Collaboration is key to accelerating diagnostics access to optimize benefits of precision medicines

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“Approximately one-third of all new drugs in development use genomic data to identify patients most likely to benefit from them”

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Precision medicine is defining the future of healthcare. In addition to providing clinically meaningful benefits to patients, delivery of the right treatment to the right patient at the right time may offer budgetary efficiencies by reducing the costs of clinical time, service use and ineffective treatment associated with a less personalized, ‘one-size-fits-all’ approach [1]. Approximately one-third of all new drugs in development use genomic data to identify patients most likely to benefit from them [2,3]. A significant proportion of the new generation of novel targeted therapies arriving in the clinic require patients to have essential tests required by a therapy’s indication, known as companion diagnostics, or tests that support treatment decisions but are not essential prior to prescription, known as complementary diagnostics.

As a result of this major change in the way pharmaceutical companies develop new medicines, there has been exponential growth of drug–diagnostic combinations seeking regulatory approval. Data from the US FDA show an increase from five to 63 approvals of drugs with associated diagnostics between 2006 and 2012 [4]. However, in only seven of these 63 drug–diagnostic combinations were the drug and the diagnostic approved at the same time [4]. Growth in precision medicines continues, with a record of 16 new products approved by the FDA in 2017, representing a third of total approvals. However, a report from the Personalized Medicine Coalition citing these figures also acknowledges the ongoing challenges, including diagnostic regulatory policy, coverage and reimbursement [3]. Without diagnostics to guide the use of these novel targeted medicines, clinicians may be reluctant to prescribe them, and payers to fund them; as a result, limiting access to these important medicines, to the detriment of patients.

Why is there a mismatch in timelines for availability of precision medicines and diagnostics, and how can the current challenges facing clinicians, payers and pharmaceutical and diagnostics companies be overcome, in order to accelerate patients’ access to the right medicines for them so that they can experience the real-world benefits of these precision treatment options?

Identifying the challenges

In most countries, suboptimal and/or delayed reimbursement and funding of diagnostics is a key barrier to identifying patients, and subsequently accessing precision medicines for those who may benefit. Pharmaceutical companies are reliant upon the availability of diagnostic tests for access to their targeted therapies, yet in many countries they are not responsible for launching and securing funding for diagnostic tests.

In 2017, we conducted research into the diagnostics market access landscape to uncover key challenges and opportunities for tackling this issue. Research was conducted across eight countries: PR China, France, Germany, Italy, Japan, Spain, the UK and the USA. This included primary research interviews with 37 clinicians, laboratory directors and payers; interviews with five leading diagnostics companies and structured secondary research of relevant literature [1].

Table 1. Archetype models.

Archetype	Definition	Country (Rx)	Country (Dx)
Budget impact	HTA-based system focused on managing access with a high potential cost to drug budgets and the overall healthcare system	Italy, Spain	N/A
Cost-effectiveness	Established HTA-based system that primarily evaluates new drug/Dx based on quantifiable cost-effectiveness measures	UK [†]	UK [†]
Comparative clinical effectiveness	Reimbursement is dependent on added clinical value relative to a comparator drug/Dx	France [†] , Germany, Japan [†]	France [†] , Japan [†]
Competitive rationalizing/free market	Free market pricing exists, but extensive negotiation and discounting is required from both government and private payers to attain attractive formulary positioning	USA [†]	Germany, Italy, Spain, USA [†]
Patient pay	Strict price control and ongoing price cutting	China [†]	China [†]

[†]Countries marked indicate those that adhere to the same archetype for both therapy and diagnostic assessments.
Dx: Diagnostic; HTA: Health technology assessment; N/A: Not applicable; Rx: Therapy.

This research identified multiple challenges that fell into three key areas: significant differences across countries in market access processes (i.e., different evidence requirements and stakeholder involvement in approval, reimbursement and funding of diagnostics), variations in timelines to achieve market access approval of companion or complementary diagnostics, and lack of early engagement between diagnostics companies, pharmaceutical manufacturers and payers to ensure diagnostics are reimbursed at the time of launch (or as close as possible to this date).

As market access processes differ from country to country, this presents a challenge for pharmaceutical companies whose core business does not include ensuring market access for diagnostics. However, the mapping out of payer archetype models allows the categorization of payers based on decision-making frameworks across countries, and illustrates differential evidence generation requirements useful for planning. The research illustrates that market access strategies, processes and evidence requirements for medicines and for diagnostics can also vary within the same country (Table 1).

In other countries, while the market access decision-making for medicines and diagnostics follow similar frameworks, different stakeholder involvement, assessment processes and evidence requirements still pose significant challenges.

In France and Japan, both the therapeutic and diagnostic market access processes can be characterized by the ‘comparative clinical effectiveness’ archetype. Technical and clinical evidence are required to support their assessment. The emphasis is on the need for a new therapeutic or diagnostic option to prove added clinical value to those already available. In France, key stakeholders for diagnostic reimbursement are the French National Cancer Institute (INCa), the National Committee for Medical Devices and Technologies Assessment (CNEDiMTS) and the National Union of Health Insurance Funds (UNCAM). While the CNEDiMTS and UNCAM process together can take up to 5 years for new complementary diagnostic tests to receive funding approval, companion diagnostics in oncology can benefit from the funding support of the INCa, improving access to the associated medicines.

The requirement for technical and clinical evidence is mirrored in Japan. But despite Japan’s emphasis on clinical efficacy, the Central Social Insurance Medical Council (Chuikyo) began a trial in 2017 of the implementation of cost-effectiveness assessment of medicines and medical devices (including diagnostics), which can be used to reprice these products. The Pharmaceutical and Medical Devices Agency (PMDA), the Ministry of Health, Labor and Welfare (MHLW) and Chuikyo, are the key stakeholders for both diagnostics and drugs for access and pricing/reimbursement, respectively. Although diagnostics and drugs can be assessed separately, companion diagnostics are more likely to secure reimbursement if assessed in parallel to a drug, and many countries are now moving away from separate reviews.

In the USA, the Center for Devices and Radiological Health (CDRH), a subcommittee of the FDA, approves diagnostics on the basis of clinical efficacy and safety. After approval, the Centers for Medicare & Medicaid Services

(CMS) and commercial payers, assess clinical, technical and economic evidence to determine test reimbursement and funding, define utilization management restrictions and support contract negotiations for limiting access of tests to the right patient subgroups. In the USA, this ‘competitive rationalizing/free market’ archetype is common to the diagnostic and therapeutic market access processes.

The differences in processes, evidence needs and stakeholders, results in wide variation in the timeframe for review of a diagnostic test for reimbursement decision-making by key stakeholders in each country, which is often accelerated for companion diagnostic tests. This can range from 4–13 months in Japan, up to 1.2 months in England, 3 months to 5 years in France, up to 3.5 years in Germany, 8–12 months in the USA and up to 15 years in China, where there is also a particularly high risk of no reimbursement leading to patient out-of-pocket purchasing. These timeframes frequently differ from those equivalent processes for achieving national availability of drugs. Pharmaceutical companies need to be cognizant of the need to factor these potential timeline disparities into marketing planning for their drugs.

Our research has identified global reimbursement challenges, common to multiple countries but present at different levels of severity. Particularly challenging is the localized approach seen in China, Italy and Spain. In China, while national access can be secured for pharmaceuticals via the National Reimbursement Drugs List (NRDL), there is still a significant need for individual provincial assessments for diagnostics. For diagnostics that are not reimbursed or are only partially reimbursed, patients are expected to pay out-of-pocket for any nonreimbursed costs. Similarly, in Italy and Spain, pricing and reimbursement processes vary across regions within the country and for diagnostics, these are the key stakeholders, whereas there is a more structured national-level assessment process for medicines through health technology assessment (HTA) agencies (the Italian Medicines Agency (AIFA) and the Spanish Medicines Agency (AEMPS), respectively). In Spain, for example, there are seven HTA regional agencies, yet only two of these, Andalucía and the Basque region, are reported to routinely assess oncology diagnostics.

A disconnect also often exists between gaining technical approval of funding, and the actual provision of this funding. A coding process is used by some countries, whereby services including diagnostic tests are allocated a code which is documented to track use and enable reimbursement. Despite having such a system in place, issues within these systems still exist. For companion diagnostics, the cost of the diagnostic test is often included in the drug reimbursement (e.g., England and Spain), without a dedicated code for the diagnostic. This poses challenges given that the medicine and test are provided by different manufacturers, and often leads to underfunding.

In the USA, codes for diagnostics are nonspecific, and instead issued for the test type, for example, *ALK*, but not the specific assay. Where reimbursement and adequate coding do exist, the complexity of systems may still result in substantial delays in reimbursement to manufacturers.

Fresh approaches to drive progress

The wide range of challenges related to the introduction of companion and complementary diagnostics is not insurmountable. There have been calls for international harmonization of the regulatory requirements for diagnostics [5], and the European Medicines Agency (EMA) has announced plans for guidelines relating to the interface between medicinal products and predictive biomarker assays, including companion diagnostics [6]. Our research reinforces the fact that alignment of processes and requirements would greatly facilitate the coordinated introduction of drug-diagnostic combinations, and the more timely delivery of targeted treatment options to patients.

We have identified examples of how a considered approach specific to the local environment can address and overcome access challenges, and help build the levels of real-world evidence that payers need to support the wider use of precision medicine in clinical practice. Potential approaches that have proven to be successful include temporary funding of companion and complementary diagnostics by pharmaceutical manufacturers while market access and reimbursement issues are addressed, and early collaboration between the multiple stakeholders involved in patient care to ensure a solid transition to long-term reimbursement and funding of diagnostics by payers.

In the UK, when Roche secured approval for Herceptin® (trastuzumab) for the treatment of HER2-positive metastatic breast cancer, it provided funding for the HER2 test to ensure availability at Herceptin launch. Funding then transitioned to the public payer as data collected during the manufacturer-funded period showed the value of testing for patient outcomes and cost-effectiveness [7]. Additionally, in 2016, special arrangements were made by the NHS in England to fund seven cancer tests aligned to NICE guidance, with no national price tariffs set for the first 3 years of their listing during which the NHS will reimburse the purchase cost [8].

In the USA, the FDA is making policy changes to facilitate earlier access to innovative medical technologies. On 15 November 2017, the FDA authorized Memorial Sloan Kettering Cancer Center’s MSK-IMPACT™, a

468-gene oncopanel intended to detect mutations in multiple tumors, and in doing so advanced policy framework that streamlined the regulatory assessment of next-generation sequencing (NGS) products [9]. Shortly after, on 30 November 2017, Foundation Medicine's FoundationOne CDx™, a comprehensive genomic profiling test that can detect genetic mutations in 324 genes, was approved by the FDA and was the first 'breakthrough-designated' NGS test to secure this [10]. The FDA's review of the evidence for FoundationOne CDx prompted their assessment of the wider published literature on the use of NGS testing in cancer. This resulted in the agency proposing a policy that applied to all NGS panels when they are used for recurrent, metastatic, or advanced Stage IV cancer patients. The CMS has proposed specific pathways through which NGS cancer panels may garner Medicare coverage. FoundationOne CDx has secured a preliminary National Coverage Determination (NCD) that grants full coverage for genetic markers on the panel that have premarket approval (PMA) from the FDA as a companion diagnostic such as *ALK* or *BRAF* mutations. Additional coverage could be secured through a pathway that addresses markers without CDx status (e.g., MSK-IMPACT), but with FDA approval for use in a patient's treatment plans with coverage with evidence development, where coverage will be granted where the lab collects patient outcomes for evidence development. Last, for lab-developed tests that are performed in a CLIA-certified lab – the majority of currently available tests – CMS is proposing coverage with evidence development when tests are included in a National Cancer Institute National Clinical Trial Network study. CMS is expected to finalize the NCD for NGS cancer diagnostics soon.

The collaboration continuum

As demonstrated in these examples, early collaboration between key stakeholders can play a significant role in overcoming some of the challenges experienced in ensuring drug-diagnostics are made available to clinicians and patients in a timely way. However, our research showed that although collaboration is common at the innovation stage, during initial scientific research and drug discovery, it is far less evident as it relates to diagnostic reimbursement and market access.

In addition to the various regulatory challenges of gaining approval for their products, diagnostic companies reported difficulties in engaging with laboratories, payers and external experts to increase understanding of the application and clinical value of diagnostics, leading to reimbursement issues. Payers also described a lack of early engagement and the real-world evidence gap as significant challenges for achieving market access for diagnostics.

Diagnostic companies taking part in our research communicated their desire for increased collaboration with pharmaceutical companies. Earlier collaboration that encompasses the clinical trial phase would create opportunities to cogenerate clinical outcomes and health economic data, and develop a greater understanding of the clinical application and value of diagnostic tools prior to acquisition of real-world evidence. This, in turn, would help create a more compelling case when looking to secure access to diagnostics for patients and their reimbursement, delivering benefits for both diagnostics and pharmaceutical companies. Interviews with payers reinforced the need for such data with a UK payer expressing a *"need to demonstrate that the diagnostic will define a subset of patients that will have the most positive effect in outcome of treatments"*, stating that *"this is the only way NICE will look at it"*. In Spain, a regional payer outlined their evidence needs, *"We want to know: what is the real benefit of using the diagnostic? What is the impact on patient management after the test is completed?"*

Engaging with payers and laboratories earlier in the process would ensure they had access to the clinical and economic data that would enable them to make value-based decisions about new diagnostics and allow potential issues to be identified and addressed. The timing of communication with stakeholders is the key; highlighted by an expert from a US Oncology Reference Laboratory, *"diagnostics manufacturers do not engage with commercial laboratories early enough. Communicating with them a year in advance makes a huge difference."* Earlier engagement with clinicians and laboratory professionals would enhance understanding of the clinical application of diagnostic technology and its potential to positively impact patient outcomes. Where appropriate, this can lead to experts recommending the inclusion of a diagnostic in clinical guidelines, a factor that influences many market access decisions. It also provides valuable hands-on experience which supports later adoption and prepares the ground for collection of real-world evidence.

Conclusion

Diagnostics are a critical part of the precision medicine equation. Currently, a global maze of multiple country access processes, with varied evidence requirements and different evaluation measures, is creating a complex environment and multiple access challenges. Greater clarity surrounding market access procedures among all stakeholders –

comparable to that already achieved with pharmaceuticals – could facilitate availability of diagnostics in a timely manner, leading to simultaneous availability of more drug-diagnostic combinations.

Greater collaboration between all stakeholders – throughout R&D, regulatory, market access and reimbursement processes and for the duration of the product lifecycle – is also important for ensuring that availability of precision medicines and diagnostics are aligned.

Such an approach can deliver more coordinated introduction of drug-diagnostic combinations, faster patient access to treatments tailored to their specific needs, increased evidence of the clinical application of diagnostics, and real-world data showing the personal and health-economic impact and value.

In a number of countries, we have identified the complexities and challenges of making precision medicines and companion/complementary diagnostics available to patients, but improvements will not be achieved without concerted action from diagnostics and pharmaceutical manufacturers, regulators, payers and other stakeholders. Examples have been provided that illustrate how reimbursement has been achieved in some countries – to benefit patients. However, as a next step, stakeholders must agree how best to act on these and other such experiences to build clear, easily applicable market access processes that can benefit patients much more widely.

Removing the compartmentalized approach to collaboration has the potential to fast-track the industry to the ‘future of medicine’.

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References

1. Barker RW. Is precision medicine the future of healthcare? *Pers. Med.* 14(6), 459–461 (2017).
2. Robinson A. Genomics – the future of healthcare and medicine. *Prescriber* 27(4), 51–55 (2016).
3. Personalized Medicine Coalition. Personalized medicine at FDA 2017 progress report (2018). www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_2017_Progress_Report.pdf
4. Agarwal A, Ressler D, Snyder G. The current and future state of companion diagnostics. *Pharmgenomics Pers. Med.* 8, 99–111 (2015).
5. Shimazawa R, Ikeda M. International differences in companion diagnostic approvals: how are we able to manage the differences? *Expert Rev. Mol. Diagn.* 15(2), 157–159 (2015).
6. European Medicines Agency. Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle (2017). www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/07/WC500232420.pdf
7. DRG Consulting. Diagnostic market access landscape – primary research with 37 payers and clinical experts, and 6 diagnostics company partners (2017). <https://decisionresourcesgroup.com/solutions/global-market-access/>
8. The Association of the British Pharmaceutical Industry. Stakeholder briefing: the new commissioning and funding arrangements for six molecular genetic tests for cancer introduced by NHS England in April 2016 (2016). www.abpi.org.uk/media/1606/commissioning_of_molecular_genetic_tests_for_cancer.pdf
9. US FDA. FDA unveils a streamlined path for the authorization of tumor profiling tests alongside its latest product action (2017). www.fda.gov/newsevents/newsroom/pressannouncements/ucm585347.htm
10. US FDA. FDA announces approval, CMS proposes coverage of first breakthrough-designated test to detect extensive number of cancer biomarkers (2017). www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587273.htm