Market access challenges in the EU for high medical value diagnostic tests

The clinical utility and medico–economic value of several personalized diagnostic tests has been well described in the literature. Development of such tests, including generation of the necessary supportive clinical validation data, is a complex and expensive endeavor. In general, sponsors of such tests lack sufficient clarity on appropriate reimbursement and regulatory pathways to provide the clear development framework necessary to incentivize the required level of investment. In the USA, an imperfect reimbursement paradigm has evolved to accommodate a small number of 'value-priced' laboratory-developed tests, although major structural barriers remain to broader implementation. In Europe, by contrast, there is virtually no precedent for value-based public sector pricing, and even such procedurally based pricing as currently exists is administered by a complex network of largely decentralized bodies. As a consequence, patient access is limited and health–economic savings are not realized. This article explores some of the European market entry barriers, with a focus on reimbursement challenges, and highlights some collaborative proposals to address such.

KEYWORDS: EU ▪ high value ▪ personalized medicine ▪ reimbursement

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The last century has seen a revolution in modern medicine with the discovery of many new treatments for common diseases. However, inter-individual variation means that response to treatment varies widely, rendering a 'one-size-fits-all' approach to patient care increasingly obsolete. With the completion of the human genome sequencing project and next-generation sequencing technologies, as well as advances in technology for the 'omics' approaches (e.g., genomics, proteomics and metabolomics), the pharmaceutical blockbuster model is gradually being challenged by a personalized medicine (PM) model. PM can be considered as the stratification of patient groups based on the molecular analysis of genes, proteins and metabolites. PM tests, or 'theranostics', can be developed as companion tests with pharmaceutical partners or as standalone tests for diagnostic or prognostic purposes. PM is enabling a paradigm shift from a treatment-centered health system to a comprehensive patient-centered care management approach with potentially enhanced efficacy and reduced adverse events. As illustrated in Figure 1, the high cost of adverse events has previously been estimated annually in the USA at US$177 billion per year and drugs overall have efficacy only approximately 50% of the time, representing a potential waste of approximately $350 billion of the worldwide $700 billion or more drug spend [1]. In addition to the well-known Herceptin® story, potentially high-impact examples of the clinical utility of PM include the use of *KRAS* testing to identify mutants unlikely to respond to large-molecule EGF receptor (EGFR) inhibitors, which could save the US health system $600 million annually [2] and, perhaps, the influence of *CYP2C9/VKORC1* genotypes on warfarin metabolism. While the latter scenario is still under investigation, and ultimate utility would be subject to complex real-world prescription and workflow dynamics, it has been suggested that integration of a genetic warfarin test could avoid 85,000 serious bleeding events and 17,000 strokes [101], providing an annual saving of $1.1 billion in the USA. Such examples highlight the health–economic potential of the field of PM, in addition to the obvious clinical advantages.

While the USA reimbursement environment for clinical diagnostics presents many challenges for the value capture for test innovators, several high value medical diagnostics are currently reimbursed by the US Centers for Medicare and Medicaid (Medicare) and commercial payers. These tests are typically reimbursed by payers in one of two ways. First, diagnostic reference laboratories can file claims using stacked Current Procedure Terminology (CPT) codes that describe generic laboratory procedures such as 'amplification, target, each nucleic sequence', and be paid based on a technical cost-derived fee schedule. This 'cost-based' approach does not explicitly reward the unique value that an innovative test may offer. The other approach to reimbursement is 'value-based',

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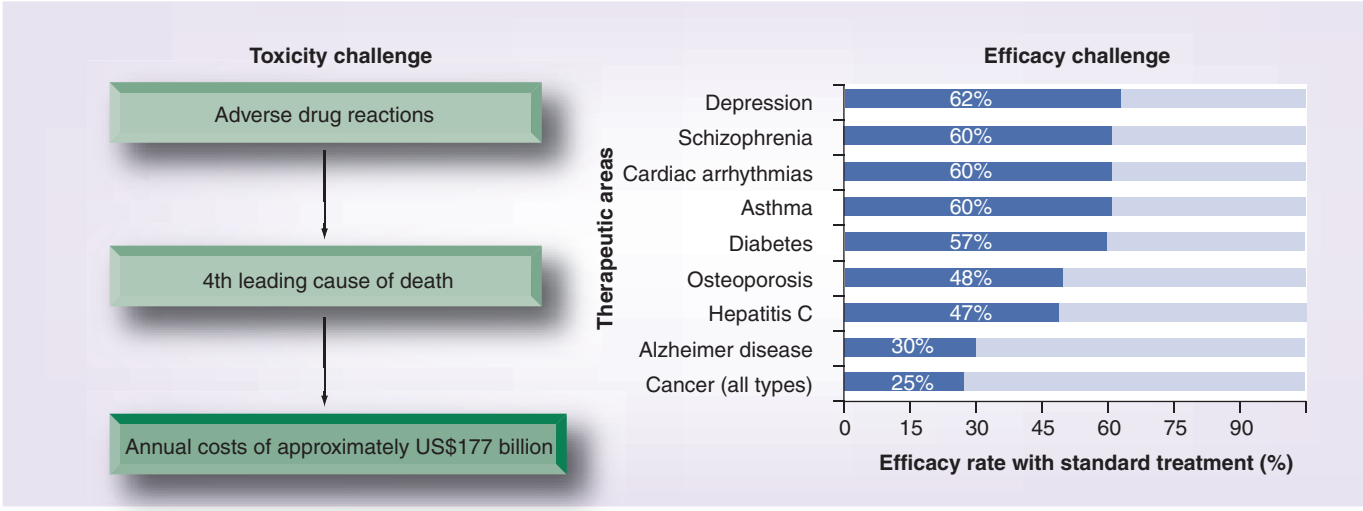


Figure 1. The dual toxicity/efficacy challenge associated with the current drug-development model.
Adapted with permission from [3,6,7].

and generally relies on the use of 'not otherwise listed codes', or catch all miscellaneous CPT codes that result in payment that is unique to the value of the specific test performed. This second approach in particular has resulted in test reimbursements of several thousand dollars for certain complex tests (e.g., Oncotype DX® breast cancer assay from Genomic Health Inc., CA, USA). While cost–effectiveness may or may not be considered by payers in their rationale for paying for these high-value tests (Medicare has historically been restricted from using cost–effectiveness data when making coverage determinations), for many payers, the cost impact is influential, particularly if use of the test results in direct cost savings such as avoidance of inappropriate drug therapy. Furthermore, initiatives such as Senator Orrin Hatch's proposed legislation regarding a novel regulatory pathway for innovative diagnostics may have a favorable impact on test reimbursement in the future. Such value-based payment arrangements are virtually unheard of in the EU.

The integration of clinical value and real-world evidence demonstration with the process of incorporating medical innovation in patient care in a timely manner is only in its infancy. PM market challenges represent only the latest manifestation of the ongoing struggle of embattled policy makers and regulators attempting to keep pace with medical advances and sophisticated technologies. These same decision-makers are now faced with the crisis brought on by new budget constraints and global financial challenges, and some, such as in the UK, are responding with strong austerity measures.

How can societies and national governments organize themselves in an attempt to modernize and improve the efficiency of healthcare delivery under these conditions? Some innovators, such as Genomic Health, have presented a partial solution to some of these dilemmas – the Oncotype DX test has demonstrated cost and clinical outcome improvements for patient, provider, payer and society, in the USA, Japan, Israel and Europe. Yet, even with this unique information set, and real-world cost offsetting demonstration, many policymakers remain unconvinced, and European market penetration, as described later in this article, is minimal.

What does this mean for diagnostic companies and others at the frontier of attempting to improve the quality of care in Europe?

In this article, the authors, several of whom are also founders of The European Personalized Medicine Coalition (EPEMED), grapple with the challenges of market access and improving patient care across the European community. Regulatory and reimbursement practices in the major European markets are reviewed, and consideration given to some specific test scenarios. The article will argue that, while barriers to rapid adoption of PM exist in both the USA and the EU, additional barriers and complexity are faced in the EU context. As will be seen later in this article, several of the major European nations have highly complex reimbursement systems.

Market access in the EU

Potential hurdles to market access in the EU

The EU currently comprises 27 member states, illustrated in Figure 2. The attached Table 1 compares the top 15 EU *in vitro* diagnostic (IVD) market sizes in the context of general healthcare spend for 2009. Accessing the market across the

EU is challenging as the EU is a heterogeneous region in terms of regulatory and reimbursement approaches, with every country having its own unique characteristics. The potential differences across member states are confounded by the problem of centralized versus decentralized systems within individual states, including the tendency of most EU nations to review tests at the local level. This local approach to coverage and reimbursement assessment of test technologies compared with national level reviews for most drugs, can present substantial barriers to consistent market access for drug/diagnostic combinations (Figure 3). Moreover, there are differences in health technology assessment (HTA) systems between, and within, countries that would benefit from standardization. While such differences are also found in the USA, the European heterogeneity is greater, and there is no precedent for value capture. While mandatory CE (originally 'CE' stood for 'Communauté Européenne' ['European Community']) markings under the IVD Directive 98/79/CE requirements does currently facilitate delivery of diagnostic tests across the EU market in a harmonized fashion, the future regulatory framework for high-risk tests, including those used in PM, is likely to evolve, and further uncertainty clouds the companion test subset, as in the USA.

Figure 2. The 27 member states of the EU.

In this article, we consider public sector practices and challenges in several of the major EU markets, including the status of two exemplar companion IVD tests (*HER2* for herceptin eligibility in breast cancer and *KRAS* for Erbitux®/Vectibix® eligibility in colon cancer). Later in this article, the situation in the EU market for the high-complexity laboratory-developed tests (LDTs) Oncotype DX and Trofile™ (Monogram Biosciences/Labcorp, CA, USA) is reviewed and contrasted with the USA.

Table 1. The European healthcare and *in vitro* diagnostic markets.

Countries	Population (thousands)	GDP (Mio €)	GDP per capita (€)	THE (Mio €)	THE/ capital (€)	THE (% GDP)	IVD market est. 08 (Mio €)	Growth rate 08 (%)	IVD market est. 08/ THE 07 (%)	IVD market est. 08 per capita (€)
EU-15	***OECD 2007 source***						***EDMA source***			
Germany	82,257	2,422,900	29,455	252,751	3073	10.4	2107	3.0	0.8	25.6
France	61,707	1,892,132	30,663	208,441	3378	11.0	1654	4.0	0.8	26.8
UK	60,975	1,764,865	28,944	148,526	2436	8.4	721	11.2	0.5	11.8
Italy	58,880	1,544,915	26,238	134,777	2289	8.7	1625	2.7	1.2	27.6
Spain	44,873	1,050,595	23,413	88,828	1980	8.5	1038	7.0	1.2	23.1
Netherlands	16,382	567,066	34,615	55,484	3387	9.8	298	3.8	0.5	18.2
Greece	11,193	228,180	20,386	21,893	1956	9.6	230	0.0	1.1	20.5
Portugal	10,604	163,119	15,383	15,786	1489	9.7	244	-1.2	1.5	23.0
Belgium	10,623	334,917	31,528	34,031	3204	10.2	315	5.7	0.9	29.6
Sweden	9148	319,194	34,892	28,957	3165	9.1	164	1.6	0.6	17.9
Austria	8315	270,837	32,572	27,453	3302	10.1	237	4.3	0.9	28.5
Denmark	5457	226,397	41,487	22,102	4050	9.8	122	5.2	0.6	22.4
Finland	5289	179,659	33,368	14,706	2780	8.2	98	-1.0	0.7	18.5
Ireland	4339	190,603	43,928	14,432	3326	7.6	81	3.8	0.6	18.7
Luxembourg	476	36,278	76,214	2461	2844	6.8				
Ref.				[3]	[4]	[5]				

EDMA: European Device Manufacturers Association; est.: Estimate; GDP: Gross domestic product; IVD: In vitro *diagnostic; Mio: Millions; OECD: Organization for Economic Cooperation and Development; THE: Total health expenditure.*
Data taken from [111].

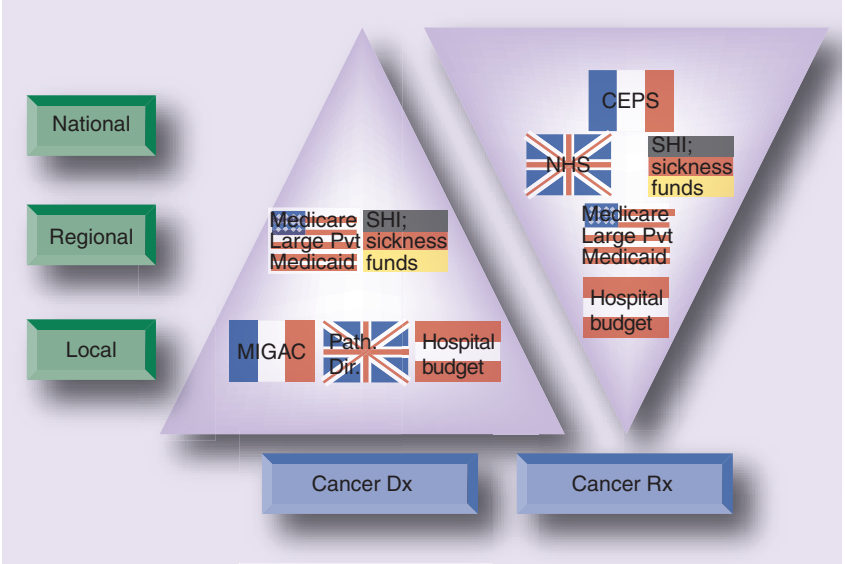


Figure 3. Key differences in reimbursement policy approaches for oncology diagnostics and therapeutics. For most countries, drugs are reviewed for reimbursement at the national level while tests are reviewed at the local or regional level.
CEPS: Comité Economique des Produits de Santé (Economic Committee for Health Products); Dx: Diagnostics; MIGAC: Missions d'Intérêt Général et d'Aide à la Contractualisation; NHS: National Health Service; Pvt: Private; Rx: Therapeutic; SHI: Statutory health insurance.
Adapted with permission from Boston Healthcare, 2010 [8].

UK

The UK is considered in detail here, as it has perhaps the best developed technology evaluation and medico–economic assessment system exemplified by the practices of NICE. Nevertheless, as with several other European countries (Figure 3), in contrast to the process for drug approval and reimbursement evaluation, the technical assessment process for diagnostics in the UK remains somewhat decentralized and lacks transparency. Until recently, there was no single HTA group responsible for the evaluation of diagnostic testing for common diseases. However in 2010, NICE was charged with the evaluation of diagnostics [102]. The scope and nature of its involvement and requirements are yet to be determined.

For technologies that are still not evaluated by NICE, the manufacturer must submit supporting evidence to local budget holders, which may apply different criteria for acceptance. Strong emphasis is on physician- and hospital-level decision-making regarding test adoption and budget impact. As discussed previously, CE-marked diagnostic tests are brought to market under the common EU *in vitro* device directive requirements (98/79/CE). In the UK, there are two options to obtain competent authority regulatory acceptance: either through self-certification by the manufacturer or conformity assessment made by a notified body (e.g., Medicines and Healthcare Products Regulatory Agency). The latter process is usually applied for the high risk tests typical of many PM scenarios. Currently, the evaluation focuses on assessment of test performance and budget impact, while there are only limited requirements to demonstrate change in patient management or impact on health outcomes by applying a test. Changes in requirements for clinical and economic impact are, however, evolving. In the 'Report of Genomic Medicine, House of Lords 2008–2009 [103] it is stated: "The [process for] evaluation of genomic tests contrasts with the evaluation system for new drugs which pass through a rigorous independent evaluation within NICE to assess their utility, validity and cost–effectiveness. At present, genetic tests for single-gene disorders are evaluated by the UK Genetic Testing Network (UKGTN) [104]. The UKGTN is a collaborative group of National Health Service (NHS) laboratory scientists, clinical geneticists, NHS commissioners and patient representatives. Tests that pass the UKGTN evaluation process, the 'Gene Dossier Process', are recommended for NHS funding. The UKGTN system works well for tests for single-gene disorders (e.g., Gaucher disease and cystic fibrosis). By contrast, it is unclear how genomic tests for common diseases, including pharmacogenetic and microarray-based tests, are evaluated".

Only in rare exceptions (mainly for companion diagnostics, a subset of PM tests) does NICE conduct HTAs, while in general, diagnostic evidence is instead submitted by test manufacturers to individual budget holders, followed by negotiation of test reimbursement and payment tariffs. Reimbursement negotiations for companion drug/diagnostic products follow the typical pathway for drug reimbursement and pricing. Where appropriate and acceptable to payers and manufacturers, risk-sharing agreements are increasingly applied. NICE reviews clinical and economic evidence and gives recommendations on reimbursements for NHS decisions. Although not explicitly mandatory for single diagnostics, health economic modeling will likely be required to support complex molecular diagnostics.

The companion tests for Herceptin and Erbitux are the current examplars in patient stratification to establish personalized treatments. Prior to NICE assessment of relevant drugs, the pharmaceutical sponsors paid for diagnostics (Roche [Basel, Switzerland] for *HER2* and Merck kGA [NJ, USA] for *KRAS* testing) in the process of establishing personalized

medicine. *KRAS* testing is now offered by multiple accredited laboratories in the UK and is fully reimbursed by the NHS, though a global IVD product offering does not yet exist for *KRAS*, and the test price does not reflect the full value, as described previously. Merck Serono provided clinical and economic evidence based on test-plus-treatment scenarios for stratified population versus all patients. In 2010, herceptin was the first guidance to be published using NICE's single technology appraisal process, first introduced in 2006. Drugs are the initial focus for single technology appraisal guidance, but the process can also be used to evaluate medical devices, diagnostic techniques, surgical procedures and other therapeutic techniques. In May 2010, the NHS agreed to pay for *EGFR* testing for the drug Iressa® indirectly via a payment to drug sponsor AstraZeneca (Paddington, London) of GB£157.50–210.00 per test, via a network of regional laboratories. No globally approved *EGFR* IVD test yet exists.

In addition to the aforementioned institutions new diagnostic approval developments will also be influenced by the UK Technology Strategy Board stratified medicines innovation platform [105]. It should also be noted that the role of NICE within the UK healthcare system is currently in flux.

While *HER2*, *EGFR* and *KRAS* testing are now reimbursed on cost-based formulae in the UK, such approvals took several years and benefitted from the interim direct sponsorship of the pharmaceutical owners of the drugs in question. Such cost-based approaches do not provide the necessary reward for medical innovation, and it is unclear whether the scenarios described earlier are scalable, can be replicated without pharma sponsors or provide timely patient access in general.

Germany

Germany is the biggest EU diagnostics market. Similar to all countries, it is struggling to introduce new technologies and to contain costs of its healthcare system. To access the market with a diagnostic product, several groups are involved, which makes successful general introduction a lengthy process.

As described earlier, products require a CE mark. In addition, medical opinion leaders define required analytical performance, clinical utility and health–economic benefit. Medical doctors support and promote the use of a test. Advocacy groups and politicians may be helpful to support reimbursement.

In Germany, approximately 88% of the population is covered by the public insurance system and 12% by a private insurance or on a self-pay basis. The reimbursement by the public system is moderate. Private insurance may reimburse services and products that are not covered by the public system and payments tend to be higher. As shown in Figure 4, public system reimbursement decisions are made by a committee (Common Health Board [GBA]) comprising health insurance, hospital, society, physicians and neutral persons. GBA makes decisions based on inputs from medical societies, companies and governmental institutes, including an independent HTA Institute (Institute for Quality and Economic Efficiency in Healthcare [IQWiG], founded in 2004) to assess therapies and diagnostic methods on quality, health and economic benefit, according to its own developed methods. The total process has no specific timelines. IQWiG receives requests from GBA but can also start its own assessments, but only GBA can implement those. As highlighted in Figure 5, final reimbursement may only be approved on an individual cases-by-case basis in each of the 16 individual LÄNDER (regions). Taken together, Figures 4 & 5 illustrate the high complexity associated with securing diagnostic test reimbursement in major European markets such as Germany.

Innovative tests are introduced often as LDTs. Particularly in oncology and genetic diseases, a majority of tests, including *HER2* and *KRAS*, are performed using laboratory developed research use only reagents (even when a CE marked product exists) and reimbursed in Germany by a CPT code-like process, thus by technical procedure cost and not clinical or economic value.

France

France is the second market in Europe for drugs, behind Germany. However, despite a very effective cost containment policy owing to a centralized control of drug budget impact from the French Ministry of Health, there is further potential for high-value diagnostics to increase pressure on drug manufacturers while capturing a part of the expected savings.

Haute Authorité de Santé (HAS) is the key HTA body in France. The related transparency committee (TC) is the commission in charge of assessing all new drugs intended for coverage in France, with associated testing being provided at up to 28 regional centers. One of the key drivers for drug pricing in France remains the TC target population estimate. In 2008, after reviewing Amgen's (CA, USA) Vectibix for metastatic

colorectal cancer treatment, TC recommended its use for wild-type *KRAS* patients only. However, at the same time, HAS did not release any guidelines or review related to *KRAS* status testing, despite the existence within the HAS of a specific commission in charge of assessing medical technologies and medical devices (Commission Nationale d'Evaluation des Dispositifs Médicaux et des Technologies de Santé [CNEDIMTS]).

This lack of interest of the HTA body in *de novo* assessment of diagnostic tests can be explained by the fact that, unlike the prevailing situation for drugs and devices for which price is negotiated at the Ministry of Health level with manufacturers, prices of the diagnostic tests are negotiated directly between the social security and physician unions. These negotiations proceed via the Nomenclature des Actes de Biologie coding system for biological tests and Nomenclature Générale des Actes Professionnels for anatomopathological tests. The Nomenclature des Actes de Biologie and Nomenclature Générale des Actes Professionnels systems allow coverage for the entire testing cost, including physician time. However, as new diagnostic test registrations on these two coding systems are a complex process, the French Cancer Institute (Institut National du Cancer) has allocated specific envelopes (Mission d'Intérêt Général et d'Aide à la Contractualisation) for *KRAS* testing, allowing the development of specialized technological 'platforms' across the French territory.

As a consequence of the *KRAS* and other high-value diagnostic market access experience, payers in France have clearly understood the interest of diagnostic tests for personalized treatments, in order to increase benefits to patients, but also from their own payer's perspective. This is why the Nomenclature Générale des Actes Professionnels coding system is being replaced by the Classification Commune des Actes Médicaux (CCAM) coding system, potentially providing for a direct review by the CNEDIMTS of new diagnostic technologies leading to coverage. This change in coding policy could also improve simultaneous assessments by TC and CNEDIMTS for the drug and its associated diagnostic, respectively, resulting in a better recognition of the added value of the global combined therapeutic–diagnostic offering. Such a scenario might also have benefited herceptin, for which testing was first authorized in 2000, but for which reimbursement has been provided only since 2007.

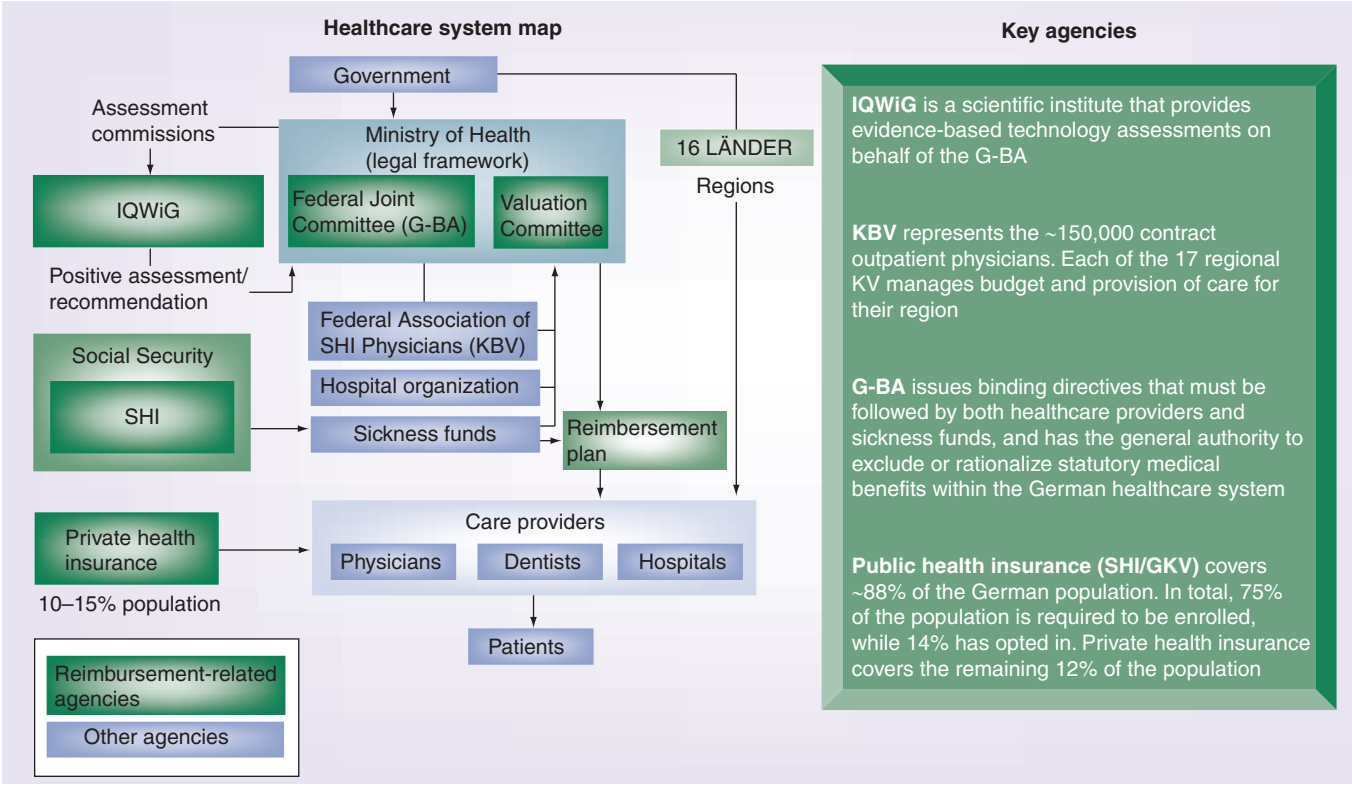


Figure 4. German healthcare system.
G-BA: Federal joint commitee; IQWiG: Institute for quality and economic efficiency in healthcare; KBV: Kassenarztliche Bundesvereinigung; KV: Kassenarztliche Vereinigungen; SHI/GKV: Statutory health insurance/German gesetzliche krankenversicherung. Adapted with permission from Scientia Advisors, LLC.

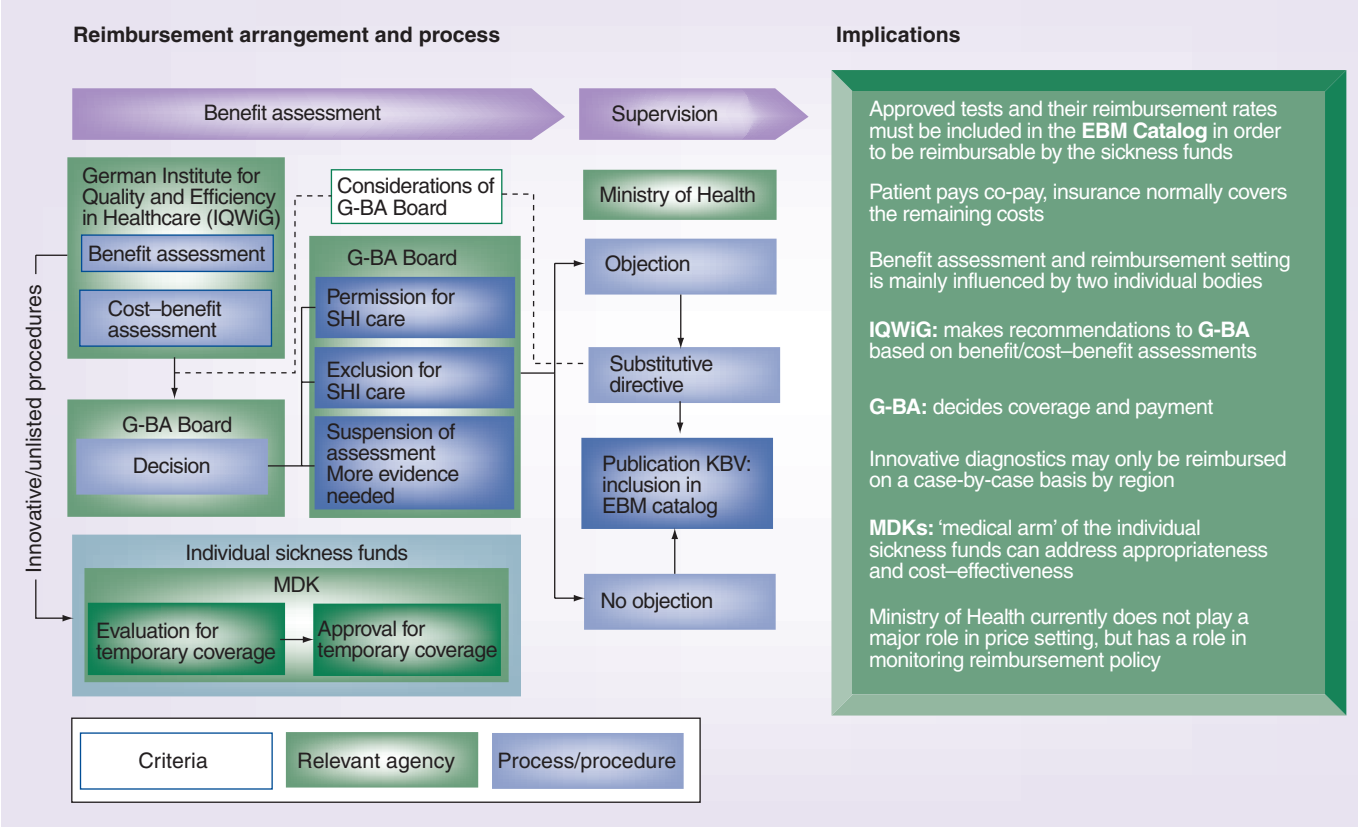


Figure 5. German reimbursement process.
EBM: Evidence-based medicine; G-BA: Federal joint commitee; IQWiG: Institute for quality and economic efficiency in healthcare; KBV: Kassenarztliche Bundesvereinigung; MDK: Medizinischer dienst der krankenversicherung; SHI: Statutory health insurance.
Adapted with permission from Scientia Advisors, LLC.

Spain

In Spain, a decentralized model applies in which the 17 autonomous regions and two autonomous cities are responsible for the delivery and financing of healthcare. National coordination amongst these regions is managed via the National Health System Interterritorial Council, chaired by the National Health Minister. This council establishes mandatory care levels that must be provided by all the regions. In 2003, regulations were introduced (Law of Cohesion and Quality of the National Health System) mandating inclusion of new technologies in the national catalog after specific review of efficacy, cost, efficiency, effectiveness, safety and therapeutic utility of the different alternatives. The council makes decisions relating to inclusion of products and services, but the central government representatives are responsible for pricing decisions. A HTA is required when incorporating new techniques, technologies or procedures, or when excluding those already provided, in the national common benefit package. The evaluation is carried out by the national HTA agency (Instituto de Salud Carlos, Madrid, Spain) in collaboration with seven regional HTA agencies, after review of the criteria listed earlier. The proposal of inclusion of new technologies that could significantly increase health expenditures also requires approval by the Fiscal and Financial Policy Council (Consejo de Politica Fiscal y Financiera, Madrid, Spain).

When marketing authorization is granted, the Ministry of Health initiates a procedure to decide on reimbursement of this new product on the national reimbursement list. The manufacturer is then invited to provide all relevant information to allow the Inter-Ministerial Pricing Commission (La Comisión Interministerial de Precios de los Medicamentos), led by Ministry of Health, to make a decision. If the outcome is positive (inclusion in the national reimbursement list), this decision is valid (mandatory) throughout the country.

Few personalized medicine tests have gone through this process. Instead, tests such as *HER2* and *KRAS* are sometimes supported by the pharmaceutical companies whose drugs they indicate (Roche for *HER2* and Merck kGA for *KRAS*), but more typically are paid out of the hospital budget. As will be discussed again later in this article, this paradigm has effectively deferred

availability of high medical value PM tests, especially when not used as true companion tests for a pharmaceutical product.

Italy

The Italian healthcare system is a decentralized version of the British NHS. Since 1978, there is a universal Healthcare system (Servizio Sanitario Nazionale) covering the whole population with national universal and compulsory health insurance. In Italy, therefore, it is not possible to opt-out of the Servizio Sanitario Nazionale. Patients are free to choose between public or private providers for many healthcare services. Since it is possible for the public sector to outsource the delivery of medical health services, an increasingly large part of healthcare services are currently provided by accredited private providers. Moreover, patients are free to buy private health insurance and to receive treatment at noncontracted private hospitals or consult private outpatient specialists, at their own expense. As in other European countries with increased personal income levels, more individuals choose to supplement their public health insurance with the purchase of personal health insurance, in a tiered system. There is a consolidation and optimization of diagnostic laboratory efficiency since 2007 resulting in larger tenders and increasing length of contracts, with a lower budget level. On the regulatory side, Italy has recently dedicated resources exclusively to improve medical vigilance of diagnostic products. Innovative tests such as *HER2* and *KRAS* are publicly funded and available via a network of public hospital laboratories organized in a network comparable to France.

Nordic countries

Healthcare costs in the Nordic countries (Denmark, Sweden, Norway, Finland and Iceland) are in general covered by their national healthcare systems. In some of the countries, patients cover part of primary care and prescription medicine costs. Expenses related to testing of specimens, for example blood, urine and tissue biopsies as part of the diagnostic workup of an individual patient as requested by the treating physician are, in general, covered by the national healthcare systems.

Personalized medicine tests must be approved by individual regions in each country before physicians can offer testing to patients. Some minor differences of approved tests can be seen from region to region. Rationale for implementation of a given test will usually be a direct link between test result and a specific treatment. This may be based on inclusion of the test in the drug labeling or on unambiguous recommendations by internationally well established groups such as St Gallen Oncology Conference or the National Comprehensive Cancer Network.

Guidelines for selection of a given test are not established in the Nordic countries although technical validation of internally developed assays is established in all laboratories offering testing of clinical specimens. Commercially available assays having IVD-CE labeling are utilized in the majority of laboratories in order to gain predictive information although some laboratories might utilize internally developed and validated assays. For *HER2* testing, the majority of test sites are using immunohistochemistry and *in situ* hybridization assays from commercial manufacturers. All clinical test laboratories in the Nordic countries participate in national or international proficiency testing programs such as NordiQC [106] and UK NEQAS [107], although the consequence of performance evaluation in these programs is limited. Accreditation of the Nordic test laboratories has been initiated with emphasis on turnaround time and logistics.

Case studies of several high-complexity LDTs

In the foregoing discussion, several European market scenarios for the *HER2* and *KRAS* tests were considered. Two further leading examples of personalized medicine tests on the US market today serve to highlight the European market's entry challenges. Both tests are high-complexity, value-based priced LDT offerings. Other LDTs will also be considered in this section. The first of these tests to be considered here is the Trofile™ companion test.

Trofile was developed as a companion test for HIV-1 coreceptor tropism. This companion test to Maraviroc (brandname Selzentry®, or Celsentri outside the USA), manufactured by Pfizer (NY, USA), is the result of a collaboration initiated in 2006 intended to demonstrate tissue tropism, or the cellular route taken by the HIV-1 virus to enter CD4 cells. This is the first such collaboration in HIV and, together with *KRAS*, is probably the most high-profile companion test developed since the *HER2* test in 1998. The Trofile assay is used to identify the CCR5-tropic patient subpopulation that responds to CCR5 antagonists. When the collaboration began, Pfizer's drug was in Phase III and the assay was used for late-stage clinical trial selection. The drug has since been approved for marketing and incorporated in the standard of

care for patients identified as CCR5 tropic by the US$1960 Trofile laboratory-developed-test (price quoted is launch price rather than current average selling price from provider Labcorp).

Recognition of the barrier to entry for the complex Trofile assay in Europe forced the partners to structure a deal specifying that Pfizer would pay Monogram for the Trofile test in Europe and other ex-US markets. This relatively unusual arrangement was structured to circumvent the significant adoption challenge the drug would otherwise have faced. In the USA, by contrast, the test received nearly 100% of payer coverage within 12 months of launch. While this centralized test offering is also available in the major European markets, it is not directly supported by the European healthcare system. It is unlikely that the Monogram–Pfizer model can be scaled across the whole industry, and not all companion test scenarios have a pharmaceutical sponsor. Furthermore, test and drug adoption have been hampered by logistical and marketing challenges. In March 2010, Pfizer partnered with US pharmacy benefits manager Medco (NJ, USA) to further build physician awareness. Outside the USA, Pfizer leads reimbursement initiatives for both the drug and the test.

It is also illustrative to consider the example of Genomic Health's Oncotype DX test, launched in the USA in 2004. This prognostic and predictive assay has been shown to quantify a patient's risk of recurrence in early-stage, node-negative, estrogen receptor-positive (ER^+) invasive breast cancer and also the likelihood of chemotherapy benefit. This assay examines a small portion of a patient's fixed and paraffin-embedded tumor tissue at a molecular level, using quantitative reverse-transcriptase (qRT) PCR technology to measure 21 cancer-related genes and controls, and provides quantitative information about the biology of the individual's disease. The test reports a computed algorithm as a single Recurrence Score™ between 0 and 100 to quantify the likelihood of distant recurrence at 10 years.

The company, collaborators, private payers and a number of other institutions have produced an array of collaborative and independent studies on thousands of patient samples demonstrating a rather robust evidence platform associated with various aspects of the test. There has also been a number of utility trials and health economic studies outlining the clinical ramifications of the test in cancer care. This represents the most robust evidence generation effort for a single indication and specific value-priced diagnostic test, and has driven the test to standard-of-care status in the USA, with approximately 50% penetration of initial target market [3]. Both the American Society of Clinical Oncology and the National Comprehensive Cancer Network (NCCN) recommend the use of Oncotype DX for patients with breast cancer in their respective clinical practice guidelines.

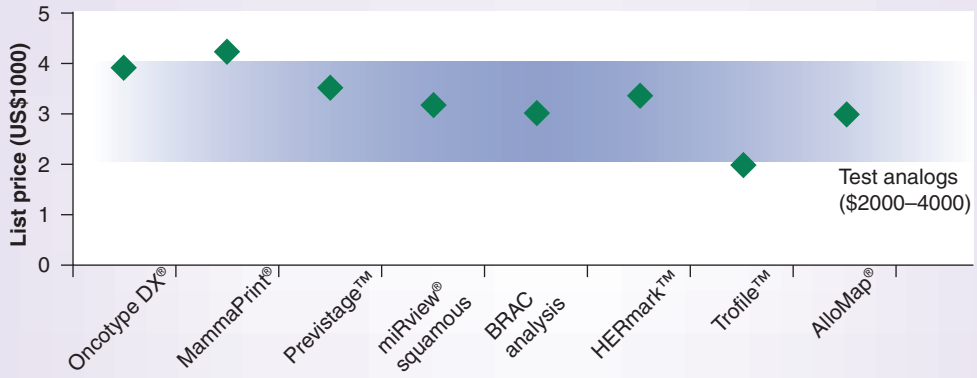
The company was able to win value-based pricing in the USA of approximately US$3900, based on its health–economic analyses. Using a 100-patient cohort from the US National Surgical Adjuvant Breast and Bowel Project, the company was able to demonstrate a $2000 per patient savings resulting from deployment of the test in the eligible population [4]. In practice, oncologists and surgeons can use the recurrence score to determine which patients are most likely to benefit from chemotherapy, thus sparing those that are not likely to benefit from the side effects, and conserving resources for payers, which is estimated to be $10,000–20,000 on average per patient.

The company currently generates approximately $170 million in annual revenue, primarily from sales of Oncotype DX. However, only approximately 6% of sales are generated outside the USA, and the company has not realized significant penetration into European markets, despite the existence of robust clinical and health-economic evidence. Most patients outside the USA pay on an out-of-pocket basis. By contrast to its USA accessible market penetration of approximately 50%, penetration outside the USA is less than 2% [3].

While Trofile and Oncotype DX represent leading US examples, they are not unique. Figure 6 shows these assays in the context of other value-priced offerings in the USA, with 2008 US prices in the range of $1000 to more than $4000. None of these assays have demonstrated significant market penetration in Europe. For example, XDx (CA, USA) CEO Pierre Cassigneul explained at the October 2010 EPEMED annual conference that the AlloMap® test was not even being marketed in Europe owing to market complexity, including reimbursement challenges [108].

Conclusion

A more personalized approach to medicine is likely to prevail in the years to come, led by more precise diagnostic, prognostic, and companion predictive and monitoring test offerings. However, with 10–30% of drugs expected to be required to include a companion diagnostic, the absence of appropriate public sector



Company	Genomic health	Agendia	DiagnoCure	Rosetta genomics	Myriad genetics	Monogram biosciences		XDx
Indication	BC recurrence risk		Colorectal cancer recurrence risk	Lung cancer subtype diagnostic	Genetic risk of developing BC	HER2 status in BC patients	Treatment selection for HIV patients	Heart transplant rejection diagnostic

Figure 6. Illustrative US pricing of leading personalized medicine tests in 2008.
BC: Breast cancer; DX: Diagnostics.
Adapted with permission from [9].

reimbursement models is likely to deprive the European population of efficient access to rapidly emerging standard of care therapy.

This article has focused on the two core issues of general reimbursement process inefficiencies in Europe associated with suboptimal procedure–cost-based payment, together with the virtual absence of precedents for the diagnostic value-based reimbursement necessary to stimulate development. Notably, even procedure-based diagnostic payment, while far from an equitable market model, faces inter- and intra-national hurdles, including lack of health technology assessment transparency, decentralization of review and occasionally complete lack of associated funding. This results in access delays and necessitates work-arounds such as subsidization by pharmaceutical companies. While each of the European nations considered has ultimately found a way to support two of the leading predictive tests available today on a modest procedurally priced basis, we argue that this has happened in a way which is not scalable and which does not foster efficient growth of the field. Furthermore, as discussed, there is no precedent for European public sector value-based test reimbursement, hence cutting-edge value-based tests are only available to a select few in Europe.

Two current work-arounds prevail in Europe. The first involves pharmaceutical subsidization or sponsorship of diagnostic test reimbursement. This has happened with *HER2*, *KRAS*, *EGFR* and *BCR-ABL* testing with sponsors such as Roche, Novartis (Basel, Switzerland), Merck kGA, Amgen and AstraZeneca. This may increasingly become the norm for co-development programs between pharmaceutical and diagnostic companies, especially when one considers that diagnostics companies, in general, lack the deep reimbursement core competency of their pharmaceutical partners. However, this solution is probably not scalable and is in any event limited to such predictive collaborations, themselves representing only a subset of the universe of PM tests. Another work-around entails the temporary targeting of private sector patients, depriving approximately 90% of the European population of timely access, especially for tests with value-oriented pricing.

Europe, with its primarily centrally managed healthcare systems, has the potential to be a leader in the emerging PM field. However, current reimbursement practices deter innovation, much of which is being driven in the USA. To foster local innovation and patient access in the EU, more process clarification, review centralization, demonstration models and clarification of economic and other utility criteria will be required.

One example of a useful attempt to foster and rationalize use of European HTA resources is the joint initiative between the European

Commission and EU member states on establishment of a European network for HTA [109]. This initiative, as described at a reimbursement workshop jointly organized by the European Device Manufacturers Association and International Association of Clinical Chemistry and Laboratory Medicine [5], comprises 35 government-appointed organizations. Also at the EU level, there is consideration, partly motivated by PM, to revisit the 1989 transparency directive 89/105/EEC, with a focus on pricing and reimbursement. Specific initiatives, such as the establishment of demonstration projects for certain PM scenarios would also be welcome, as has been proposed in the context of healthcare reform in the USA.

The authors look forward to development of these and related initiatives, and to a time when the value of emerging PM tests is expeditiously recognized and incorporated in routine patient care across Europe. To contribute to the realization of this objective, some of the authors have joined others in forming EPEMED [110], a not-for-profit organization founded to address some of the complex issues in PM which confront industry, regulators, payers and governments.

Financial & competing interests disclosure

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Executive summary

Background

- Global reimbursement challenges for high-value diagnostics tests are significant.
- In the USA, while there are several examples of 'value-priced' laboratory-developed tests (LDTs), there are no comparable examples of *in vitro* diagnostic (IVD) tests.
- In Europe, however, there is no precedent for public sector value pricing to incentivize high-value diagnostic development for either LDTs or IVDs, and European patients are effectively denied access.

Specific challenges in Europe

- Europe presents specific inter- and intra-national heterogeneity in terms of diagnostic reimbursement.
- The complex European IVD reimbursement paradigm is reviewed for several major markets in this article, and specific challenges for test developers are highlighted.
- It is noted that diagnostic reimbursement is less centralized and less transparent than its therapeutic counterpart, which has a significant adverse impact on European innovation.

Possible solutions

- This article describes several initiatives to address Europe-specific challenges.
- Several of the authors, in addition to serving in leading personalized medicine companies, are also founders of The European Personalized Medicine Coalition, an emerging European advocacy organization formed to address market challenges.

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