Commission Expert Group on Rare Diseases

Recommendation on

CROSS BORDER GENETIC TESTING OF RARE DISEASES IN THE EUROPEAN UNION

13 November 2015

Background to the Recommendation

Introduction

Methods for carrying out genetic testing are developing at an unprecedented and unforeseen rate. Simultaneously, the overall number of genes linked to rare diseases (RD) is increasing. This means that it is now possible to provide an etiological diagnosis for several thousand RD (or 'Mendelian' diseases). Although accurate diagnosis enables specific treatment for only a minority of RD at present, the outcomes of genetic testing may allow a better understanding of their prognosis and in all cases clarify the origin of the disease (preventing further unnecessary clinical and laboratory differential diagnostic investigations), and elucidate the mode of inheritance, thereby facilitating life planning and reproductive choices for the entire whole family.

A recent analysis of the Orphanet database[1] reveals that at the end of 2014 there were 1674 laboratories registered in Orphanet in Europe, providing tests for 2557 genes and 3378 diseases. The same analysis of Orphanet data demonstrates that the genetic testing offer differs greatly, even between countries of comparable size. For some of the larger countries, for instance, the results were as follows: Germany (testing for 2116 RD-associated genes), Spain (1708 genes), France (1579 genes), Italy (1148 genes), and United Kingdom (896 genes). For medium and smaller-sized countries the genetic testing offer differs substantially, since it ranges from 18 to 1171 genes tested. Furthermore, as of December 2014, 915 RD - equating to 27% of the diseases for which a test for the relevant gene exists- can only be tested in laboratories located in *one* country in Europe. The logical implication of these statistics is that for a significant proportion of RD a test can only be ordered from *outside* the subject's country of residence, concurring with the findings of the EJA Survey (see below).

The rapid developments in next generation sequencing (NGS), together with the development of national and international variant databases which support the interpretation of sequencing results, means that improving national genetic testing capacities may become a more achievable goal than previously envisioned[2]. Nonetheless, cross border genetic testing (CBGT) for RD will remain necessary in the foreseeable future, due to differences in the national/regional testing offer. For this reason -and based on the observations and discussions during the 2012 European Workshop on Genetic Testing Offer in Europe, organized by the European Commission's Joint Research Centre, EUCERD and EuroGentest (EuGT) - the EUCERD Joint Action (EJA) decided to further investigate the issues related to genome–based diagnostics and CBGT, with the aim to create **specific Recommendations for the European Commission and the Member States in their reflections or policy developments on how to ensure timely and accurate genetic diagnostics for RD.**

Policy background

The necessity of a collaborative, European approach to genetic testing for RD is stipulated in several EU policy documents:

[1] Analysis of the Orphanet (www.orpha.net) database concerning the genetic test offer in 33 European countries on 8 December 2014.

[2] Indeed, some Member States (MS) may opt to pursue self-sufficiency in NGS, and any such efforts to improve facilities and services close to patients themselves should be encouraged.

- The Council Recommendation on an action in the field of Rare Diseases (2009/ C151/02) asks MS to "Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts **in order to support the development of European guidelines on diagnostic tests or population screening, while respecting national decisions and competences**".
- The Commission Communication *Rare Diseases: Europe's Challenge* (COM(2008) 679) states that "Given the large number of tests and the need to design and validate a specific set of diagnostic assays for each, no single country can be self-sufficient in the provision of testing and in an efficient external quality assessment of the provided tests. **There is a need to enable and facilitate the exchange of expertise through clearly stated, transparent, EU agreed standards and procedures**".
- Directive 2011/24/EU on the application of patients' rights in cross-border healthcare emphasises the potential for European Reference Networks (ERNs) "**to facilitate improvements in diagnosis** and the delivery of high-quality, accessible and cost-effective healthcare for all patients with a medical condition requiring a particular concentration of expertise in medical domains where expertise is rare" (preface 54).

Against this background, fundamental issues related to genetic testing for RD were discussed during the 2012 European Workshop on Genetic Testing Offer in Europe, in Ispra, Italy. The discussions are summarized in Report EUR 25684 EN.2013[3]. This workshop gathered experts to discuss a range of areas where European cooperation could provide added-value in terms of quality and organisation of genetic services. In its Report, the workshop recommended several action points relating to the organisation of genetic testing for RD in Europe, quality assurance of genetic testing, NGS, and 'Direct-to-Consumer' (DTC) testing. The workshop specifically recognized the unequal accessibility of genetic testing across Europe. In order to reduce these inequalities, the following action points were agreed:

- Document the differences in the organization of genetic testing services which prevent equitable access to such tests and provide a basis for discussion between MS on ways how to improve the current situation;
- Ensure that MS include provision for CBGT in their national plans or strategies for RD (NP/NS);
- Ensure that undiagnosed patients with RD have timely access to newly developed NGS diagnostic testing services where clinically appropriate and when available at MS level. The access to genetic testing laboratories (GTL) providing NGS should be ensured within RD ERNs when appropriate.

The action points identified were presented in the final EUCERD meeting in June 2013, as possible topics for recommendations of the EUCERD in the field of genetic testing. It was agreed that this important topic - and the drafting of a subsequent recommendation - should be followed-up under the newly-formed Commission Expert Group on Rare Diseases (CEGRD).

Methodology for the elaboration of Commission Expert Group on Rare Diseases Recommendations on cross-border genetic testing of Rare Diseases in the European Union

The EUCERD Joint Action (EJA, contract N° 2011 22 01) performed a Survey of Clinical Genetics Units and Genetics Laboratories in the EU MS, to investigate their experiences with CBGT for RD. The aim was to identify challenges that could realistically be addressed, for instance, sharing guidelines for the processes of offering and commissioning gene tests on a cross-border basis, whilst respecting the principles of MS

[3] http://www.eurogentest.org/fileadmin/templates/eugt/pdf/News_documents/JRC_Genetic_testing_offer_in_Europe.pdf

subsidiarity in healthcare. Harmonizing procedures in this way could facilitate CBGT even though the fundamental challenges related to healthcare funding cannot be solved at the EU level.

The Survey was performed between January and March 2014. The responses from the sample of laboratories and clinics participating in the Survey demonstrates that the **amount of CBGT for RD in EU MS is substantial** (an estimated 90 000 – 100 000 samples were subjected to CBGT in 2013 alone). **The Survey provided evidence, as initially outlined by the Ispra Workshop, that currently there is significant inequity of access to genetic testing for RD across the EU.** The EJA Survey also identified several issues which compounded the difficulties of CBGT, relating to affordability, logistics and local bureaucracy. A subsequent workshop was organised by the EJA in December 2014 to translate the outcomes of the Survey into Recommendations for consideration by the CEGRD in 2015, in order to alleviate the challenges identified[4]. The resulting draft Recommendation was ultimately based on the EJA Survey, the discussions at the EJA Workshop, and Report EUR 25684 EN.2013 of the Ispra Workshop. Draft versions of the Recommendation were presented and discussed at the CEGRD meetings in March and June 2015. The document was revised via a drafting group meeting on 14th September 2015, to enable the presentation of a pre-final draft to the CEGRD members for consideration at the November 2015 meeting.

Scope of the Recommendations

The specific focus of these Recommendations is to support the EC and the MS in facilitating the process of **Cross-Border Genetic Testing (CBGT) of RD**. The document does not seek to provide guidance on the vast array of topics pertaining to genetic testing *per se*; notably, the Recommendations do not address the following:

- the scientific and technical application of NGS
- the ethical, legal and social issues relating to genetic testing
- preconception, prenatal, or postnatal genetic screening programmes
- Direct-To-Consumer testing
- potential for research-generated data to support clinical diagnostics and patient management[5]

A select list of international genetic testing guidelines with a clear relevance to the process of CBGT of RD may be found in the Annex to these Recommendations – the principles enshrined in these annexed guidelines should also apply to CBGT.

Finally, these Recommendations acknowledge that the organisation and funding of healthcare systems fall within the competence of MS, which have adopted widely varying healthcare and funding systems. CBGT should be offered and commissioned in accordance with relevant MS legal provisions and the following Recommendations should be viewed in the light of MS subsidiarity in healthcare, taking due account of the decisions taken at the MS level.

[4] Report available at http://www.eucerd.eu/wp-content/uploads/2015/03/WP8_WS_GeneticTesting2014.pdf

[5] Genomics data generated through RD research initiatives holds major potential to support clinical diagnoses and patient management. It is important to develop standards to support the validation and utility of such data in the clinical sphere. In the absence of these, the Recommendations refrain from specific guidance on this subject, on the grounds that methods which are not yet validated should be performed in the legal framework adopted for research in each MS.

RECOMMENDATIONS TO THE EUROPEAN COMMISSION AND MEMBER STATES

1. Obtaining an accurate and timely diagnosis is a priority for all people with a potentially genetic RD; therefore, access to genetic testing -whether provided locally or on a cross-border basis - should be ensured, to facilitate such diagnoses, when there is a clear clinical indication.

1.1 The importance of adequate access to genetic testing for RD - including cross border genetic testing (CBGT) - when there is a clear clinical indication, should be stipulated in future National Plans and Strategies (NP/NS) for RD and should be incorporated when existing NP/NS are evaluated and revised.

1.2 MS should provide openly accessible information on genetic testing availability at the national level.

1.3 MS should have a transparent policy pertaining to CBGT: such policies should seek to streamline the process of CBGT, as far as possible.

1.4 The possibility of developing shared resources to facilitate CBGT of RD should be explored at the EU level.

2. The expert group underlines the importance of assessing genetic testing, on the basis that early diagnosis through clinically-guided genetic testing may avoid the need for further invasive and/or unnecessary exploratory and therapeutic procedures.

2.1 MS should consider, where possible, to share data on the assessment of genetic tests for RD - with full regard of the need to preserve patient anonymity - and further explore whether this exchange could be taken into consideration within the framework of the Joint Action 3 EUnetHTA on this basis.

2.2 Decisions on the purchasing/procurement of CBGT should be made on the same basis as any other medical investigations that are considered clinically indicated.

3. Whether genetic testing is provided on the national/regional level or on a cross-border basis, expertise should be shared at the EU (or global) level.

3.1 MS should promote the use of - and active contribution to - international variant databases when conducting genetic testing for RD, to improve the assessment of the pathogenic potential of genomic variants.

3.2. Cross border collaboration between laboratories, clinical genetics centres, and research initiatives dedicated to RD diagnostics should be supported, as this holds major potential for the RD field.

3.3 The organization of the collaboration between expert laboratories should be set within the context of European Reference Networks (ERNs), as per Directive 2011/24/EU by integrating expert laboratories in the different thematic networks linked to their area of expertise. The potential for ERNs to support the process of CBGT for RD should be explored.

4. Appropriate information on genetic testing laboratories should be made available to facilitate cross-border genetic testing of rare diseases, particularly when pertaining to the quality of laboratories.

4.1 MS should support laboratories within the national territory in contributing - and updating - defined data elements to the Orphanet database (which at present is the main source of information on genetic testing laboratories for the RD field at European level).

4.2 To facilitate informed decision-making when selecting laboratories for CBGT, laboratory testing websites should display as a minimum their accreditation status, scope of the test offered, turn-around-time, and transparent pricing parameters.

4.3 Given the critical importance of quality for genetic testing of RD, MS should promote accreditation and the participation of laboratories in EQA.

Annex

Professional Guidelines and Recommendations relevant to the process of cross-border genetic testing of Rare Diseases should be followed alongside the Recommendations defined in this document, in particular:

EuroGentest (2015) *Guidelines for Diagnostic Next Generation Sequencing* http://www.nature.com/ejhg/journal/vaop/ncurrent/full/ejhg2015226a.html

EuroGentest (2015) *Guidelines for Diagnostic Next Generation Sequencing : Supplementary Information* *http://www.nature.com/ejhg/journal/vaop/ncurrent/suppinfo/ejhg2015226s1.html*

European Commission (2004) *Recommendation on the ethical, legal and social implication of the genetic testing* https://ec.europa.eu/research/conferences/2004/genetic/pdf/recommendations_en.pdf

OECD (2007) *Guidelines for Quality Assurance in Molecular Genetic Testing* - http://www.oecd.org/sti/biotech/38839788.pdf