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European Commission
Commissioner for Health and Food Safety
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European Commission

Equity, excellence and innovation – modern cancer care for all

Europe's Beating Cancer Plan – eradicating inequalities within cancer care

High-level conference on cancer
31 January – 1 February 2023, Stockholm, Sweden

Innovative solutions as a tool for expanding early detections and eliminating inequalities

Introductory remarks on early detection
Prof. Anna Martling, Karolinska Institutet

The importance of early detection: lessons learned from breast cancer
Dr. Alberto Costa, Special Adviser to the European Commissioner for Health and Food Safety on cancer policy

Screening for prostate cancer: benefits, harms and organisation
Prof. Ola Bratt, University of Gothenburg

Lunch

The implementation and benefits of population-based lung cancer screening
Prof. Miroslaw Samarzija, University of Zagreb

Biomarkers as a tool for early detection of cancer
*Prof. Ettore Domenico Capoluongo, Università degli Studi di Napoli Federico II*

Panel discussion

Full Professor of Clinical Biochemistry and Clinical Molecular Biology - Department of Excellence in Molecular Medicine and Medical Biotechnology, Federico II University, Naples
Director of Dept. of Clinical Pathology and Genomics – Ospedale per l'Emergenza Cannizzaro – Catania
Member of the European Commission Expert Panel ('Expamed') on *medical devices and invitro diagnostic.*
Member of the Committee on Molecular Diagnostics (C-MD) – IFCC (International Federation of Clinical Chemistry and Laboratory Medicine)
Coordinator of the Operational Group on "*Use of genomic technologies in the field of treatment personalization***" - Italian Society of Clinical Biochemistry and Clinical Molecular Biology - SIBioC-Laboratory Medicine**
Elected member of the Board of Directors of the "*Multicenter Italian Trials in Ovarian cancer and gynecological malignancies (MITO-Group)***"**
Member of the *European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Task Force: European Regulatory Affairs (TF-ERA)*

❑ The **earliest stages of cancer detection** are when our existing clinical interventions can be **MORE SUCCESSFUL**

❑ Detecting **pre-invasive tumours before clinical** symptoms appear is likely to enhance the effect of medical interventions such as surgical resection, which can be curative for most types of localized cancers that have not metastasized

❑ When **ACCURATE TESTS** are available, **risk- based cancer screening of populations is recommended** by regulatory agencies, and contributes to **lowering cancer deaths**
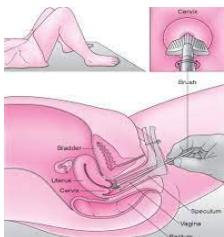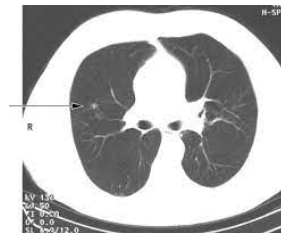
Examples include
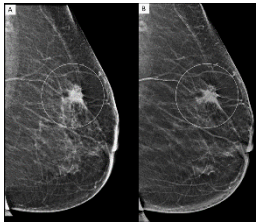
MAMMOGRAPHY for **Breast Cancer**
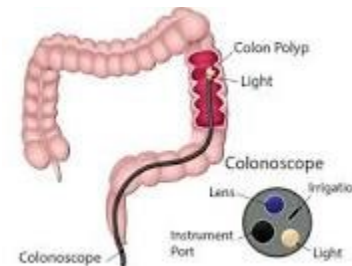
COLONOSCOPY for **Colorectal Cancer**

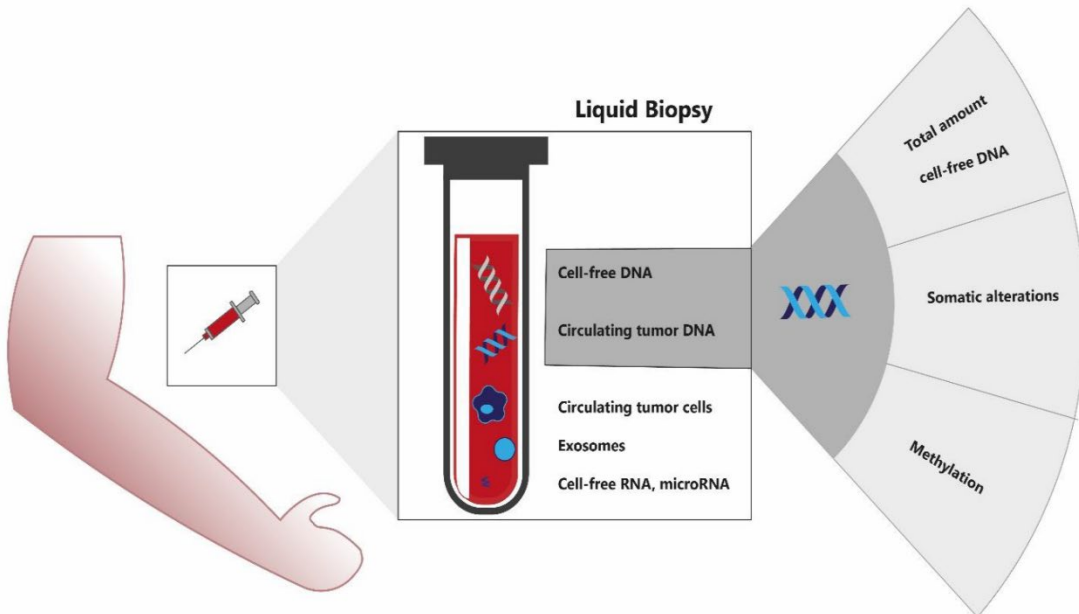**Papanicolaou test (Pap smear)** for **Cervical Cancer**

Low- dose chest computed tomography for those at high risk of **Lung Cancer**

❑There are several ongoing **efforts towards detecting other endogenous biomarkers:**

- **CELL-FREE NUCLEIC ACIDS**
- PROTEINS
- LIPIDS
- METABOLITES

Blood/Other biofluids

❑ Significant achievements have been made by sequencing of **cancer genes from circulating tumour DNA (ctDNA),** as evidenced by the recent success of a **multianalyte, multicancer** test in a prospective **study of women** without a history of cancer in which the feasibility **of using a BLOOD TEST to detect multiple cancers was established**

Liquid Biopsy

Total amount cell-free DNA

Cell-free DNA

Circulating tumor DNA

Somatic alterations

Circulating tumor cells

Exosomes

Cell-free RNA, microRNA

Methylation

❑ **cfDNA/ctDNA** is considered an **emerging biomarker in cancer care**

❑ **No major conclusions** can be drawn about the potential of **pre-surgery cfDNA/ctDNA** to **predict outcomes** in some cancers

❏ However, accurate tests based on **imaging and/or non- invasive analysis of patient fluids** such as **blood** (*LIQUID BIOPSY*) **are NOT AVAILABLE** for the **vast majority** of **cancer types**

❏ The **diagnostic specificity** of current tests **is INSUFFICIENT** to **allow ROUTINE SCREENING of asymptomatic** population of individuals where the **cancer prevalence is low**

❏ A **TEST** with **low positive predictive value would lead to:**

- ▪ **an unacceptably high percentage of FALSE POSITIVES**
- ▪ **UNNECESSARY MEDICAL INTERVENTIONS**
- ▪ **precluding broad deployment**

❏ The **continuing debate** over whether the only widely **used blood biomarker test**, the prostate-specific antigen (PSA) test, is useful for reducing prostate **cancer mortality despite its drawbacks** (overdiagnosis and overtreatment) serves as an **important lesson for future tests**

EFLM Paper

Matthias F. Froelich, Ettore Capoluongo, Zsolt Kovacs, Simon J. Patton, Evi S. Lianidou and Verena Haselmann*, on behalf of the EFLM interdisciplinary Task and Finish Group "CNAPS/CTC for early detection of cancer"

The value proposition of integrative diagnostics for (early) detection of cancer. On behalf of the EFLM interdisciplinary Task and Finish Group "CNAPS/CTC for early detection of cancer"
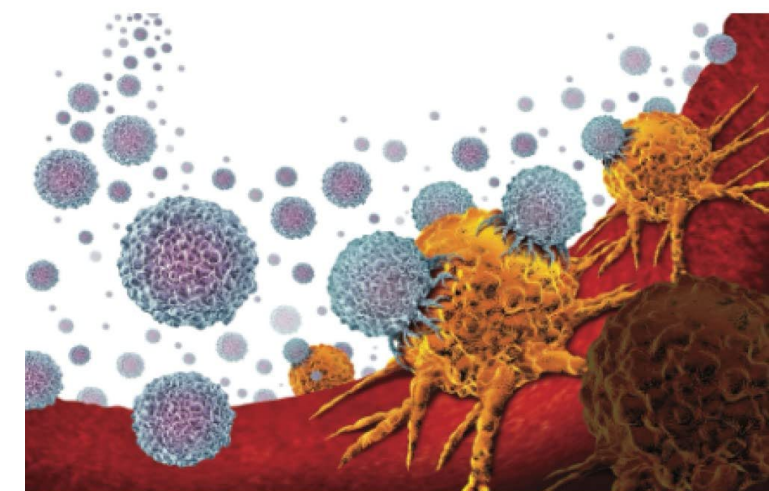

Figure 1: Benefits and limitations of disruptive diagnostic technologies in laboratory medicine, imaging and data-driven medicine.
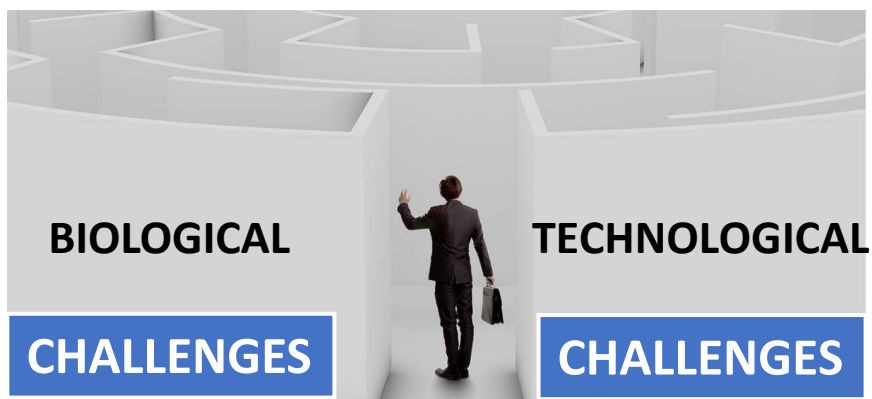*As compared to standard of care techniques.

LIQUID BIOPSY

New Challenges in the Era of Immunotherapy and Precision Oncology

Edited by
Antonio Russo, Ettore Capoluongo, Antonio Galvano, Antonio Giordano

BIOLOGICAL **CHALLENGES**   TECHNOLOGICAL **CHALLENGES**

❑**Biological and Technical challenges remain obstacles to the early detection of cancer, especially before symptoms are apparent**

❑A test with **high sensitivity** would be required to **detect very low signal levels**, but such a test **must not contribute substantially** to the **OVERDIAGNOSIS** of inconsequential cancers

❑The **expression or release of biomarkers is variable and compounded by:**

- **Interpatient Variation**
- **Tumour Heterogeneity**
- **Comorbidities**
- **Background Secretion by Healthy Cells**

The challenge of early detection

❑ For continuously **shed biomarkers such as proteins**
- ▪ Patient's **tumours** are **not universally biomarker positive**
- ▪ **secretion rates can vary** by as much as four orders of magnitude, even for cells of **the same tumour type**

❑ **Biomarkers** that are released only **by dead** or **dying cells** are shed **just once**, and **their detection is confounded by background shedding** from **healthy tissues**

❑ **Cell-free DNA** (**cfDNA**) is **released** from **non-cancerous cells** throughout the body, which makes the **proportion of somatic mutations** in malignant cells versus normal cells (namely, variant allele frequency - **VAF**), increasingly **difficult to detect at low tumour burden**

Studies on **Non- Small- Cell Lung Cancer** Evolution Through Therapy (TRACERx) predicted that **primary tumour burdens** of:

Primary tumour burdens	Average clonal plasma VAFs
1 cm^3	0.006%
10 cm^3	0.1%
100 cm^3	1.3%

FINDING A NEEDLE IN A HAYSTACK
1. THE SLOW WAY

Needle

Not a Needle

Tumor

Circulating Tumor Cells

Cell-free DNA (cfDNA)
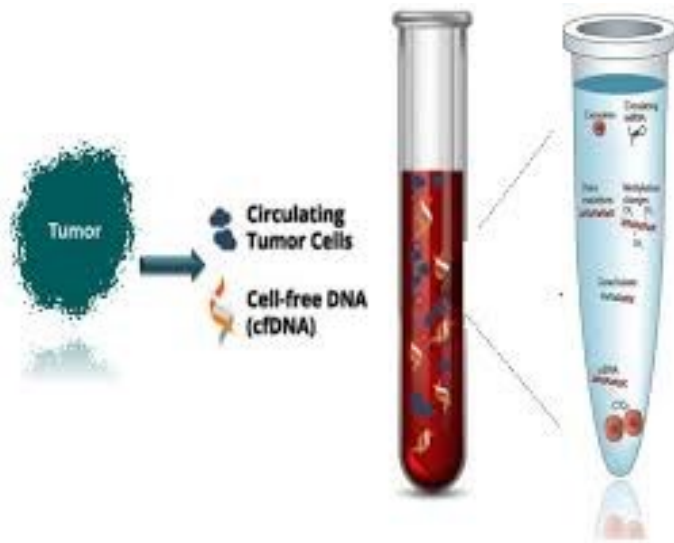
For a **conventional 4 ml of plasma** from a **10-ml blood draw** and **a VAF of 0.1%,** it has been estimated that there would be an **average of just 6 molecules per tube** carrying the **respective somatic mutation**

❑ Further compounding the **TECHNICAL** challenge, **shed biomarkers are:**

- **diluted** by a **large pool of blood (~5 l)**

- **circulate for short periods** owing to **degradation** or clearance

- **ctDNAs**: a circulation **half-life ≤1.5 h** in **blood**
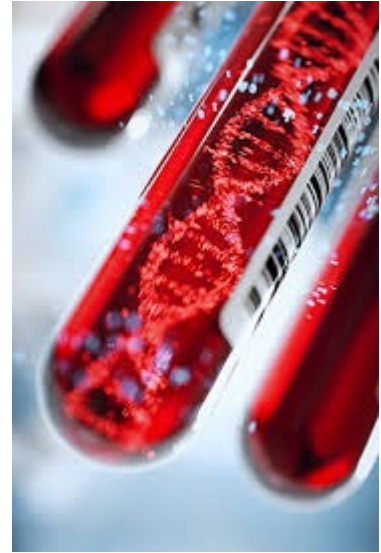
❑Individual **biomarkers often LACK SPECIFICITY** because their levels can be elevated in **non-cancerous** conditions, as in the case of:

- **DNA mutations from non- malignant clonal haematopoiesis** of indeterminate potential (CHIP)

- **PSA** level increase from **benign prostatic hyperplasia**

- or they are **shed across many types of cancer**, as is the case for carcinoembryonic antigen (**CEA**), the level of which is elevated in cancers of the **colon, breast, lung and other organs**

❑It is necessary to identify **MULTIANALYTE** **panels** which **combine different classes of biomarkers** into **a single predictive score** to :

- ▪ **Assess** the **presence of disease**

- ▪ **Localize** the **cancer to anatomical sites**

By comparison, the **RESOLUTION** of **clinical positron emission tomography (PET)**-based **molecular imaging** (using fluorine-18) reported as~**200 mm³** (equivalent to a tumour diameter of ~ **7 mm**)

Tumours could remain undetectable for more than 10 years following initiation of tumorigenesis
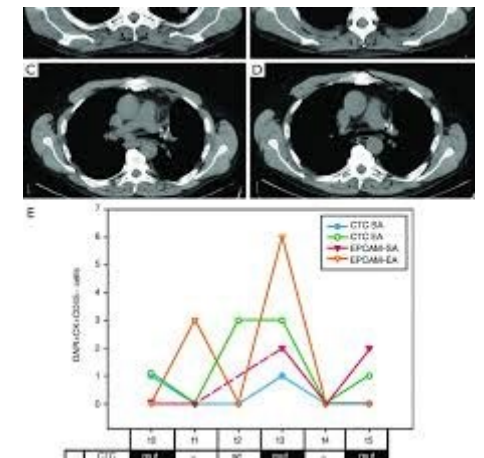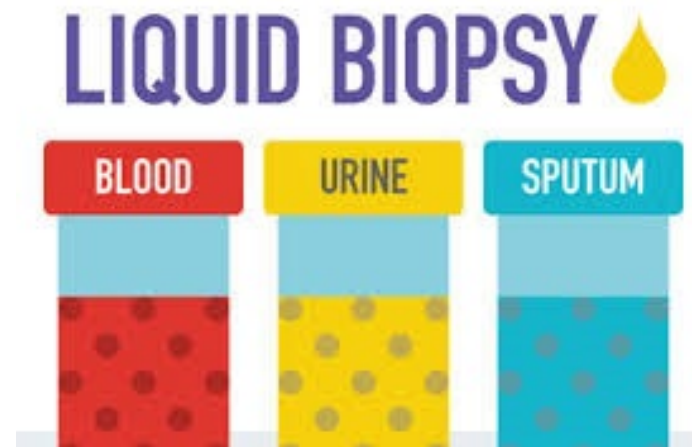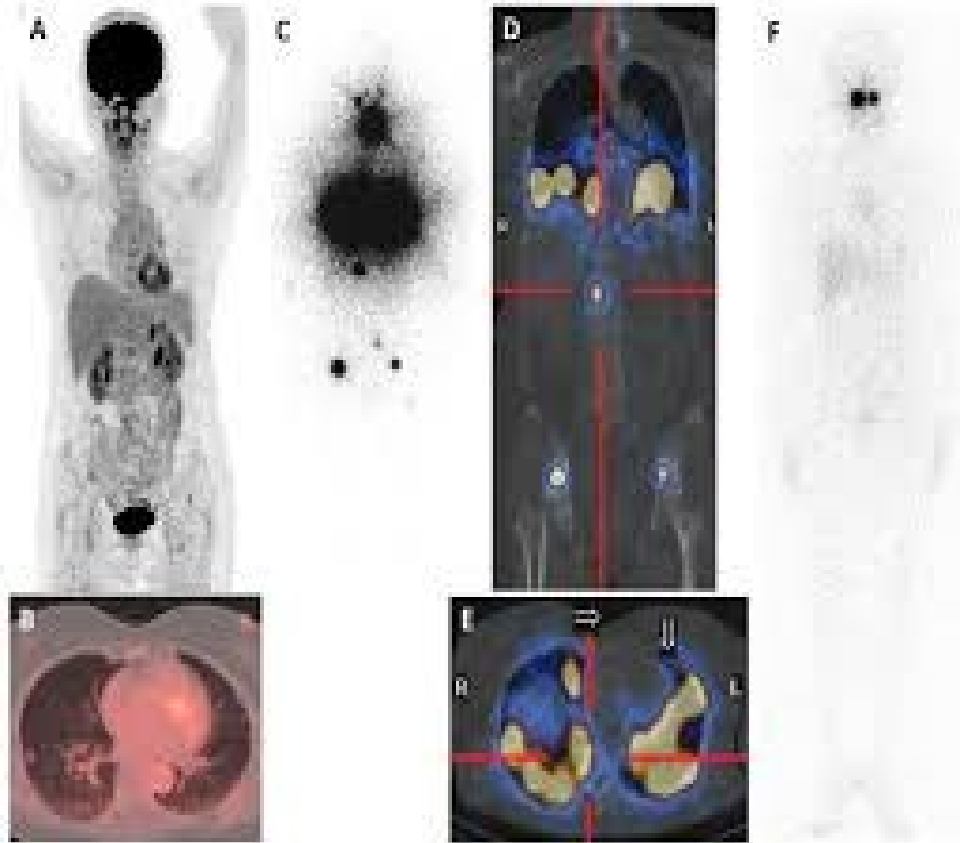
DON'T GET FRUSTRATED. GET FASCINATED.

Incipient tumour
$d < 5$ mm (10^6 cells/mm³)
~10^8 times smaller than the human body

Tumour cell

Biomarker

Healthy cell

Circulation
Biomarker half-life (approximately minutes to hours)
~10^1–10^{21}-fold degradation in 24 h

Δt

Dilution into blood (~5 l)
>75,000-fold dilution

Detection
Sampling volume (~5 ml)
~1/1,000th of blood volume

Renal clearance
Renal filtration (MW < 60,000)
Circulation time ~10–20 s
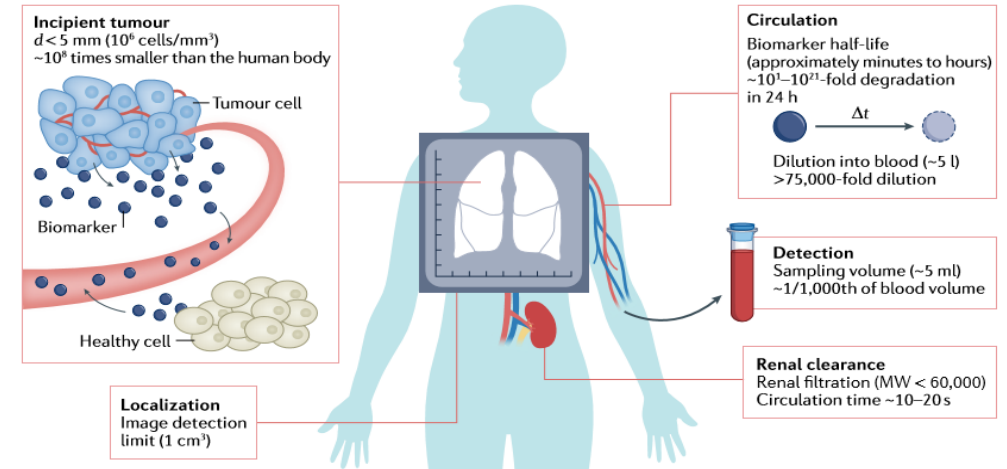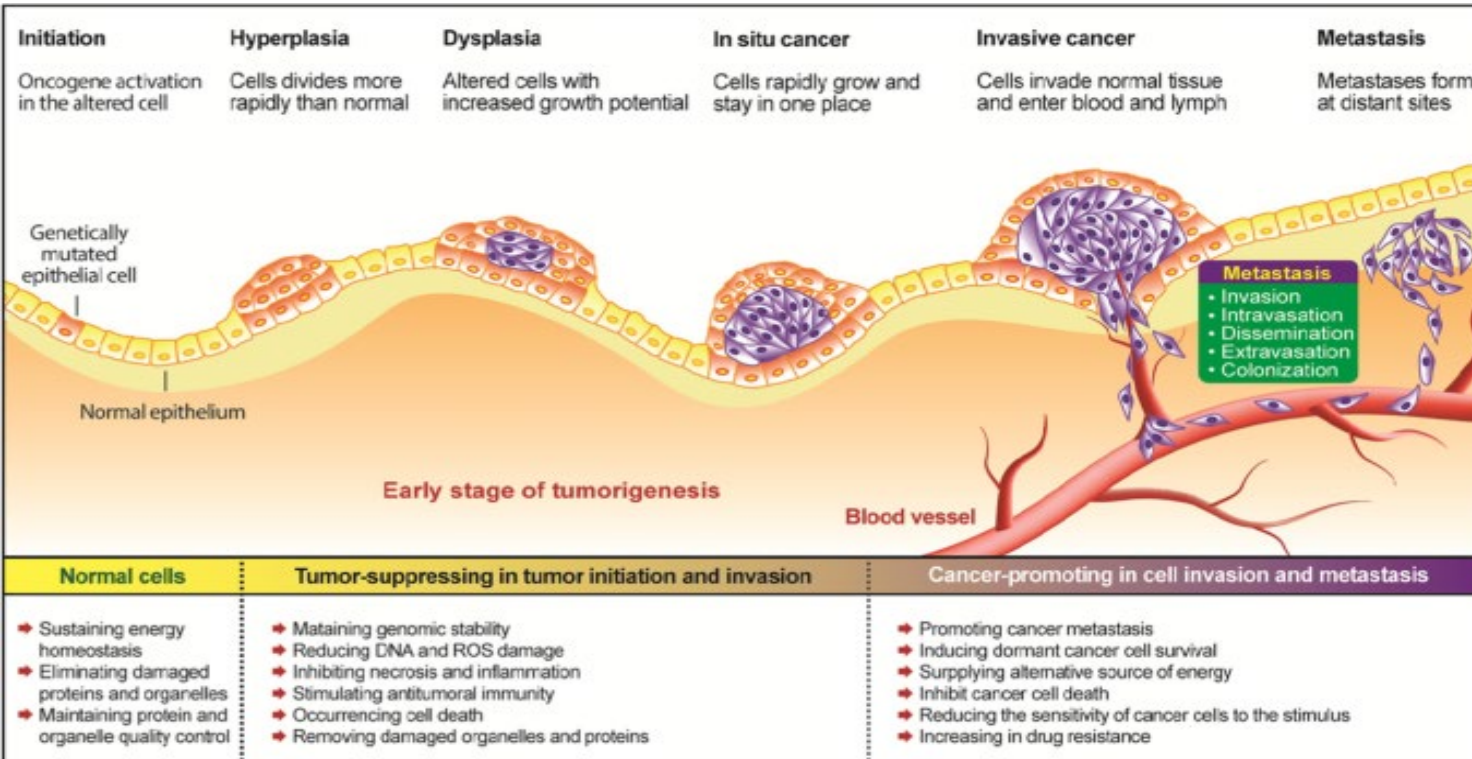
Localization
Image detection limit (1 cm³)

Fig. 1 | **Challenges associated with detecting early-stage tumours.** An early-stage tumour (smaller than 5 mm in diameter) is on average eight orders of magnitude smaller in volume than the human body. Several factors hinder the ability to detect biomarkers shed from tumours, including transport challenges from the tumour microenvironment (TME) into the circulation, an approximately five orders of magnitude-fold dilution into blood and short circulation times owing to degradation and renal filtration. These factors decrease the number of tumour-associated biomarkers (for example, cell-free nucleic acids, proteins, metabolites and circulating tumour cells) that can be found in a typical 5–10 ml blood draw, which represents only ~1/1,000th of the total circulation volume. d, diameter; MW, molecular weight; Δt, change in time.

0 1 2 3 4 5 6 7 8 9 10 yrs

Initiation	Hyperplasia	Dysplasia	In situ cancer	Invasive cancer	Metastasis
Oncogene activation in the altered cell	Cells divides more rapidly than normal	Altered cells with increased growth potential	Cells rapidly grow and stay in one place	Cells invade normal tissue and enter blood and lymph	Metastases form at distant sites

Genetically mutated epithelial cell

Normal epithelium

Metastasis
- Invasion
- Intravasation
- Dissemination
- Extravasation
- Colonization

Early stage of tumorigenesis

Blood vessel

Normal cells	Tumor-suppressing in tumor initiation and invasion	Cancer-promoting in cell invasion and metastasis
→ Sustaining energy homeostasis → Eliminating damaged proteins and organelles → Maintaining protein and organelle quality control	→ Mataining genomic stability → Reducing DNA and ROS damage → Inhibiting necrosis and inflammation → Stimulating antitumoral immunity → Occurrencing cell death → Removing damaged organelles and proteins	→ Promoting cancer metastasis → Inducing dormant cancer cell survival → Supplying alternative source of energy → Inhibit cancer cell death → Reducing the sensitivity of cancer cells to the stimulus → Increasing in drug resistance

~7 years or more from the birth of a founder carcinoma cell to macro metastatic tumours, due to the **inherent inefficiency** of individual tumour **cells to seed and survive in distant organs**

Kwong GA et al. Nat Rev, 2021

Cancer - Screening and early detection

16 May 2010
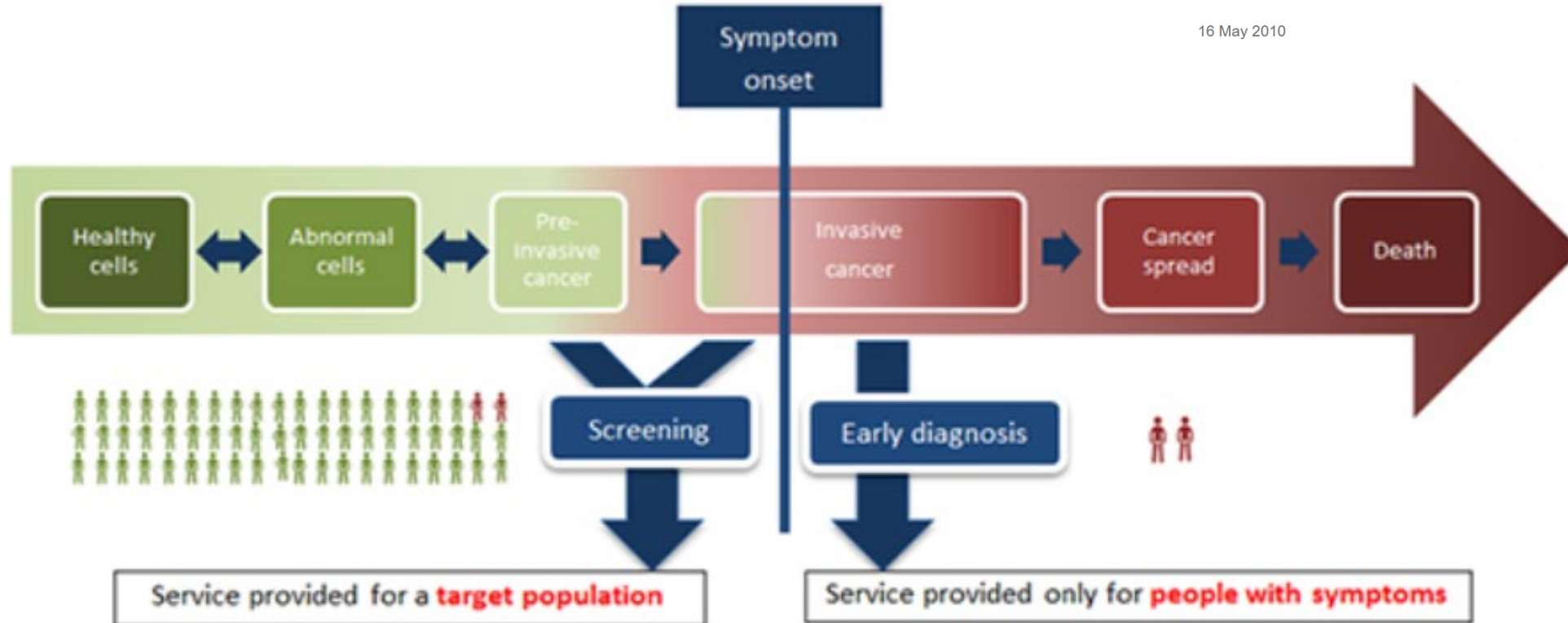
Distinguishing CANCER SCREENING from EARLY DIAGNOSIS: as defined by WHO

❑ **Early DIAGNOSIS requires ensuring:**

- ▪ **Rapid patient presentation**
- ▪ **DIAGNOSIS**
- ▪ **TREATMENT** as soon as first symptoms appear.

❑ It is **RELEVANT TO ALL TYPES OF CANCER**

❑ **SCREENING** is relevant to a **subset of cancer types only:**

- ▪ **CERVICAL** (PAP + HPV screen)
- ▪ **COLORECTAL** (fecal occult blood test)
- ▪ **BREAST** (NMR; mammography and self/medical-examination)

which together **represent 28% of cancer cases** in the WHO EU Region

- ▪ In the case of **CERVICAL CANCER**, screening enables cure at **a precancerous stage of the disease with minor surgical treatments**.

- ▪ This is **not the case for breast cancer** or for **colorectal cancer screening**

❑ **Fast-growing** and **highly aggressive cancers** may **rapidly progress** within a relatively **narrow window of months to years and** are associated with **poor clinical outcomes**

❑ Triple negative cancer
❑ High-grade serous ovarian carcinoma (HGSOC)

in women whose tumours have *BRCA1 or BRCA2 mutations*, or *homologous recombination deficiency*

The performance of multi-gene panels for breast/ovarian cancer predisposition

Marcella Nunziato [a,b,1], Giovanni Luca Scaglione [a,b,c,1], Federica Di Maggio [a,b], Carmela Nardelli [a,b], Ettore Capoluongo [a,b,d,*], Francesco Salvatore [a,b,*]

BRCA Mutation Status in Triple-Negative Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: A Pivotal Role for Treatment Decision-Making

Francesco Pavese [1], Ettore Domenico Capoluongo [2,3], Margherita Muratore [1], Angelo Minucci [4], Concetta Santonocito [4], Paola Fuso [1], Paola Concolino [4], Enrico Di Stasio [4], Luisa Carbognin [1], Giordana Tiberi [1], Giorgia Garganese [5,6], Giacomo Corrado [1], Alba Di Leone [1], Daniele Generali [7], Simona Maria Fragomeni [1], Tatiana D'Angelo [1], Gianluca Franceschini [1], Riccardo Masetti [1], Alessandra Fabi [8], Antonino Mulè [9], Angela Santoro [9], Paolo Belli [10], Giampaolo Tortora [11,12], Giovanni Scambia [1] and Ida Paris [1,*]

ORIGINAL RESEARCH

Alternative academic approaches for testing homologous recombination deficiency in ovarian cancer in the MITO16A/MaNGO-OV2 trial

E. D. Capoluongo [1,2†], B. Pellegrino [3,4,5†], L. Arenare [6], D. Califano [7], G. Scambia [8,9], L. Beltrame [10], V. Serra [11], G. L. Scaglione [12,13], A. Spina [7], S. C. Cecere [14], R. De Cecio [15], N. Normanno [16], N. Colombo [17], D. Lorusso [8,9], D. Russo [7], C. Nardelli [1,12], M. D'Incalci [10,18], A. Llop-Guevara [11], C. Pisano [14], G. Baldassarre [19], D. Mezzanzanica [20], G. Artioli [21], M. Setaro [12], G. Tasca [22], C. Roma [16], N. Campanini [23], S. Cinieri [24], A. Sergi [10,25], A. Musolino [3,4,5], F. Perrone [6], P. Chiodini [26], S. Marchini [10‡] & S. Pignata [14‡,*]

INTRODUCTION

BRCA to the future: towards best testing practice in the era of personalised healthcare

Ettore Capoluongo*

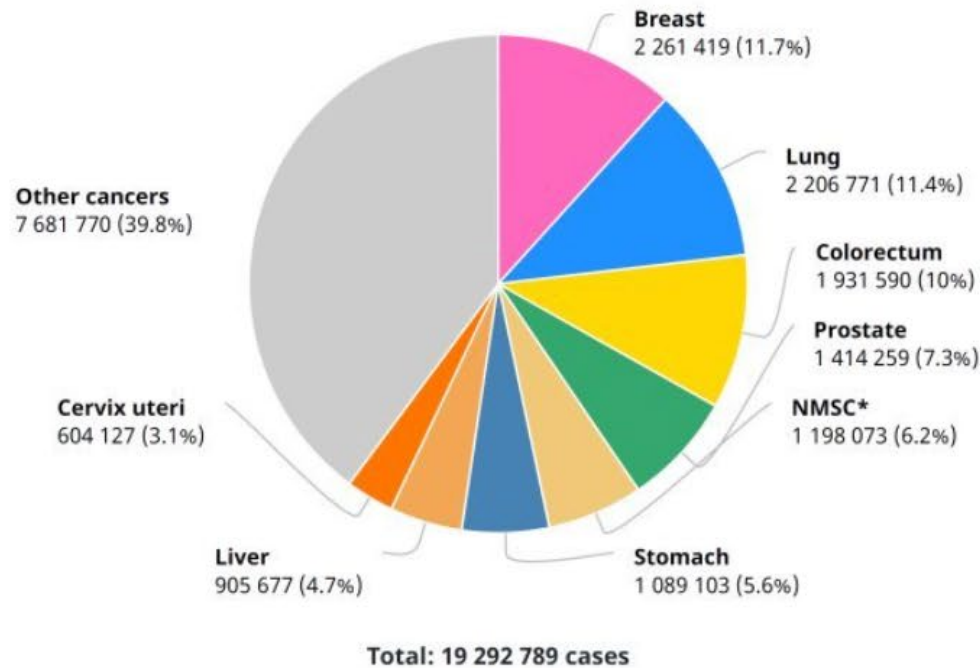❑**Detecting such aggressive cancers** at an **EARLY STAGE** **would likely require identification** of **CANCER PRECURSORS** (as for **HGSOC**) and the development of new **ultrasensitive approaches** **that permit increased frequency of testing**

❑**Use of synthetic biomarker** could ddress **these challenges**, with the main approaches being those that **leverage activity- based or genetically encoded mechanisms for EARLY DETECTION**
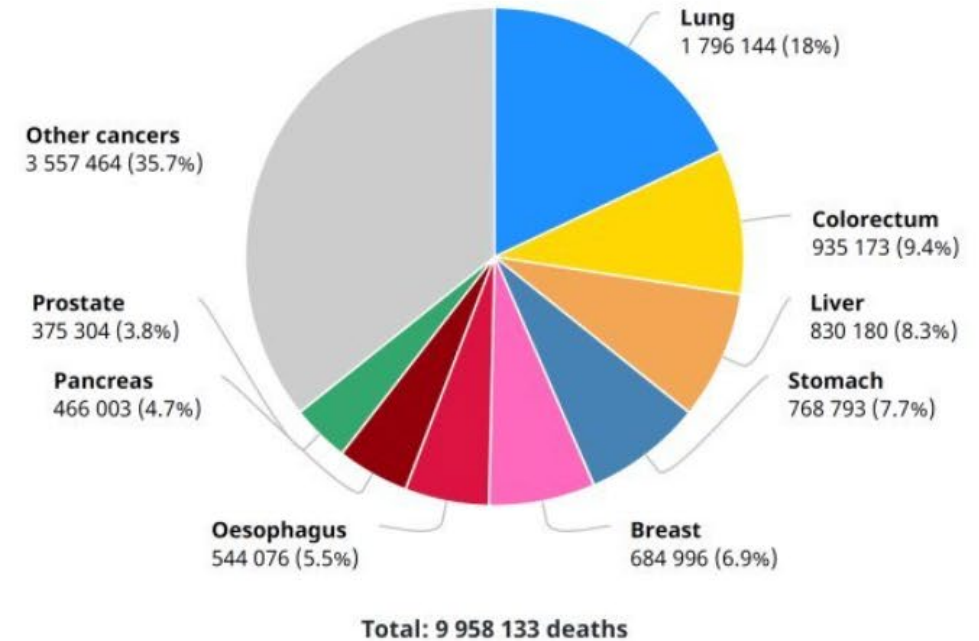
However, the **WHO 2010 model is disavowed** by research data which tell us that:

- **tumors cases continue to increase worldwide every year**

Number of new cases in 2020, both sexes, all ages

Breast
2 261 419 (11.7%)

Lung
2 206 771 (11.4%)

Colorectum
1 931 590 (10%)

Prostate
1 414 259 (7.3%)

NMSC*
1 198 073 (6.2%)

Stomach
1 089 103 (5.6%)

Liver
905 677 (4.7%)

Cervix uteri
604 127 (3.1%)

Other cancers
7 681 770 (39.8%)

Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages

Lung
1 796 144 (18%)

Colorectum
935 173 (9.4%)

Liver
830 180 (8.3%)

Stomach
768 793 (7.7%)

Breast
684 996 (6.9%)

Oesophagus
544 076 (5.5%)

Pancreas
466 003 (4.7%)

Prostate
375 304 (3.8%)

Other cancers
3 557 464 (35.7%)

Total: 9 958 133 deaths

International Agency for Research on Cancer
World Health Organization

GLOBAL CANCER OBSERVATORY
GCO

#GCO #365

Estimated number of incident cases all cancers, both sexes, all ages

China

United States of America

India

Japan

Germany

Brazil

Russian Federation

France

United Kingdom

Italy

0   1 000 000   2 000 000   3 000 000   4 000 000

Numbers

International Agency for Research on Cancer

World Health Organization
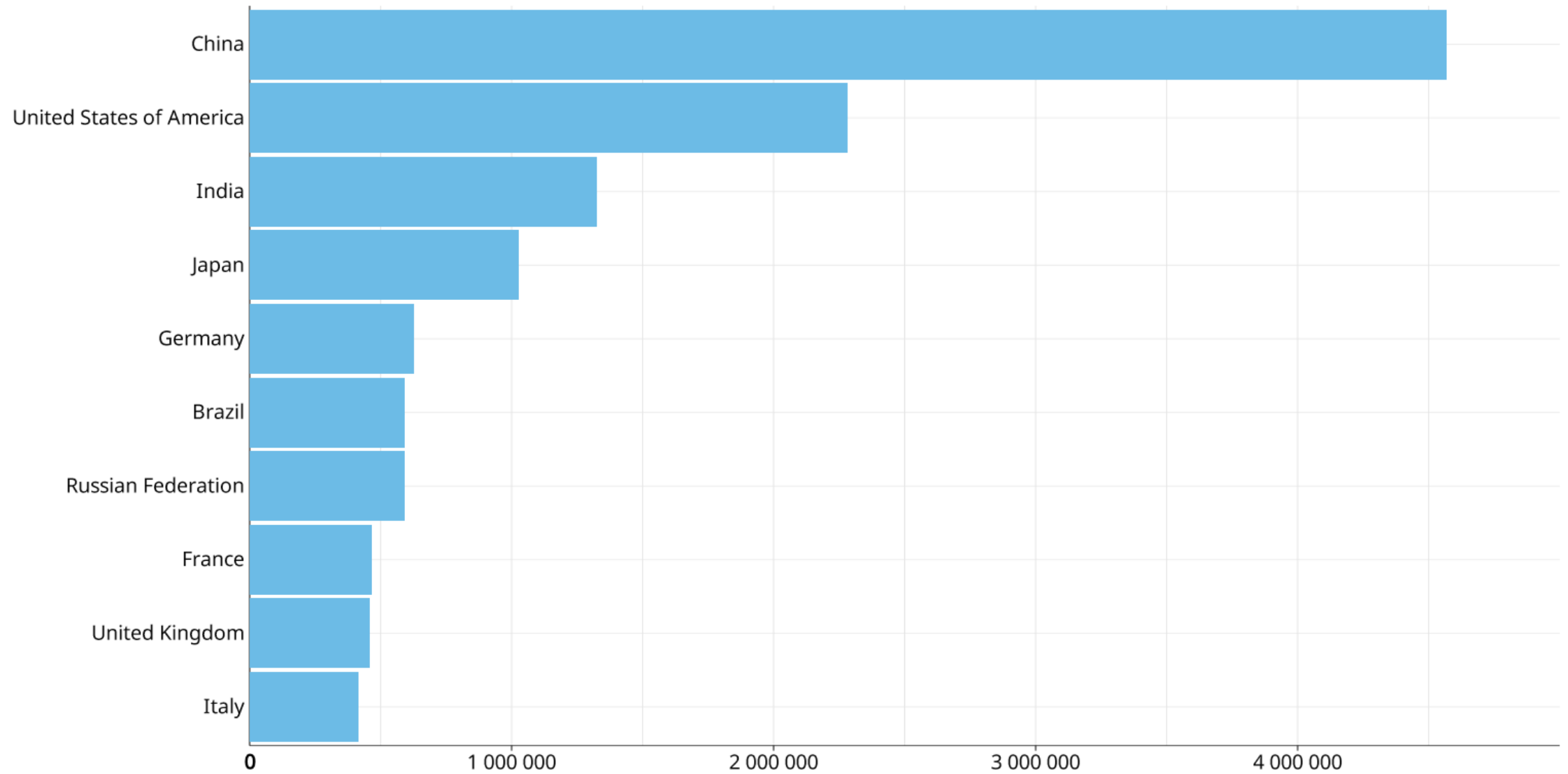
When the diagnosis is made in the presence of symptoms, for some tumors the **stage is higher** and **negatively impacts** the **prognosis**

EARLY AND LATE CANCER DIAGNOSIS
STAGE OF CANCER WHEN DIAGNOSED, ENGLAND 2013

EARLY (STAGE I + II)   LATE (STAGE III + IV)

ALL CANCERS
54% 46%

BREAST
84% 16%

COLORECTAL
45% 55%
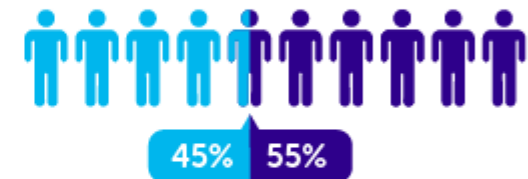
LUNG
23% 77%

MALIGNANT MELANOMA
91% 9%

NON-HODGKIN LYMPHOMA
35% 65%

OVARIAN
43% 57%

Emerging strategies to discover cancer biomarkers very early in apparently HEALTHY INDIVIDUALS

cerebrospinal fluid
tear fluid
saliva
pleural effusion
bronchoalveolar lavage
blood
ascites
peritoneal lavage
urine
seminal fluid

cerebrospinal fluid
tear fluid
saliva
pleural effusion
bronchoalveolar lavage
breast milk
breast ductal fluid
blood
ascites
peritoneal lavage
urine
cervical and vaginal secretion
uterine / utero-tubular lavage

Liquid Biopsy

The science of sniffs: disease smelling dogs

Is this the cheapest solution?

Fig. 5 | **Characteristics of synthetic biomarkers for early-stage cancer detection.** Enzymatic, small-molecule, DNA-based, mammalian cell-based and bacterial cell-based sensors leverage synthetic biomarkers to enhance early cancer detection. Each technology senses dysregulated activity (that is, the 'input') associated with the tumour microenvironment (TME), such as protease activity, metabolic activity or biophysical features. Through diverse modes of amplification and strategies for improving signal specificity, these approaches lower the limit of detection below current clinical thresholds (~1 cm³). ECM, extracellular matrix; IONP, iron oxide nanoparticle; PEG, polyethylene glycol; VOCs, volatile organic compounds; NA, not available.

Although these approaches are very PROMISING, they are still confined to the PRECLINICAL SETTING

SAME PROBLEMS ALL ALONG, WITH LACK OF EFFECTIVE ANSWERS

AIM TO BE EARLY
shutterstock.com · 1492145477

There is a need for **extensive profiling of early- stage** and *in situ* **tumours** as well as **lethal precursors** that have a **high propensity** for malignancy

World Health Organization | Health topics ⌄ | Our work ⌄ | Newsroom ⌄ | Data ⌄ | Emerg

What causes delays in cancer diagnosis and treatment?

| 1st symptom | 1st visit to doctor | Diagnosis | 1st treatment |

Time

| | "Access delay" | "Diagnosis delay" | "Treatment delay" |

Causes of delay:

- Poor cancer awareness
- Poor performance
- Referral issues
- Waiting lists, sub-optimal resources
- Financial barriers
- Logistical barriers
- Psychosocial barriers
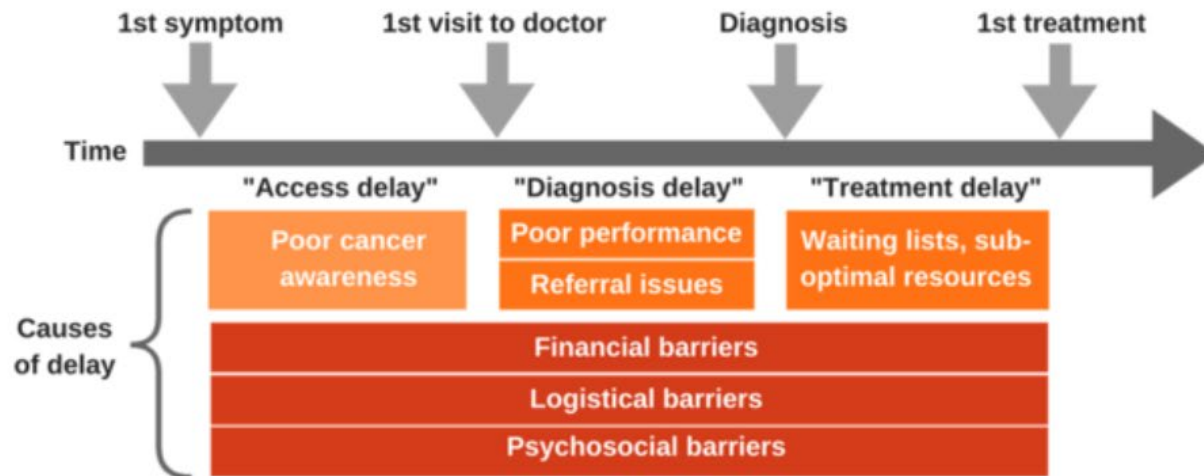
❑ **Although the nascent field of synthetic biomarkers** is **exciting** and full of **promise**, there are gaps in our current **knowledge of cancer pathogenesis** that need to be filled alongside addressing **technical challenges to guide future advances**

❑ There **is a limited understanding of:**

- the **BIOLOGY** of **EARLY LESIONS**

- **WHEN** and **HOW** a **precursor lesion transitions into malignancy**

The **Cancer Genome Atlas (TCGA)** has generated a **tremendous knowledge base** for the biomedical community but there is a **bias towards ADVANCED** and **LOCALLY ADVANCED TUMOURS**

Detection and localization of surgically resectable cancers with a multi-analyte blood test

Joshua D. Cohen[1,2,3,4,5], Lu Li[6], Yuxuan Wang[1,2,3,4], Christopher Thoburn[3], Bahman Afsari[7], Ludmila Danilova[7], Christopher Douville[1,2,3,4], Ammar A. Javed[8], Fay Wong[1,3,4], Austin Mattox[1,2,3,4], Ralph. H. Hruban[3,4,9], Christopher L. Wolfgang[8], Michael G. Goggins[3,4,9,10,11], Marco Dal Molin[4], Tian-Li Wang[3,9], Richard Roden[3,9], Alison P. Klein[3,4,12], Janine Ptak[1,2,3,4], Lisa Dobbyn[1,3,4], Joy Schaefer[1,3,4], Natalie Silliman[1,2,3,4], Maria Popoli[1,3,4], Joshua T. Vogelstein[13], James D. Browne[14], Robert E. Schoen[15,16], Randall E. Brand[15], Jeanne Tie[17,18,19,20], Peter Gibbs[17,18,19,20], Hui-Li Wong[17], Aaron S. Mansfield[21], Jin Jen[22], Samir M. Hanash[23], Massimo Falconi[24], Peter J. Allen[25], Shibin Zhou[1,3,4], Chetan Bettegowda[1,3,4], Luis A. Diaz Jr.[1,3,4,*], Cristian Tomasetti[3,6,7,†], Kenneth W. Kinzler[1,3,4,†], Bert Vogelstein[1,2,3,4,†], Anne Marie Lennon[3,4,8,10,11,†], and Nickolas Papadopoulos[1,3,4,†]

A **blood test** can detect **8 common cancer types** through assessment of the levels of:

- **circulating proteins** (CA-125, CEA, CA19-9, Prolactin, Epatocyte growth factor (HGF), Osteopontin (OPN), Myeloperoxidase, TIMP-1)

- **mutations in cell-free DNA**

⚠️ **Very few studies** have examined **a large number** of **healthy control individuals**, which is essential for evaluation of the **specificity of such tests**

Fig. 3.

Science. 2020;369(6499): eabb9601

Overview of cancers incident during the DETECT-A study.

(A) Twenty-six cancers (blue) in 10 organs were first detected by blood testing. (B) Ninety-six cancers were identified in the study (see Supplementary Materials). The location, and number of those first detected by blood testing (blue), standard-of-care screening (green) or by other means (grey) are shown.

- 10,000 women (65 to 75 years of age) with **no personal history of cancer** from a population with **high adherence to SOC screening**

Detection and localization of surgically resectable cancers with a multi-analyte blood test

⚠️ **Diagnostic sensitivity** is also an **ISSUE** for LB

⚠️ Available evidence indicates that **patients with early-stage cancers** can **harbor less than 1 mutant** template molecule **per milliliter of plasma,** which is often **beyond the LOD** of **technologies** that assess multiple mutations simultaneously

Detection and localization of surgically resectable cancers with a multi-analyte blood test

Another issue with LB is the identification of the **underlying tissue of origin**

Actionability or **druggability** of the variants with **low VAF**

Accelerating the Development and Validation of Liquid Biopsy for Early Cancer Screening and Treatment Tailoring

Denis Horgan [1,2,*], Tanja Čufer [3], Francesco Gatto [4], Iwona Lugowska [5], Donatella Verbanac [6], Ângela Carvalho [7,8], Jonathan A. Lal [2,9], Marta Kozaric [1], Sinead Toomey [10], Hristo Y. Ivanov [11], John Longshore [12], Umberto Malapelle [13], Samantha Hasenleithner [14], Paul Hofman [15] and Catherine Alix-Panabières [16]

Figure 6.1.1 Schematic representation of correlation among Limit of Detection, type of technology. [Real Time PCR (RT − PCR), Next-Generation Sequencing (NGS) and digital-PCR (dPCR)] and probability of false positive (FP) results.

Biological fluid withdrawal: how much sample volume is enough?

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Learning objectives

By the end of the chapter the reader will:

- understand the fundament of liquid biopsy
- have a deep knowledge of ctDNA analysis in earlier diagnosis or screening

6.2.1 Introduction

Cancer biomarkers can be detected in different bodily fluids, such as blood, urine, saliva, cerebrospinal fluid, stool, and lavage effusions (Fig. 6.2.1). Concentrations of cfDNA in blood plasma were reported
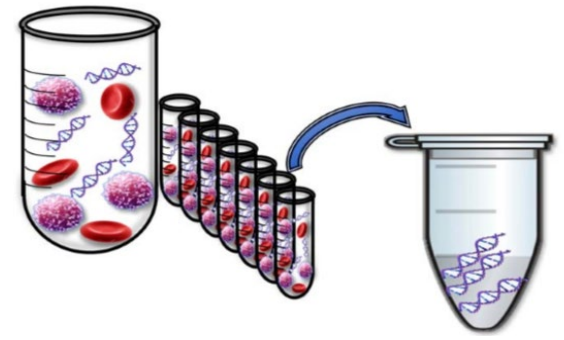
❑**LB** makes it possible to **detect cancers, including early cancers**, in individuals **without any history of the disease**

❑It is possible intervene by **SURGERY** on the **BASIS OF LB+ RESULT**

❑LB can be **incorporated into routine medical care** without discouraging patients from engaging in other forms of screening

❑Such testing **MUST be performed in a SAFE manner** without incurring a large number of **futile**, **invasive follow-up tests**, also avoiding the **patient's anxiety**

❑ There is also an **urgent unmet clinical** **need to detect aggressive cancers**, and **early detection efforts** would be greatly empowered by the **ability** to **predict:**

✓ **TUMOUR AGGRESSIVENESS**

✓ **LETHALITY**

❑ The **US National Cancer Institute (NCI)** initiated the Human Tumor Atlas Network (HTAN) to **create detailed molecular, cellular and spatial maps** of a variety of **PRECANCERS**, *in situ* **cancers** and **ADVANCED CANCERS** as a function of time

This will **lead to a deep understanding of:**

❑ **how precancers** transition to malignancy for those cancer types
❑ **how invasive cancers**:

- Progress
- Metastasize
- respond to or develop resistance to treatment

Vision

Interministerial Collaboration:

Ministry of Economy and the sea

Ministry of Finance

Ministry of Labour, Solidarity and Social Security

Ministry of Science, Technology and Higher Education

Ministry of environment and climate action

Ministry of Justice

National Cancer Control Strategy
2021-2030

National Program for Oncological Diseases

Citizen centered

Prevention | Early Detection | Diagnosis Treatment | Survivors

Teamwork; Communication; Motivation
Knowledge (data/research)
Leadership of the Ministry of Health

EARLY DETECTION ROAD MAP

❑Ensuring **fair** and **quality ACCESS** to **screening**

❑ Ensure **quality and safety** of **procedures**

❑Ensure **training** of the **professionals involved**

Bringing Onco-Innovation to Europe's Healthcare Systems: The Potential of Biomarker Testing, Real World Evidence, Tumour Agnostic Therapies to Empower Personalised Medicine

Denis Horgan [1,*], Gennaro Ciliberto [2], Pierfranco Conte [3], Giuseppe Curigliano [4], Luis Seijo [5,6], Luis M. Montuenga [7,8], Marina Garassino [9], Frederique Penault-Llorca [10], Fabrizia Galli [11], Isabelle Ray-Coquard [12], Denis Querleu [13], Peter Riegman [14], Keith Kerr [15], Hein Van Poppel [16], Anders Bjartell [17], Giovanni Codacci-Pisanelli [18], Jasmina Koeva-Balabanova [19], Angelo Paradiso [20], Zorana Maravic [21], Vassiliki Fotaki [21], Nuria Malats [8,22], Chiara Bernini [1], Simonetta Buglioni [2], Alastair Kent [23], Elisabetta Munzone [24], Ivica Belina [25], Jan Van Meerbeeck [26], Michael Duffy [27], Beata Jagielska [28] and Ettore Capoluongo [29,30,*]

"Numerous declarations made by the EU institutions both before and during the coronavirus crisis, ***suggest a growing recognition of the need to innovate—at*** the level of both policymakers and of the health community.

The **renewed attention to disparities** in **cancer care and access across Europe is also driving new assessments of obstacles** and new pursuits of solutions, and **promoting greater networking and collaboration among cancer institutions**"

❑ **Oncology Referral Network**

❑ **Qualify Access** and **Increase Equity**

❑ **Valuing Professionals** and **Institutions**

Barriers to the LB implementation

ESMO Precision Medicine Working Group, has strongly underlined the **incomplete sensitivity of LB** which represents a major limits for **its use in clinical practice**, particularly due to the **lower sensitivity** for:

- **gene fusions**
- **copy number**

As the EU's plan itself suggests, improvements in screening and **EARLY DIAGNOSIS** will require:

- **Updates on the practical tools (choice of the best technological platforms)**

- **Policy pronouncements (fundamental for the harmonization)**

No mention is made of LB, but for full effect, **updating recommendations** should reflect the full **potential of screening technology**

Together with **continued technological and scientific advances bringing greater precision and predictability** to **LB**, there is a **role for policy in enhancing** the **environment for further development**

❑ Advances in **genomic sequencing** mean that generating genomic data **is no longer a major barrier**

❑ The main challenge is **being able to interpret a genomic finding** in the **context of the individual**

❑ This requires the **KNOWLEDGE GAINED** from data at a population level to sort through the "**noise" of variation** in an individual's genome and to identify an **individual change** or **pattern that may be unique to an individual**

❑ To **improve reproducibility**, not only **ISO 15189 is important**, but should be complemented with standards on the **pre-analytical phase**.

❑ **For Biomarker testing**, data is the indispensable component of **CREDIBILITY, which means: to do what is clinically valid and usefull!**

. Pictorial representation of data sources for predictive biomarker development and barriers that prevent successful clinical translation. Individual data variables (blue)
e predictive but some may be prognostic (such as TNM) but in combination form a predictive tool.
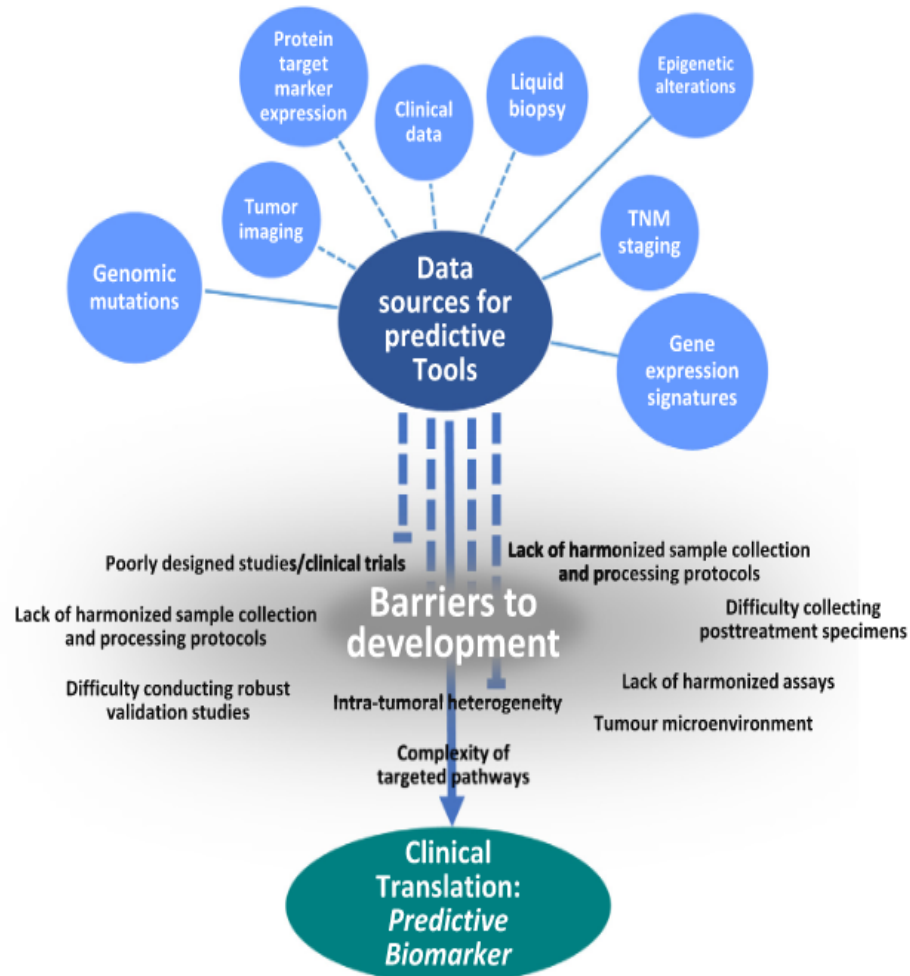
Aa long as data is seen as **sub-optimal**, **any technologies dependent on it** will **REMAIN MARGINAL**

Without clear directives on **Quality Standards** for **different biomarker tests**, the consequences could be:

- **Inaccuracies in lab reports**
- **Results** that may need further **clarification**
- **CONFUSION**

CREDIBILITY: do not test something that is useless!

CREDIBILITY: do not reimburse useless tests!

Biomedicine Hub

DE GRUYTER

Perspectives

Denis Horgan*, Mario Plebani, Matthias Orth, Elizabeth Macintyre, Stan Jackson, Jonathan A. Lal, France Dube, Marta Kozaric, Birute Tumiene, Roberto Salgado, Jack A. Schalken, Ettore D. Capoluongo and Marta Carnielli

The gaps between the new EU legislation on *in vitro* diagnostics and the on-the-ground reality

Review

Florent Vanstapel*, Matthias Orth, Thomas Streichert, Ettore D. Capoluongo, Wytze P. Oosterhuis, Hikmet Can Çubukçu, Francisco A. Bernabeu-Andreu, Marc Thelen, Leo H. J. Jacobs, Solveig Linko, Harjit Pal Bhattoa, Patrick M. M. Bossuyt, Pika Meško Brguljan, Guilaine Boursier, Christa Cobbaert and Michael Neumaier

ISO 15189 is a sufficient instrument to guarantee high-quality manufacture of laboratory developed tests for in-house-use conform requirements of the European *in-vitro*-diagnostics regulation. Joint opinion of task force on European regulatory affairs and working group accreditation and ISO/ CEN standards of the European federation of chemistry and laboratory medicine

Abstract: The EU *In-Vitro* Diagnostic Device Regulation (IVDR) aims for transparent risk-and purpose-based validation of diagnostic devices, traceability of results to uniquely

Fig. 3. Main areas of barriers.
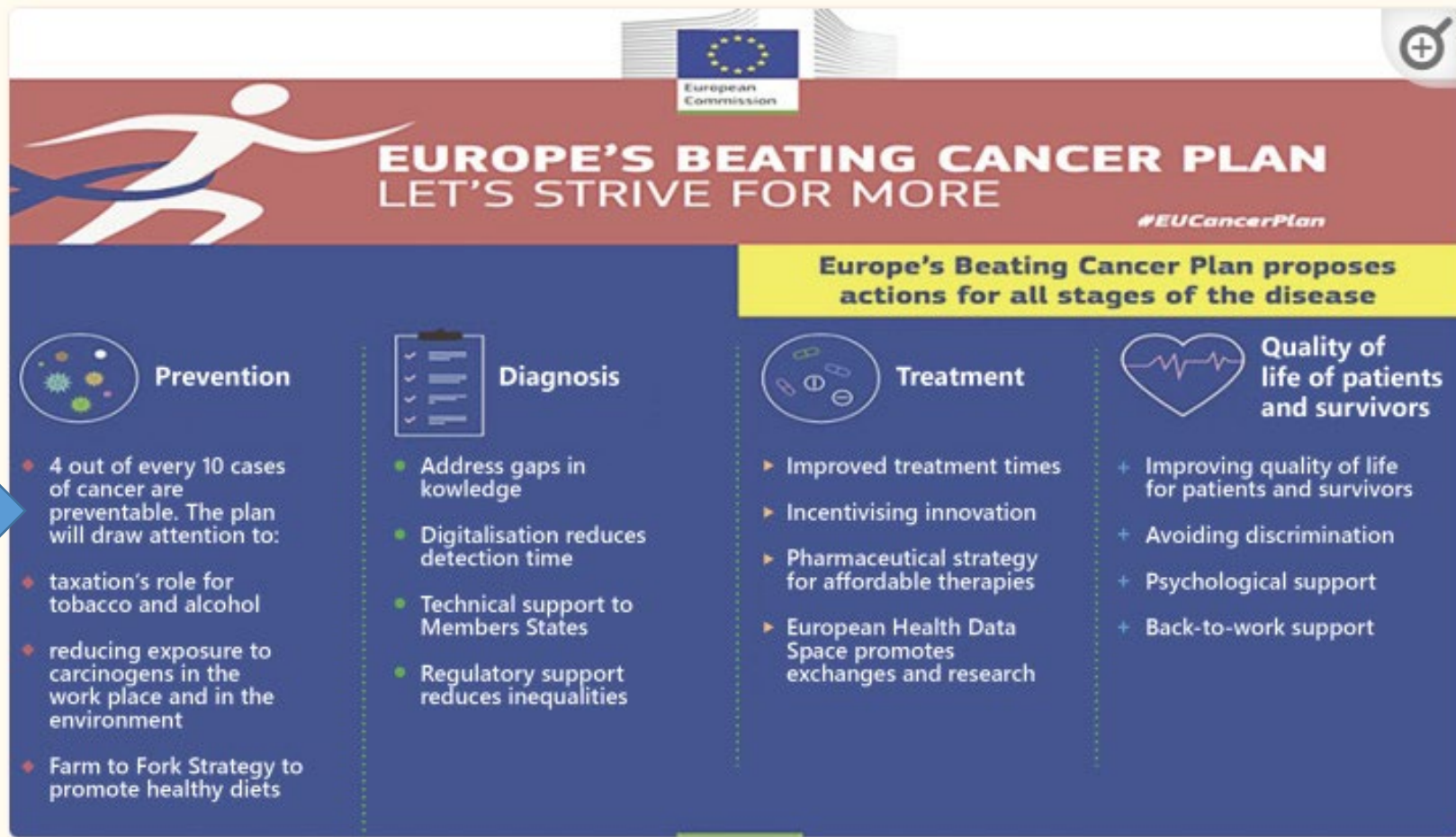
Horgan et al.: Bringing Greater Accuracy to Europe's Healthcare Systems: The Unexploited Potential of Biomarker Testing in Oncology

Section	Subsection
Science	System biology and data
	Research
	Clinical study design
Operational	Information delivery
	Education and training
	Inform, educate, empower patients
	Regulations
Economics	Reimbursement
	Single technology evaluation
	Costs of testing
EU-level	Bio-banks
	Translation
	Reimbursement
	Legal and ethical

Fig. 2

European Commission's Beating Cancer Plan.

Predisposition Biomarkers

A genetic predisposition (genetic susceptibility) is an increased likelihood of **developing a health disorder based** on the presence of a particular genetic biomarker:

Screen for these every population for:

PREVENTABLE diseases	Types of Cancer/Syndromes
HEREDITARY CANCERS	Ov; Breast; Pancreatic, Prostate, Melanoma, Gastric
CARDIOVASCULAR DISEASES	Brugada S, Hearth failure; Sudden death
NEURODEGENERATIVE CONDITIONS	Alzheimer
METABOLIC DISEASES	Hypercholesterolemia; diabetes; Inflammatory disorders

Thank you