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EU-Wide Access to High-quality, Affordable Precision Diagnostics: An EHA Position Paper

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For a given disease, if prevention is not possible, the ideal treatment cures or controls a maximum number of patients with minimal side effects and the highest possible quality of life, for an optimized cost to the individual and society. The increasing number of treatment options available creates exciting challenges for individually adapted, so-called, Precision Medicine. All treatment starts with diagnosis, so Precision Diagnostics precedes and is indissociable from Precision Therapeutics.

While applicable to all diseases, hematological cancers (eg, leukemia, lymphoma, and myeloma) are an important model, justified first by the exponential rise in the number and cost of cancer drugs and cellular therapies. These cancers have also disproportionately provided proof-of-concept innovation, including in diagnostics, in part because they are relatively accessible to sampling for both diagnostics and assessing response to treatment. The latter is referred to as minimal (or measurable) residual disease (MRD) and is increasingly being used both as a surrogate to overall/progression-free survival in clinical trials and for modulation of individual treatment.

If a diagnostic test can determine which patients are most likely to benefit from a drug, its targeted use will facilitate identification of the advantages of the drug, avoid potential side effects in patients who are unlikely to respond and reduce overall drug requirement, while optimizing benefit/risk ratio. From an economic point of view, the cost effectiveness of more widespread use of a diagnostic test needs to be assessed in order to determine whether this extra cost is offset by the reduced therapeutic costs, thus providing a health benefit at an acceptable cost/effectiveness ratio. Such Health Technology Assessments (HTA) should ideally be performed at a European level, in order to optimize equal access to state-of-the-art care. While this article was written on the eve of the Covid-19 pandemic, many considerations also apply to testing for viral presence and/or immune status.

Challenges

Significant hurdles to EU-wide implementation of high-quality, accessible and affordable precision diagnostics exist.

Access to specialized tests

Each cancer is being divided into smaller and smaller subgroups based on the enormous heterogeneity of the disease, and this is predominantly thanks to the exponential increase in our capacity to detect acquired (onco)genetic abnormalities. There is therefore an increasing demand for diagnostic expertise, putting strains on access to appropriate specialized cancer diagnostic platforms. While these are predominantly molecular, they must function in synergy with the tissue/cell-based specialists who, in addition to performing phenotypic diagnostics, select and appropriately process the material for molecular analysis, thus avoiding 'rubbish-in, rubbish-out' risks incurred by analysis of inappropriate material as well as choosing the most appropriate diagnostic tests/panels for assessment.

It is accepted by most that reference-grade expertise requires sufficient experience and sample throughput in the relevant field, providing a strong argument for centralization. Individual EU Member States are primarily responsible for implementing the choice between local and centralized diagnostics, in a current environment where there are clear disparities, both between and within Member States, in access to specialized tests such as Next-Generation Sequencing (NGS also known as High-Throughput Sequencing or HTS), and other specialized molecular and tissue/cellular tests.

NGS/HTS testing can either be global (whole genome/exome approaches), which tend to be disease-subtype-discovery orientated, or targeted, and currently more diagnostic, prognostic and

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theranostic orientated, although these approaches may converge in the foreseeable future with technological and bio-informatic developments. This will lead to increased processivity in data generation, with a logical decrease in the cost of production, particularly if panels and bio-informatic pipelines become increasingly uniform. Whether this will translate into increasingly accessible, reasonably priced diagnostic testing will be largely determined by the attendant intellectual property issues, which in turn depend on how the diagnostic kits are developed, validated and marketed.

From development to patient

Classically, the academic sector identifies interesting new diagnostic markers, publishes their relevance within the context of a clinical trial in a peer-reviewed journal, occasionally preceded by patent deposition. Only a minority of patented diagnostic tests are subsequently licensed and brought to market, usually by the biotechnology sector. Understanding and appreciation of this academic-biotechnology-commercial chain is not universal amongst diagnostic and academic actors, although this is gradually improving with increasing awareness of the importance of Health Technology Assessment (HTA).

Academic development of precision diagnostics (often publicly funded) is vital, as is appropriate dissemination of relevant diagnostic advances, in order to allow rapid patient benefit throughout the EU. This process is currently one of the black boxes in health care, both with respect to the partnerships between academia and the biotechnology sector and to the pricing of tests, which can be exorbitant. The relative contributions to the cost of a diagnostic test between kit production, intellectual property protection and/or value-added approaches to diagnostic reimbursement are currently unclear. Cultural and political differences in the appreciation of the appropriate interaction between public and private actors in healthcare exist both within and between countries.

Health care systems are often underpowered and/or ill-prepared (including in health sector education systems) for HTA approaches to rationalizing diagnostic priorities and access. The uptake of precision diagnostics would benefit from increased transparency and a concerted optimization effort within the EU, as piloted by EUnetHTA.[1,2] The European Hematology Association (EHA) is therefore in favor of a permanent mechanism for joint clinical assessments along the lines of the European Commission's HTA proposal,[3] with a focus on innovative technologies, including in-vitro diagnostic devices that target unmet medical needs or have major public health impact.

Regulation: the IVDR

New and far-reaching EU legislation will have to be implemented in all EU Member States by May 2022: the In Vitro Diagnostic Medical Devices Regulation (IVDR).[4] Succinctly, IVDR will strengthen the requirements for clinical evidence used to demonstrate the clinical benefit and safety of the device, including post-market surveillance. It will also increase the involvement of notified bodies, which are independent conformity assessment bodies nominated by national competent authorities. Assessments and audits by Notified Bodies will be necessary under IVDR for the vast majority of diagnostic tests. Importantly, this must now be complemented by validation by EC-nominated EU Reference Laboratories (EURLs) for selected, high individual and public risk tests (Class D).

Class D tests are essentially restricted to infectious agents (including CMV, EBV, hepatitis) and blood group testing (eg, Kell, Duffy). Genetic (constitutional and acquired) and immunophenotypic (histological and cellular) tests are classified as Class C tests. The implementation of IVDR is managed by the European Commission (DG SANTE) and National Competent Authorities, through an IVD subsection of the Medical Devices Coordination Group (MDCG).[5]

IVDR represents both an opportunity and a threat for the cancer research and diagnostics sectors, as it does for the diagnostics industry. Small-scale biotechnology companies with limited portfolios may find it difficult to comply with IVDR and some kits may no longer be marketed. Interaction between Notified Bodies and the diagnostic sector will be necessary for more specialized tests and for market and post-market surveillance, under economic models which are being identified. There is accepted exemption for in-house, laboratory-developed tests (LDTs) to be used in patient care, as long as an equivalent-performance commercial kit does not exist, but the economic impact of widespread replacement of LDTs by commercial kits has yet to be addressed. Companion diagnostics with theranostic impact are being treated jointly with EMA. The details of implementation regarding these 'niche' tests, which are the mainstay of a specialized hemato-oncology laboratory, are currently being explored within the MDCG-IVD group.

The optimal scenario would be that the consolidated diagnostic budget, which currently represents 2% to 3% of cancer care,[6] will be modernized and streamlined by benefitting from diagnostic innovation and stakeholder synergy to contribute to the objective described in the opening sentence of this article. IVDR would also stimulate the European biotechnology industry, by encouraging development of precision diagnostic kits. The scenario to be avoided is a sub-optimal choice of validated diagnostic tests which prevent or discourage diagnostic research and innovation.

Task force and partnerships

EHA created an IVD Task Force in early 2019, covering molecular and cellular cancer diagnostics and benign hematological diagnostics, including blood grouping. This task force works closely with the BioMed Alliance,[7] a non-profit organization representing over 30 leading European research and medical societies involved in both diagnostic and therapeutic care of all EU citizens. Indeed, the IVDR section of the BioMed Alliance Medical Devices Task Force is chaired by the EHA president-elect, who is a designated stakeholder in the MDCG.

Optimal synergy between the public healthcare and industrial diagnostic sectors will depend on a clear understanding on the part of diagnostic specialists on how we can help the European Commission to:

1. prioritize optimal use of diagnostic budgets;
2. encourage and accompany academic, public development of innovative, reproducible diagnostics;
3. facilitate appropriate synergy between the academic and industrial sectors in the developmental chain from ideas to proof of concept, clinical trials, product development, health care system integration and (proven) patient benefit, including in post-market surveillance and real-life trials.

This opportunity must not be missed. For the public academic diagnostic sector, this will require working closely with National Competent Authorities and regulators in encouraging constructive interaction with the biotechnological and diagnostic sectors at the European level, and active participation in the implementation of IVDR through the appropriate EU advisory structures,

particularly in post-market surveillance and LDT aspects. It represents an opportunity to develop appropriate novel partnerships between academia and industry which are in keeping with current evolutions in clinical trial design, data management and, particularly, inclusion of patient representatives and HTA and ethical/legal experts. For genetic testing in hematological cancers, we have the choice between a national approach or a European concerted approach to IVDR implementation. Given the rarity of many of our diseases and diagnostic tests, the latter approach is clearly preferable.

Multistakeholder collaboration will be indispensable if a harmonized model for the use, storage and accessibility of test results is ever to become reality – an ambitious and long-term goal that, in EHA's view, is crucial to enabling equal access to appropriately priced, expert-developed precision diagnostics and effective data sharing across the EU. One example is HARMONY, the pioneering public-private partnership for big data in hematology.[8] Such partnerships will be key in facing up to the challenges of precision diagnostics in the digital medicine era.

EHA's messages for policymakers:

EU-wide access to high-quality, reproducible, affordable precision diagnostics is essential for realizing true personalized medicine. Benefits include improved, tailored treatment with minimized side effects, the highest possible quality of life for patients and optimized cost effectiveness for society.

We discern 4 key needs:

1. **Concerted implementation of the in-vitro diagnostic medical devices regulation (IVDR)** across Europe in a way that optimizes use of diagnostic budgets, protects publicly funded, academically developed precision diagnostics and facilitates synergy between the academic and industrial sectors along the development-to-market chain.
2. **A mechanism for joint clinical assessments** along the lines of the European Commission's HTA proposal, to rationalize reimbursement decisions and optimize the uptake of precision diagnostics.
3. **EU funding for (public-private) multistakeholder partnerships**, which must include patients that will take on the challenges of advancing precision diagnostics in the digital medicine era (incl. development of a harmonized model for storing and accessing test results).
4. **EU funding for academic development of precision diagnostic tests**, developed and evaluated in concertation within the context of clinical trials. Such tests are of vital importance for enabling targeted and avoiding unnecessary treatments, thus improving patient outcomes.

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