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DEVELOPING AN ADVANCED DIAGNOSTICS ECOSYSTEM IN EUROPE:

A PROPOSAL FOR CHANGE

A White Paper prepared by the EUCOPE Genomics Working Group and Charles River Associates

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DEVELOPING AN ECOSYSTEM THAT ENHANCES PATIENT ACCESS TO ADVANCED DIAGNOSTICS IN EUROPE

Clinical practice is rapidly evolving with increased uptake of precision medicine and the ability to conduct large-scale, high-quality genetic and genomic profiling of patients. The science around the application of genomics is accelerating, with advanced diagnostic technologies delivering transformative benefits to patients today and contributing to improving the health of patients in the future.

The health benefits of genomics and advanced genomic testing are significant. These innovations facilitate earlier diagnosis of disease, improve prognosis of disease outcome and enable targeted therapeutic interventions based on an unprecedented understanding of the underlying molecular characteristics of patients. Today we can deliver the right treatment for the right patient at the right time – with widespread adoption, the potential is enormous to derive exponential benefit to healthcare systems alongside more targeted and efficient use of resources.

Investment in genomics technologies and applications provides societal benefits beyond our health systems, with dynamic advanced diagnostic “ecosystems” stimulating innovation, growth and employment, in particular in mature healthcare and biotechnology sectors.

However, despite the many scientific breakthroughs across European academic centres and hospitals, the adoption of advanced diagnostics and technologies in the clinic and healthcare systems is not a foregone conclusion, and the rate of adoption in Europe is falling behind that of other regions globally.

There are several factors to explain this:

- The value of advanced diagnostics is not sufficiently recognised. Funding is insufficient and support not well suited to increase their role in the clinical setting, resulting in clinical practices not keeping up with the accelerating cycle of innovation in novel diagnostics.
- The time to market for advanced diagnostics is too long, complex and fraught with uncertainty. There is a lack of pathways for appraisal that are time-bound and flexible and that can accommodate the unique characteristics of advanced diagnostics.
- Essential clinical supporting infrastructure is lacking in Europe. This includes an appropriately trained workforce, data sharing and data storage infrastructure capabilities, and digital health recording within healthcare systems.

The lack of widespread access to advanced diagnostics in clinical practice is leading to missed healthcare gains and socio-economic benefits from an emerging innovation sector. The consequences will limit transformation of healthcare systems and impact the global competitiveness of the biopharmaceutical sector in Europe with the loss of intellectual property, capital and talent to other regions.

A PROPOSAL FOR CHANGE

Given these challenges, the genomics industry group of EUCOPE – with the support of Charles River Associates (CRA) – has developed a set of policy proposals to support understanding of the advanced diagnostics sector, the benefits it brings and related requirements for success.
In order to support the evolving ecosystem for advanced diagnostics, policymakers will need to balance actions across three themes:

1. The need for supportive and well-funded advanced diagnostics ecosystems
2. The need for value and appraisal processes that are fit for purpose for advanced diagnostics assays
3. Leveraging existing infrastructure with national genomics policy initiatives

This will require specific actions from European governments and EU institutions:

1. Investing in an R&D ecosystem that fosters development, encourages innovation, and facilitates uptake of advanced diagnostics
2. Developing specific and clear regulatory pathways for advanced diagnostics
3. Developing clear pathways for fast and efficient reimbursement for advanced diagnostics
4. Facilitating the integration of advanced diagnostics into clinical practice
5. Increasing the appreciation of the value of advanced diagnostics

Integrating these measures into well-articulated genomics strategies that address the need for broader access to advanced diagnostics and promote innovation will be essential. This will not only deliver benefits in terms of better health outcomes for patients but also help attract companies to invest in surrounding infrastructure and lead to the creation of high-value jobs in companies that specialise in sequencing, processing, storing, analysing, and sharing genomic data. The organisations involved in this work wish to partner with healthcare systems to improve outcomes for patients, improve healthcare resource use and ensure Europe continues to be a leading region for healthcare innovation.

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1. INTRODUCTION

The decades-long focus on developing "personalised" medicines has led to the emergence of technologies targeted at individual patients' or groups of patients' needs, ensuring that patients get the right treatment at the right time. Clinical practice is now shifting towards an era of precision medicine and large-scale, high-quality genetic profiling of patients with technologies focusing on the structure, function, evolution, mapping, and editing of genomes.[1] This transition is centred on a continuous cycle of insight generation, driven by data, technology and advanced analytics, coming from a variety of sources including imaging, genomics, clinical trials, and electronic health records.

Europe has been the source of much of scientific development in genomics with important contributions to the first genome sequencing project.[2] In the late 1990s, British scientists worked closely with academics in the US to complete the first draft of the entire human genome – the first map of the three billion base pairs that make up human DNA.[3] Since then, the European Union (EU) has continued to support scientific developments in genomics and retains some of the leading genomics scientists in the world. Europe remains a global player in genomics through the enablement of national programmes or pan-European programmes – such as the "1+ Million Genomes" initiative, involving 23 countries across Europe – looking to improve the uptake of genomics by healthcare systems and in personalised healthcare.[4] As the science around genomics continues to evolve, advanced diagnostics technologies are delivering benefits to today's patients while supporting future research and clinical development. However, beyond research programmes, many of these technologies are not reaching patients in clinical routine care in Europe. Patients' health outcomes in diseases like cancer continue to vary because of stark differences in the availability of and access to innovative and personalised healthcare. Their fragmentation across countries and healthcare systems is largely due to knowledge gaps as well as a lack of infrastructure and healthcare system funding.[5]

The objective of this paper is to review the evidence on the value of "advanced diagnostics" but also the barriers that impede the development and uptake of advanced diagnostic technologies, and to consider the need for an ecosystem that fosters the development of commercial advanced diagnostics and their uptake in the clinical setting. We argue that this effort should be integrated into the multitude of national genomic-medicine initiatives that have been established in many countries over the past 15 years.[6]

1.1. WHAT ARE "ADVANCED DIAGNOSTICS"?

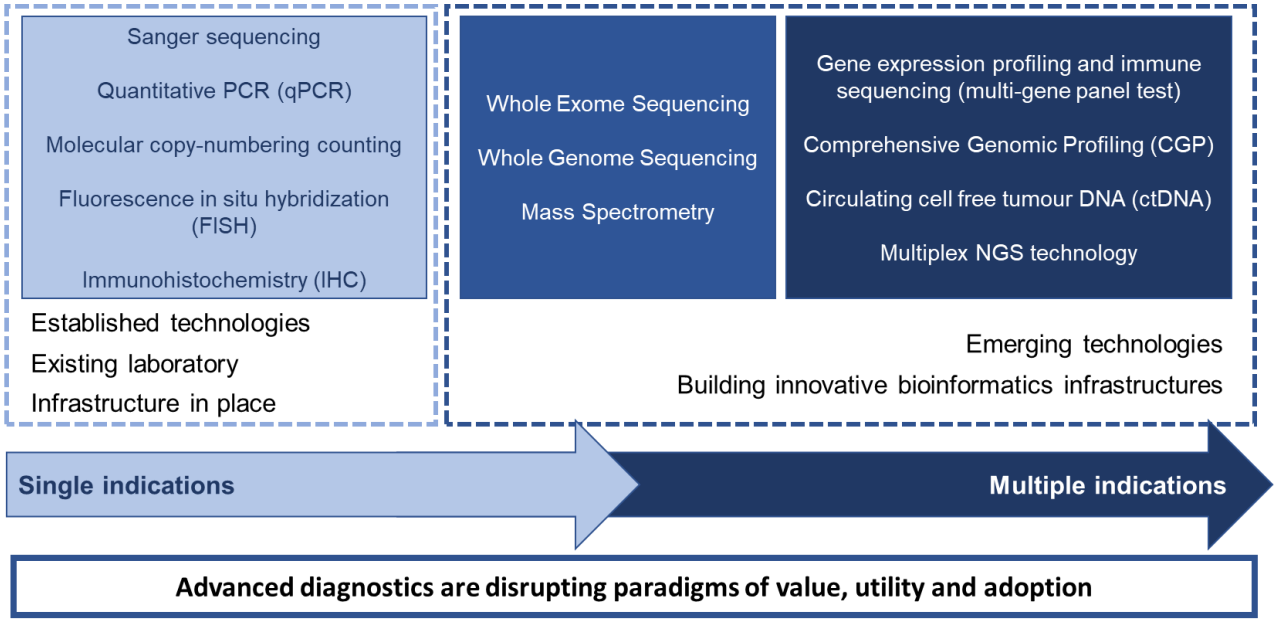
This paper focuses on "advanced diagnostics" that exploit the improved understanding of genomics – i.e. the study of genes and their functions, and related techniques.[7] This includes DNA arrays, High-throughput Sequencing (HTS), Comprehensive Genomic Profiling (CGP), Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS).[8] Advanced diagnostics are used for a variety of clinical purposes that span both research and clinical decision-making, including: screening for disease, diagnosis, prognosis, therapy selection and prediction of treatment benefits, monitoring risk of recurrence as well as support in clinical trial designs.

The progress in advanced diagnostics is partially driven by Next Generation Sequencing (NGS) technology, which has revolutionised the ability to sequence nucleic acids by increasing the amount of sequence data

that can be obtained in a rapid and cost-effective manner.[9] As illustrated in Figure 1, NGS is utilised in technologies such as WES and WGS. However, these technologies – unlike technologies which perform single or limited gene sequencing – are largely limited to research settings and are not yet widely available in clinical practice. This is partially due to the data science capabilities that are required to interpret and action the results obtained from more advanced diagnostics.

Advanced diagnostics are evolving with new cutting-edge techniques rapidly being developed, such as gene expression profiling, immune sequencing and liquid biopsy methods from blood plasma, e.g. mutation testing from circulating cell-free tumour DNA (ctDNA), which may also use multiplex NGS technology.

Figure 1: Defining advanced diagnostics



Source: CRA analysis

2. THE VALUE OF ADVANCED DIAGNOSTICS

Advanced diagnostics represent a paradigm shift in medical care, primarily because of the vast amount of relevant information they generate. Delayed or wrong treatments lead to worse health outcomes and unnecessary costs for both patients and healthcare systems. Advanced diagnostics have the potential to reduce the financial burden of trial-and-error and one-size-fits-all approaches, with both immediate and longer-term cost savings to the healthcare system along with personal benefit to the patient due to more timely and correct diagnoses. Oncology care is a prime example of the continuous personalisation of medicines, where more than 200 clinically relevant genomic alterations have been identified.[10] Lung cancer exemplifies the need for multiple genes to be interrogated in order to guide treatment (e.g. BRAF, EGFR,

MET, ROS1, NTRK, ALK and RET), and further biomarker discovery will continue to drive the need for testing more genetic mutations (e.g. homologous recombination deficiency [HRD], tumour mutational burden [TMB]). These early successes in identifying and targeting individual oncogenic drivers, together with the increasing feasibility of sequencing tumour genomes, have already started to deliver short-term successes – such as increased patient survival – and have brought forth the promise of genome-driven oncology care, leading to a new era of personalised healthcare.[11] Thus, these advances deliver several layers of benefits across the patient care pathway, including value to patients but also the benefits they deliver to healthcare systems and payers as well as the broader societal and economic impacts.

OPTIMISING TREATMENT SELECTION – DELIVERING BETTER HEALTH OUTCOMES FOR PATIENTS

Genomics currently allows a range of medicines to target specific molecular characteristics with improved outcomes and reduced side effects. In oncology and rare diseases, this also includes non-pharmacologic approaches that are informed by specific diagnoses. Genomics reveals prognostic markers that can indicate how a disease may develop and the correct treatment modality, while pharmacogenomic testing accurately predicts what medications at what doses will be safest for a person with a specific genetic makeup. For example, new diagnostics technology such as ctDNA can inform treatment selection at all stages of disease progression. It is estimated that in the US this will help more than 700,000 advanced cancer patients with their therapy selection, over 15 million early-stage survivors through recurrence monitoring, and more than 100 million individuals with early-stage cancer detection through cancer screening.[12] Genomics delivers direct benefits to patients, as set out in Figure 2.

Figure 2: The benefits of genomic testing to patients – examples from a variety of applications

Choosing the right clinical pathway for the right patient	• Genomic testing indicates better suited and more effective therapies for patients based on their individual needs, leading to improved patient outcomes and fewer adverse events, and identifies which treatment options not to use. • The breadth of diagnostic data that it unlocks allows for both faster diagnosis and greater diagnostic accuracy. Advanced diagnostics can identify genomic alterations missed by other testing approaches and improve access to existing and new treatment options. • In cases where innovative therapies are still in development, it enables more targeted clinical trial enrolment and thus improves patient access to targeted treatments. • Integrating advanced diagnostics into clinical care has the potential to cut short an otherwise expensive and burdensome diagnostic odyssey for the patient with previously undiagnosed disease.[13] • Genomic testing allows for a prompt diagnosis when multiple genes need to be sequenced at once, ensuring an appropriate treatment is initiated as quickly as possible.

- Knowing the risks and chances associated with a disease can enable informed decision-making, e.g. family planning, treatment adherence or preventative measures. It further has the potential to increase quality of life and reduce the mental burden of disease, with increased well-being and sense of personal control as a result of the patient's increased knowledge about the disease.[14]

PREDICTIVE AND PROGNOSTIC BIOMARKERS – BROADER IMPACT ON PATIENTS, FAMILIES AND CARERS

Patients benefit from patient-centred care with an increased understanding of their condition, treatment choices and associated risks – resulting in patients being more involved in the treatment decision-making. Some examples of this are given in Figure 3 below.

Figure 3: Broader benefits of advanced diagnostics to patients, families and carers – examples from a variety of applications

Engaged patients, families and carers	• Being equipped with more specific and accurate diagnostic information, clinicians can make better informed medical decisions in accordance with a patient's own interests and preferences.[15,16] • Diagnostic information can result in earlier diagnosis of acute conditions such as cancer and thus the chance of sequelae with disability.[17] • In some situations, diagnosing a condition may not change treatment choices or drive improved clinical outcomes yet may still provide personal or clinical utility (e.g. prognosis).[18] Diagnostic information may support families' and carers' decisions about family planning, future plans, or end-of-life patient care. • Improved outcomes for patients mean they can potentially make a faster return to their normal lives, including returning to work sooner.

MORE EFFECTIVE AND EFFICIENT HEALTHCARE SYSTEMS

Advanced diagnostics offer vastly increased opportunities for early detection of disease and even prevention and allow clinicians to make more informed decisions about treatment, including faster decisions about appropriate treatment by streamlining (i.e. integrating multiple diagnostic tests into one test) and enhancing diagnosis (i.e. providing information that would not have been accessible otherwise). By current estimates, in vitro testing accounts for less than one percent of healthcare spending yet influences 70% of clinical decisions.[19] This introduces potential savings in healthcare systems due to less inefficiency in healthcare, and supports mapping out multiple lines of treatment in a patient's treatment plan, leading to a reduction in trial-and-error medicine and adverse events, and thus of ineffective spending.

Figure 4: The benefits of genomics testing to healthcare systems and payers – examples from a variety of applications

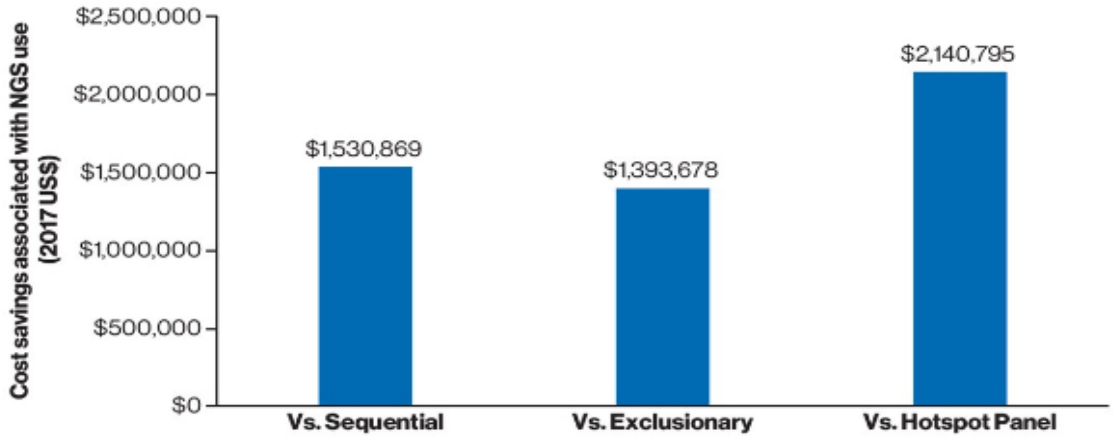
Delivering benefits to healthcare systems, healthcare professionals and payers	• Healthcare professionals and patients both can be involved in treatment decision-making, while healthcare professionals are better equipped to provide patients with more accurate information on their treatment and potential treatment outcomes. This can help determine which patients need medications and which do not, and prevent overtreatment. • The consolidation of genetic testing into a single test enables streamlining and cost offsets whilst the reliability and reproducibility of advanced diagnostics reduces the need for retesting or collection of additional tissue samples, resulting in a faster diagnosis. • Refraining from a 'trial-and-error' approach means less need for additional tests, fewer adverse events, and less dispensing of medicines or other treatments that would have been ineffectual. • Genomics testing has potential to bring both immediate and longer-term cost savings to the healthcare system by reducing ineffective healthcare spending on suboptimal or potentially harmful treatments. It can also reduce inefficient healthcare resource allocation – assigning the right targeted treatment or no treatment to the right patients.[20]

Contrary to some concerns that the vast amount of genetic information would potentially lead to growing downstream costs due to increased healthcare utilisation, research actually shows that uptake of genomic testing is cost saving for diverse patient groups ranging from paediatric patients with rare and undiagnosed genetic diseases to oncological patients.[21,22,23,24,25,26,27]

In oncology alone, it is estimated that as many as 30%–40% of patients receive inefficient treatment.[28] One example of the cost savings that advanced diagnostics can generate can be found with Oncotype DX®, which informs chemotherapy treatment decisions in patients with HR+ (hormone receptor positive), HER2- (human epidermal growth factor receptor 2 negative) invasive breast cancer. Oncotype DX® has been shown to generate cost savings to many healthcare systems in the EU, including in Ireland where a real-world study showed that the net reduction in chemotherapy following its use resulted in a saving of EUR 1,238 per patient.[29,30,31]

A study demonstrating the cost savings associated with NGS is illustrated in Figure 5. This shows that NGS testing generates more cost savings when compared to single gene sequential or exclusionary testing as well as versus hotspot panels (in non-small-cell lung carcinoma, NSCLC).[32] Furthermore, another study conducted in the UK shows that performing panel sequencing, which has an estimated cost of £339 (€395) per patient, is less expensive than performing more than two or three single gene tests, which are estimated to cost between £71 and £141 (€82–€164) per test (depending on the mutation type).[33]

Figure 5: Cost savings associated with NGS use vs other testing strategies in NSCLC (N= 2,066)



Source: Pennell et al,[34] define patients as having received *sequential testing* if they received a sequence of single-gene tests for alterations with FDA-approved therapies (EGFR, ALK, ROS1, and BRAF). See endnote for additional details.[35]

FUTURE PERSPECTIVES – BENEFITS FOR RESEARCH

Advanced diagnostics have facilitated the discovery of numerous genomic predictive biomarkers that are used in today's treatment decision-making, especially in oncology. For example, through NGS, researchers can aim to classify biomarkers to describe solid tumours effectively, which will impact future treatment and prognosis.[36] A good example of such a successful implementation is Myriad's myChoice CDx PLUS assay, used to detect HRD by assessing a genomic instability score and BRCA1 and BRCA2 gene mutations in genomic DNA extracted from tumour specimens. This complex composite biomarker includes a combination of a platinum sensitivity, a genomic scar or mutational signature test and a functional assay to determine the eligibility of patients with breast, ovarian and other cancer types for treatment with PARP inhibitor drugs. Other examples include circulating tumour DNA blood-based biomarkers for the early detection of cancer [37] and the tumour mutational burden (TMB), for which the immunotherapy Pembrolizumab has been FDA-approved for the treatment of adult and paediatric patients with unresectable or metastatic high-TMB (TMB-H) solid tumours.[38]

Outside oncology, advanced diagnostics have also contributed towards the rapid development of the COVID-19 vaccine. Genomic sequencing has helped in determining how quickly the virus is adapting as it spreads, identifying new variants and targets to therapies, and accelerating vaccine development.[39]

These highly complex assays are currently being launched in Europe and are "live" case studies showcasing the ability of European regulatory and healthcare systems to provide swift access to advanced diagnostic technologies alongside those pharmaceuticals receiving a relevant companion diagnostic (CDx) indication.

Figure 6: Benefits of advanced diagnostics in directing future areas of research – examples from a variety of applications

Helps direct future areas of research	• As healthcare systems contribute genomic data to national genomic databanks and biobanks, it will be possible to capitalise on a large and heterogeneous population and achieve the larger samples needed to achieve real breakthroughs in personalised medicine, cancer research, brain-related diseases, etc. This potential further increases with international data sharing. • Advanced diagnostics have enabled the development of novel trial designs, which permit the testing of patients with multiple tumour histologies and/or tumour molecular aberrations. These are also known as master protocols. Both umbrella trials and basket trials fall into this category.[40]

BENEFITS TO SOCIETY AND THE ECONOMY

It is clear that advanced diagnostic technologies represent value to patients and the healthcare system, but this value also extends beyond health budgets. Health and well-being are well known to contribute to economic and social progress; and in turn, economic security and social cohesion are two key determinants of health. This then has a significant positive impact on the economic performance of other sectors in the national economy, through the jobs they generate and from the purchase of goods and services.[41]

There is little evidence on the wider impact of advanced diagnostics in Europe, but according to a US study on the "Economic Impact of the Human Genome Project", the benefits are widespread and increasing over time. The Human Genome Project (HGP) alone has produced 3.8 million job-years of employment in the US, or one job-year for each $1,000 invested.[42] Personal income generated by HGP (wages and benefits) exceeded $244 billion over the time frame, averaging out to $63,700 income per job-year. Back in 2010 (latest figures available), genomics directly supported more than 51,000 jobs in the US, and indirectly supported more than 310,000 jobs, according to the study. This created $20 billion in personal income and added $67 billion to the US economy. There are no equivalent studies in Europe at this time, but the UK government predicts there could be more than 18,000 new jobs created by gene and cell therapy in Britain alone by 2030.[43]

Therefore, investing in genomics will provide benefit to society at large, as a vibrant advanced diagnostic ecosystem will spur innovation in the health sector, especially in biotechnologies and personalised treatments; increase quality of life; and increase educational and employment opportunities – all of which are drivers of growth in countries with mature healthcare systems.[44]

Figure 7: Broader societal and economic benefits of advanced diagnostics

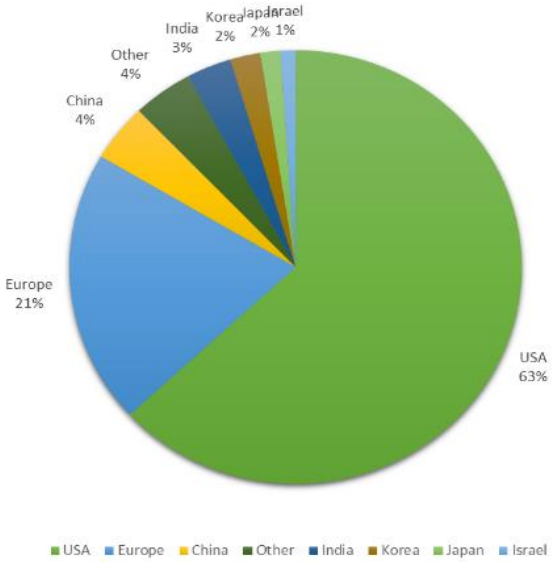
A valuable societal investment	• Timely investment in advanced diagnostics will help attract companies to invest in surrounding infrastructure and lead to the creation of high-value jobs. Initial investments will help attract risk capital to invest in companies that are expanding into or based in the region, and help build a globally relevant workforce. • Data-driven practices can accelerate health delivery and allow better allocation of resources while delivering better health outcomes.[45] Improved outcomes help alleviate the growing burden on social security systems as there is less need for services like disability pensions, while data-driven practices better allow for financial integration across health and social care budgets. • The increased demand for genomic data in healthcare will, if properly supported, lead to the creation of a considerable number of jobs and business opportunities in response to the need for companies that specialise in sequencing, processing, storing, analysing and sharing genomic data.

3. THE IMPORTANCE OF A EUROPEAN ECOSYSTEM FOR DELIVERING THE BENEFITS OF ADVANCED DIAGNOSTICS

Personalised healthcare is centred on a continuous cycle of insight generation, driven by data, technology and advanced analytics, using large-scale datasets supported by technology development in imaging, genomics, and digital health (wearables, apps, etc).[46] Technology and advanced analytics – driven in part by the emergence of genomics – provide the tools needed to derive meaningful, actionable insights from these data. This has, in turn, improved our understanding of cancer biology and opened up new ways of diagnosing and treating many new diseases such as rare cancers.

Despite the involvement of many European universities in scientific breakthroughs, Europe has fallen behind in exploiting the commercial potential of genomics testing and is being outpaced by other regions such as the United States. In the US, demand has led to the emergence of private genetics services that have grown into successful companies by marketing advanced diagnostics. As illustrated in Figure 8, out of the 279 genetics and genomics companies worldwide, over 63% (176) are currently based in the US, compared to 21% located in Europe.

Figure 8: Percentage of genomics companies by location (region/country)



Source: CRA analysis based on listing from biopharmguy

The lack of access to advanced diagnostics in clinical research and clinical practice is leading to a fundamental market failure in a hugely important emergent market sector. This not only results in patients failing to be identified for highly effective targeted therapies but also has important consequences for the overall competitiveness of biopharmaceutical research. There is a lack of resources to prepare countries for the emergence of technologies that identify people with potentially fatal diseases much earlier.

This section identifies some of the key barriers that impede the development and adoption of advanced diagnostics such as comprehensive genomic profiling and, more broadly, NGS-based technologies.

3.1. EUROPEAN R&D ECOSYSTEM FOR ADVANCED DIAGNOSTICS

Europe has top tier universities which contribute to scientific breakthroughs and some of the most advanced scientific knowledge. European universities and local advanced diagnostic companies have benefited from public investment (discussed further below); however, the number of new companies derived from research institutes developing advanced diagnostics remains small. This suggests that more can be done to ensure Europe has an R&D ecosystem that is favourable for advanced diagnostics.

An unfavourable ecosystem in Europe means that the smaller companies being set up are not developing into larger European companies, which prevents the advanced diagnostics industry from establishing in Europe and stymies growth and innovation. Furthermore, this is resulting in Europe's skilled workforce in this field looking to other regions for employment due to limited career prospects. One example of this is Solexa, a spin-out company from Cambridge University in the UK. To gain access to funds, Solexa acquired a San Francisco based US company called Lynx, which then obtained sufficient seed funds to launch the Genome Analyzer.[47] However, Solexa was subsequently purchased by Illumina and was key to

development of the revolutionary sequencing by synthesis (SBS) technology that is the foundation of Illumina sequencing instruments. Illumina now has a market capitalisation of approximately $50 billion. It is an illustrative case of inadequate support or incentives for companies seeking to develop advanced diagnostics and establish themselves in Europe.

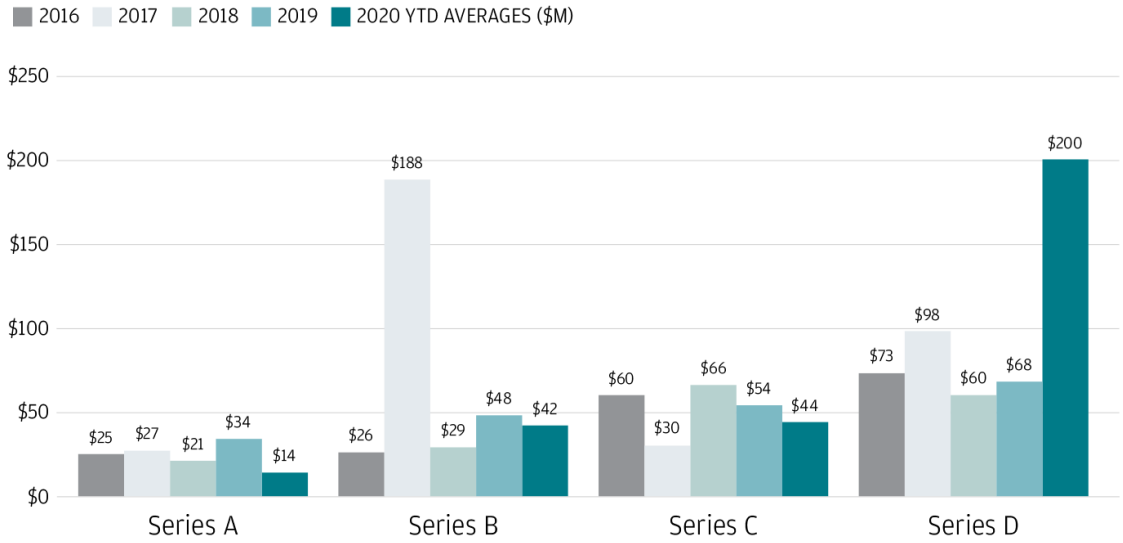
Another example of a European molecular diagnostics company that decided to primarily invest and grow in the US is Agendia, a spin-off of the Netherlands Cancer Institute. One of its products, the MammaPrint test, obtained regulatory approval in 2003 and has been empowering women diagnosed with breast cancer to make informed decisions about whether to undergo systemic (neo)adjuvant therapies ever since. The pivotal randomised clinical trial MINDACT was entirely set up by European physicians, and the study was funded with European sponsorship.[48] However, as US payers recognised the value of the diagnostic test more than their European counterparts, Agendia set up its headquarters in the US, where the majority of its workforce is stationed. This demonstrates the need for European spin-out companies to find the necessary support in their countries of origin, and in turn such companies can support their local economies through high-skilled employment opportunities.

LACK OF ACCESS TO SEED FUNDING AND RISK CAPITAL

Despite European institutions playing an important role in supporting R&D – with one third of the total R&D expenditure in the EU being publicly funded[49] – the EU lags the US in access to capital for seed-stage and early-stage companies. Venture capital (VC) financing as a share of gross domestic product (GDP) is significantly lower in Europe than in the US. Over the last couple of years, VC investments across industries averaged 0.20% of GDP in the US but only 0.03% in the EU.[50] Not only is the absolute size of VC financing in Europe disadvantageous, but so is its composition. The gap is largest for early-stage needs, where only about half as many firms receive VC funding in Europe compared to the US. However, as demonstrated in Figure 9, total venture funds invested in the field has increased in recent years, and the COVID-19 crisis appears to have contributed to more venture capital being invested in the diagnostic space.[51]

Without existing commercialised products, advanced diagnostic companies require capital to develop their technologies; capital is needed to develop the assay and supporting software and to obtain clinical utility data. As a result of limited access to funding and commercialisation potential, seed-stage and early-stage advanced diagnostic companies in Europe are struggling to cope.[52] Companies in the US, on the other hand, have much greater access to capital, which has fostered an entrepreneurial risk-taking spirit and has enabled companies to grow. For example, the pricing of US-based Adaptive Biotechnologies' initial public offering of 15 million shares was $20 per share in June 2019 – resulting in gross proceeds of $300 million.[53] This offering has enabled the company to grow, and the share price to increase by over 130% in the first year of public trading. The problem with a lacking European ecosystem, then, is that technologies initially developed in European labs are commercialised by companies with greater access to US capital markets – often those located outside the EU.

Figure 9: Tools and diagnostics average venture rounds: diagnostics, sequencing, genomics, proteomics, and research tools



Source: J.P Morgan (21 August 2020) – Life Sciences in a Changing World: Startup Outlook Through 2020 – figure based on data from DealForma Database. Updated through July 1, 2020. Series A funding refers to the first venture capital funding received by a start-up company, and which precedes the Series B funding round. As the company grows, it seeks Series B, C and D funding.

COLLABORATIONS WITH ACADEMIA AND OTHER SECTORS

The development of advanced diagnostics is often a collaborative effort. Many advanced diagnostic companies have benefited from the guidance provided by universities, which have developed innovation centres and IP managers to support "bench scientists" in establishing companies to commercialise their research. One successful company to spring from such efforts is Thrive Earlier Detection Corp., which has developed a DNA- and protein-based liquid biopsy test called CancerSEEK, designed to detect multiple cancer types at earlier stages of disease. This technology was discovered by the Vogelstein lab at Johns Hopkins University. The company spun out of Johns Hopkins in 2019 with an initial $110 million in venture capital backing.[54] In October 2020, it was announced that Exact Sciences acquired Thrive for cash and stock consideration of up to $2.15 billion.[55]

Another key driver of growth for advanced diagnostic companies is the extent to which they have benefited from collaborations with other global companies – such as pharmaceutical and technology firms – and from the human capital of high-tech industries, particularly in the specialty of bioinformatics. This has been the case for Guardant Health, which has collaborated with pharmaceutical companies such as Janssen and Amgen to develop a global liquid biopsy companion diagnostic for lung cancer drug amivantamab.[56] In 2018, Adaptive Biotechnologies and Microsoft partnered to create a TCR-Antigen Map, an approach to translating the genetics of the adaptive immune system to understand at scale how it works, and this partnership has been expanded to decode COVID-19.[57]

Such collaboration is also happening in Europe. There are successful examples of emerging advanced diagnostic companies where government investments are supporting the translation of advanced diagnostics into the clinical setting. Through the allocation of government investments to genomics, advanced diagnostic companies have succeeded in attracting capital and developing early commercialisation potential. Countries such as the UK and France have introduced national policies designed to increase investments in genomics and greater diagnostic capacity. The UK launched Genomics England in 2013 and ran the 100,000 Genomes Project, while France launched its public genomics initiative in 2016, saying it would invest €670 million over the first five years.[58,59] Securing government contracts has helped some early companies, such as the British genomics start-up Congenica, to secure risk capital. In October 2018, Genomics England chose Congenica as its Clinical Decision Support Service partner to help deliver the new NHS Genomic Medicine Service, which aims to make genetic testing a routine element of delivering healthcare.[60]

However, the number of successful collaborations is still low, reflecting the smaller number of new companies developing advanced diagnostics in Europe. Furthermore, in order to incentivise innovation, a marketplace is needed where new technologies can be rapidly commercialised and where value is recognised.

Recommendations

Develop an R&D ecosystem for advanced diagnostics: Concerted support is needed from European governments to foster an ecosystem for advanced diagnostics.

- Rationalise funding and provide opportunities for the industry to collaborate with academic institutions and other industries (e.g. biotech and high-tech industries).
- Introduce business incentives (e.g. tax breaks) and develop innovation hubs focused on advanced diagnostics, which would support researchers in starting up companies in the commercialisation process. Such incentives will foster an entrepreneurial risk-taking spirit and enable companies to grow.
- Establish specific funding and risk capital for advanced diagnostics at both EU and national level to facilitate the creation of advanced diagnostic companies at early stage.
- Provide additional tailored funds and tax incentives for the development of cutting-edge products (e.g. genomics or personalised medicine), and public investment to enable technological transformation (e.g. data analytics and digital tools).

3.2. THE REGULATORY FRAMEWORK FOR ADVANCED DIAGNOSTICS

Another key factor in the success and commercialisation of early-stage advanced diagnostic companies is the potential to access the market and generate early revenue. One of the defining aspects of advanced diagnostics is the ongoing development of the technology as usage develops. Only as the number of participating patients increases is it possible to optimise the algorithms which deliver additional value to the patient, the healthcare system and society. The implication of this is that a flexible regulatory approach that

enables early adoption and allows the technology to develop is a key part of the ecosystem for advanced diagnostics.

PRODUCT DEVELOPMENT AND REGULATORY APPROVAL

The European approach to regulating advanced diagnostics is under transition. Through the new In Vitro Diagnostic Regulation (IVDR), a number of qualified notified bodies will carry out conformity assessment procedures and grant conformity certificates for advanced diagnostics. Quite how this will work in practice is still being developed, but it is clear that unlike the approach adopted by Medicare in the US, there will be no direct link between regulatory approval and the reimbursement process. There is also little clarity on whether formal accreditation will result in a more favourable assessment by payers.

In the US, the Clinical Laboratory Improvement Amendments (CLIA) regulate laboratory testing and require clinical laboratories to be certified by the Centers for Medicare & Medicaid Services (CMS) before they can accept human samples for diagnostic testing. The FDA Pre-Submission and the CLIA Waiver pathways are two options that have enabled genomics companies (with a Certificate of Compliance by CMS) to perform high-complexity tests through Medicare without the need for full FDA approval.[61,62] Unlike in the US, there is no single port of call in Europe for advanced diagnostic companies to help develop regulatory strategy and there is no equivalent to the FDA Pre-Submission or the CLIA Waiver pathway. The primary benefit of the CLIA exemption is that it gives a pathologist located in one state the ability to approve tests performed across the whole country.

In Europe, the regulatory framework is more fragmented than in the US, and the lack of harmonisation of standards means that genomics companies do not have the capacity to shift samples across countries easily; i.e. a pathologist localised in the Netherlands would not be able to sign off on reports for German and French samples. Having a single lab in Europe which can approve tests across all 27 EU member states would facilitate access to lab-based commercial genomics testing. As illustrated in Table 1, the new IVDR will bring benefits and challenges for advanced diagnostics. For Europe to be competitive in terms of advanced diagnostics, increased clarity regarding how this will work, and flexible application, will be vital.

Table 1: Benefits and challenges of the new EU In Vitro Diagnostic Regulation (IVDR)

Key benefits of the new IVDR	Key challenges with the new IVDR
• **Private–public partnerships**: The new IVDR provides greater private–public partnership opportunities, as it is unlikely that public labs will meet the data requirements stipulated by the IVDR. • **Develop quality standards to ensure patient safety:** Through the new IVDR new harmonised standards will be developed, which manufacturers would need to comply with[63] • **External experts or subcontractors**: The IVDR will enable notified bodies to utilise external experts or subcontractors for certain activities, such as for conformity assessment.[64] However, the notified body needs to have permanently available personnel who are able to assess the manufacturer's performance and make a clinical judgement.	• **Increase in the evidence requirements**: There are concerns that through the new IVDR, companies will be required to produce more extensive evidence to have a product on the market. • **Exemptions**: The IVDR differentiates between commercial assays and in-house tests and provides some exemptions to in-house tests (through Article 5.5). However, a Guidance on in-house testing and the criteria that will be used to grant these exemptions have not been published yet.[65]

PUBLIC ACCEPTABILITY AND LEGAL UNCERTAINTIES

A person's genetic and genomic data represent the most private information about the past, present and future of the individual. Keeping this information safe and confidential is of the utmost importance, and research groups, companies and governments must facilitate data access while ensuring it does not end up in the wrong hands.

Currently, the European regulatory framework is not well adapted to enable citizens to control the use of their information or to freely share their genomic data with either individual companies or institutes of research. In the EU, data management is covered and protected through the General Data Protection Regulation (GDPR), which provides protection for "natural persons" regarding the processing of personal data and the free movement of such data.[66] However, the GDPR allows Member States to implement variations and sets out the requirements to comply with EU or Member State law.[67] Because of this, patient consents are not harmonised across European Member States, and thus it is difficult to merge European datasets and to access critical data. Europe needs a solid legal framework on data ownership and data usability – that provides a simple and convenient enrolment process.[68] Additionally, European citizens must be fully informed about all aspects of genomic sequencing, including its benefits and implications.

Recommendations

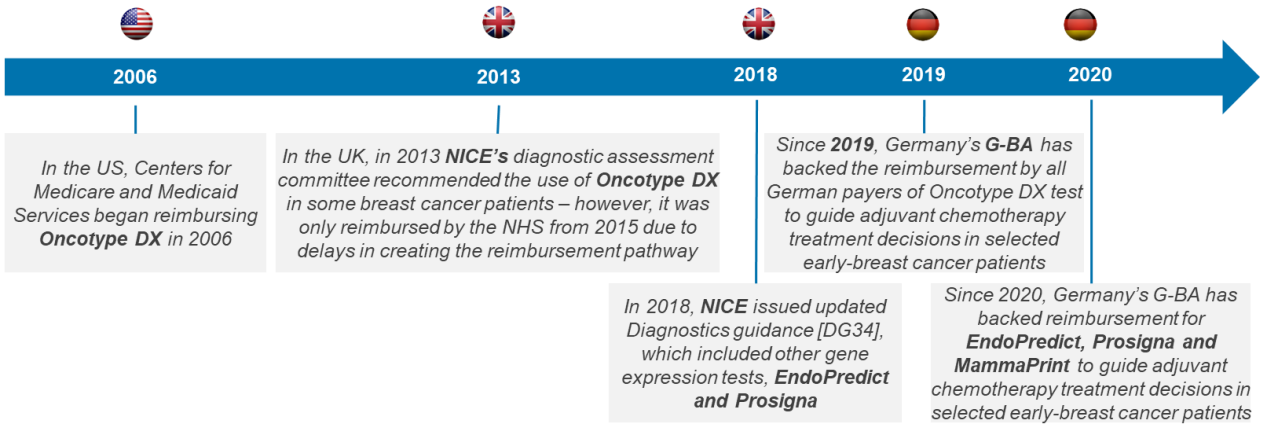
- Regulatory bodies should provide more dialogue opportunities, so advanced diagnostic companies can obtain guidance on the regulatory pathways available and on early evidence generation, which in turn will enable manufacturers to shape studies to meet regulators' evidence requirements.
- An ISO standard specific to advanced diagnostic laboratories should be established, and external quality assessment (EQA) schemes set up, to ensure that the operating laboratories meet certain performance standards.
- More legal clarity needs to be provided on data ownership and data usability – and the code of conduct needs to have the same legal interpretation of the GDPR across Member States.
- Future regulatory frameworks should allow the flexibility to accommodate product improvements with NGS test panels by including the most up-to-date scientific knowledge, while ensuring that the tests are safe, effective and accurate, with timely access provided to patients – and the feedback of advanced diagnostic companies should be taken into account in the development of regulatory frameworks.

3.3. COMMERCIALISATION, REIMBURSEMENT AND FUNDING OF ADVANCED DIAGNOSTICS

Ultimately, a commercial market is needed in order to incentivise the development and delivery of genomic tests. The lack of clarity regarding regulatory pathways and the prospect for appropriate reimbursement is a significant barrier to commercialisation in Europe.[69] While some countries, such as the US, have developed a reimbursement system designed to accommodate "value-priced" diagnostic tests, in Europe, by contrast, reimbursement of advanced diagnostic tests mostly relies on non-specific hospital funding ("DRG-type") or a centralised limited fund.

Advanced diagnostic manufacturers are facing significant market access barriers in Europe; a typical example of this is illustrated in Figure 10. Europe's reimbursement and funding models – which have generally been slow to adapt to advanced diagnostics and rely on pharmaceutical companies paying for precision tests[70] – are resulting in patients having access to advanced diagnostics technologies through the public healthcare system with a 5-to-10-year delay from initial launch. In the example of Figure 10, it took seven years from US to EU first reimbursement, with a still-evolving landscape in Europe after 15 years.

Figure 10: Market access timeline for gene expression testing for breast cancer (e.g. Oncotype Dx, EndoPredict, Prosigna and MammaPrint)

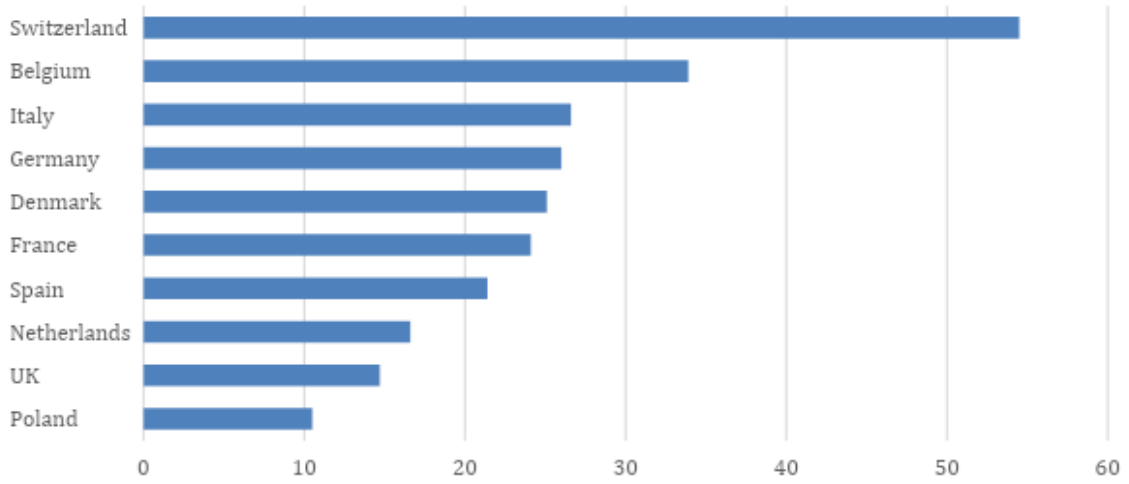


Source: CRA analysis based on multiple sources[71,72,73] (NICE = The National Institute for Health and Care Excellence. NHS = National Health Service. G-BA = Federal Joint Committee, Germany)

While some countries provide faster reimbursement to diagnostics, other countries experience reimbursement challenges. For example, at the end of 2020, the reimbursement authorities in Germany removed the *prior authorisation* requirements on the national reimbursement codes for CGP, WES and WGS, allowing more flexibility in the reimbursement process.[74] This has contributed to some German health insurers (e.g. Barmer, AOK) starting to cover WES and WGS as part of their reimbursement policies, demonstrating payers' confidence in the need to reimburse genomic tests to drive patient access to advanced diagnostics in the clinical setting.[75,76] However, there still exist key market access challenges in other markets, and such challenges are associated with variation in approaches for assessment and reimbursement across and within Member States (national vs regional); the general lack of linkage between assessments and decision-making; and the lack of established clear processes for reimbursement, funding and uptake of diagnostic innovation.

Furthermore, advanced diagnostics face funding challenges, with the budgets set aside often a fraction of what is required. This is illustrated by the difference in levels of investment by countries. Figure 11 highlights the per capita expenditure on in vitro diagnostics (IVD) across selected countries in Europe; there is a wide variation across countries, from a low of €10.5 in Poland, to €14.7 in the UK, to the highest, €54.5, in Switzerland. However, these figures exclude government investments towards national programmes such as Genomics England and Germany's genomDE.[77] The way diagnostics are funded varies depending on the therapy area and the country.

Figure 11: Per capita expenditure on in vitro diagnostics (€) (2019)



Source: MedTech Europe,[78] where France data includes only the Central Laboratory IVD Market, and UK data reflects the consolidated sales of the participating companies in Global Diagnostic Market Statistics (GDMS), plus the figures published by NHS England for glucose test strip sales adjusted to represent the whole of the UK.

Key to enabling further competition and more flexible development of publicly owned services is ensuring that funding for advanced diagnostic tests is available, and that it can be effectively accessed by providers, and implemented in a similar time frame to that of access to medicines. Both centralised funding and a tariff-based approach have a role. As we move to genetic profiling or WGS, the funding model needs to take into account the required investment in infrastructure and capacity development, as well as the need to encourage competition between diagnostic providers.

Recommendations

Develop a clear pathway to fast and efficient reimbursement: European governments should provide a clear reimbursement pathway for commercial advanced diagnostic tests.

- Ensure faster access to market via innovative reimbursement mechanisms: To ensure timelier patient access and allow for an accurate evaluation of the value in clinical practice, positive diagnostic appraisals should lead to automatic funding within a stipulated time frame (akin to the EU Transparency Directive introduced for pharmaceutical reimbursement) and payers should be more willing to utilise novel reiterative reimbursement models that reward value.
- Continue developing dedicated funding pathways to ensure access to diagnostics. This can be facilitated through sharing best practices on how to fund different types of diagnostics and ensure high levels of access. Both centralised funding and a tariff-based approach have a role. This should consider alternative funding mechanisms for advanced diagnostics, such as lump sum or budgetary funding for diagnostic services, in order to address long-term funding sustainability.

- Participate in European-level discussions on how to improve access to advanced diagnostics. Public and private bodies can discuss the importance of patients in Europe having access to advanced diagnostics. This dialogue can be facilitated through EU-level initiatives, such as the European Partnerships in Horizon Europe.
- Make the significant investment needed to scale up programmes – including the adaptation of early access programmes to accommodate the use of companion diagnostics and advanced diagnostics. This should aim to speed up access to diagnostics and increase diagnostic capacity to support the broader needs of the population.

3.4. CHALLENGES IN VALUE ASSESSMENT

Widespread insurance coverage requires evidence that demonstrates value, with streamlined ways to validate tests using standardised criteria and procedures across the EU. The value assessment mechanism as part of the reimbursement pathway, however, remains a major hurdle since it often involves not-fit-for-purpose evidence requirements, with added complexity and costs for developers seeking to generate necessary clinical validation data. The lack of sufficient clarity on appropriate reimbursement pathways makes it challenging to develop the appropriate evidence and harder to justify the required level of investment.

In comparable markets, such as the US, payers' prior assessment frameworks have been identified as unsuitable for evaluating advanced diagnostics, and a subset of Medicare providers have explored partnerships with private bodies that are specifically equipped to assess such technologies. As a result, an external company (Palmetto GBA) was commissioned to establish a framework able to assess the clinical utility of genomics tests.[79] Palmetto GBA then developed the MoIDX framework, which establishes the clinical utility; conducts the technical assessments; and establishes reimbursement of new molecular diagnostics – and this is utilised by a number of Medicare Jurisdictions.[80] In order to establish a product's clinical utility, MoIDX does not require manufacturers to conduct a randomised controlled trial (RCT) for each product and each indication. This initiative ensures that Medicare patients obtain access to these technologies quicker and that advanced diagnostic companies are provided with clear guidance on the required evidence in order for the product to be reimbursed.

While the tailored framework has allowed faster patient access and helped increase investor confidence, the US has also been receptive to experimenting with novel reimbursement models through which real-world evidence (RWE) can be collected as part of an iterative process. For example, US public payer Medicare issues national coverage decisions (NCDs) with or without evidence development requirements for NGS cancer tests that are approved by the FDA as a "companion" IVD device and those that are used for planning treatment for patients with "recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer".[81] Another landmark risk-sharing agreement was negotiated between UnitedHealthcare and Genomic Health in 2007 that allowed Oncotype DX to be reimbursed at a predetermined price. If too many women were still receiving chemotherapy despite low-risk scores, however, UnitedHealthcare retained the option to reopen the contract at a lower price.[82] More recently, Harvard Pilgrim Health Care and Illumina

negotiated a value-based agreement for NGS for non-invasive prenatal testing (NIPT) in 2018 and for WGS in 2020.[83,84]

In Europe, there are some initiatives aiming to introduce value-based public sector pricing for advanced diagnostics (such as the RIHN in France and the GGG program in the Netherlands).[85,86] However, where such procedurally based pricing currently exists, it is not administered effectively, and this is at times due to the complex network of largely decentralised bodies. In the absence of clarity on evidence requirements, patient access to advanced diagnostics remains limited, and health-economic savings are not realised.

Recommendations

- Reimbursement frameworks need to be adapted to ensure they can appropriately evaluate new advanced diagnostics: A framework should be developed and implemented that can be used to evaluate the analytical and clinical evidence of advanced diagnostics and that can capture the dynamic nature of their value. To achieve this, novel elements of clinical utility, including personal utility, need to be considered for advanced diagnostics.
- A value assessment framework should be created that is fit to assess advanced diagnostics: This should be able to evaluate various types of evidence and incorporate various stakeholders (including physicians, patients and the manufacturer's representatives) in the assessment process. Furthermore, the professionals conducting the assessment should have no conflicts of interest.
- Greater collaboration is needed between public and private on value assessment of advanced diagnostics: More flexibility for public and private bodies to collaborate on the value assessment of advanced diagnostics is necessary to ensure that the assessment frameworks reflect the latest scientific advancements.
- HTA bodies should acknowledge the challenges of implementing traditional study designs for advanced diagnostics – as they are not fit for these technologies – and accept novel study designs (e.g. basket trials, umbrella trials, and retrospective studies) that demonstrate the clinical utility of advanced diagnostics and prioritise timely patient access.

3.5. UPTAKE OF DIAGNOSTICS

If Europe invests in an ecosystem that fosters advanced diagnostics and develops clear regulatory and reimbursement pathways, their utilisation in the research and clinical setting will increase, and patients, clinicians and healthcare systems will experience the broader benefits of these tests.

LACK OF INFRASTRUCTURE, DIGITALISATION AND WORKFORCE CAPACITY

Unlike other diagnostic tests, advanced diagnostics necessitate dedicated infrastructure and qualified personnel to ensure their reliable clinical execution and interpretation. Thus, to further the uptake of advanced diagnostics, healthcare systems need to invest in their laboratory and analytic services in addition to their infrastructure, which would need to facilitate data capture and electronic health records.[87,88]

In Europe, genomic tests have traditionally been performed in public laboratories within hospitals, limited to the research setting, and largely focused on oncology – and it is only recently that decision makers have begun considering commercial tests. With a rapidly growing number of advanced diagnostic tests available to patients, serious consideration needs to be given to ensure a robust and healthy diagnostics ecosystem in Europe that allows innovators to thrive. The infrastructure to support sequencing on a large scale is still being built, while basic supporting digital infrastructure such as electronic health records is severely limited across European healthcare systems. There is furthermore a lack of bioinformatics infrastructure and computational tools needed to interpret sequencing results, including data storage and periodic re-evaluation of incidental findings that may attain clinical relevance over time.

Private–public partnerships can enable faster adoption of advanced diagnostics in the clinical setting. For example, Genomics England has recently created an interface and in-depth collaboration between NHS commissioning and technology companies. There are many examples of this in Europe.

Genomics England has partnered with Illumina to ensure its WGS targets are met. In January 2020, Genomics England and Illumina announced a new agreement to deliver up to 300,000 whole genome equivalents over the next five years, with an option to increase to 500,000.[89] Samples will be provided through the NHS Genomic Medicine Service and the network of seven genomic laboratory hubs across England, which were established in 2018.[90] The Genomics England Clinical Interpretation Partnership (GeCIP) Domains are UK-led consortia of researchers, clinicians and trainees which work on improving the clinical application and interpretation of the data in the 100,000 Genomes Project.[91]

Similarly, a leading precision oncology company, Guardant Health, has recently entered into a partnership with the Vall d'Hebron Institute of Oncology (VHIO) in Barcelona, Spain, to establish the first Guardant-based liquid biopsy testing service in Europe. The opening of this service is expected to significantly increase the number of cancer patients identified as eligible for clinical trials based on available precision medicines and help accelerate research and development of the next wave of cancer therapeutics.[92]

Recommendations

Integrate advanced diagnostics into clinical practice: A coherent strategy for personalised medicines should articulate the approach to disease profiling and consider the integration of advanced diagnostics into clinical practice.

- Investment in private–public partnerships is needed to enable the faster adoption of advanced diagnostics in the clinical setting: Private–public partnerships lead to better communication and data sharing between the industry, genomic centres, and clinics.
- Health systems should invest in infrastructure, centralised laboratories and appropriate and up-to-date Dx training for healthcare professionals.
- The strategy should both facilitate the uptake of home-brewed diagnostics – those developed in individual laboratories – and integrate the latest advances in commercial diagnostics technologies. It should include a model which seeks to establish partnerships with leading advanced diagnostics providers, wherever they are in the world, and then partners with them to bring the technologies into the region and countries both at development and at commercial stages

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