but less attractive from a commercial perspective.

6.4.2 Medical factors: growing need for systematic demonstration of clinical functionality

Clinicians using tissue and cell grafts are often involved in the set-up of tissue establishments, which also have a legal requirement to nominate a registered clinician to review clinical outcomes of applied tissues and cells[82]. While clinicians document follow-up on clinical functionality in patient files, they also publish a significant number of their findings in publications in scientific journals on safety, quality and health outcomes of tissue and cell transplants (Cell and Tissue Banking, Bone and Joint Surgery, Bone Marrow Transplantation etc.). This is the traditional way, in which (groups of) clinicians

[80] http://www.who.int/transplantation/ReportOttawaCTTx.pdf

[81] http://www.gewebenetzwerk.de/

[82] Point A. 3 of Annex I of Commission Directive 2006/86/EC

share their (newly acquired) knowledge with colleagues. Such knowledge-sharing is also an essential part of the many congresses organized by the relevant professional associations of healthcare professionals.

Several of these professional communities and associations have further organised their common efforts to collect information on safety, quality and health outcomes of their activities, by creating systematic data collection registries:

- EBMT runs a central registry where transplant centres can enter data on bone marrow/cord blood transplants. Data entry is well structured and access and governance are decided commonly.[83]
- ESHRE runs the European IVM Monitoring Consortium (EIM) which collects data on IVF cycles in 39 European countries, which covers clinical results (pregnancies), side-effects as well as follow-up of children.[84]

These professional associations are also actively developing best practice guidelines how patients should be treated with tissues and cells, including their follow-up.

This strong interest and involvement of clinicians in patient follow-up allows for continuously monitoring and improvement of treatments for patients, and can be the basis for reassuring the authorities of the safety, quality and clinical functionality of these therapies. Such follow-up data are in particular important in case of novel processes or novel therapies. In times of financial constraints, such data on the benefit of tissue and cell therapies are also increasingly important to justify (public) funding and reimbursement of certain treatments. Some of the public organisations specialised in Health Technology Assessment (HTA) like NICE (UK), IQWIG (DE) and ANSM (FR) have already published reports on the cost/benefit and made recommendations on the use of specific tissue and cell therapies[85].

There are increasing reflections at European and international level on common (standardized) approaches to follow-up and assess the use of tissue grafts, involving professionals (who provide and analyse data) as well as authorities (who need data for their assessments). Early reflections on this topic have already started at EU-level[86] and the indications are that tissue and cell clinical safety and functionality will be increasingly important in the field and will in the future demand a more structured approach involving professionals as well as authorities.

6.4.3 Social factors: media, altruism and trust

The media play a key role in building awareness and willingness of citizens to donate. While a recently published Eurobarometer[87] indicates a limited public awareness of the tissue and cell sectors in general, it also found a significant willingness amongst EU citizens to make donations, most importantly for replacement tissues (50-55%) and

[83] https://www.ebmt.org/Contents/Data-Management/Registrystructure/Pages/Registry-structure.aspx

[84] http://www.eshre.eu/Data-collection-and-research.aspx

[85] https://www.nice.org.uk/guidance/ipg257

[86] http://www.iss.it/binary/tvmp/AmmAperta/TRSF/2015/10/tr-2015-10-1216-j1h.pdf

[87] http://ec.europa.eu/COMMFrontOffice/PublicOpinion/index.cfm/Survey/getSurveyDetail/search/426/surveyKy/2030

hematopoietic stem cells (bone marrow, 45%). Willingness to donate sperm or egg cells was lower (20-25%).

Altruism is a key driver for citizens to make donations. The Eurobarometer exercise reports that 75% of citizens willing to donate mention 'to help people in need' as their main reason to donate. Only a much smaller number (13%) of respondents would find it acceptable to receive monetary remuneration in return for donations. The future development of the tissue and cell (-based) sectors, and therefore of the need for tissues and cell donations, need to take account of these public sensitivities. The current lack of clarity regarding what is acceptable as compensation could present a risk to sustained public support.

While the media can be a powerful ally in the promotion of tissue and cell donation, news about scandals (manipulations, excessive salaries) can provide the media with stories that have the opposite effect and could pose serious threats to the sustainability of activities that rely on donation. Donation in the EU is in general made on a voluntary and unpaid basis as encouraged by EU law.[88] In the related organs and blood/plasma sectors, public reaction to media stories have shown that there is a strong sensitivity and reduction in public willingness to make donations wherever some actors in the system are perceived to make illegal profits and have engaged in manipulations/fraudulent activities.[89]

Social media so far play a limited role in donor recruitment for tissues and cells. Nevertheless, several recent developments in the organs sector can also be expected in the tissues and cells sector. Most notably Facebook has allowed its members to share their organ donor status as a life event.[90] These Facebook members are subsequently referred to the national registries managed by National Competent Authorities. It needs to be noted that in many countries the registration as an organ donor after death also implies the donation of tissues and cells.

Media coverage feeds much of the interest in possible new therapies, in particular in the field of stem cells. Such media coverage can put some unrealistic and premature expectations on novel treatments. While many of the publicised possibilities are still many years away from becoming proven as safe and effective therapies, there have been some cases where less-scrupulous actors offer them to treat patients profiting from lack of regulation, typically targeting patients with very serious conditions and without alternative therapeutic options. Some companies such as X-Cell (DE) and Stamina (IT) have been convicted and the investigations received significant media attention. Such cases affect the credibility of the entire sector and risk to impact negatively on public willingness to donate tissue and cells as well as on the willingness to be treated with stem-based therapies.

Societal trust and support is a key prerequisite for new technologies. Society at large expects that appropriate controls are put in place to protect them, not only from adverse events but also from products that lack efficacy. It is important to prevent events that will alienate society to new medical therapies, by ensuring a robust system is in place to monitor and oversee these products.

6.4.4 Ethical factors

[88] Article 12 of Directive 2004/23/EC

89 http://www.dso.de/uploads/tx_dsodl/DSO_JB_D_2012_e.pdf

[90] https://www.facebook.com/help/416967021677693/

Transplant medicine and reproductive medicine are highly innovative sectors. With some of those innovations come new ethical questions. A recent example is the decision by the UK Parliament to allow for IVF/ART establishments to create so-called 'three-person' babies (mitochondrial transfer).[91] The accompanying discussions in the UK and European Parliaments and media clearly indicate that different views, hopes and fears come with such innovations.

Many of these and other innovations require policy makers to have in-depth reflections and discussions with a need to get access to good technical information on this complex sector. This has led to increasing importance of activities of dedicated ethical bodies looking at these sciences, such as the Nuffield Council on Bioethics in the UK[92] or the European Group on Ethics (EGE) for the European Commission[93]. Fact-based and transparent discussions, often well covered by media, are important to maintain public awareness and support for the activities of this sector. Furthermore, some general ethical principles will require continuous attention to ensure public trust in the sector is not undermined. In 2006, the World Health Organisation organised the Zurich Symposium on ethics and regulation of human cell and tissue transplantation.[94] This symposium identified and addressed key ethical elements like donor consent, protection of donor data, unpaid donation, fair procurement, stewardship of donated tissues and cells, quality and safety, fair distribution and recipient consent.

More recently, additional points have been subject to ethical debates:

- One is the need for robust donor protection. Demand for donors is expected to increase with the increased demand for tissues and cells (for transplants, for fertility treatment or for developing advanced therapies). Donor protection is well defined and addressed in the organ transplant sector, partly due to the introduction of a legal requirement in Directive 2010/53/EU,[95] and has been the subject of multiple EU-funded projects.[96] Many of these learnings can be useful to apply also in the tissue and cell sector in order to maintain public trust in this sector so that services will continue to be sustained by the willingness of the public to donate.
- The possibility to patent (or not) processes, products and therapies derived from human tissues and cells may also have a major impact on the development of the sector. Some first CJEU Rulings[97] have put conditions and limitations on patenting of therapies based on human embryos. Similar court cases and rulings can be expected in the rapidly developing tissue and cells sector, which brings a degree of uncertainty for clinicians, professionals and investors (regardless of what the rulings conclude).

[91] (http://www.bbc.com/news/health-31594856).

[92] http://nuffieldbioethics.org

[93] http://ec.europa.eu/epsc/ege_en.htm

[94] http://www.who.int/bulletin/volumes/85/12/06-038703/en/

[95] Article 15 of Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation

[96] See annex 2 of Commission Staff Working Document on the mid-term review of the "Action Plan on Organ Donation and Transplantation (2009-2015): Strengthened Cooperation between Member States"

[97] Case C-34/10 Brüstle v. Greenpeace, Case C-364/13 International Stem Cell Corporation v. Comptroller General of Patents, Designs and Marks

6.4.5 New technologies and their impact on the T&C sector

Section 6.3 already described the expected impact of developments in ATMPs which work with human tissues and cells as starting materials. On the one hand they can require an increased supply of tissues and cells, mainly if new therapies are developed based on allogeneic tissues and cells. On the other hand, these new therapies might replace in future the need for some of the existing tissues and cell transplant therapies, for example by culturing grafts in the laboratory, rather than working with donated materials.

Many of the safety and quality measures, applied by tissue establishments to donors/donations, are also subject to continuous technological innovation. The most notable example in recent years is a shift towards more sensitive NAT/PCR testing to detect infectious diseases in donors. Also the application of novel microbial inactivation techniques, applied to different tissues and cell types, are increasingly becoming standard practice. Awareness regarding the risks of emerging diseases like West Nile virus and Ebola help promote and increase the use of new tests. Policy makers tend to be risk-averse and very susceptible to suggestions that ever greater risk mitigation steps are justified.

However, while these technologies are very much welcomed to help ensure safe supply of substances of human origin, their application needs to be carefully evaluated within the overall safety and economic context of the existing measures. Typically, in line with EU regulations, safety and quality measures include (1) a good donor selection, (2) testing of donors and (3) quality measures for handling substances of human origin. Introducing a new measure will therefore bring an incremental improvement in safety and quality compared to the existing measures. This is to be assessed together with the incremental cost when assessing cost/benefit prior to introducing such new measure. Depending on the state of the health system, this can lead to different conclusions in terms of cost/QALYs gained, and eventually to different investment decisions in different countries. A comparable example can be given in the well-established blood sector, where investment costs of $1,5-2 million per QALY have been reported (while the usual cut-off to fund a new medical measure is usually not above $50,000).[98] While in less established blood systems, typically in Member States with less GDP and purchasing power, the QALY gained can be more significant, but the threshold of acceptable incremental cost might also be lower. Similar considerations are relevant for the tissue and cells sector. The adoption of these new technologies therefore is also expected to call on expertise in (health) technology assessment, a field that is in full development in the EU.

6.5 CONCLUDING REMARKS AND SUMMARY NOVEL THERAPIES

- Innovation in the tissues and cells sector is advancing continuously by progress in immunology, microsurgery and cryopreservation. More recently developments in tissue engineering, gene and somatic therapies add to this progress. These innovations are therefore ongoing within and outside the legal framework of Directive 2004/23 of Tissues and Cells.

- In replacement tissues, growth trends vary per type of tissue, each one being subject to different factors. Overall, the use of ophthalmologic grafts is expected to increase due to higher needs of our ageing population, while the use of bone

[98] Cost per QALY gained by introducing NAT testing for HIV, HBV or HCV, analyses by and for Belgian Red Cross (Flanders)

grafts is expected to grow due to an increased commercialisation, evidenced by the entry of private operators. The growth trends in use of skin and cardiovascular grafts are less clear due to different, partly opposing, factors.

- Annual transplantation numbers of allogeneic HPC in Europe have tripled between 1998 and 2013, and are likely to continue increasing. Some new techniques like using haplo-identical (i.e. family-related) donors might decrease this need, while others, like the development of new HPC-based therapies like tumor-infiltrating vaccines, might increase the need for HPC.

- The continuing growth for assisted reproductive technologies (ART) is driven by medical (increasing infertility rates), social (e.g., new family compositions), technological (e.g. freezing of genetic material for future use) and commercial (e.g., online and cross-border services) factors.

- The development of the tissue and cells sector might also be affected by the developments in neighboring sectors like advanced therapy medicinal products (ATMP) and medical device industry. This might in first place impact demand and possible competition by commercial actors for allogenic human tissues and cells. However, so far ATMP developments seem mainly to take place with autologous cell products. Whenever novel therapies bring significant benefits in terms of efficacy, safety and quality, they might replace traditional transplant therapies. It seems however difficult to have a central overview on this, as oversight on the traditional tissues and cells sector is organised at national level, and as many ATMPs are currently offered within the decentralized setting of hospital exemptions.

- The developments in the ATMP sector offer opportunities for tissue establishments to supply not only starting materials, but also infrastructure and expertise in GMP-cleanrooms or dedicated cell culture facilities. Several public banks, like NHS Blood and Transplant (UK) have set up such cell culture facilities, and also the research for several of the (5) centrally approved ATMPs has been initiated in tissue establishments within academic hospitals.

- However the developments of ATMP also bring challenges, including due to legal uncertainties and borderline issues which make it difficult for professionals and companies to know which safety and quality requirements to apply: those under the Tissue/Cells legislation or those under the (Advanced Therapy) Medicinal Product legislation. Classifications often depend on technical details and the Committee on Advanced Therapies (CAT) makes scientific recommendations on whether products fall within the definition of ATMP. However these recommendations are not binding at EU level, leading to different Member States to apply different legal frameworks for similar products. Tissue establishments regularly complain on classifications which force them to stop preparing well-established therapies. In parallel, pharmaceutical companies complain of a lack of level playing field, forcing them to undergo costly clinical trials and marketing authorization procedures, which translate into the need to charge high prices which are hard to obtain reimbursement for.

- Future developments of the tissue and cell sector will also reflect general economic trends related to the entry of the private sector and the need for efficiency. Private sector entry is driven a.o. by the possibility of direct-to-consumer activities (e.g., internet sales of sperm), of organizing large-scale processing (e.g., to make bone powder) and by changes in societal demand (e.g., ageing or delaying childbirth). In order to ensure supply of all types of tissues/cells, public actors will have to focus on economically less interesting activities and will have to undertake some actions to increase their cost-efficiency, like cost-sharing or consolidation of establishments.

- The strong involvement of clinicians, and significant data-collection efforts led by professional societies, are an important facilitator for innovation in the sector. These data will allow authorities to monitor and ensure safety, quality and functionality of novel therapies. In times of financial constraints, these data will also be helpful to justify public investments to ensure overall availability of tissue and cell therapies.

- Media play an increasingly important role to ensure public awareness and willingness to donate, without which this sector cannot exist. While there is an overall public support for this sector, thrust can easily erode when there is coverage of (monetary) scandals, and with it donation rates go down. Media will therefore require specific attention, also to help leverage the possibilities of social media, and to manage often premature coverage and expectations on novel therapies.

- With new therapies come new ethical concerns and hopes, which require dedicated political debates. Ethical opinions can oppose strongly, in particular as each comes with valid arguments. It is therefore important that a good basis of facts and sector-knowledge is available to support policy makers in these difficult ethical discussions. Some of the ethical discussions that are needed, concern directly some important preconditions for the sector like the need for donor protection and the possibility of patenting (or not) therapies based on human materials.

- The future development of the sector also depends a lot on enabling technologies, like the availability of new testing technologies. Some of these new technologies can however be very expensive, in particular for EU Member States with lower GDP rates. Their added value therefore needs to be assessed within the (national) context of existing safety and quality measures, which will require dedicated (health) technology assessment (HTA) knowledge.

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8 ANNEX 2: TABLES

8.1 Tables replacement tissues

No additional tables for replacement tissues.

8.2 Tables HPC

Table 28 Provision of HPC-M products in 2012

Country	%	No HPC BM products
Japan	32	1,318
Germany	31	1,210
USA	21	947
Brazil	3	131
France	3	83
Italy	3	65

Source: WMDA Annual Report, 2012

Table 29*4* Provision of HPC-A products in 2012

Country	%	No HPC BM products
Germany	46	5,055
USA	23	2,573
China	6	638
UK	5	522
Korea	3	448
Taiwan	3	344

Source: WMDA Annual Report, 2012

Table 35 Provision of HPC-CB products in 2012

Continent	Intra-continent	Imported	Exported
Asia	1,358	43	41
North America	1,285	239	490
Europe	581	317	299
Australia	38	73	40
South America	18	198	0
Africa	0	0	0

Source: WMDA Annual Report, 2012

Table 30 Overview Growth European HPC Donor Registries[$]

EU MS*	HPC donor registry	No of Donors 2010	No of Donors 2012	% of global Donor Inventory	Size in 2012
AT	Austrian Bone Marrow Donors	62,452	63,274	0.313	Medium
BE	Marrow Donor Program Belgium	49,709	31,366	0.155	Medium
BU	Bulgarian Bone Marrow Donor Registry	444	634	0.003	Small
BU	Bulgaria Pirogov (DC)	659	669	0.003	Small
HR	Croatian Bone Marrow Donor Registry	19,315	31,758	0.157	Medium
CY	Cyprus Bone Marrow Donors Registry	110,481	117,139	0.579	Large
CY	Cyprus Paraskevaidio Bone Marrow Donor Registry	6,058	5,884	0.029	Small
CZ	Czech National Marrow Donors Registry	35,533	39,715	0.196	Medium
CZ.	Czech Stem Cells Registry	20,199	21,568	0.107	Medium
DK	The Danish Bone Marrow Donors Registry	24,925	27,012	0.134	Medium
DK	Bone Marrow Donors Copenhagen	12,923	13,575	0.67	Small
FI	Finnish Stem Cell Registry	20,493	20,649	0.102	Medium
FR	Registre France Greffe de Moelle	187,519	205,967	1.018	Large
DE	Zentrales Knochenmark Register Deutschland	4,062,456	4,767,127	23.568	extra large
EL	Unrelated Hematopoietic Stem Cell Donor Registry	29,608	33,737	0.167	Medium
HU	Hungarian Bone Marrow Donor Registry	4,962	6,452	0.032	Small
IE	Irish Unrelated Bone Marrow Registry	20,362	20,816	0.103	Medium
IT	Italian Bone Marrow Donor Registry	331,544	337,302	1.668	Large
LT	Lithuanian National Bone Marrow Donor Registry	5,169	7,762	0.038	Small
NL	Europdonor Foundation	38,645	41,639	0.206	Medium
PL	DKMS Baza Dawcow Komorek Macierzystych Polska (DC)	94,781	251,399	1.243	Large
PL	Central Bone Marrow Donor Registry Poltransplant	31,281	115,565	0.571	Large
PL	Against Leukemia Fdt Marrow Donor Registry (DC)	10,586	15,145	0.075	Small
PL	Poland FUJ (DC)	12,632	--		n.a.
PT	Cedace Portuguese Bone Marrow Donors Registry	248,425	310,935	1.537	Large
RO	Romanian Nat Registry of Hematopoietic stem cells voluntary donors	645	1,058	0.005	Small
SK	Slovak National Bone Marrow Donor Registry	1,728	3,544	0.018	Small
SI	Slovenia Donor		15,568	0.077	Small
ES	REDMO, Jose Carreras Leukemia Foundation	86,361	106,521	0.527	Medium
ES	DKMS Espana (donor center)		1,375	0.007	Small
SE	The Tobias Registy	40,478	39,878	0.197	Medium
UK	Anthony Nolan	418,306	468,997	2.319	Large
UK	British Bone Marrow Registry	320,018	324,645	1.605	Large
UK	Welsh Bone Marrow Donor Registry	61,193	51,669	0.255	Medium
Total* **		6,182,390	7,499,769	37.078	

Table: Overview growth of European HPC Donor Registries;

[$] In some countries DC are operating independent from the national registry, these are marked as (DC).

* There were no registries in Estonia, Latvia, Luxembourg and Malta; ** The Poland FUJ registry became part of the National Polish Poltransplant Registry after 2010. Due to Polish legislation they are in the process towards the establishment of one national registry.

***In 2012, the total number of donors worldwide was **20,226,863** (source BMDW).

In 2012, **4.126** HPC-M and **10.988** HPA-A donations were made through an unrelated donor registry (percentage of global no of donations is given). Data provided by BMDW and WMDA.

NB – Registry information is confidential; according to BMDW Houserules 12.2.3: "Publication of method where data from individual contributors are needed and shown as specific examples may be published "anonymizing" the contributing registries. Otherwise the registries shown or easily identified have to be asked and given the opportunity to review and object their names and/or data to be shown."

Table 37 Overview growth European Public Cord Blood Registries[$]

EU MS	Public Cord Blood Registry	No of available Public CBs 2010	No of available Public CBs 2012	% of global CB Inventory
AT	Austrian Cord Blood Registry	1,153		
BE	Belgium Cord Blood Registry	7,706	16,952	2.62
BE	Leuven Cord Blood Bank	7,053		
HR	Croatian Cord Blood Bank	1,003	2,026	0.31
CY	Cyprus Cord Blood Bank		1,535	0.24
CZ.	Czech Cord Blood Registry	3,581	3,923	0.70
FI	Finnish Cord Blood Registry	3,121	3,369	0.61
FR	The French Cord Blood Registry	10,984	22,960	3.55
DE	Jose Carreras Stem Cell Bank Duesseldorf	15,762	17,852	2.76
DE	ZKRD - German Cord Blood Bank	9,677	15,375	2.74
EL	Hellenic Cord Blood Bank	313	1,251	0.19
EL	Thessaloniki Public Cord Blood Bank		462	0.07
IT	Italian Cord Blood Bank Network	22,848	28,430	4.40
NL	Europdonor Foundation	2,636	3,237	0.50
PL	Central Cord Blood Registry (POLtransplant)	303	852	0.13
PL	Unrelated Cord Blood Registry	50		
PT	Luscoord	3,754		
SK	Eurocord Slovakia - Slovak Placental Stem Cell Registry	1,510	1,724	0.27
SI	Slovenia Cord	146	245	0.04
ES	REDMO Spanish Cord Blood Registry	46,899	55,424	8.57
SE	Tobias Cord Blood Registry	1,338	2,526	0.39
UK	Anthony Nolan Cord Blood Registry	187	1,520	0.24
UK	British Bone Marrow Registry - Cord Blood Bank	11,958	17,334	2.68
Total**		**151,982**	**196,997**	**30.46**

Table: Overview growth European Public Cord Blood Registries

[$] In some countries cord blood banks operate under the authority of a national HPC donor registry

* The Leuven Cord Blood Bank was integrated into the Belgium Cord Blood Registry

** In 2012, the total number of publicly available cord blood units was 646,772. The total number of globally provided public CB units was 4,054 in 2010 and 4,150 in 2012. Data provided by BMDW and WMDA.

NB Registry information is confidential; according to BMDW Houserules 12.2.3: "Publication of method where data from individual contributors are needed and shown as specific examples may be published "anonymizing" the contributing registries. Otherwise the registries shown or easily identified have to be asked and given the opportunity to review and object their names and/or data to be shown."

Table 38 FACT/Netcord accredited HPC-CB banks in Europe

EU-MS	Name of Organization	Type of Cord Blood Unit	
		Public Use	Private/Family directed Use
AT	Vivocell Biosolutions GmbH & Co KG	X	Private
BE	Banque de Sang de Cordon Cliniques Universitaries Saint-Luc	X	Family
BE	Institut Jules Bordet	X	Family
BE	Navelstrengbloedbank Universitair Ziekenhuis Gent	X	Family
BE	Leuvense Navelstrengbloedbank (Cord Blood Bank Leuven - Belgium)	X	Family
BE	Liège Cord Blood Bank	X	Family
FI	The Finnish Cord Blood Bank (Currently Not Accepting New Units)	X	
FR	Cord Blood Bank: Cellular Therapy Engineering Department, Banque de sang placentaire de Bordeaux (Bordeaux CBB), Etablissement Français du Sang Aquitaine-Limousin	X	
FR	Besançon Cord Blood Bank of the Etablissement Français du Sang	X	Family
FR	Banque de Sang Placentaire du CHRU de Montpellier		Family
DE	DKMS Lifeline Cord Blood Bank	X	Family
DE	José Carreras Cord Blood Bank Düsseldorf	X	Family
DE	Bayerische Stammzellbank gGmbH	X	Family
DE	Cord Blood Bank Mannheim	X	
EL	Hellenic Cord Blood Bank	X	Family
EL	Stem Health Hellas S.A.	X	Private
IT	Emilia Romagna Cord Blood Bank (ERCB)	X	Family
IT	Milano Cord Blood Bank	X	Family
IT	Pavia Cord Blood Bank	X	Family
IT	Treviso Cord Blood Bank	X	Family
NL	Sanquin Cord Blood Bank	X	Family
San Marino	InScientiaFides s.p.a.		Private
ES	Programa Concordia Banc de Sang i Teixits	X	Family
ES	Banco de Sangre de Cordón Umbilical Andalucia	X	Family
SE	The Swedish National Cord Blood Bank	X	Family
UK	NHS Cord Blood Bank	X	
UK	The Anthony Nolan Cord Blood Bank	X	Family

Table *39* Percentage of population registered as donor, availability rate and number of donations per EU MS in 2012

EU MS	Population 20-60 yr	No of donors	% of population	Availability rate (%)	No of donations in 2012	% of registered donors donating
AT	4,720,678	63,272	1.3	76	24	0.04
BE	5,991,425	62,731	1.0	72	36	0.06
BU	4,079,174	1,303	0.03	100	1	0.08
CY	500,429	123,023	**24.6**	86	23	0.02
CZ	5,977,923	61,889	1.0	69	33	0.05
DE	45,152,402	4,783,529	**10.6**	77	6.239	0.13
DK	2,915,996	40,456	1.4	88	6	0.01
EL	6,103,338	37,740	0.6	27	1	0.00
ES	29,946,584	107,896	0.4	76	35	0.03
FI	2,809,656	21,752	0.8	100	24	0.11
FR	33,888,169	205,967	0.6	70	255	0.12
HR	2,348,495	31,758	1.4	45	11	0.03
HU	5,571,194	6,491	0.1	83	2	0.03
IE	2,552,340	20,816	0.8	54	7	0.03
IT	32,148,600	339,472	1.1	68	163	0.05
LT	1,646,626	7,810	0.5	94	4	0.05
NL	9,048,736	41,667	0.5	68	35	0.08
PL	22,608,184	396,525	1.8	84	298	0.08
PT	5,769,013	314,146	**5.4**	95	96	0.03
RO	11,438,347	1,244	0.01	100	0	0.00
SE	4,924,120	3,878	0.8	69	20	0.05
SI	1,186,742	16,025	1.4	53	4	0.02
SK	3,225,959	4,079	0.1	58	1	0.02
UK	34,020,020	845,499	**2.5**	67	648	0.08

Table 31 EBMT registered patients receiving 1st allogeneic and autologous HPCT (2012)

	Allogeneic	Autologous	Total
All patients	14.165 (42%)	19.513 (58%)	**33.678**
>18 yr	11.288	18.349	**29.637**
<18 yr	2.877	1.164	**4.041 (12%)**

Table 41 Allogeneic HPCT – donor source in 2012

	HLA identical sib/twin	Non-identical/other	Unrelated	Total
All allogeneic procedures	5.910 (38%)	1.217 (8%)	8.224 (54%)	**15.351**
>18 yr	4.760	863	6.851 (55%)	**12.474**
<18 yr	1.150	354	1.373 (48%)	**2.877**

Table 42 Allogeneic and autologous HPCT – stem cell source in 2012

	HPC-M	HPC-A	HPC-CB	Total
All autologous procedures	176	22.285	6	**22.467**
All allogeneic procedures	3.476	11.117	758	**15.351**
>18 yr	1.751	10.281	442	**12.474**
<18 yr	1.725	836	316	**2.877**

Table *43* Allogeneic HPCT with unrelated donors/cord blood (2012)

	HPC-M	HPC-A	HPC-CB	Total
All allogeneic procedures	1.454 (18%)	6.076 (74%)	694 (8%)	**8.224**
>18 yr (%)	717 (10%)	5.712 (84%)	422 (6%)	**6.851**
<18 yr *%)	737 (54%)	364 (26%)	272 (20%)	**1.373**

Source: Passweg et al. 2014

Table 44 Average cost for HPCT with autologous donor, sibling donor, unrelated donor and unrelated cord blood in euros

	Selection / harvesting	Transplantation	Follow-Up 1st yr.	Total
Autologous (range)	11.935 (2.944-13.539)	21.124 (10.963-37.472)	12.609 (2.851-80.315)	**45.668**
Allogeneic sib (range)	31.480 (14.14.-61.950)	24.894 (14.384-54.393)	45.549 (15.435-175.257)	**101.923**
Allogeneic UD (range)	64.876 (43.726-113.447)	28.581 (16.727-80.088)	78.025 (13.646-454.609)	**171.482**
Allogeneic UCB (range)	65.398 (47.131-104.352)	56.277 (28.008-209.999)	133.015 (21.464-526.808)	**254.690**

Source: Blommenstein et al. 2012

Table 45 BMDW fees, actual November 2014

# Donors and/or CBU's (n)	Fee
N<=20,000	€1,180
20,000 < N <= 100,000	€2,950
100,000 < N <= 1,000,000	€5,900
N>1,000,000	€11,800

Table 46 WMDA fees, actual May 2015

# Donors and/or CBU's (n)	Fee
N<=20,000	€1,000 + 50 per product provided in 2013
20,000 < N <= 100,000	€1,000+ 50 per product provided in 2013
100,000 < N <= 1,000,000	€1,000+ 50 per product provided in 2013
N>1,000,000	€1,000+ 50 per product provided in 2013

Table 47 Fee schedules actual November 2014*

Country/Registry	BM / HPC-A procurement	Cancellation fee	Remarks
Marrow Donor program Belgium,	€13,650	€400-1,250	fee schedule donor 2011.
Bulgarian Bone Marrow Donor Registry,	€11,250	€750-1,500	fee schedule October 2014.
Cyprus	Reciprocal	Reciprocal	
Czech National Marrow Donors Registry	€14,500	€700-1,800	fee schedule 2013
Danish Bone Marrow Donor Registry (Aarhus),	102,208-110,190 DKK (€13,731–14,803)	15.000 DKK (€2,015)	fee schedule April 2014.
Finland	€ 20,846,64	€1,240-2,775	Red Cross Finland, fee schedule January 2014.
France	€12,400	€2,775,19	Registre France Greffe de Moelle, fee schedule 1.1.2014. Excl VAT
Germany, ZKRD Germany, DKMS	€13,500 €14,500	€2,800 + €2,000 G-CSF €770-1,800	
Hungarian Stem cell donor registry	€15,000	€700 + €2,000 (G-CSF)	fee schedule February 2012.
Irish unrelated bone marrow registry	€21,560 – 21,310	€1,040	international fee schedule 2009.
Italian Bone Marrow Donor Registry	€ 17,000	€399-1,228	fee schedule 2012
Lithuanian Bone Marrow Donor Registry	€14,500	€700-2,000	fee schedule May 2014
Europdonor Foundation, Netherlands	€14,935	€2,575	fee schedule January 2014.
REDMO - Fundación Joseph Carreras, Spain	€13,800	varies	fee schedule June 2010

*Fee schedules were not received from registries in AT, HR, EL, PL, PT, RO, SI, SK, SE, UK.

Table 48 Examples of financial funding

Country	Financial resource
Romania	Funding through State Budget, Ministry of Health
Austria	Donations, health insurance,
Belgium	Belgium National Institute for Health and Invalidity Insurance Structural support operating costs and fixed sum per transplant for support
Czech Rep	Funding by the BMT Foundation and insurance
Europdonor NL	Some governmental funding for recruitment (2600 donors/yr)
United Kingdom	Charity
DKMS, Germany	Donations from donors (contribution for HLA typing)public and business

Source: WMDA Handbook 2013

Table 49 Cost of processing umbilical cord units

Process Stages	€/Unit	N=3243
Collection	17.10	x 3,243=5,540.4
Processing	310.15	x 3,243=75,366.45
Quality control	180.86	x 3,243=586,528.98
Human resources	163.84	x 3,243=531,333.12
External preventive Maint enance	35.2	x 3,243=114,153.8
External corrective maintenance	13.26	x 3,243=43,002.18
Total	720.41€	2,336,289.63€

Source: Arojo et al 2012

Table 50 Some major private cord blood banks active in EU MS

CBB	No of samples stored	Banks operating under main organisation	Remark
Vita34	100,000	Secuvita; Stem Sure; Stem Care; Izvorna Celica; Vidaplus; Bio-Save	Revenue 2013 €1,494. Stock market listed
Cryo Save	250,000	Crio Cord; Esperite	Active in 70 countries Stock market listed
Future Health Biobank	75,000		Active in 54 countries
Cells4Life	75,000		Active in 13 countries, licensed by UK HTA (11083); No bank in UK
SeraCell	23,000	BabyStem; Bioteca	Active in 2 countries
Smart Cells	30,000		UK HTA licensed (22522); ISO 9001
Biovault	22,000	Biocord	Active in 10 countries
New England Cord Blood Bank	53,000		USA based CBB
Vivocell	13,000		
Cord Blood Center Group	135,000		
Crioestaminal	50,000		
Stella Cure		Vidaplus; Vita Futura	
Precious Cells Group			Active in 25 countries

8.3 TABLES NOVEL THERAPIES

Table 51 Licensed ATMP in Europe (EMA)

Name product	Indication for treatment
ChondroCelect	A tissue engineered product indicated for repairing single symptomatic cartilage defects of the femoral condyle of the knee in adults.
Glybera	A gene therapy medicinal product indicated for adult patients with lipoprotein lipase deficiency and suffering from severe or multiple attacks of pancreatitis (inflammation of the pancreas) despite dietary fat restrictions.
MACI	A combined ATMP indicated for the repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3-20 cm2 in skeletally mature adult patients.
Provenge	A somatic cell therapy medicinal product indicated for the treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated.
Holoclar	Treatment for moderate to severe limbal stem cell deficiency due to physical or chemical burns to the eye(s) in adults.

8.4 Tables ART

8.4.1 Table A1: Prices sperm banks

	Spermbank	Straw ICSI (anonymous)	*Straw ICSI (non-anonymous)*	*Straw IUI (anonymous)*	Straw IUI (non-anonymous)	Straw IVF (anonymous)	Straw IVF (non-anonymous)	Exclusive donor	Extended donor profile
CZ	Spermbank International	€76-€100 *(Price depends on quality and volume)*	*No non-anonymous samples*	*€160-€184 (Price depends on quality)*	*No non-anonymous samples*	€120	*No non-anonymous samples*	No exclusive donors	Free of charge
DE	Berliner Samenbank - Berlin Sperm Bank	Price not listed	*No non-anonymous samples*	*Base fee: €1,800,- Preparation of specimen: €135,- Sperm sample €200,- Each additional insemination cycle €335,-*	*No non-anonymous samples*	€900,-	*No non-anonymous samples*	No exclusive donors	Not available
DE	Erlanger Samenbank	€400,- per sample (excl. 150 laboratory costs)	*No non-anonymous samples*	€400,- per sample (excl. 150 laboratory costs)	*No non-anonymous samples*	€400,- per sample (excl. 150 laboratory costs)	*No non-anonymous samples*	No exclusive donors	Not available
DK	Cryos International	€178 excl. VAT (2 straws, MOT 10) 60 Euro for 5 MOT	€398 excl. VAT (2 straws, MOT 10) 142 Euro 5 MOT ICI	Prices range from €59 to €399	prices range from €59 to €399	60 Euro for 5 MOT	142 Euro 5 MOT ICI	€12000,-	Free of charge
DK	European spermbank	€195 excl. VAT (min MOT 20)	€295 excl. VAT (min MOT 20)	€239 excl. VAT (min MOT 20)	€379 excl. VAT (min MOT 20)	Price not listed	Price not listed		€25
EL	Cryogonia	Price not listed	*No non-anonymous samples*	Price not listed	*No non-anonymous samples*	Price not listed	*No non-anonymous samples*	Possible, prices are not listed.	Free of charge
UK	London Sperm Bank	No anonymous samples	£850,- per treatment cycle	No anonymous samples	£850,- per treatment cycle	No anonymous samples	£850,- per treatment cycle	Not listed on website	Free of charge

UK	Birmingham Sperm Bank	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website
USA	European spermbank USA (Seattle Sperm Bank)	NA	$525 (= €385.45)	NA	$635 (= €466.20)	NA	NA	NA	$10,-
USA	California Cryobank	$595	$695	$695	$795	NA	NA	NA	$25
USA	Xytex Cryo International	$295,-	$395,-	$610,-	$730,-	$375,	$485	NA	from $65
USA	Fairfax Cryobank	$545,-	$665	$670,-	$780,-	$380,-	$525,-	NA	Personal Profile (9-14) $26;

8.4.2 Table A2: Prices sperm and delivery 2

	Spermbank	Pick up (dry ice)	Pick up and return (nitrogen tank)	Within the country (dry ice)	Within the country (nitrogen tank)	Europe (dry ice)	Europe (nitrogen tank)	Rest of the world (nitrogen tank)	Other
CZ	Spermbank International	Only transport to clinics (not individual users) (nationally and internationally, prices not listed							
DE	Berliner Samenbank - Berlin Sperm Bank	Only transport to clinics (not individual users) shipping to other countries is not referenced on the website. Prices are not listed							
DE	Erlanger Samenbank	Only transport to clinics (not individual users) shipping to other countries is not referenced on the website. Prices are not listed							
DK	Cryos International	€39,	€45	€55	€79	€169	€219	€349	
DK	European spermbank	Not offered	Not offered	Not offered	€100	Not offered	€269	Please contact us	€500,- shipping to Israel in nitrogen tank
EL	Cryogonia	Only transport to clinics (not individual users) shipping to other countries is not referenced on the website. Prices are not listed							
UK	London Sperm Bank	Only transported to the London Women's Clinic or the Bridge Centre, extra fee of £150,-							
UK	Birmingham Sperm Bank	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website
USA	European spermbank USA (Seattle Sperm Bank)	Not offered	Not offered	Not offered	$150: Two-day shipping to Washingt on,	Price not listed on website	Price not listed on website	Price not listed on website	$200: Two-day shipping to AK and HI, $250 for overnight.

					Oregon and California. $200 for overnight. $180: Two-day shipping to all other continental U.S. states, $230 for overnight				
USA	California Cryobank	Not offered	$55,-	Not offered	$150,-	Price not listed on website	Price not listed on website	Price not listed on website	
USA	Xytex Cryo International	Not offered	$50,-	Not offered	$180,- to $240,- (depending on speed and time of delivery)	Price not listed on website	Price not listed on website	Price not listed on website	Alaska/Hawaii Shipping Two-day delivery by 5:00 p.m. $200
USA	Fairfax Cryobank	Not offered	Not offered	Not offered	$185 - $240 / container	Price not listed on website	Price not listed on website	Prices not listed on website	

Source: internet search Rathenau Instituut 2014

8.4.3 Table A3: Prices of reservation depot (storage for future use)

	Spermbank	3 months	6 months	1 year	2 years	3 years	4 years	5 years	10 years
CZ	Spermbank International	Storage is offered, prices are not listed							
DE	Berliner Samenbank - Berlin Sperm Bank	No storage offered							
DE	Erlanger Samenbank	Cryopreservation €250 for one cycle, €450,- for two cycles. Additional cost for laboratory test €75,- Costs for storage €360,- per year/ temperate storage €180,- per year							
DK	Cryos International	€39	€68	€117	€196	€275	€354	€430	€820
DK	European spermbank	€50	€75	€135	€237.50	€343.75	€ 406.25	€ 468.75	€ 843.75
EL	Cryogonia	Storage is offered, prices are not listed							
UK	London Sperm Bank	No storage offered							
UK	Birmingham Sperm Bank	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website	Not listed on website
USA	European spermbank USA (Seattle Sperm Bank)	$200	$200	$350	$600	Price not listed	Price not listed	$1,200	Price not listed
USA	California Cryobank	Not offered	$275	$475	$800	$1,050	N Price not listed	$1,570	$2,680
USA	Xytex Cryo International	Not offered	$200 (Six-Month Storage Fee First 6	$350	Price not listed	Price not listed	Price not listed	Price not listed	Price not listed

			Months free for purchases of six or more units; thereafter billed in advance bi-annually)						
USA	Fairfax Cryobank	$40 monthly, so 3 months $120	Price not listed	$395	$670	$985	Price not listed	$1,340	$2,400

Source: internet search Rathenau Instituut 2014

8.4.4 Table A4: Volumes embryo

Country code	Year data	Number of women in fertile age (between 15 and 45) relative to year data	Donors	*% relative to women in reproductive age*	Donated	*% relative to women in reproductive age*	Received from other MS	Imported	Distributed to other MS	Exported	FET with donor sperm and donor oocyte - cycles started	*% relative to women in reproductive age*	FET number of recipients	*% relative to women in reproductive age*	FET number of embryos donated	*% relative to women in reproductive age*	FET number of embryo transfers	*% relative to women in reproductive age*	FET ber of pryos ferred	*% tive to men in roducti e age*
AT	2011 **	1.745.857	NA	NA	NA	NA	data not collected **	data not collected **	data not collected **	data not collected **	NA	NA								
BE	2012	2.202.885	NA	NA	230	0,01	0	0	0	0	NA	NA			230	0,01			27	0,001
BG	2012	1.457.281	12	0	22	0,002	0	0	0	0	11	0	0	0	0	0	0	0	0	0
CY	2012	212.338	NA	NA	7	0,003	0	0	0	0	3	0	5	0,002	19	0,009	5	0,002	12	0,006
CZ	2012	2.215.635	NA	NA	1341	0,061	7	0	28	1013	123	0,01	NA	NA	1341	0,061	473	0,021	902	0,041
DE	2012	######	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
DK	2012	1.098.026	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EE	2012	269.711	NA	NA	103	0,038	NA	NA	NA	NA	9	0	15	0,006	103	0,038	19	0,007	37	0,014

EL	2011 *	2.304.293	NA	NA	NA	NA	NA	106329 *	NA	NA	NA	NA							
ES	2012	9.933.955	NA	NA	1233	0,012	NA	NA	NA	NA	NA	NA	640	0,006	1233	0,012	721	0,007	1384	0,014
FI	2012	1.015.868	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	55	0,005	NA	NA
FR	2012	######	143	0,001	332	0,003	NA	NA	NA	NA	NA	NA	117	0	332	0,003	136	0,001	247	0,002
HR	2012	843.778	NA	NA	NA	NA	0	0	0	0	NA	NA								
HU	2012	2.093.084	NA	NA	6	0	0	0	0	0	0	0	6	0	6	0	6	0	NA	NA
IE	2012 ****	1.038.623	NA	NA	NA	NA	0 (2013 TE annual report)****	993 (all from Ukraine 2013 TE annual report)*****	NA	NA	NA	NA								
IT	2012	######	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NE (?)		NE (?)		NE (?)		NE (?)	
LT	2012	623.283	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
LU	2012	114.369	0	0	0	0	0	0	0	0	NA	NA	0	0	0	0	0	0	0	0
LV	2012	421.711	7	0,002	13	0,003	0	0	19	10	56	0,01	7	0,002	13	0,003	7	0,002	13	0,003

MT	2012	85.050	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA							
NL	2011 **	3.334.966	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA							
PL	2012	8.477.637	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA							
PT	2011 ***/ 2012 ****	2.201.556 (2011) / 2.172.315 (2012	7***	0	NA	NA	NA****	0***	NA****	0***	NA	NA	NA	NA	13	0	6	0	NA	NA
RO	2011 **/ 2012/ 2012 ****	4.379.369 (2011) / 4.341.679 (2012)	79 (2012) ****/ 1 (2013) ****	0,002 (2012) ; 0 (2013)	0	0	0	0	0****	NA**	0	0	7	0	43	0	6	0	16	0
SE	2011 ***	1.876.556	0***	0	0** *	0	0***	0***	0***	0***		NA	NE (?)		NE (?)		NE (?)		NE (?)	
SI	2012	411.037	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SK	2011 ***	1.219.202	NA	NA	84* **	0,007	NA	NA	NA	NA	NA	NA	40	0,003	92	0,008	48	0,004		

UK	2011 **/ 2011 ***/ 2012	13.218.614 (2011) / 13.191.613 (2012)	19***	0	78***	0	Yes, but disclosure of information is prohibited**	Yes, but disclosure of information is prohibited**	32; Germany, Ireland and Spain**	96; American Samoa, Australia, Canada, India, Israel, Japan, New Zealand, Singapore, South Africa and the USA**	145	0	73	0	315	0,002	102	0	177	0,001

8.4.5 Table A5: Volumes oocyte

Geo-graphical name	Coun try code	Year data	Number of women in fertile age (between 15 and 45) relative to year data	Donors	*% relative to women in repro-ductive age*	Dona-tions	*% relative to women in reproduc-tive age*	Donated	*% relative to women in repro-ductive age*	Received from other MS	Impor-ted	Distribu-ted to other MS	Expor-ted	IVF & ICSI with donor oocyte-cycles started	*% relative to women in repro-ductive age*	IVF & ICSI with donor oocyte–aspi-rations	*% relative to women in repro-ductive age*
Austria	**AT**	2011**	1.745.857	NA	NA	NA	NA	NA	NA	data not collected **	data not collected **	data not collected **	data not collected **	NA	NA		NA
Belgium	**BE**	2011**/ 2012	2.199.162 (2011) / 2.202.885 (2012)	492	0	NA	NA	NA	NA	760 all from the Netherlan ds**/0	0	0	0	NA	NA		NA
Bulgaria	**BG**	2012	1.457.281	194	0	247	0	###	0,2	0	0	0	0	354	0		NA
Cyprus	**CY**	2012	212.338	147	0,1	197	0,1	###	0,6	0	0	0	0	260	0,1		NA
Czech Republic	**CZ**	2012/ 2012****	2.215.635	NA	NA	NA	NA	37621****	1,7	0	0	0	0	###	0,2		NA
Germany	**DE**	2012	15.462.554	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
Denmark	**DK**	2012	1.098.026	106****	0	194****	0	1089****	0,1	0	0	0	0	106****	0		NA

Estonia	**EE**	2012	269.711	48	0	NA	NA	840	0,3	NA	NA	NA	NA	63	0		NA
Greece	**EL**	2012	2.272.242	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
Spain	**ES**	2012	9.933.955	###	0,1	###	0,1	###	1,2	NA	NA	NA	NA	###	0,1		NA
Finland	**FI**	2012	1.015.868	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
France	**FR**	2012	12.461.307	422	0	422	0	###	0	NA	NA	NA	NA	795	0		NA
Croatia	**HR**	2012	843.778	NA	NA	NA	NA	NA	NA	0	0	0	0	NA	NA		NA
Hungary	**HU**	2012	2.093.084	NA	NA	52	0	NA	NA	0	0	0	0	NA	NA		NA
Ireland	**IE**	2011	1.054.270	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	18***	0		NA
Italy	**IT**	2012	11.606.065	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
Lithuania	**LT**	2012	623.283	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
Luxem-bourg	**LU**	2012	114.369	0	0	0	0	0	0	0	0	0	0	NA	NA		NA
Latvia	**LV**	2012/ 2012****	421.711	239****	0,1	336	0,1	###	1	0	0	0	0	294	0,1		NA
Malta	**MT**	2012	85.050	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA

Nether-lands	**NL**	2011**/ 2011***	3.334.966	NA	NA	612***	0	5***	0	NA	NA	745 (auto logous) **	0***	NA	NA		NA
Poland	**PL**	2012	8.477.637	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
Portugal	**PT**	2011***/ 2012****	2.201.556 (2011) / 2.172.315 (2012)	315***	0	NA	NA	NA	NA	NA****	0***	NA****	0***	NA	NA		NA
Romania	**RO**	2011/ 2012****	4.341.679	16 (2012) ****/29 (2013)\ ****	0 (2012); 0 (2013)	79 (2012) ****/88 (2013) ****	0,002 (2012); 0,002 (2013)	240	0	0****	0	0****	0	0 (2012)/ 37 (2013)	0 (2012) / 0		NA
Sweden	**SE**	2012	1.874.204	211	0	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA
Slovenia	**SI**	2012	411.037	6	0	6	0	58	0	0	0	0	0	10	0		NA
Slovakia	**SK**	2011	1.227.837	NA	NA	66***	0	NA	NA	NA	NA	NA	NA	NA	NA		NA
United Kingdom	**UK**	2011**/ 2011***	13.218.614	1485***	0	1618***	0	14568***	0,1	NA**	297; Australia, Russia and USA**	NA**	NA**	1415***	0		NA

8.4.6 Table A6: Volumes sperm banks

Geographical name	Country code	Year data	Number of women in fertile age (between 15 and 45) relative to year data	Donors	*% relative to women in reproductive age*	Donations	*% relative to women in reproductive age*	Donated	*% relative to women in reproductive age*	Received from other MS	Imported	Distributed to other MS	Exported	IUI with donor sperm - couples treated	*% relative to women in reproductive age*	IUI with donor sperm - cycles started	*% relative to women in reproductive age*	IUI with donor sperm - aspirations	*% relative to women in reproductive age*	IVF & ICSI with donor sperm - couples treated	*% relative to women in reproductive age*	IVF & ICSI with donor sperm - cycles started	*% relative to women in reproductive age*	IVF & ICSI with donor sperm - aspirations	*% relative to women in reproductive age*
Austria	**AT**	2011 **	1.745.857	NA	NA	NA	NA	NA	NA	data not collected**	data not collected**	data not collected**	data not collected**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
Belgium	**BE**	2011 **/ 2012	2.202.885	NA	NA	1447	0,066	NA	NA	7824 (total) from Denmark, Italy, Germany, France, Spain and the Netherlands**/ 9056	0	46 (total) to Germany, France, Spain, the Netherlands and Denmark**/ 37	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N

Bulgaria	**BG**	2011 ***/ 2012	1.457.281	260***	0,018	932 ***	0,063	NA***	NA	287*** (all from Denmark)	0***	0***	0***	561	0,04	613	0,04	598	0,04	339	0,02	474	0,03	440	0,(
Cyprus	**CY**	2012	212.338	38	0,018	97	0,046	NA	NA	40	0	27	0	25	0,01	37	0,02	25	0,01	56	0,03	76	0,04	21	0,(
Czech Republic	**CZ**	2012 / 2012 ****	2.215.635	NA	NA	NA	NA	NA	NA	598 (no distinction between cross-border distribution or import)***	598 (no distingtion between cross-border distribution or import***	5 (no distinction between cross-border distribution and export)****	5 (no distinction between cross-border distribution and export)****	NA	NA	NA	NA	NA	NA	NA	NA	737	0,03	732	0,(
Germany	**DE**	2011 **	15.462.554	NA	NA	NA	NA	NA	NA	1007 (no differentiation made between cross border distribution and import/export)**	1007 (no differentiation made between cross border distribution and import/export)**	325 (no differentiation made between cross border distribution and import/ export)**	325 (no differentiation made between cross border distribution and import/ export)**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
Denmark	**DK**	2012	1.098.026	NA	NA	NA	NA	42223^	3,845	0^	3000^	45224^	2662^	NA	NA	10612^	0,97	NA	NA	NA	NA	NA	NA	NA	N

Estonia	**EE**	2011 */ 2011 **/ 2012 / 2012 ****	269.711	52*	0,019	596 **	0,217	NA	NA	249 (all from Denmar) - Substantial part of that 249 sperm straws (235) were imported by one larger public ART center in 2011. This does not happen every year and the sperm straws are not used up in one year.**/ ****	NA	NA	NA	74	0,03	NA	NA	131	0,05	141	0,05	NA	NA	154	0,(
Greece	**EL**	2012	2.304.293	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
Spain	**ES**	2012	9.933.955	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7035	0,07	3812	0,03	NA	NA	NA	N
Finland	**FI**	2011 **/ 2012	1.015.868	NA	NA	NA	NA	NA	NA	Received sperm from Denmark, but exact figure unknown	NA	NA	0**	NA	NA	1049	0,1	NA	NA	NA	NA	NA	NA	NA	N

										**														
France	**FR**	2012	12.461.307	235	0,002	235	0,002	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3870	0,03	NA	NA	NA	NA	1222	0,(
Croatia	**HR**	2012	843.778	NA	NA	NA	NA	NA	NA	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
Hungary	**HU**	2012	2.093.084	NA	NA	158	0,008	NA	NA	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	156	0,01	NA	N
Ireland	**IE**	2011 ***/ 2012 ****	1.038.623	0***	0	0***	0	0***	0	1270 (all from Denmark 2013 TE annual report)** **	25 (all from USA 2013 TE annual report) ****	0***	776 (partner) 2013 TE annual report** **	NA ***	NA	445 ***	0,04	NA ***	NA	NA ***	NA	184 ***	0,02	NA ***	N
Italy	**IT**	2012	11.606.065	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
Lithuania	**LT**	2012	623.283	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
Luxem-bourg	**LU**	2012	114.369	0	0	0	0	0	0	0	0	0	0	25	0,02	47	0,04	44	0,04	16	0,01	18	0,02	17	0,(
Latvia	**LV**	2012	421.711	29	0,007	76	0,018	0	0	177	0	0	0	129	0,03	140	0,03	140	0,03	69	0,02	69	0,02	43	0,(
Malta	**MT**	2012	85.050	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N

Nether-lands	**NL**	2011 ***	3.334.966	NA	NA	2752 ***	0,083	8317* **	0,249	NA	NA	156** *	0***	141 5** *	0,04	8185 ***	0,25	NA	NA	132 ***	0	151 ***	0	NA	N
Poland	**PL**	2012	8.477.637	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
Portugal	**PT**	2011 ***/ 2012 /201 2*** *	2.201.556 (2011) / 2.172.315 (2012	140 ***	0,006	NA	NA	NA	NA	NA*** *	0***	NA** **	0***	NA	NA	239	0,01	NA	NA	NA	NA	119 ****	0,01	NA	N
Romania	**RO**	2012 / 2012 ****	4.379.369 (2011) / 4.341.679 (2012)	96 (2012) ****/ 144 (2013)****	0,002 (2012) ; 0,003 (2013)	126 (201 2)** **/ 140 (201 3)** **	0,003 (2012) ; 0,003 (2013)	NA	NA	166 (2012) ****/ 714 (2013) ****	0	0 (2012)**** / 0 (2013)****	0	153 (201 2)/ 184 (201 3)		174 (2012)/ 212 (2013)		0 (2012)/ 90 (2013)		62 (201 2)/ 112 (201 3)		53 (2012)/ 110 (2013)		0 (201 2)/ 74 (201 3)	
Sweden	**SE**	2012	1.876.556	647	0,035	NA	NA	NA	NA	NA	NA	12	0	133	0,01	NA	NA	NA	NA		NA		NA	NA	N
Slovenia	**SI**	2012	411.037	22	0,005	65	0,016	NA	NA	0	0	0	0	NA	NA	NA	NA	NA	NA	41	0,01	41	0,01	51	0,(
Slovakia	**SK**	2011 ***	1.219.202	NA	NA	121* **	0,01	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N

United Kingdom	**UK**	2011 **/ 2011 ***/ 2012	13.218.614 (2011) / 13.191.613 (2012)	NA	NA	NA	NA	NA	NA	1003; Cyprus Denmark, Germany, Norway and Spain.**	1104; Australia, USA and Uruguay **	42; Cyprus, Denmar, Germany, Greec, Ireland and Spain.**	47; Australi, USA and Uzbekistan**	2060 ***	0,02	4015 ***	0,03		NA	1917	0,01	2208	0,02		N

8.4.7 Table A7: Donor compensation

Geographical name	Country code	Description of compensation	Compensation of sperm donors	Compensation of oocyte donors	Compensation of sperm donors - internet fertility search	Compensation of oocyte donors - internet fertility search
Austria	AT	NA	Compensation, amount not specified	Data not available	One (n=1/6*) clinic actively recruits sperm donors with no reference to compensation.	None of the clinics in the sample
Belgium	BE	It is not allowed to offer any advantage in exchange for the donation of human body material. The donor may receive reimbursement of costs linked to travel (to and from place of donation), and receive compensation for income loss due to the donation.	Compensation, amount not specified.	Compensation, amount not specified.	Four (n=4/12*) clinics actively recruits sperm donors with reference compensation but not to amount of compensation.	One (n=1/12*) clinics actively recruits oocyte donors with reference compensation but not to amount of compensation.

Bulgaria	BG	Payment is allowed	Average is €50,- with a maximum of €200,-	Average is €1000,- with a maximum of €1500,-	One (n=1/7*) clinic actively recruits sperm donors with reference compensation but no amount.	One (n=1/7*) clinic actively recruits oocyte donors with no reference to compensation
Cyprus	CY	NA	No Compensation	No Compensation	None of the clinics in the sample	None of the clinics in the sample
Czech Republic	CZ	Donor may receive compensation only for costs efficiently, economically and provably incurred in relation to the donation	Compensation, amount not specified.	Compensation, amount not specified.	Two (n=2/7*) clinics actively recruit sperm donors, both reference compensation, one clinic with the amount of 10.000CZK per 10 donations, the other clinic with the amount of 40 euro per one donation	Two (n=2/7*) clinics actively recruit oocyte donors, all reference compensation one of the amount of 15000CZK and the other of €60-€100 per donation.
Germany	DE	NA	Compensation, amount not specified.	Oocyte donation not allowed.	Two spermbanks offer €105 per sample. One spermbank expects donors to donate regularly (roughly every 14 days for at least 1 year). The other spermbank has a maximum compensation	Oocyte donation not allowed.

					per donor of €630.	
Denmark	DK	To be kept economically indemnified, e.g. loss of earning, expenses to medicines, expenses to transport. The donor must document expenses such as loss of earning, medical costs and cost linked to travel	Compensation, amount not specified.	Compensation, amount not specified.	One spermbank (n=1) offers €67 per sample. At this spermbank a minimum of 10 samples is required. The other spermbank (n=1) offers a small financial remuneration. No minimum or maximum listed. One spermbank (n=1) gives a bonus in compensation to sperm donors they are particularly seeking. Non-anonymous sperm donors with Extended profile get 10% extra.	Oocyte donors are recruited by one (n=1/9*) of the clinics with no reference to compensation

Estonia	EE	Payment of donors of reproductive cells is allowed. Living donors and recipients covered by health insurance shall be paid benefits for temporary incapacity for work by the Estonian Health Insurance Fund pursuant to the procedure provided in the Health Insurance Act.	Compensation, amount not specified.	Compensation, amount not specified.	None of the clinics in the sample	None of the clinics in the sample
Greece	EL	Yes,the principle of non-payment donation shall not prevent living donors from receiving compensation, provided it is strictly limited to making good the expenses and loss of income related to the donation so that any financial incentives or benefit for a potential donor should be avoided.	Compensation, amount not specified.	Compensation, amount not specified.	One spermbank states donors are compensated for travel expenses and loss of income justified from their absence of work but amount of compensation is not specified.	None of the clinics in the sample

Spain	ES	Living donors may receive compensation, strictly limited to making good the expenses and inconveniences of the donation	€100,- per donor semen	€900,- per oocyte donor	Three (n=3/13*) clinics actively recruit sperm donors of which two reference compensation but do not mention amount of compensation.	Five (n=5/13*) clinics actively recruit oocyte donors, all reference compensation but do not mention amount of compensation.
Finland	FI	NA	Tissue establishment considering e.g. compensation of travel expenses)	Tissue establishment considering e.g. compensation of travel expenses	Two (n=2/3*) clinics actively recruit sperm donors one with reference to compensation but no amount, one (n=1/3*) without reference to compensation	Three (n=3/4*) clinics actively recruit oocyte donors one with reference to compensation but no amount, one (n=1/4*) without reference to compensation
France	FR	Non-paid donation is laid down in the law on bioethics as a key principle. However, the law sets that donors must be reimbursed for all the expenses they have for the donation.	Compensation, amount not specified.	Compensation, amount not specified.	None of the clinics in the sample	None of the clinics in the sample

Croatia	HR	Compensation of living donors for loss of earnings and any other justifiable expenses caused by the removal of tissues or by the related medical examinations. A justifiable fee for the necessary medical or technical services rendered in connection with the removal of tissues	Compensation, amount not specified.	Compensation, amount not specified.	None of the clinics in the sample	None of the clinics in the sample
Hungary	HU	(1) Donation of organs and tissues shall only take place without consideration given in return. (2) The donors shall be eligible for recompense of loss of income related to the donation, and of his justified costs incurred in connection with making his statement of donation and with travelling, which are not reimbursed under his social insurance coverage.	Compensation, amount not specified.	Compensation, amount not specified.	None of the clinics in the sample	None of the clinics in the sample

Ireland	IE	NA	No Compensation	No Compensation	None of the clinics in the sample	None of the clinics in the sample
Italy	IT	NA	No Compensation	No Compensation	None of the clinics in the sample	None of the clinics in the sample
Lithuania	LT	Gamete donation is not allowed	Gamete donation is not allowed	Gamete donation is not allowed	Gamete donation is not allowed	Gamete donation is not allowed
Luxembourg	LU	NA	No Compensation	Oocyte donation not allowed	None of the clinics in the sample	None of the clinics in the sample
Latvia	LV	NA	Compensation, amount not specified.	Compensation, amount not specified.	Two (n=2/5*) clinics actively recruit sperm donors both reference compensation but no amount.	Two (n=2/5*) clinics actively recruit oocyte donors both reference compensation but no amount.
Malta	MT	Gamete donation is not allowed	Gamete donation is not allowed	Gamete donation is not allowed	Gamete donation is not allowed	Gamete donation is not allowed

Netherlands	NL	Yes. Only financial compensation of costs, including loss of income, directly following on the removal of an organ (includes tissues and cells) is allowed.	Compensation, amount not specified.	Compensation, amount not specified.	Four (n=4/10*) clinics actively recruit sperm donors, one with reference to compensation but no amount and one only less waiting time for treatment	Five (n=5/10*) clinics actively recruit oocyte donors one with reference to compensation and amount of €900,- one with reference to compensation but no amount; one only for donation to intended parents in the own social environment and one only less waiting time for treatment.
Poland	PL	NA	No Compensation	No Compensation	One (n=1/11*) clinic actively recruits sperm donors with reference to compensation and amount of 200PLN	Two (n=2/11*) clinics actively recruit oocyte donors, all with reference compensation, one references the amount of 4000PLN, and the other one an amount of 1000 $ or when willing to travel to another country 1500 $

Portugal	PT	A maximum amount considered fair to compensate gamete donors for the loss of earnings or inconveniences related to donation, that establish different criteria for egg and sperm donation; no compensation allowed for embryo donation. Couples declares in the informed consent their intention to donate the supranumerary embryos after completing 3 years of the cryopreservation period imposed by law	For sperm, there is an overall maximum of 1/10 of the social support index (€419,22) for each course of donation, that is €41,92.	For eggs the overall maximum of 1.5 of the social support index (€419,22) that is €628,83	One (n=1/2*) clinic actively recruits sperm donors with no reference to compensation	One (n=1/2*) clinic actively recruits sperm donors with no reference to compensation
Romania	RO	No	No Compensation	No Compensation	None of the clinics in the sample	None of the clinics in the sample
Sweden	SE	No	In Sweden the routines for compensation are not the same for all county councils. Additionally there is a variety of the levels of compensation.	In Sweden the routines for compensation are not the same for all county councils. Additionally there is a variety of the levels of compensation.	None of the clinics in the sample	None of the clinics in the sample

Slovenia	SI	Compensation of living donors for loss of earning and any other justifiable expenses caused by the removal or by the related medical examinations; Compensation is given for covering travel costs, possible medical support and eventual hospitalization.	Compensation, amount not specified.	Compensation, amount not specified.	NA	NA
Slovakia	SK	The cost will be reimbursed only for documented costs, strictly related to donation.	Compensation, amount not specified.	Compensation, amount not specified.	One (n=1/2*) clinic actively recruits sperm donors with reference compensation but no amount	One (n=1/2*) clinic actively recruits oocyte and embryo donors, reference to compensation but not amount
United Kingdom	UK	Reproductive cells: The HFEA Direction 0001 provides the guiding principles for clinics when compensating sperm, egg and embryo donors. The HFEA Code of Practice, guidance note on 'Payments to donors' provides further guidance: http://www.hfea.gov.uk/500.html \	up to £35 per clinic visit	up to £750 per cycle of donation	Two (n=2/11*) clinics actively recruit sperm donors of which one references compensation of £35,- per visit to the clinic. Two sperm banks referer compensation of £35,- per visit to the clinic (total n=2).There is no maximum amount of	Six clinics actively recruit oocyte donors, of which four reference compensation and amount of £750 for each donation cycle. (total n=11)

					donation listed. But on average men donate between 10 and 20 times.	

8.4.8 Table A8: Donor anonymity

Geographical name	Country code	Donor anonymity	Donor anonymity
Austria	AT	Not allowed: Parents will just get any necessary medical information or information regarding physical appearance of the sperm donor. However to the child the personal data of the sperm donor will be disclosed when he or she is 14 year old.	Non-anonyous, identity disclosure to the child at a certain age
Belgium	BE	anonymous donation	Anonymous
Bulgaria	BG	anonymous donation	Anonymous
Croatia	HR	identity disclosure allowed, non-anonymous donation	Non-anonyous, identity disclosure to the child at a certain age
Cyprus	CY	anonymous donation	Anonymous
Czech Republic	CZ	anonymous donation	Anonymous

Denmark	DK	identity disclosure allowed, anonymous donation allowed	Anonymous and non-anonymous donation
Estonia	EE	anonymous donation	Anonymous
Finland	FI	Children have the right to know the identity of the donor at age 18	Non-anonyous, identity disclosure to the child at a certain age
France	FR	anonymous donation	Anonymous
Germany	DE	identity disclosure allowed, non-anonymous donation	Non-anonyous, identity disclosure to the child at a certain age
Greece	EL	No data available	Data not available
Hungary	HU	anonymous donation	Anonymous
Ireland	IE	There is no legislation in Ireland in this area. No donor sperm is procured here in Ireland. All donor sperm is obtained from another EU Member State. The donor disclosure rules in that MS would have to be applied to these donors. Guidelines on anonymity to be drafted.	Anonymous and non-anonymous donation
Italy	IT	anonymous donation	Anonymous
Latvia	LV	anonymous donation	Anonymous

Lithuania	LT	Gamete donation not allowed	Gamete donation not allowed
Luxembourg	LU	identity disclosure allowed, non-anonymous donation	Non-anonyous, identity disclosure to the child at a certain age
Malta	MT	Gamete donation not allowed	Gamete donation not allowed
Netherlands	NL	Donor identity disclosure is only applicable for treatments in the Netherlands; donor characteristics are registered after amalgamation. The law is not applicable for the donation, but for the trajectory after amalgamation.	Non-anonyous, identity disclosure to the child at a certain age
Poland	PL	NA	No legislation
Portugal	PT	No, (CNPMA- NCA3): Donor's identity is kept confidential except if the donor express consent on contrary and only when the children born turns 18. Any other case, disclosure of donor data is only allowed for weighty reasons recognized by a judicial decision. Since 2013 there is a centralized registry with restricted access	Anonymous and non-anonymous donation

Romania	RO	anonymous donation	Anonymous
Slovakia	SK	anonymous donation	Anonymous
Slovenia	SI	Donor identity disclosure is allowed, anonymous donatino	Data not available
Spain	ES	anonymous donation	Anonymous
Sweden	SE	The donor is anonymous to the recipient (couple) but the child has the right to know its biological father/mother when it reaches mature age. Accordingly the TE (IVF-clinic) performing ART with donor gametes has to keep records of their donors for 70 years.	Non-anonyous, identity disclosure to the child at a certain age
United Kingdom	UK	Donor identity disclosure is allowed, non-anonymous donation	Non-anonymous, identity disclosure to the child at a certain age

8.4.9 Table A9: Prices of ART treatments from internet search per Member State (N=180)

	No. clinics/ prices listed	Clinic	IUI partner	IUI non-partner	IVF partner	IVF non part-ner	ICSI partner	ICSI non part-ner	FET part-ner	FET non part-ner	Oocyte dona-tion	Sperm dona-tion (straw)	Embryo dona-tion	Remarks
AT	(n=6/6)	KinderWunshKliniken Dr. Loimer	€495*	€1320*	€2970*/ €854**/ €911,42 ***		€3410*/ €945.52 **/ €1002.93 ***							* *self- financing couples (private)* ** *IVF fund, patients up to 35* *** *IVF fund, patients between 35 and 40* **** *package price, medication not included*
		Das Kinderwunsch Institut			€2200*/ €854**/ €911,42 *** /		€2500*/ €945,52 ** / €1002,94 *** /							
		Fertilitätszentrum Döbling			€2750 ****		€3190 ****							
		Institut für In-Vitro-Fertilisierung und Endokrinologie Dr. Hans-Peter Steiner			€2850*/ €853,99 **/ €911,41 ***		€2850*/ €945,51*/ €1002,92 ***							

		Kinderwunsch Zentrum Goldenes Kreuz			€854**/ €911,42 ***		€945,52** / €1.002,93 ***						
		Private Kinderwunsch-Clinic Dres. med. Josef und Sonja Zech	€ 440*		€3590*/ €854**/ €911,42 ***		€3890*/ € 945,52 **/ €1.002,93 ***						

	No. clinics/ prices listed	Clinic	IUI part-ner	IUI non-partner	IVF partner	IVF non part-ner	ICSI partner	ICSI non partner	FET partner	FET non partner	Oocyte dona-tion	Sperm donatio n (straw)	Embryo dona-tion	Remarks
BE	(n=5/12)	ZNA Middelheim Centr. voor Reproductieve Geneeskunde	± €100	± €100	± €400 / €1200 *	± €400 / €1200 *	± €400 / €1200 *	± €400 / €1200 *						** €400 is the price for Belgian citizens with the correct health insurance and a payback form, €1200 accounts for those without the correct pay back form* *** When a patient is part of a Belgium Mutality, treatment is free of cost, otherwise it is the second price stated* **** Lab cost, reimbursed for those with a Belgium health insurance* ***** Price for a Belgian couple with health insurance*
		Fertiliteitskliniek CRG-Brugge-Kortrijk	€0 / €250 **		€0 / €1383**		€0 / €1383**							
		Vrouwenkliniek, UZ Gent	€ 335		€1500***							€150		
		The In Vitro Fertilization team - Universite de Liege			€1350/ €1650									

		Centrum voor Medisch Begeleide Voortplanting van het UMC Sint-Pieter	€150 / €170		€250****									

	No. clinics/ prices listed	Clinic	IUI part-ner	IUI non-partner	IVF partner	IVF non partner	ICSI partner	ICSI non partner	FET part-ner	FET non partner	Oocyte donation	Sperm donation (straw)	Embryo dona-tion	Remarks
BG	(n= 7/7)	Medical Center - Clinical Institute for reproductive medicine St. Elisaveta			€1.380		€1.482					€306		** €990 (stimulated with donor sperm); €650 (unstimulated with donor sperm) ** Donor-egg IVF treatment, ICSI included *** € 890 (stimulated cycle); € 210 (unstimulated cycle) **** €1170 (stimulated cycle) ; €320 (unstimulated cycle) ***** €772 IVF on natural cycle €977 IVF on*
		Nadezhda		€650 / €990 *	€2.900						€5300 **			
		Sofia Hospital	€200	€210 / €890	€210 / €890		€320 / €1170 ****							
		In Vitro OB Medical Center "Dimitrov"	€179	€281	€772 / €977 *****	€925 / €1130 ^								

		OLIMED In vitro center	€256	€360	€1.125		€256						*limited cycle + medicine costs. ^ €925 ICSI on natural cycle*
		Dr. Shterev Hospital	€23 / €613								€296/ €5132		*€1130 ICSI on limited cycle + medicine cost ^^ for IVF/ICSI treatment*
		Radost	400 lev		2700 lev		3000 lev					600 lev ^^	
CY	(n= 1/8)												** 2 straws*
		Pedieos									£2750	£450*	
CZ	(n=7/7)	IVF Cube									€6.100		** One donor embryo; one donor embryo + PGD; two donor embryos; two donor embryos + PGD*
		Reprofit	€130	€200	€1.950		€1.950		€320	€1140 / €1500 / €1680 / €3000*	€4500/ €4000 **	€200	€1.140	*** Includes IVF and fresh donor oocytes; IVF and frozen donor oocytes *** 2 embryos **** Incl. donor oocyte; incl. donor oocyte and ICSI; incl. donor oocyte and PICSI ***** ICSI 0,5 - 1 mil / dose, 0,2 ml, over 10 quantities, from: 84 €; ICSI 1 - 2*

													mil / dose, 0,5 ml, over 10 quantities, from: 100 € IVF; 2 - 10 mil / dose, 0,5 ml, over 10 quantities, from: 120 €; IUI 2, under 15 mil / dose, 1,8 ml, under 10, From: 160 € ****** €1040 (basic IVF cycle) ; €1800 (complete IVF cycle)* ******* IVF with ICSI, minimal stimulation* ********€3500 (donated eggs IVF cycle) ; €3800 (Donated eggs IVF cycle with best sperm and embryo selection)* *^ €4980 (IVF cycles with Donated oocytes - Standard) ; €6600 (IVF cycles with Donated oocytes - Standard + PGS) ; €6200 (IVF cycles with Donated oocytes - Individual); €7900 (IVF cycles with Donated oocytes - Individual + PGS); €9900 (IVF cycles with Donated oocytes - ,, All Inclusive")* *^^ €1000 (1*

													donated embryo, assisted hatching); €1500 (2 donated embryos, assisted hatching) ^^ Embryo Adoption- two top quality embryos
		ReproGenesis			€2.000				€600	€1.800	€4.500			
		Gynem	€450		€1990		€1990		€1500 ***		€4000/ €4500/ €4800	€150		
		Center of Ass. Reproduction, Univ. Hospital Brno			€1040/ €1800 ******		€600 *******		€ 220		€3500/ €3800 ********	€150	€1000/ €1500 ^^	
		Sanatorium Repromeda	€110	€350	€2.200	€4980/ €9900^	€400		€300			€240	€2.200	
		Arleta Centre for Reproductive Medicine												

	No. clinics/ prices listed	Clinic	IUI part-ner	IUI non-part-ner	IVF partner	IVF non partner	ICSI partner	ICSI non part-ner	FET part-ner	FET non part-ner	Oocyte dona-tion	Sperm dona-tion (straw)	Embry o dona-tion	Remarks
DE	(n=5/10)	Kinderwunsch-Zentrum Wiesbaden	€260 (without hormone inject-tion) / €1000 **		€3.000		€3.500							* without hormone injections ** with hormone injections *** Insemination without stimulation **** Insemination with stimulation ^ In vitro fertilisation (IVF) incl. embryo transfer ^^ Intracytoplasmic sperm injection (ICSI) incl. embryo transfer ^^^ €400 excl. cost for sending €510 incl. cost for sending
		Kinderwunschzentrum Praxisklinik City Leipzig	€150 - 160		€1.500		€1.800							
		Praxis für Fertilität	€400 - €600		€2000 - €3000		€3500 - €5500							
		Kinderwunsch Klinik IVF – Bayreuth	€400 - €500		€2200 - €2800		€3200 - €5200							
		Fertility Center Berlin	€59,82 ***; €82,32		€523,42^		€705,06 ^^							

			****											

	No. clinics/ prices listed	Clinic	IUI part-ner	IUI non-part-ner	IVF partner	IVF non partner	ICSI partner	ICSI non part-ner	FET part-ner	FET non part-ner	Oocyte dona-tion	Sperm dona-tion (straw)	Embryo dona-tion	Remarks
DK	(n=11/11)	Ciconia Aarhus Privathospital og Fertilitetsklinik	DKK 1.500 (+/- €200)	DKK 1.500 (+/- €200)*	DKK 22.000 (+/- €2950)	DKK 23.250	DKK 25.000				DK 40.000	DKK 2.750		* If referred by family doctor, treatment is free of charge ** Free of charge for Danish inhabitants second price applies for foreigners **** First price for open donor sperm, second for anonymous donor ^ DKK 0 if referred by GP, DKK 600 if referral for woman using washed semen, DKK 1200 if referral for woman with non-washed semen ^^ DKK 26.000 if
		AAGAARD Gynækologi & Fertilitet	DKK 1.500*	DKK 2.600	DKK 17.000 - DKK 21.000		DKK 24.000		DKK 8.000		DKK 34.000	DKK 1.300		
		Maigaard Fertiliteitsklinik	DKK 1.500	DKK 2.750	DKK 22.000		DKK 25.000						DKK 8.000	
		Dansk Fertilitetsklinik	€0/€430		€2.975		€3.450					€375 /		

			**									€200 ***		using own donor and IVF, DKK 29.000 if using own donor and ICSI, DKK 42.000 if using anonymous donor ^^^ €195,- ICI anonymous, min MOT 20, €295 ICI non-anonymous, min MOT 20, €239 IUI anonymous, min MOT 20, €379 IUI non-anonymous, min MOT 20 ^^^^^ First is for anonymous donor, second price for open donor ^^^^^^^ Dkk 4.500 (non-contact donor); DKK 5.200 (non-contact donor, extended profile); DKK 6.000 (open donor); DKK 6.900 (open donor, extended profile)
		Fertilitetsklinikken Trianglen	DKK 0 / DKK 600/ DKK 1.200^		DKK 22.000		DKK 25.000				DKK 26.000 / DKK 29.000 / DKK 42.000 ^^		
		Nordic Cryo Bank										€195 / €295 / €239 / €379 ^^^	
		Stork Klinik	DKK 3.800		DKK 22.500	DKK 24.000	DKK 26.000		DKK 5.000		DKK 45.000	DKK 1.500 / 2.500^ ^^^	
		Copenhagen Fertility Center	DKK 2.000	DKK 3.500	DKK 18.500		DKK 22.000				DKK 35.000	DKK 1.500	
		Vitanova			€3.000	€3230 / €3340 ^^^^^	€3.600						
		IVF-Syd Fertilitetsklinik	€350	€500	€3.000	€ 3.150	€3.450	€3.600					

		Diers Klinik	DKK 3.800	Dkk 4.500 / DKK 5.200 / DKK 6.000 / DKK 6.900 ^^^^ ^^										
EE	(n=1/2)	Elite Kliinik						€ 390	€1650 / €5100 *	€1650 / €5100 *		€ 260		* fresh embryo
IE	(n=5/5)	Sims IVF			€4.600	€5150 *	€ 4.920	€5470 *			€8700 ** / €9500			* Additional charges will be incurred for non-anonymous donors and those with extended profiles ** included IVF treatment *** IVF with ICSI **** natural cycle or Clomid ***** IUI and FSH
		Repromed Ireland	€ 950		€4.500		€5000 ***		€ 1.250		€ 8.500	^		
		Merrion Fertility Clinic	€520 **** €720		€ 4.500		€ 4.900		€ 1.100					

			*****										****** with FSH ^ Donor Sperm is charged on an individual basis as costs vary depending on the type and profile of donor chosen. ^^ Price varies in accordance with donor profile.
		Cork Fertility Centre	€650 ******		€ 3.750		€ 4.250		€ 990		€ 8.000	^^	
		HARI	€ 400		€ 4.400		€ 4.900		€ 1.000				

	No. clinics/ prices listed	Clinic	IUI part-ner	IUI non-part-ner	IVF partner	IVF non partner	ICSI partner	ICSI non partner	FET part-ner	FET non partner	Oocyte dona-tion	Sperm dona-tion (straw)	Embryo dona-tion	Remarks
EL	(n=7/15)	EmBio IVF Center	€200		€2.000		€300		€700,-		€4300 / €4800	€500		* IVF + ICSI ** €3000 for one OE cycle or you can pay €4000 for two *** including all the donor's meds etc.
		Mediterranean Fertility Center & Genetic Services	£350	£600	£1,100				£700		£2,200		£2,700	
		Embryoland IVF Center Athens	€2600 / €3000						€4500 / €4800					
		Life Clinic	€800		€3.200		€3.600*		€1.600			€250		
		Serum IVF			€3000**						€5000 ***			
		Gennima	€836	€836	€3.747		€3.953	€1.455			€6.245			
		Neogenesis			€1.500		€800		€1.000		€3.600			
		NewLife IVF Center			€3.200						€5000,-			
ES	(n=11/13)	IVI			€6490*									* Starting price ** Spanish

		IVF Spain		€1000/ €1500 **	€1650/ €2950 / €6500***					€5500 ****			donation bank; Central European donation bank *** Natural cycle; IVF Basic, a controlled ovarian stimulation; IVF Plus **** 5-7 guaranteed eggs from the recent cycle of the donor ***** With 24 chromosome PGS ****** Fresh egg donation cycle with 24 chromosome PGS; all donor costs included ******* Up to 7this price
		Centro Médico Manzanera			€4.250								
		UR Clinica Vistahermosa			€6950 *****		€6950 *****				€9950 / €25.000 ******		
		Institut Marquès											€3.585
		Ginefiv									€5.665		
		Clinica Tambra							€1.200		€6.045		
		FIV Madrid							€1.500		€7.000		
		Juaneda Fertility Center	€875		€5.000	€ 5.500	€5.000		€1.500		€6.250		
		AISA reproducion y biotecnologia					€3.700						€6.000
		Irema	€750 - €1195		€4.150 *******		€4.150 *******		€1620 ****** *				

FI	(n=3/3)	Väestöliitto Lapsettomuusklinikka	€395*/ €503	€707*/ €783	€1819–2158 * / €2296–2784 **	€2470 * / €3064 ** / €5411 * €5707 ***	€2353–2692 * / €2973–3461 **		€920 * / €1102 ****		€5411*/ €5707 ***			* co-payment ** total price, 1-3 follow up visits *** total price, donor eggs **** total price ^ own cost ^^ total cost, 2-3 follow up visits included ^^^ one treatment included # €5500 – 5600 (total price with IVF, 2- 3 visits included), €5000 – 5200 (own cost) ; €6200 – 6400 (total price with ICSI, 2-3 visits included), €5700 – 5900 (own cost)
		Fertinova	€366.50*/ €458****		€2536 **** €2004 * / €2536 ****		€2394 * / €3069 ****		€809 * / €1001 ****		€6354,75 - €6911,50 * / €6950 - €7400 ***			
		Ovumia	€412 – 584 ^ / €515 – 687 ^^	€737 ^^^	€1815 – 1954 ^ / €2327 – 2499 ^^		€2392 – 2531 ^ / €3047 – 3219 ^^		€712 ^/ €894 ***		€5500 – 5600 / €5000 - 5200 / €6200 – 6400 / €5700 – 5900 #	€737 ^^^		
FR	(n=0/3)	Prices are not listed on any of the websites												
HR	(n=0/2)	Prices are not listed on any of the websites												

HU	(n=2/2)	Versys Clinics			€3000 - €9000*								* €3000 - €9000 (depending on the technique used (ICSI, PICSI, assisted hatching, PGD) ** €1520 (IVF-ET), €1680 (IVF-Assisted hatching) *** €1840 (IVF-ICSI); €1960 (IVF-ICSI-Assisted hatching)
		Róbert Károly Private Clinic	€440		€1520 / €1680**		€1840/ €1960 ***		€800				
IT	(n=3/5)	Livet	€700		€3.900		€3.900		€900				* stimulated ** unstimulated *** with egg donation **** IVF with egg donation
		CFA centro fecondazione assistita	€62/ €375 **		€ 2.373	€87 43 ***	€ 2.373		€375		€8.743 ****		
		Gamete Donation									€7.000		
LT	(n=3/5)	Nord Fertility	€160		€1880 / €3050 *				€580				* €1,880 IVF (without the medications) + ICSI; €3,050 IVF (including the medications) ** IVF + ICSI
		Grazinos Bogdanskiene Fertility Center	€600		€2.200		€2900 **						
		Jolsana medical centre	€145		€1.304		€435						
LU	(n=0/1)												

		Prices are not listed on any of the websites											

	No. clinics/ prices listed	Clinic	IUI part-ner	IUI non-part-ner	IVF partner	IVF non partner	ICSI partner	ICSI non part-ner	FET part-ner	FET non part-ner	Oocyte dona-tion	Sperm dona-tion (straw)	Embryo dona-tion	Remarks
LV	(n=5/5)	Ava clinic Riga	€540	€910	€ 2.080	€2.450	€3.040	€3.410	€1.250		€6.450	€370		* with donor sperm ** with whole treatment ***for five treatments **** IVF with ICSI includes medication, embryoscope, embryoglue, PICSI, CultActive ***** IVF with ICSI with donor sperm includes medication, embryoscope, embryoglue, PICSI, CultActive ^ includes embryo glue, assisted hatching
		Embrions	€150	€300	€ 950	€1100 *	€1.250		€300					
		Jusu Arsti	€242	€570	€ 1.053		€1.381	€1708 *			€4938 **			
		IVF Riga	€1500 ***	€2300 ***			€6000 ****	€6300 *****	€1800 ^		€8250 ^^		€8600 ^^^	
		EGV - Effective infertility treatment	€400	€550	€2.000		€2.600				€3690 / €6210 ^^^^	€150		

														^^ package: egg donation, medication, PICSI, embryoscop, embryoglue, assisted hatching ^^^ package: embryo donation,medication,embryoscope, embryoglue, assisted hatching ^^^^ Egg donor program (with embryo freezing) total fee €6210
MT	(n=0/1)	Prices are not listed on any of the websites												
NL	(n=4/10)	Nij Barrahûs	€ 724,83	€724,83 + €1200 *	€1338,86 **		€1338,86 ***		€286,62 ****					* buying 6 straws with sperm ** IVF/ICSI transport, stimulation, monitoring, punction at Nij Barrahus extra: €916,81 for treatment in Leer; extra €668,85 for IVF treatment in Zwolle *** IVF/ICSI transport, stimulation, monitoring, punction at Nij Barrahus extra:
		Nij Geertgen	€ 724,83	€724,83 + €111,31 + €50,00 ^	€1.338,86 ^^		€ 2.306,91		€286,62 + €372,62 + €300,00 ^^^^					
		Medisch Centrum Kinderwens			€1100,00 + €900 ^^^^ ; €1800 ^^^^^		€ 1100,00 + €900 ^^^^ ; €2100 ^^^^^		€600		€2400 *****	€213	€425	

		IVF-kliniek VU medisch centrum	€750		€2.050		€2.300							€1293,98 for ICSI treatment in Leer; extra € 959,09 for ICSI treatment in Zwolle **** cryo-cyclus monitoring extra: €442,51 for transfer in Leer; extra €230 for transfer in Dusseldorf; extra €204,42 for transfer in Zwolle ***** for 4 eggs ^ psychological counseling and administrative cost for sending straws ^^ IVF/ICSI stimulation, monitoring en punction ^^^ cryo-cyclus-monitoring + lab phase + transfer in Genk ^^^^ phase 1 and 2 + phase 3 and 4 ^^^^^ if treatment can't be reimbursed
PL	(n=11/11)	Invicta	€164	€260	€3.248	€4.000 *					€4.000			* With egg donor ** IVF IMSI GOLD Package (including consultation, medical examination, medicaments) €3300
		Gyncentrum	€200		€2.200		€2.200				€4.500	€490		
		Center for Reproductive	€100	€220	€1150 - €1300		€1.000		€300					

		Medicine Bocian											*** Surrogacy packages. Two Surrogate mother Program (without donor) resulting in one confirmed pregnancy: €36.300; Two Surrogate mother program with frozen embryo transfer- resulting in one confirmed pregnancy: €32.300
		InviMed			5.780 zl		6.780 zl		1.500 zl		18.000 zl		18.000 zl
		NeoMed Poland			2200 **						€4.500	€150	
		nOvum fertility clinic	€192		€1.437		€1.653		€383				
		Artvimed	€125	€275	€875		€875		€250				
		Gravita	€650	€1.250					€500				
		VitroLive	700zl	1500zl	5500 zl	6500zl	5500zl	6500zl	1200zl				
		Klinika Bocian	€100	€220	€1.000		€1.000		€300				
		New Life Poland									€8000 ***		
PT	(n=1/2)	AVA Clinic - centro de fertilidade de Lisboa	€680	€970	€2.950	€2950 + €290 *	€3.900	€3900 + €290 *	€900		€5.950	€290		* for sperm donation
RO	(n=2/5)	Mures Fertility Center	€ 245		€1514 / €1759 *		€293							* €1514 (IVF on natural cycle) €1759 (IVF on stimulated cycle) ** Discounted IVF Standard IVF 2nd cycle €2250; Standard IVF 3rd
		Gynera Fertility Center	€ 200		€2550 **		€ 400		€ 400					

														cycle €1800; Minimal IVF (Natural cycle or maximum 3 oocytes retrieved) €1800; Share IVF €1000
SE	(n=5/5)	IVF-kliniken Falun	1700 kr; 7200 kr *		26.500 kr 20500 kr **				13.000 kr					* with hormone stimulation ** local doctor, Package price IVF: 54000 kr *** insemination with donor sperm and hormone stimulation **** IVF with ICSI ***** with hormone stimulation and injections ^ natural cycle ^^ partner insemination ^^^ Package price for 3 IVF/ICSI treatments: 60.000kr; 3 IVF/ICSI treatments with donor sperm: 84.000 kr # Package price for 3 IVF/ICSI treatments under 39 years old: 68.000 kr; package price for 3 IVF/ICSI treatments 39-41 years old: 76.000 kr
		IVF-Kliniken Umeå		15.000 kr ***	32.000 kr ^^^	42.000 kr ^^^	32.000 kr **** ^^^				70.000 kr			
		IVF-Kliniken Stockholm	6500 kr		34.000 kr #		34.000 kr #		13.000 kr					
		IVF-Kliniken CuraÖresund	10.000 kr *****		32.000 kr ##				13.000 kr					
		Fertilitetscentrum Stockholm	7000 kr ^ / 9000 kr ^^		34.000 kr ###				13.000 kr					

														## Package price 3 IVF treatments under 39 years old: 59.000 kr; price for 3 IVF treatments 39-41 years old: 68.000 kr ### Package price 3 IVF treatments under 38 years old: 68.000 kr; package price 3 treatments between 39 - 41 years old: 76.000 kr
SI		No English language websites found												
SK	**(n=2/2)**	Ferticent	€100		€1.300		€1.300							* package, includes ICSI ** egg donation ivf package *** frozen embryo adoption
		Gyn-Fiv			€1990 *				€ 500		€4450 **	€ 200	€1450 ***	
UK	(n=11/11)	Harley Street Fertility Clinic	£1000 = €1250		£3600 = €4496		£2800 = €3497		£1100 = €1374			£1000 = €1250		* IVF 3 Cycle Package – £7,200 ** £795 (unstimulated) £1,295 (stimulated) *** £5,750 (5 fresh eggs) £3,350 (6 frozen eggs) **** IVF 3 cycle package £8,400.
		Assisted Reproduction and Gynaecology Centre	£600 = €751		£3000 = €3758 *		£1200 = €1503							

		The London Women's Clinic	£795 / £1,295 **		£3,350 ****				£1,150	£2,700	£5,750 / £3,350 ***	£850		Three cycle egg donation package from UK based, registered donors (6 frozen eggs per cycle) £7,700 ***** £5020 (shared donor for eggs) £8135 (exclusive egg donor) £5020 (from a known donor) ****** £5,750 (Egg donation from a UK based, registered donor (5 fresh eggs)) or £3,350 (Egg donation from a UK based, registered donor (6 frozen eggs)) or £7,700 (Three cycle egg donation package from UK based, registered donors (6 frozen eggs per cycle)) additional to these costs always £3,050 administration cost ******* IVF 3 cycle package: £8,000 ********£ 5,790 (with IVF); £ 6,390 (with ICSI) ^ £835 ; £1025 for stimulated IUI ^^ excludes medication ^^^ £6,790 with IVF ; £6,990 with ICSI ; £1,720 egg sharing and IVF ; £2,020 egg sharing
		Lister Fertility Clinic		£ 872.50	£3555		£1390		£ 995		£5730	£1675	
		Care Fertility	£760		£3050	£5020 / £8135 *****	£1050		£1125			£720	£3150
		Bourn Hall Clinic	£750		£2,950	£5,700	£950		£1,200			£500	
		The Bridge Centre	£795 / £1,295		£3,300 *******		£1,250		£1,100	£2,700	£3,350 / £5,750 / £7,700 ******	£850	
		Midland Fertility Services	£ 995		£ 2,920		£ 3,520		£1,200		£ 5,790 / £ 6,390 ********	£ 300	£ 3,590
		Bristol Centre for Reproductive Medicine	£835 / £1025 ^		£3210		£4280		£990		£2600	Variable	

		St. Jude's Hospitals and Clinics	£780 ^^		£2,990 ^^		£3,290 ^^		£990		£1,720 / £2,020 / £6,790 / £6,990 / ^^^	£2,550 ^^^^		and ICSI ^^^^ Excludes cost of screening donors ^^^^^ IVF + ICSI # per 5 vials ## one vial of donor sperm
		Body Bureau	£250		£1,275		£1,800 ^^^^^		£510					

Source: Internet search N=180 fertility clinics Rathenau Instituut 2014

9 ANNEX 3: COUNTRY CLASSIFICATION ACTIVITY ART

This annex contains an overview of EU Member States as categorised on level of activity for ART.

Restrictive, average and liberal access and reimbursement

In this paragraph we discuss countries with relatively large activity in gamete donation and countries with relatively limited activity in gamete donation. We integrate here findings on number of donors/donations, number of fertility treatments and access and reimbursement criteria and treatments offered as indicated by the internet search on fertility clinics. Furthermore we discuss which countries can be considered hubs for fertility treatment as they have relatively large activity and as indicated by the internet search many clinics communicate to patients from abroad, for instance by means of a multi-language website.

Many Member States do not have significantly large or small activity in gamete donation related practices or data is lacking to make such a classification. These countries are not specifically addressed in this paragraph.

Countries with large activity

Countries with relatively large activity in sperm donation are Denmark and Belgium. For Denmark this is based on number of donors and cross-border distribution, import and export of sperm. Belgium does not have an exceptionally large number of sperm donors but a considerable amount of sperm is received from other Member States.

For oocyte donation countries with large activity are Czech Republic and Spain.

Czech Republic, Spain, Estonia and Ireland have relatively large embryo related activity. For Estonia the number of donated embryo is not exceptionally high but relative to the number of women in reproductive age the number of donated embryo is considerable. In Ireland the classification is based on the high number of imported embryo.

For Poland there are no legal regulations on fertility treatment in Poland. Polish authorities have no basis for collecting data on number of fertility clinics, donors, treatments etc. The internet fertility search however indicates activity in Poland might be considerable and Poland might be an actor in cross-border fertility care. Therefor Poland is also discussed in this section.

Below these figures are integrated with information on access, reimbursement and compensation of donors and cross-border fertility care.

Denmark (DK)

Denmark has by far the largest activity in sperm donation with 4223 donated units of sperm, 3000 imported, 45224 distributed and 2662 exported units. Several EU Member States indicate to rely partly or entirely on the DK sperm banks for their supply of donor sperm. Our understanding is that Cryos International operates from a monopoly in the EU, although the European Sperm Bank also has considerable activity. Our understanding is that a substantial part of distribution of sperm takes place directly to consumers (and less so via tissue establishments or clinics) in other Member States. As found in the internet search on fertility clinics, one DK sperm bank indicates donor compensation of €67 per sample (with a minimum of 10 donations). It cannot be

concluded though that higher amounts of compensation lead to a larger availability of donors and of donor sperm.

Czech Republic (CZ)

Large numbers of oocyte donation are reported in comparison to other Member States (36414 oocytes donated) but only small numbers (4) for distribution in the EU, and none (0) for export. Furthermore a relatively high number of donated embryos are reported to EUROCET compared to other EU Member States (1341) of which a large share (of 1013) for extra EU export (to non-EU countries).

A classification for sperm donation related activity cannot be made as the number of sperm donors and sperm donations is not available. To EUROCET (over year 2012) a total number of 903 sperm straws was reported as received from another Member State. In the opinion of the competent authority there is a high probability that most imports are partner reproductive cells, indicating cross-border fertility treatments. Furthermore to EUROCET (over the year 2012) only 8 sperm straws distributed to other Member States are reported (8 are reported to EUROCET and 5 are reported by the Competent Authority). It is unclear how this relates to the existence of a large sperm bank in CZ offering online samples to all EU Member States.

The internet search of clinics indicates compensation amounts for sperm donors of around €40 per donation, and another clinic about €360 (CZK 10.000) per 10 donations. For oocyte donation amounts are offered of 15000 CZK or €60-100 per donation by different clinics.

Availability of oocyte and embryo might make Czech Republic a popular destination for cross-border fertility care. Also the internet fertility search indicates Czech Republic is a destination for cross-border fertility care as many CZ fertility clinics have websites in English, German, Italian, Russian, or French. Our provisional finding is that CZ is a popular destination for cross border fertility care from AT, DE, IT, FR and UK (and perhaps other countries). This is also confirmed by the Competent Authority. Our internet search indicates that prices for fertility services offered in CZ are relatively less costly compared to most other EU Member States. Our provisional finding is that CZ is an attractive destination for cross border fertility care not only because of availability of gametes but also based on low cost of treatments.

Spain (ES)

For Spain overall, our impression is that it is one of the largest providers of fertility services in the EU, both for citizens of Spain and for nationals of other countries, thereby serving as popular destination for fertility treatments/ reproductive tourism .

In EUROCET 2012 it is indicated that ES has 6457 oocyte donors with 123.447 oocytes donated. Our understanding is very little or none of these oocytes are distributed to other EU Member States or exported to third countries.

Reported in EUROCET 2012 IVF/ICSI with donor oocytes is more performed (11.155 cycles started) compared to IVF/ICSI with donor sperm (3812 couples treated). Donor activity in sperm or number of sperm straws received from other Member States or imported from third countries is not reported. It is our understanding ES is not self-sufficient when it comes to donor sperm and intended parents traveling to ES can also have sperm from other Member States (for instance from DK) sent to clinics in ES for fertility treatments. The internet search indicates some of the fertility clinics in ES also have an English, Italian, French, German, Russian, Portugese, Norwegian, Chinese, Japanese, Finnish and Swedish language website. Our provisional finding would be that

ES may be a destination for cross border fertility care, for many countries in the EU including UK, IT, FR, DE, PT, NO, FI, SE, NL, BE and AT.

It is our provisional finding that the cross border fertility care to Spain might foster also a flow of sperm straws from other EU Member States, specifically from Denmark to Spain.

Belgium

Between Belgium and the Netherlands cross-border fertility care specifically takes place because of different legislations on donor anonymity and identity disclosure. Also between Belgium and France there is cross-border fertility care due to restrictive access to ART treatments in France.

Poland (PL)

There are no legal regulations on fertility treatment in Poland. Polish authorities have no basis for collecting data on number of fertility clinics, donors, treatments etc. ART treatement with non-partner donation is not prohibited and no specific access criteria apply, but ART treatment with non-partner donation is not reimbursed either. Our internet search shows that IUI, ICSI, IVF, FET with both partner and non-partner donation, sperm donation, oocyte donation and embryo donation are offered by clinics in PL. Our internet search of clinics indicates compensation amounts for sperm donors of about 200 PLN (around €50) (offered by one clinic). For oocyte donation amounts are offered of 4000 PLN by one clinic or $1000 and $1500 when willing to travel to another country to donate by another clinic. The internet search indicates some of the fertility clinics in PL also have an English, Italian, Swedish, German, Russian language website. Our provisional finding would be that PL may be a destination for cross border fertility care, for different countries in the EU including UK, IT, DE, AT and SE.

Average sperm activity: Bulgaria, Ireland, the Netherlands, Estonia and the UK. Average Oocyte activity: Belgium, Bulgaria, Cyprus, Denmark, Estonia, Latvia and United Kingdom. Average embryo activity: Belgium and UK

In the UK activity is average for sperm, oocyte and embryo. In Bulgaria sperm and oocyte donation are average but embryo donation is limited. In Belgium and Estonia sperm and oocyte donation are average but embryo donation related activity is relatively high. Ireland has average sperm related activity, but high embryo related activity and low oocyte related activity.

Denmark had average oocyte related activity but high sperm related activity and no embryo donation. Denmark is therefor already discussed in the paragraph on large activity. Cyprus and Latvia have average oocyte related activity but limited sperm and embryo related activity and are therefor discussed in the paragraph on limited activity.

Sweden, Finland and Greece: not enough data available to make classification for neither sperm, oocyte nor embryo. Discussed further here as indication is activity is not limited.

Countries with relatively limited activity

In Malta and Lithuania gamete donation is prohibited. These are therefor not further discussed in this chapter. In Italy gamete donation was prohibited at the time of data collection. Sperm donation activity is limited in Hungary, Cyprus, Latvia, Luxembourg, Portugal, Romania, France and Slovenia.

In Germany and Luxembourg oocyte (and embryo donation) is not allowed while sperm donation is allowed. In Hungary, Romania, France, Slovenia and Ireland oocyte donation related activity is limited.

In Denmark Germany, Luxembourg, Sweden and Slovak Republic embryo donation is not allowed. In Austria and Slovenia it is unclear if embryo donation is allowed, but no embryo donation is reported(in Sweden, Denmark and Slovak Republic oocyte donation is allowed). Embryo donation related activity is limited in Hungary, Cyprus, Latvia, Portugal, Romania and Bulgaria.

In Hungary, Romania and Slovenia gamete donation related activity is limited for sperm, oocyte and embryo, compared to other Member States where this activity is allowed. In Cyprus and Latvia sperm and embryo donation related activity is limited, while oocyte donation related activity is average. In Portugal sperm and embryo donation related activity is limited, oocyte donation related activity however cannot be classified due to limited data. In France sperm and oocyte donation related activity is limited but embryo donation related activity cannot be classified due to limited data (data on cross-border exchange, import and export is not available). Ireland has limited oocyte related activity. Sperm and embryo related activity is classified as average or high even though donation of sperm and embryo in Ireland is non-existent or very limited because large quantities of these gametes are received from other Member States or imported from third countries. Bulgaria has average sperm and oocyte donation but limited embryo donation.

For Austria and Croatia data on donation activity (e.g. donors, cross-border distribution, import, export and treatments) is not available (Austria) or to limited to make a classification of activity (Croatia). Based on access and reimbursement criteria and the internet fertility search it can be inferred activity in Austria and Croatia is limited.

Below these figures are integrated with information on access, reimbursement and compensation of donors and cross-border fertility care.

Austria (AT)

Since February 2015 there has been a change in legislation however and since the following is allowed: donation of oocytes, the use of donated sperm for IVF, ICSI and FET are allowed in Austria. Furthermore this change in legislation entails ART treatment is offered to homosexual women. Our internet search supports that the activity level is limited for non-partner donation: IUI for non-partner donation is only offered by a small number of clinics in our sample; treatments such as ICSI and IVF for non-partner are not offered by clinics in our sample.

Activities in Austria are nationally oriented where many tissue establishments in the Member State supply many of the clinics in the country, without much cross-border exchange of gametes. This might be due to the fact that oocyte donation was prohibited so far and to the fact that sperm donors are rare in Austria, due to the fact that the name of the donor will be disclosed to the child at a certain age. The previous restrictions suggest some cross-border fertility care from Austria to neighbouring Member States, intended parents from AT going abroad for fertility treatments. It is also the experience of the Competent Authority that in previous years women needing an oocyte donor or homosexual couples made use of cross-border care due to previous restrictions in national law.

Croatia (HR)

In Croatia IUI, IVF, ICSI and FET with partner and non-partner donation are all allowed and reimbursed in HR, as indicated in the competent authorities' survey sent out by the consortium. Our internet fertility search indicated that IUI, IVF or ICSI with non-partner donation are not offered within our sample of clinics. Treatments with non-partner donor sperm or oocytes are not reported to EUROCET (year 2012). Our preliminary finding is that although non-partner donation is allowed and reimbursed it is not practiced in HR.

Hungary (HU)

Hungary has limited non-partner activities and is nationally oriented with no flows of oocyte, sperm or embryo to or from other EU Member States or third countries. The number of cross border exchange and import/export for sperm, oocyte and embryo is 0 in EUROCET (2012). The number of donated sperm straws (158 donations) or donated oocyte (52 donations) is not exceptionally high. Also the number of fertility treatments with non-partner donation is relatively low.

The internet search indicates some (2 out of 4 in our sample) of the fertility clinics in HU also have a Romanian language website (besides an English language website). The number of donated sperm straws (158 donations) or donated oocyte (52 donations) is not exceptionally high. Also the number of fertility treatments with non-partner donation is relatively low. Furthermore considering the relatively small number of clinics addressing intended parents from abroad (indicated in our internet search) our provisional finding is that HU is not a major destination for cross-border fertility care, except for partner donation treatments for RO couples.

Latvia (LV)

In EUROCET 2012 it is indicated Latvia has 72 oocyte donors with 4277 oocytes donated. None of these 4277 donated oocytes are reported to be distributed to other Member States or exported to third countries. The internet search indicates some of the fertility clinics in LV also have an Norwegian and Swedish language website. As confirmed by the Competent Authority LV is a destination for cross border fertility care, most notably from Sweden, Norway and UK, but also from Russia, Lithuania, Israel and USA (as stated by the CA). Our internet search indicates that prices for fertility services offered in LV are relatively less costly compared to most other EU Member States. Our provisional finding is that LV is an attractive destination for cross border fertility care based on low cost.

Portugal (PT)

For Portugal the figures available on partner and non-partner donation indicate that most treatments are with partner gametes, not with non-partner donor material. In 2013, 91% of IVF/ICSI cycles performed were with partner gametes (as indicated by the Competent Authority). IUI, ICSI, IVF and FET with both partner and non-partner donation are allowed and regulated by law. Maximum age of men: 60 in private sector and public sector. There is no access for singles or for gay or lesbian people.

The perception of the Competent Authority is that cross-border reproductive care with for instance Spain occurs because of national restrictions, namely single or gay people seeking ART treatment.

10 ANNEX 4: GLOSSARY

Term	Definition	Source
Assisted reproductive technology (ART)	Methods used to achieve pregnancy by artificial or partially artificial means. This includes, but is not limited to, in vitro fertilisation, intracytoplasmic sperm injection, cryopreservation of gametes and/ or embryos and intra-uterine insemination.	CoE Guide
Abuse of medicinal products	Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effets.	Directive 2001/83/EC
Advanced Therapy Medicinal Product (ATMP)	A medicinal product that is either a gene therapy medicinal product, a somatic cell therapy medicinal product, a tissue engineered product, or a combined advanced therapy medicinal product (which are medicinal products incorporating cells and medical devices or actively implantable medical devices).	CoE Guide
Agency	The European Agency for the Evaluation of Medicinal Products established by Regulation (EEC) No 2309/93.	Directive 2001/83/EC
Allogeneic use	Cells or tissues removed from one person and applied to another	Directive 2004/23/EC
Audit	Periodic, independent, and documented examination and verification of activities, records, processes, and other elements of a quality system to determine their conformity with specific internal or external requirements. They may be conducted by professional peers, internal quality system auditors or auditors from certification bodies.	CoE Guide
Autologous use	Cells or tissues removed from and applied in the same person..	Directive 2004/23/EC
Banking	Processing, preservation, storage and distribution of tissues and cells for therapeutic and/or research purposes.	CoE Guide
Biobank	A collection of biological material and the associated data and information stored in an organised system for a population or a subset of a population.	CoE Guide
Broker for tissues	Intermediairy organisation, not necessarily a tissue establishment, involved in management	Contractor

and cells	of supply and demand of human tissues and cells	
Cell processing unit	A medical laboratory facility where HPC are manipulated prior to transplantation. These activities may include the depletion of specific cell types from the graft, selection for specific cell types for infusion, ex vivo manipulation of cells in the graft, or concentration of the cell product.	World Marrow Donor Association International Standards for Unrelated Hematopoietic Progenitor Cell Donor Registries. Jan 1, 2014
Cells	Individual human cells or a collection of human cells when not bound by any form of connective tissue	Directive 2004/23/EC
Centre	A healthcare facility comprising a tissue establishment and a unit responsible for clinical application at the same location.	Definition proposed by SANTE
Commercial operators	See private operators	Contractor
Common name	The international non-proprietary name recommended by the World Health Organization, or, if one does not exist, the usual common name.	Directive 2001/83/EC
Compensation	Reparation strictly limited to making good the expenses and inconveniences related to the donation	Definition proposed by SANTE
Consent	Consent to donation, either directly from the donor him/herself or as a result of family approach. In countries with a presumed consent legislation, consent to donation can be the result of absence of objection, either in a national non-donor registry, and/or after consulting the donor's relatives after death.	EUROCET 14-02-2014
Cord blood collection site	A location where the infant donor is delivered and the cord blood unit is collected.	World Marrow Donor Association International Standards for Unrelated Hematopoietic Progenitor Cell Donor Registries. 2014
Cross border reproductive care (CBRC)	Refers to the movement of patients within the EU Member States or to neighbouring non EU-countries to seek ART treatment outside their country of residence.	SOHO VS

Direct use	Any procedure where tissues/cells are donated and used without any banking/ storage.	CoE Guide
Distribution	Transportation and delivery of tissues or cells intended for human applications. [Refers to the transport of tissues/cells from one Member State to another but also to transport from the tissue establishment to the organization responsible for human application].	Directive 2004/23/EC and edited by SANTE
Donation	Donating human tissues or cells intended for human applications	Directive 2004/23/EC
Donor	Every human source, whether living or deceased, of human cells or tissues	Directive 2004/23/EC
Donor evaluation	The procedure of determining the suitability of a potential donor, living or deceased, to donate.	CoE Guide
Donor profile	Non-phenotypical (or social) characteristics of a donor	Contractor
Egg sharing	Arrangement by which a woman undergoing IVF makes some of her eggs available for another woman's treatment, or for research, in return for free treatment or significantly reduced treatment costs.	Nuffield Council on Bioethics, Human bodies; donation for medicine and research
Embryo donation	The transfer of an embryo resulting from gametes (spermatozoa and oocytes) that did not originate from the recipient and her partner.	International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009
Embryo transfer (ET)	The procedure in which one or more embryos are placed in the uterus or fallopian tube.	International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009
End user	A healthcare practitioner who performs transplantation procedures.	CoE Guide

Export	The act of transporting human bodies, body parts, cells or tissues intended for human application to another country where they are to be further processed or used.	CoE Guide
Final product	Any tissue or cell preparation intended to be transplanted or administered after the final release step.	CoE Guide
Homeopathic medicinal product	Any medicinal product prepared from products, substances or compositions called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may also contain a number of principles.	Directive 2001/83/EC
Human application	The use of tissues or cells on or in a human recipient and extracorporal applications.	Directive 2004/23/EC
Immediate packaging	The container or other form of packaging immediately in contact with the medicinal product.	Directive 2001/83/EC
Immunological medicinal product	Any medicinal product consisting of vaccines, toxins, serums or allergen products: (a) vaccines, toxins and serums shall cover in particular: (i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine; (ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin; (iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin; (b) allergen product shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent	Directive 2001/83/EC
Import	The act of bringing tissues or cells into one country from another for the purpose of transplantation.	CoE Guide
Incentive	Inducement/stimulus for donation with a view to seeking financial gain or comparable advantage.	Definition proposed by SANTE

Intermediary	Individuals, organisations and institutions that mediate the (often long and complex) chain of transactions between donor and eventual recipient (whether the recipient is another person or an organisation). 'Intermediary' is also used as a specific designation for those personnel who facilitate the donation process in face to face contact with donors and recipients.	Nuffield Council on Bioethics, Human bodies; donation for medicine and research
Medicinal prescription	Any medicinal prescription issued by a professional person qualified to do so.	Directive 2001/83/EC
Medicinal product	Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product.	Directive 2001/83/EC
Medicinal products derived from human blood or human plasma	Medicinal products based on blood constitutents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin.	Directive 2001/83/EC
National self-sufficiency	Fulfilling the needs of human tissue and cell products for medical application (e.g. transplantation, ART procedures) of the resident population by accessing resources from within the country's population	Definition proposed by SANTE
National sufficiency	Fulfilling the needs of human tissue and cell products for medical application (e.g. transplantation, ART procedures) of the resident population by accessing resources from within the country and through regional/international cooperation.	Definition proposed by SANTE
Non-partner donation	Means that the donor is another person apart from the couple.	SOHO VS
Organ	A differentiated and vital part of the human body, formed by different tissues, that maintains its structure, vascularisation and capacity to develop physiological functions with an important level of autonomy.	Directive 2004/23/EC
Organisations responsible for human application (OHRA)	A health care establishment or a unit of a hospital or another body which carries out human application of human tissues and cells.	Directive2006/86/EC

Outer packaging	The packaging into which is placed the immediate packaging.	Directive 2001/83/EC
Package leaflet	A leaflet containing information for the user which accompanies the medicinal product.	Directive 2001/83/EC
Partner donation	The donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship.	Directive2006/86/EC
Payment	A generic term covering all kinds of transactions involving money, and goods with monetary value, whether those transactions are understood as recompense, reward or purchase.	Nuffield Council on Bioethics, Human bodies; donation for medicine and research
Periodic safety update reports	The periodical reports containing the records referred to in Article 104 [of directive 2001/83/EC].	Directive 2001/83/EC
Post-authorisation safety study	A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.	Directive 2001/83/EC
Preservation	The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues.	Directive 2004/23/EC
Primary packaging	Any material employed in the packaging of tissues and cells, excluding any outer packaging used for transportation or shipment, intended to be in direct contact with the graft.	CoE Guide
Private operator	Actor involved on for-profit basis	Contractor
Processing	All operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications.	Directive 2004/23/EC
Procurement	A process by which tissue or cells are made available.	Directive 2004/23/EC
Procurement organisation	A health care establishment or a unit of a hospital or another body that undertakes the procurement of human tissues and cells and that may not be accredited, designated, authorised or licensed as a tissue	Directive2006/86/EC

	establishment.	
Proprietary medicinal product	Any ready-prepared medicinal product placed on the market under a special name and in a special pack.	Directive 2001/83/EC
Public service obligation	The obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.	Directive 2001/83/EC
Quality management	The coordinated activities to direct and control an organisation with regard to quality.	Directive2006/86/EC
Quality system	The organisational structure, defined responsibilities, procedures, processes, and resources for implementing quality management and includes all activities which contribute to quality, directly or indirectly.	Directive2006/86/EC
Quarantine	The status of retrieved tissue or cells, or tissue isolated physically or by other effective means, whilst awaiting a decision on their acceptance or rejection.	Directive 2004/23/EC
Radionuclide generator	Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical	Directive 2001/83/EC
Radiopharmaceutical	Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.	Directive 2001/83/EC
Registry	A repository of data collected on cell, tissue and organ donors and/or transplant recipients for the purpose of outcome assessment, quality assurance, healthcare organisation, research and surveillance.	CoE Guide
Reimbursement	Payment to a person to cover expenses actually incurred in the act of donation, such as travel expenses, meals and lost earnings. Reimbursement returns the person to the same financial position they would have occupied had they not donated, and does not enrich the donor in any way. See also recompense, compensation and reward.	Nuffield Council on Bioethics, Human bodies; donation for medicine and research

Remuneration	Material advantage gained by a person as a result of donating bodily material (reward), where this is calculated as a wage or equivalent.	Nuffield Council on Bioethics, Human bodies; donation for medicine and research
Reproductive cells	All tissues and cells intended to be used for the purpose of assisted reproduction.	Directive2006/86/EC
Risk to public health	All risks with regard to the quality, safety and efficacy of the medicinal product.	Directive 2001/83/EC
Secondary packaging	Any material employed in the packaging of tissues and cells, excluding any outer packaging used for transportation or shipment, intended to be in direct contact with the graft.	CoE Guide
Serious adverse event	Any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.	Directive 2004/23/EC
Serious adverse reaction	An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity	Directive 2004/23/EC
Standard operating procedures (SOPs):	Written instructions describing the steps in a specific process, including the materials and methods to be used and the expected end product.	Directive2006/86/EC
Storage	Maintaining the product under appropriate controlled conditions until distribution.	Directive 2004/23/EC
Strength of the medicinal product	The content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form.	Directive 2001/83/EC
Substance	-human, e.g. human blood and human blood products; -animal, e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products; -vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretions, extracts; -chemical, e.g. elements, naturally occurring	Directive 2001/83/EC

	chemical materials and chemical products obtained by chemical change or synthesis.	
Testing laboratories	These laboratories perform the histocompatibility, blood group, infectious disease, and other testing of the prospective donors and patients. They may be under the direction of a registry, donor centre or transplant centre or may be separate from these entities.	World Marrow Donor Association International Standards for Unrelated Hematopoietic Progenitor Cell Donor Registries. 2014
Third countries	Term used within the EU to refer to countries that are not members of the EU.	CoE Guide
Tissue	All constituent parts of the human body formed by cells	Directive 2004/23/EC
Tissue establishment	A tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells.	Directive 2004/23/EC
Tissue establishment	A tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells.	Directive 2004/23/EC
Traceability	The ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells.	Directive2006/86/EC
Unexpected adverse reaction	An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.	Directive 2001/83/EC

Validation (or 'qualification' in the case of equipment or environments)	Establishing documented evidence that provides a high degree of assurance that a specific process, piece of equipment or environment will consistently produce a product meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.	Directive2006/86/EC
Waiting List	A waiting list is a collection of patients who are awaiting an organ, tissue or cell transplant. All patients are counted regardless as to whether they are "actively" participating or are suspended (temporally not transplantable) on the date of the reporting of the waiting list information.	EUROCET 14-02-2014
Wholesale distribution of medicinal products	All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned.	Directive 2001/83/EC

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