Bringing onco-innovation to Europe's healthcare systems: the unexploited potential of biomarker testing, real world evidence and the potential of Tumour Agnostics. The lesson from *BRCA1/2* genetic testing

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Abstract

Rapid and continuing advances in biomarker testing are not being matched by take-up in health systems, and this is hampering both patient care and innovation. It also risks costing health systems the opportunity to make their services more efficient and, over time, more economical. The potential that genomics has brought to biomarker testing in diagnosis, prediction and research is being realised, pre-eminently in many cancers, but also in an ever-wider range of conditions. One of the paradigmatic examples is *BRCA1/2* testing in ovarian, breast, pancreatic and prostate cancers. Nevertheless, the implementation of genetic testing in clinical routine setting is still challenging. Also for BRCA testing there is a great country-dependent heterogeneity. In fact, development is impeded by data deficiencies, and lack of policy alignment on standards, approval – and the role of real-world evidence in the process - and reimbursement. The acute nature of the problem is compellingly illustrated by the particular challenges facing the development and use of tumour agnostic therapies, where the gaps in preparedness for taking advantage of this innovative approach to cancer therapy are sharply exposed. Europe should already have in place a guarantee of universal access to a minimum suite of biomarker tests and should be planning for an optimum testing scenario with a wider range of biomarker tests integrated into a more sophisticated health system articulated around personalised medicine. Improving healthcare and winning advantages for Europe's industrial competitiveness and innovation require an appropriate policy framework – starting with an update to outdated recommendations.

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Introduction: Healthcare efficiencies

Europe is missing out on major opportunities. The rapid growth in the availability of biomarker testing based on molecular diagnostics has made it possible to improve European citizens' health. Widespread adoption would support continued improvements in outcomes for diseases, already for cancer, and increasingly across a wide range of conditions. And the prospects are even more attractive if the development and deployment of more sophisticated biomarkers is encouraged. This would open the path to exploiting the new possibilities of tumour agnostic therapies - and would drive the evolution of much-needed debate and definition of the role of real-world evidence. The impact on patients' health would be more informed treatment decisions and increased access to targeted treatments, with improved outcomes. The impact on health systems would be the better deployment of resources that precision medicine allows. [1]

Minimum and optimum testing

The short-term need is for the provision of a regime of high-quality minimum biomarker testing across the EU. This would be an "essential package" of tests offered to all EU patients for diagnosis and prevention, detailing the type, the technique and the methods of implementation, and ensuring access to testing in time to inform treatment decisions. This would be backed by clarity over reimbursement, and up-to-date testing guidance to clinicians. Consistent access would be guaranteed for cancer patients to clinically meaningful testing results based on long-term validated biomarkers such as EGFR, HER2, and ALK. [2]

Further ahead, in an optimum biomarker-testing scenario, excellent clinical teams all over Europe would deliver a high standard of care for every patient with cancer, and increasingly for patients with other conditions. Complex multi-modality teams of experts, adequately trained in molecular diagnostics, would be the norm to allow effective decision making as more information and more biomarkers become available. Pan-cancer studies would operate on the basis of standardized data between multiple platforms, with agreed criteria among different groups of researchers to work on the data and present the results. Registries, with opt-in and-out criteria for each disease area would provide more robust data sets – including the patient's disease history, outcomes, treatments and genomic aspects, and information on the use of biomarker tests themselves, such as how often and on which patients. [3] Fuller use of real-world evidence would support the acceptance of valuable new biomarkers. And prospects would mature for wider endorsement of – and engagement with – tumour agnostic therapies, where genomic data would allow a focus on specific anomalies or molecular features regardless of the tumour site of origin, rather than dependence on histological data.

In both paradigms, the aim is to secure the best standard of care for patients. Even the minimum scenario presupposes readiness to overcome the objective limitations of resources, capital (human, financial, infrastructure etc.) from country to country, region to region, even hospital to hospital. And a situation where these limitations were no longer the principal issue would be the optimum scenario. The longer-range question is how willingly – and how soon - the EU will embrace an optimum biomarker scenario. This will require not only adequate resources but also political will to be deployed. [4]

Gaps, and need for action.

At present, progress is impeded by a wide range of barriers.

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Although the scientific community has risen well to the innate scientific challenges of developing sophisticated biomarkers, their deployment still faces many operational barriers in outdated regulations, inadequate infrastructure for data collection and laboratory analysis, insufficient training of healthcare professionals, and fragmented approval and funding systems. There are wide variations in provision across technologies, disease areas, and patient populations across Europe. Europe's apparatus for product approval of biomarkers is under-developed, lacking the clearer procedures – and related support – for obtaining drug approvals. While the number and complexity of available tests continues to increase, inconsistency persists among evidence frameworks for diagnostics, and among standards for demonstrating clinical utility, which has the effect of perpetuating inconsistency and uncertainty on reimbursement arrangements.

There is insufficient familiarity in health systems with complex testing systems. Reimbursement of biomarker tests that are matched to treatments with positive clinical trial data, or for patients with single mutations, is often easier because of the link to a single medicine. In these cases, it is clear that performing the biomarker test is useful and provides access to treatment that improves a patient's chance for survival and quality of life. The problem arises when health systems need to be able to assess value in more complex testing services, such as testing for biomarkers that look at monitoring disease or patients' health, that prognose for future disease progression or that predict whether a patient will have an adverse reaction to a medicine. And even then, reimbursement remains a challenge. There are Europe-wide variations in the levels of background knowledge and literacy on biomarker education, as well as learning motivation, across stakeholders and geographical regions. There is a lack of understanding of the value of the information delivered by biomarker testing due to knowledge gaps across stakeholder groups and unbalanced knowledge across disease areas. And there is a general requirement in most countries and regions that new tests save costs, rather than a general prevailing view that cost effectiveness is a more appropriate metric of value. [5]

The uncertainty on access, funding and uptake of biomarkers based on molecular diagnostics has a direct negative influence on investment decisions, further hampering progress and the integration of innovation. The disproportion of attention is striking: diagnostics account for less than 2% of total healthcare spending – but they influence 60% of clinical decision making. Current policy in Europe -and particularly in respect of reimbursement - fails to take this into account, and urgently needs updating.
Upcoming EU policy changes. [6]

It is not just the coronavirus pandemic that has given new prominence to health in EU policy – although it has imparted additional impetus. Already the EU was conscious of the twin perils of sub-optimal health services becoming unsustainable in the face of demographic change and spiralling chronic disease, and of the EU losing out at world level to scientific innovation, on which its prosperity largely depends.

This is why the inception of the twenties has seen EU plans for a Cancer Mission, [7] a Beating Cancer plan, a European Health Data Space [8] fed by high volumes of new data drawn from the growing availability of real world evidence and by early signs of readiness of national health data organisations to exchange information, and by the promise of a new EU pharmaceutical strategy by the end of 2020. These initiatives – now complemented by the urgent and heavily-funded search for vaccines and treatments to counter Covid-19 – will depend heavily for their success on the extent to which sensitive and sophisticated testing is available – in other words, for greater use of biomarkers.

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Tumour-agnostic therapies

These potentially game-changing therapies constitute a paradigm shift in how oncology patients are diagnosed and treated, superseding the traditional “one size fits all” approach. Products with tumour-agnostic approval are already a reality, marking a concrete step towards precision medicine. But they present a challenge for regulators, health technology assessment bodies and payers because of the new complexities of identifying and demonstrating effectiveness in what have until now been largely unexplored avenues of evidence generation, with a dependence on still-unfamiliar approaches such as basket trials and innovative methods such as optimized diagnostic algorithms. The advent of these therapies has also thrown a sharper light on the urgency of reaching wider understanding of the potential of and the requirements for real-word evidence.

Need for updating 2003 Recommendations.

Nearly two decades have passed since the emergence in 2003 of EU recommendations relating to early diagnosis and screening, and in that time the possibilities for better and more interventive healthcare have increased dramatically. But the operating context – for physicians and specialists, for researchers and innovators, and for regulators and payers – remains influenced by obsolete thinking. There is an urgent need for updating to take account of progress over the intervening years and the prospects of greater advances in coming years if the operating climate is conducive rather than restrictive.

Biomarkers in action: clinical use cases

It is in oncology that biomarker testing has made its most progress to date, and is proving its worth in breast, ovarian, prostate, lung, thyroid and colon cancers, as well as more generally.

In breast cancer, testing of tumour biopsy now makes it possible to identify certain mutations that drive treatment resistance This already permits better risk assessment of patients, and also assists the search for therapies that specifically target these mutations, so that testing can then help guide treatment decisions. [9]

In ovarian cancer - the deadliest gynaecological cancer – the presence of germline mutations in genes such as *BRCA1 and BRCA2* may also support identification of potentially at-risk family members through cascade testing, or the offer of germline testing to the direct family members of a positive patient. [10] HRD testing, which incorporates new genomic instability assessment algorithms, offers the opportunity to enhance the utility for BRCA testing in ovarian, breast, pancreatic and other cancers. Nevertheless, the implementation of genetic testing in clinical routine setting is still challenging. Also for BRCA testing there is a great country-dependent heterogeneity, needing a urgent process of harmonization world-wide.

Multi-gene expression profiling can prognose outcomes in early-stage breast cancer, and the aggressiveness of prostate cancer, informing decisions over chemotherapy, radiotherapy or surgery. This can support clinical decision making in patients with early stage breast cancer who may require adjuvant chemotherapy, in whom standard of diagnostic care yields an indeterminate prognosis. And in prostate cancer, it can support clinical decision making in patients with indeterminate risk based on other testing data.

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In non-small cell lung cancer, the current range of tests for mutations identifies patients that are eligible for targeted therapies. And a wide range of possibilities are emerging for biomarker testing in defining lung cancer options, ranging from optimized image-based screening to the use of autoantibodies or other circulating biomarkers such as microRNAs and protein panels. [11]

Molecular testing for colorectal cancer helps to guide decisions, adapting treatment to targeted therapies to reduce the risk of disease progression or death. In thyroid cancer, knowing the oncogenic molecular driver helps to determine the aggressiveness of the tumour and/or to identify the most appropriate systemic or targeted therapy.

Across the entire range of cancer – 'pan-cancer' – there is also rich potential in the integration of molecular information, identifying actionable mutations with broad molecular profiling, matching the right targeted therapy to the detected actionable mutation, and evaluating treatment outcome. Applications combining testing using next generation sequencing with artificial intelligence and machine learning may ultimately help chart entire clinical pathways.

Potential solutions

The list of deficiencies and barriers to exploiting the potential of biomarkers is long, but so too is the list of solutions that are already available – or should be.

Many of the issues relating to funding can be solved with only marginal adjustments to healthcare funding. European health authorities should put in place a policy framework to support diagnostics in the EU by 2022, with a ring-fenced budget allowance for biomarker testing development and clinical validation. Research on biomarkers discovery and early testing should benefit from policies that promote investment and funding. What is currently missing for innovative diagnostic technologies is a dedicated and specific reimbursement pathway, on the basis of the value of information delivered, implemented consistently across Europe. Models of well-evolved HTA mechanisms – if connected to a reimbursement decision - would inspire other countries without relevant structures [12]. In such a system, decision makers, including HTA bodies informed by input from patients, would define evidentiary standards for diagnostics and would commit to pay for products that met them. [13]

Much of this can be achieved by more effective collaboration. The EU should agree by 2023 a business model for public-private cooperation for optimal biomarker testing available across the EU, based on a recognition of the business and value case to provide infrastructure to meet testing requirements. This would make it possible to build the evidence base on biomarker testing, and define how this is accessed, such as on a pan-cancer registry across the EU.

Since data collection, data quality, data standards and data interoperability are notoriously deficient in many of Europe's health and research systems, with frequently incomplete, non-standardised, retrospective, non-accessible and siloed methods, health authorities should provide guidelines on how clinically-relevant biomarkers should be measured and reported. Member states should agree on a federated structure of national databases, and regulatory barriers to data transmission and the transport of human samples should be eased to permit large international multi-centre clinical validation studies of biomarkers (especially early diagnostic and prognostic biomarkers), which require large and long-lasting cohorts.

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The EU should establish a framework for quality of testing and value of diagnostics information. Testing data should come from standardised laboratories where samples are collected, transported stabilised and stored under standardised conditions and include sample metadata on the complete preanalytical phase. This way the data can be compared and analysed as it is not polluted with irreproducible and or unusable data for further analysis. This would facilitate centralised and standardised registries of diagnosis including sequence and biomarker data, pre- analytical sample metadata, and treatment and outcome data. It would feed into a fast track approval mechanism for biomarker validation, accompanied by guidance on minimal testing standards and resource allocation. [14]

Clarity for clinicians on where and when tests should be performed should be provided, within a system capable of allowing for evolving testing needs and permitting new tests to be rapidly made available to patients. In a virtuous feedback loop, the captured testing data would inform service improvement, benchmarking and research. The clinical infrastructure would turn fit-for-purpose real world data into real world evidence to help close evidence gaps, overcoming the deficiencies of existing datasets, Global or even pan European pan-cancer registry could demonstrate the insights possible from a large data set of high quality and provide valuable learning on what is needed to share data across borders [15].

Collaboration also would have to be systemised to provide for the engagement of multiple specialties in shifting testing objectives from risk assessment to informing treatment decisions, with drug and diagnostic developers, clinicians, biologists, biostatisticians and digital technology groups routinely cooperating on studies. Member states should promote engagement between payer organizations, biomarker developers and the wider healthcare stakeholder community, through vertical and horizontal integration, and member states should ensure that new validated biomarker tests are rapidly made available to patients without unrealistic evidentiary burdens being imposed by regulators.

There are opportunities still to be explored – such as providing simpler testing kits for complex conditions, and notably the development of blood biopsy, or the convergence of complex test offerings with predictive protein-, genetic-, epigenetic-based biomarkers or NGS panels, or the development of predictive potential of prognostic tests (effectively as companion diagnostics) with emerging drugs. [16]

The particular challenges of tumour agnostic therapies

The catalogue of gaps and possible solutions in biomarker testing and evidence generation applies with added intensity to tumour agnostic therapies (TAx), also known as histology-independent therapies, and an important emerging subcategory of personalised healthcare. These represent a new way of thinking about how cancer is treated, markedly different from how treatment plans have been developed in the past. and are seen as representing a new era in patient care and drug development. They are distinct from conventional anti-cancer treatments, in that they target cancer based on specific genomic or molecular alterations of cancer cells rather the tissue of origin. As such, the same drug has potential to be used to treat various unique types of cancer, included very rare tumours, as long as the common biomarker targeted by the drug is present. These potentially game-changing therapies constitute a paradigm shift in how oncology patients are diagnosed and treated, moving away from the traditional “one size fits all” approach.

Trials of TAx differ from traditional anti-cancer trials, especially in the assessment of tumour-agnostic drugs for rare and ultra-rare populations, and this limits the possibility of generating comparative evidence. In tumour types where the genomic alteration targeted has a very

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low prevalence, RCTs are often not possible. In addition, low patient numbers for single tumour entities with the specific biomarker mean that statistical proof of effect and estimation of between-tumour heterogeneity are challenging. Also, given the heterogeneity of the target population, it is very difficult to identify a clear standard of care to serve as an appropriate comparator.

The basis of approval for these products is a biomarker present across many tumour types, and biomarkers that measure response, establishing the effects of context, and deciphering mechanisms of treatment resistance across a variety of tumour types. [17]

The difficulties assessing treatments designed to respond to unmet clinical need in patients with rare or ultrarare diseases are multiplied in the case of TAx. Regulatory bodies have implemented flexible approaches to regulatory approval, providing options to accelerate the regulatory review process for many orphan or other rare disease treatments, notably through adaptive pathways. These adaptive pathways and their application have also been considered for TAx in some contexts.

Because of the intrinsic difficulties in demonstrating effectiveness in the small target populations currently typical of advances in TAx, evidence in submissions for product approval has been derived in many cases from the use of basket trials. By focusing on specific molecular features regardless of tumour type, these trials can broaden the target patient population and include niche and rare cancers that are often underrepresented in traditional clinical trials. But while basket trials benefit from relatively small sample sizes and can offer early evidence of clinical activity by focusing on tumour response end points, they are typically early phase, single-arm studies, owing in part to the challenge in defining appropriate controls across disparate tumour types. [18]

Nonetheless, the EMA and the FDA have considered that a high response rate with a long duration of response in a basket trial can be enough to support a histology independent cancer drug's efficacy. While regulatory agencies are demonstrating openness to an approach that recognises the histologically independent nature of these therapies and the associated evidence challenges, it is anticipated that current approaches to value assessment and the diagnostic infrastructure are not fully adequate for this, and new approaches have not yet been broadly validated. HTA bodies are increasingly confronted with large uncertainty in the evidence base available to inform coverage and reimbursement decisions.

Surveying national attitudes to TAx

An extensive survey of attitudes among clinicians, regulators and academics in several leading countries revealed just how wide-ranging the challenges to exploiting TAx are. The study focused on the challenges faced by all stakeholders when assessing their value, but identified issues along the pathway from regulatory approval to HTA and reimbursement decisions, as well as potential opportunities to overcome barriers. Respondents were quizzed for their views on general awareness of TAx beyond specialist oncologists, researchers and academics, on the role of manufacturers in increasing awareness, and on cooperation between regulators and national HTA to align on support for innovation and faster patient access to TAx.

The survey assessed national acceptability of basket trials for HTA, for therapies in general, and specifically in the case of TAx. For TAx, questions related to how far HTA recommendations included efficacy endpoints beyond overall survival, such as quality of life

or clearly measurable biomarkers, such as the size of tumour; and whether HTA agencies should accept evidence from uncontrolled, multicentre, open-label, single arm clinical trials.

It explored healthcare system reliance on post-authorisation evidence generation to facilitate patient access to histology independent cancer drugs, the existence of dedicated HTA pathways for specialised, innovative technologies like TAx, national readiness to grant conditional patient access until a final recommendation is made on the basis of further evidence is available (such as after the finalisation of post authorisation studies, or through the UK Cancer Drugs Fund, and opportunities for conditional reimbursement arrangements, in general, and specifically for TAx.

On testing, the survey inquired into whether routine availability of diagnostic tests - such as broad panel NGS - is considered a prerequisite for TAx, and whether mechanisms for reimbursement of diagnostic tests (such as broad panel NGS or WGS) should be separate from HTA / reimbursement assessments of TAx.

Frequently mentioned barriers to assessing TAx included the lack of comparative effectiveness, poorly characterized prognostic value of the genomic alteration defining the tumour-agnostic approach, and limited knowledge on natural history of identified patients' populations. Lack of clarity in the diagnosis pathway, the use of surrogate endpoints (without evidence on the drug's efficacy on progression-free survival and overall survival), inappropriate design and low prevalence / low number of patients enrolled in studies, often with heterogeneity of previous treatment, were also highlighted. The innate complexity of the healthcare sector and lack of appropriate regulation were seen as further obstacles.

The survey detected some willingness to create alignment between regulators and HTA bodies in terms of evidence sources, endpoint requirements and acceptability of relevant post-authorisation data collection models, but there was wide recognition of a lack of consensus over priorities. There appears at present little common ground on the potentially influential factors to improve the situation – across a range that runs from government support to adequate infrastructure, via involvement of key stakeholder groups, increased awareness and understanding of TAx, and adaptive HTA processes. Crucially, there is currently only little movement to create alignment between regulators and HTA bodies in terms of evidence sources, endpoint requirements and acceptability of relevant post authorisation data collection models. And readiness in principle to evolve managed entry agreements beyond discounts is not widely matched by corresponding action. Similarly, appropriate diagnostic and data infrastructure is not available everywhere, and is not a priority everywhere.

From the UK, some serious gaps were reported – including "a disconnect between regulators, who are thinking and evolving, and HTA, who are slow behind the curve", lacking awareness of basket trials, "and are not adapting as quickly." This is compounded by the perception that "there's little willingness to make this evolution really happen", with "a general reluctance in the UK to think about more creative ways of managing uncertainty (i.e. evidence generation, pricing schemes, innovative payment mechanisms that go beyond discounts)."

Regulatory scepticism over inadequate substantiation of claims was clear in French responses: "There's no real scientific reason to accept a weak clinical endpoint when you already have a weak design if it is a very severe cancer, because if it is a very severe cancer you have short PFS and short OS so you can observe it."

Differential responses to basket trials were flagged up in responses from Canada: "Basket trials present challenges for the HTA. Regulators have a different purpose as they want to know that the drug reasonably works, and so a basket design can be appropriate, but in Canada it will be difficult to convince a payer that the basket solves the problem." And in the absence of widespread and economically acceptable testing, progress in TAx is constrained, as one comment graphically demonstrated: "Companies had a grand vision for TA, but to start with screening hundreds to find 1 person who might benefit is a risky strategy, especially given that testing is expensive. The numbers of patients are so little that the strategy does not help policy makers, it barely makes sense from clinical and economic standpoint."

In Spain, the 1990 legislation in force provides for no structure that could work for Taks: no conditional reimbursement / adaptive pathway / fast track, and "there is no plan to change the current state of things." In addition, ethere's little experience in Spain of combining the two different pathways for drugs and for techniques, technologies, and processes."

In Germany, "currently not many new genetic tests are reimbursed," and problems experienced with TAx applications have included uncertainty of the evidence, issues with its presentation, and the design of clinical trials, often lacking subgroup analysis. In addition, there is a view among some engaged in pricing issues that pricing negotiations are comparable to "a bazaar and deal-making, where bargaining is the most important part needed to reach the market."

From Italian regulators came the view that "the most important aspect for TAx candidates is whether they can capture information in a systematic way in a protocol and include information of response rate in the dossier for pricing and reimbursement." For Italian payers, "Uncertainty is very high: we can accept phase II clinical trials, but for moving from adaptive to confirmation trials the payers want more. Uncertainty is very high especially is there is a low number of patients for each histology." There is also hesitancy over basket trials, "due to lack of knowledge, uncertainty coming not only from low numbers of population sample but also characterisation of those populations."

In South Korea, the unique nature of TAx means regulatory evaluation could be difficult. HTA would also be problematic: "The national payer doesn't change the approach because there's no need yet. Generally, the national payer will change regulation and policy or guideline if there's need."

A representative from Canada identified the fundamental problem as "the lack of comparative evidence to demonstrate a proven tumour agnostic effect." And the view was widely shared. But the lack of comparative data was also perceived by respondents as an understandable – and at present inevitable - challenge, given the nature of the new entities under study, from a molecular point of view. The immediate issue, therefore, is to identify the level of uncertainty the different agencies are ready to tolerate, since unflinching insistence on historical methods for assessing drugs precludes any chance of progress.

Early dialogue is seen as key to mitigating uncertainty, through initial discussion with relevant bodies at European level to evolve some shared views that could be translated to the national level and have some influence on discussions on price and reimbursement. Discussion of uncertainty from a clinical point of view has also led to – for instance – a framework developed by ESMO to rank genomic alteration, and work of this type could help advance understanding of the genomic alteration with respect to different cancer types. Giving specific weight to alterations could help in prioritising treatment options.

Real-world evidence

The discussions of data adequacy are already turning towards the use of real-world evidence, and highlighting the need for better access so as to confirm where therapies are - or are not - bringing value to patients. The emerging experience with TAx serves only to reinforce that need. Fragmentation and low prevalence of digitalised systems currently inhibit collection of data, with many hospitals and centres still working on paper, and with the lack of interoperability hampering the exchange digitalised data even where local systems exist. It is still not possible in certain countries to upload or share patient data for consultation on cloud platforms with physicians in other countries. Policy decisions are needed to initiate improvements, and funding is a further challenge.

The situation on acquisition and use of real-word evidence in health care has been compared adversely to other high-technology and highly-regulated industries – notably aviation – where real-time data on critical issues is shared as a matter of course, using the most advanced communications and technology, both to enhance safety and to feed into product development and design. Future learning and rapid feed-back loops are in place between use and R&D, built into the system from scratch to promote ‘data-driven innovation’.

There are signs of some longer-term thinking and even some policy shifts to improve the situation. OECD Health Ministers have agreed that governments establish a national health data governance framework to encourage the availability and use of personal health data to serve health-related public interest purposes while promoting the protection of privacy, personal health data and data security," and to “encourage common data elements and formats; quality assurance; data interoperability standards; common policies that minimise barriers to sharing data for health system management, statistics, research and other health-related purposes that serve the public interest. [19]

There is growing recognition that ensuring that, in future, each doctor, patient and researcher has access to the information they require, while allowing individuals to maintain control over their personal data, will lead to more precise diagnostics, and better treatment decisions. It will yield new insights for research and medicine. And it will improve patient care and help combat diseases more effectively. It is conceivable to harness the flood of data generated every single day in healthcare and research environments to the benefit of individual patients, to better understand illnesses, and to tailor treatments to the needs of the individual.

Challenges of development of RWE data including provision of informed consent, and that requires clear communication with appropriate stakeholder involvement at all stages, the inclusion of outcomes relevant to patients, the collection and analysis of meaningful data, and motivation and reward for patient and clinician. It also requires accuracy, quality and point of entry, and to be collected in a “real world” setting (e.g. community or primary care).

But its use in post-marketing follow up is easily demonstrated in principle. It can identify adverse effects in a larger (non-trial) population, and in population sub-groups. It can link with other data sources to gain a broader overview including cause and long-term follow up in assessment of co-morbidities and use of other anonymised non-disease/treatment specific registries and public data. It can factor in seasonal variations (e.g. allergies), and its capacity to predict adverse effects gives it potential use in future clinical trials. But of course

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there is a need for adequate statistical methods to extract, analyze and interpret RWE before it can translate into credible evidence.

There are growing calls (for instance from senior EMA staff – HG Eichler) to reinforce the urgency that opportunities for patients are lost. Science is progressing faster than the "system", impeding the development and best use of novel treatment options. The myth that patient-data protection and secondary data use are a trade-off is overdue for elimination: both can be achieved at the same time. The argument is that it is time to shift the debate: instead of considering that analysing personal health data is a risk to individuals, it should be accepted that the reverse is the case: not analysing personal health data is a risk to individuals. [20]

Gaia-x is a multi-stakeholder initiative to create a federated, interoperable, cross border data infrastructure. Representatives from politics, business and science from France and Germany, together with other European partners, are aiming for a secure, federated system that meets the highest standards of digital sovereignty while promoting innovation, with an open, transparent digital ecosystem, where data and services can be made available, collated and shared in an environment of trust. More than 300 organizations from various countries are already involved in GAIA-X. [21]

The Medical Informatics initiative in Germany is a multi-stakeholder consortium aimed at building a framework for data sharing and integration. It was created to close the gap between research and healthcare, and all of Germany's university hospitals have joined forces with research institutions, businesses, health insurers, and patient advocacy groups to create a framework that harnesses research findings to the direct benefit of patients. The German Federal Ministry of Education and Research (BMBF) is investing around 160 million euros in the programme through 2021, on the conviction that the digitisation of medicine is creating new opportunities for patient care and research. In a first phase, university hospitals and partner organisations will establish and link data integration centres, allowing research and healthcare data to be aggregated and integrated across multiple entities and sites.

At the same time, innovative IT solutions for specific medical applications will be developed to demonstrate the benefits of high-tech digital healthcare services and infrastructures. Participating university hospitals and their partners have formed consortia tasked with developing strategies for shared data use and exchange, and they will subsequently establish data integration centres, and create IT solutions for concrete use cases. According to Federal Minister of Education and Researc, digitisation can make personalised medicine a reality. But we have to make the switch now. Digital products and applications, not only in healthcare but also in medical research, are generating more and more data, and at an accelerating pace. These data must be aggregated and analysed – then they can help us to better understand and treat diseases. Our goal is a learning, digital and connected health system, where the right information is available at the right time, to the right person. With the launch of the medical informatics initiative, we've taken a major step in the right direction. [22]

Other recent initiatives in Europe include MedMij, a non-profit organisation in the Netherlands building an infrastructure based on HL7 FHIR to enable and promote the digital exchange of personal health data between patients and professionals "and building trust, in a safe, user-friendly, sustainable and affordable way, [23] and HealthdataHub, a French government initiative
aimed to cross-reference health databases and to facilitate their use by the research and development teams, while respecting the privacy of users of the health system. The aim is

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to link data from various databases and EHR for specific research questions, to allow subsequent analysis by AI. [24]

A recent change in US legislation, the ONC Final Rule, goes some way to combating fragmentation by limiting the actions that holders of data can employ to actively prevent sharing. It identifies and finalizes the reasonable and necessary activities that do not constitute information blocking while establishing new rules to prevent “information blocking” practices (e.g., anti-competitive behaviours) by healthcare providers, developers of certified health IT, health information exchanges, and health information networks as required by the Cures Act. [25] Currently, many EHR contracts contain provisions that either prevent or are perceived to prevent users from sharing information related to the EHRs in use, such as screen shots or video. The ONC final rule requires electronic health records to provide the clinical data necessary, including core data classes and elements, to promote new business models of care. This rule advances common data through the U.S. Core Data for Interoperability, a standardized set of health data classes and data elements that includes “clinical notes,” allergies, and medications, to help improve the flow of electronic health information and ensure that the information can be effectively understood when it is received. It also includes essential demographic data to support patient matching across care settings. [26]

To further advance the mission of fostering innovation, the CMS final rule establishes a new Condition of Participation for all Medicare and Medicaid participating hospitals, requiring them to send electronic notifications to another healthcare facility or community provider or practitioner when a patient is admitted, discharged, or transferred. These notifications can facilitate better care coordination and improve patient outcomes by allowing a receiving provider, facility, or practitioner to reach out to the patient and deliver appropriate follow-up care in a timely manner. Additionally, CMS is requiring states to send enrollee data daily beginning April 1, 2022 for beneficiaries enrolled in both Medicare and Medicaid, improving the coordination of care for this population. This ensures beneficiaries are getting access to appropriate services and that these services are billed appropriately the first time, eliminating waste and burden. Beneficiaries will get the right services at the right time at the right cost, with no administrative burden to rebill services. [27]

Tentative conclusion

Ultimately, successful development and deployment of biomarker testing depends on a policy framework in which countries would find it easier to reach consistent decisions and to provide clearer funding arrangements, thus boosting access and continued development. The EU should take the lead in developing or promoting clear and updated guidance for regulators and payers, for public and private laboratories, for clinicians and healthcare providers, on the active development and use of biomarker testing.

There are some signals that could justify guarded hopes of an improved environment. Recent demonstrations of wide support for EU initiatives such as its Beating Cancer Plan or its Cancer Mission, as well as 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.

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But nothing will happen by accident. Constructive change to the health care context could ensure better use of the potential offered by new technologies in testing, in diagnosis and in treatment of cancer, through development and use of biomarkers and the advanced treatments – such as personalised medicine and TAx – that they enable. But this will result only from vigorous debate among all stakeholders, and agreement on recommendations of a technical and political nature that will result in a better deal for patients and a more sustainable approach to healthcare.

Recommendations

Recommendations to the EU

- The European Commission to update by 2021 its recommendation on early detection strategies allowing for risk stratification through molecular diagnostics/biomarker testing

- European health authorities to put in place a policy framework to support diagnostics in the EU by 2022, with a ring-fenced budget allowance for biomarker testing development (clinical validation). Research on biomarkers discovery and early testing should also be a matter of concern and funding promoting policies.

- The EU to agree by 2023 a business model for public-private cooperation for optimal biomarker testing available across the EU.

- The EU to provide guidance on minimal testing standards and resource allocation by 2025.

- The EU to establish a framework for quality of testing and value of diagnostics information, with a fast track approval mechanism for biomarker validation

- The EU to facilitate centralised and standardised registries of diagnosis including sequence and biomarker data, pre- analytical sample metadata, treatment and outcome

- The EU to fund laboratory capacity, accreditation, clear guidelines, stricter regulation, quality control and relevant education, and quality assurance mechanisms.

- The EU to promote accredited methodologies for cancer detection and treatment and encourage research and excellence.

- The EU to promote the therapeutic value of digital tools in diagnostics, patient monitoring

- The European Commission should consider a 12 month postponement of the date of application of the IVDR, to mitigate capacity challenges within the notified bodies and the effect of COVID-19 on European stakeholder's preparations for this new regulation. This would be in line with a recent decision for a 12 month postponement of the MDR.

- The European Commission's Medical Devices Coordination Group and the member states' National Competent Authorities for IVDs should develop clear guidance for

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public and private laboratories on how they should move forward with the development of lab developed tests under the new regulation.

Recommendations to EMA

- EMA to progress its plans for early engagement on regulatory qualification of novel biomarkers
- EMA to review its biomarker clinical and analytical validation process
- EMA to evaluate clinical outcomes measured by biomarkers
- EMA to progress multi-stakeholder scientific advice on the use of companion diagnostics.
- EMA to promote consensus on how to optimally design and set up confirmatory basket trials.

Recommendations to Member States

- Member states to agree on a federated structure of national databases.
- Member states should ensure that new validated biomarker tests are rapidly made available to patients”
- Member States have incentivize the development and uptake of biomarkers of limited interest to commercial companies (early detection biomarkers & risk biomarkers)
- Member states/EMA to better synchronise CDx approval processes with drug approval
- Member states to provide clarity on funding routes for biomarker testing.
- Member states to allocate resources specifically for discovery and validation of biomarkers, and promote engagement between payer organizations, biomarker developers and the wider healthcare stakeholder community. (vertical integration and horizontal integration)
- Member States to ensure horizon scanning processes are in place to support early multi-stakeholder engagement on potential challenges for reimbursement and implementation of new tests, and to ensure clear reimbursement structures are in place for biomarker testing.
- Member States to find a uniform agreement for online consultations through standardized exchange platforms across Europe

Healthcare System - Stakeholders Recommendations

- Healthcare systems across Europe to create a systematic reference framework for clinical laboratories
- Regulators and payers to align on standardized outcome measures, systematic data collection, and data standards and sharing.
- Developers of biomarkers to support applications with robust data.

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- Developers of biomarkers, PAGs, HCPs medical societies to cooperate on information and education, including literacy for the public and for professionals.

- Drug and diagnostic developers, clinicians, biologists, biostatisticians and digital technology groups to cooperate on pan-cancer studies, with more, and more targeted, screening, exploiting the potential of stratification and of genomics, AI, biomarker testing.

- Laboratories to obtain the general medical laboratory standards ISO 15189 or equivalent accreditation and undertake a minimum of 100 tests per month.

- Laboratories to obtain accreditation on the pre-analytical ISO/CEN standards

- Central biobank facility at each medical academic centre collecting biomaterials from the existing diagnostic pathways for research accredited for the general biobank standard ISO 20387 and the pre-analytical ISO CEN standards

Funding solutions:

- Biomarker testing should be of high quality, with defined testing pre-analytical and analytical standards and clear criteria on minimum performance characteristics of biomarker tests.

- Data sets accompanying biomarker tests should be robust and clearly demonstrate a relationship between the biomarker and its expected value.

- Member states should each create a centralised national system aligned with European standards to validate and set up tests, and Europe should move towards data centralisation, to permit the creation of robust data-sets across the continent to generate cost-benefit evidence. This should include clear minimum criteria and formats for reporting in terms of standardised metrics taking account different stages of testing.

- Data sharing policies across member states should be revisited to facilitate European multi-institutional and multi-national studies every 3 years.

Data solutions:

- Biomarker testing should be of high quality, with defined testing pre-analytical and analytical standards and clear criteria on minimum performance characteristics of biomarker tests.

- Data sets accompanying biomarker tests should be robust and clearly demonstrate a relationship between the biomarker and its expected value.

- Member states should each create a centralised national system aligned with European standards to validate and set up tests, and Europe should move towards data centralisation, to permit the creation of robust data-sets across the continent to generate cost-benefit evidence. This should include clear minimum criteria and formats for reporting in terms of standardised metrics taking account different stages of testing.

- Data sharing policies across member states should be revisited to facilitate European multi-institutional and multi-national studies every 3 years.

- Structures should be in place to collect and share research data and real-world data and standardized registries of genomics and outcome data.

Information and education solutions:

- Stakeholders should receive tailored biomarker education to ensure appropriate timing and breadth of information, including ethical and compliance considerations

- The short-term focus should be on educating groups highly influential in widening access to biomarker testing, notably payers.

- Biomarker education should be maintained to keep stakeholders upskilled so that they can make informed decisions.

- Information bearers should be identified at a Europe-wide and member state level, along with support for their role and visibility.

Implementation solutions:

- Early engagement with regulatory bodies should be routine to address challenges and provide clarity on the infrastructure needed.

- Authorities should pre-emptively organise meetings or courses on how to implement biomarker tests

- Authorities should provide clarity for all stakeholders on the procedures needed to implement a biomarker test, to allow timely access across testing centres.

- All actions to be realistic and measurable, with indicators monitored, to enable evaluation through agreed performance indicators.

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