

PERSONALISED MEDICINE IN EUROPE – ENHANCING PATIENT ACCESS TO PHARMACEUTICAL DRUG-DIAGNOSTIC COMPANION PRODUCTS

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EXECUTIVE SUMMARY

With our growing understanding of the molecular basis of human disease, there has been unprecedented investment in research and development of personalised medicines - drugs that rely on biomarkers to optimize therapeutic interventions. Targeted therapeutic interventions offer the potential to improve clinical outcomes, increase patient safety, and reduce spending on unnecessary or ineffective prescription drugs. Personalised medicine uses (mainly molecular) biomarkers for purposes of risk assessment, diagnosis, prognosis, monitoring and guiding therapeutic decisions. This report focuses on companion diagnostics, tests which use biomarker status to stratify patient populations into subpopulations of differential drug response and adverse reactions. Beyond this, stratification according to predictive biomarkers can also be beneficial during the drug development process.

More than 75% of the pharmaceuticals associated with companion diagnostics are approved in oncology. In the future, patients with autoimmune, inflammatory and neurodegenerative and other diseases are also expected to benefit from stratification by predictive biomarkers. The development of companion diagnostics is therefore expected to accelerate. Often a commercially available *in vitro* diagnostic test for one biomarker is associated with one pharmaceutical drug. However, with an increasing number of predictive biomarkers in the same indication, the amount of the biospecimen, especially tissue samples in the case of oncology, becomes the limiting factor for test access. Therefore, diagnostic developers seek to develop so-called multiplex tests that combine several biomarkers in a single analysis or even more ambitious comprehensive analyses like whole genome tests.

Apart from these medical-scientific challenges, patient access to stratified pharmaceutical drug therapy faces a different, more structural challenge: In-vitro diagnostics and pharmaceutical drugs traditionally follow separate routes to patient access at an institutional level. In contrast, pharmaceutical drugs conditional on a particular biomarker status can only be used after companion diagnostic testing, which inevitably links a pharmaceutical drug to a companion diagnostic. This study aims to identify factors impeding or facilitating patient access and to develop policy recommendations for improving patient access in Europe, analysing patient access pathways to pharmaceutical drug-diagnostic companion products from a patient perspective.

Patient access in the European Union (EU) was analysed with respect to the most important stages of patient access: regulatory approval/certification, health technology assessment, pricing reimbursement/funding, providers (clinicians and pathologists/laboratories) and patients. For stages with large differences between countries, the five most populated countries in the EU – France, Germany, Italy, the United Kingdom and Spain – were chosen as examples. Current relevant publications were reviewed (peer-reviewed articles, company reports, presentations, abstracts from congresses) and exploratory interviews with expert stakeholders were conducted to get up-to-date primary data from practitioners in the field. Ideally, systematically collected data on actual patient access in terms of drug and companion diagnostic utilization would provide the evidence base for this study. However, such data rarely exist in the EU-5. Recommendations for improved patient access are given based on the identified facilitating and impeding factors for patient access.

The current EU framework separates regulatory approval for pharmaceutical drugs from conformity assessment for companion diagnostics. Recommendations by the European Medicines Agency (EMA) allow any validated companion diagnostic that is in line with the licensed indication to be used in association with the approved pharmaceutical drug. It is easier to bring new tests (e.g. different versions of the test used in regulatory trials) to the market and use them alongside an approved pharmaceutical drug in the European environment than in the US – a situation that fosters innovation. Having said this, recommending minimum requirements for companion diagnostics may improve quality of testing and reduce the risk of misclassifications.

Health technology assessment, pricing and reimbursement/funding processes differ markedly between countries. Pharmaceutical drugs and the associated companion diagnostics are evaluated separately in France, Germany, Italy and Spain. Separate evaluation processes are neither coordinated nor synchronized. In the United Kingdom (England), companion diagnostic evaluation is integrated into the technology appraisal of the associated pharmaceutical drug which avoids delays or inconsistent decisions. Integrated evaluation is therefore recommended for other countries, too. The United Kingdom also established an assessment programme for situations in which several tests for the same biomarker are available. Pricing in most countries involves elements of value-based pricing approaches and external reference pricing. In fee-schedule systems like Germany, France and Italy, availability of generic codes facilitates access to companion diagnostic testing at the time of drug launch, provided that tariffs associated with reimbursement codes sufficiently reflect current testing costs of laboratories. If new codes have to be generated, patient access may be delayed, because code generation processes are not subject to time limits. In systems with global annual laboratory budgets like Spain and the United Kingdom, code generation is not necessary for reimbursement. However, patient access may be delayed when positive reimbursement decisions imply mandatory funding but local budget holders' budgets are not adapted. In the United Kingdom, funding mechanisms for companion diagnostic testing are not clear among stakeholders; therefore companies pay for a considerable proportion of companion diagnostic tests on a temporary basis. In Spain, companion diagnostic testing is typically paid for by pharmaceutical companies.

There are other country-specific characteristics. In Germany, funding of companion diagnostic testing is mandatory if required by the drug label. In France, the National Institute of Cancer (INCa) facilitates access to pharmaceutical drugs associated with companion diagnostics in oncology by providing molecular testing free of charge at the time of drug launch. However, promotion by INCa is temporary, and managing the transfer of molecular testing to the institutions of the health care system remains a challenge yet to be addressed. Furthermore, promotion of companion diagnostic testing in France is limited to oncology and does not comprise other therapeutic areas. Italy is the country with the largest number of risk-sharing agreements in place. Such risk-sharing agreements depend on data about the utilization of select drugs in their various indications. Funding of companion diagnostic testing in a hospital setting is based on diagnosis-related group systems in all of the EU-5 countries. Diagnosis-related groups pay a fee per case which includes companion diagnostic testing expenditures.

Laboratory testing performance varies within countries. In the worst case, errors in the testing process may lead to misclassifications of patients, thus undermining the key principle of personalised medicine, i.e. providing the right drug for the right patient. Therefore, providing high testing quality is important in order to select the right patients for a pharmaceutical drug. Implementation of quality assurance measures helps to maintain a high quality standard. The most extensive quality assurance measure is accreditation, which is already mandatory for laboratories performing companion diagnostic testing in some countries, and will become mandatory in others. Part of the accreditation requirements is participation in external quality assessment schemes. However, external quality assessment schemes for molecular testing still need to be institutionalized, e.g. in Germany. Testing quality may be incentivized by linking testing performance criteria to reimbursement/funding of companion diagnostic testing.

Little is known about the knowledge and attitudes of European clinicians and especially oncologists. Therefore, further research is needed to determine whether clinicians' attitudes and behaviours are impeding or facilitating patient access. Finally, the role of patients has changed in recent years as the majority of patients now wish to play a more active role in the clinical decision-making process.

In conclusion, patients in the five largest EU countries do have access to companion diagnostic testing and drugs associated with companion diagnostics. However, countries differ with regard to the scope and timing of patient access. Integrated health technology assessments and consistent reimbursement/funding decisions for pharmaceutical drugs and the associated companion diagnostics are key facilitators for patient access, along with ensuring high quality of the testing process.

Personalised medicine (PM) has been defined in various ways. In the Medical Subject Headings – the vocabulary controlled by National Library of Medicine – the synonymous term individualized medicine is defined as follows: “[A] therapeutic approach tailoring therapy for genetically defined subgroups of patients.” However, it has been argued that personalised medicine is more than genomic medicine (Simmons, Dinan, Robinson, & Snyderman, 2012). A broader definition was developed in a workshop of the European Commission health research directorate: “A medical model using molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, and determine the predisposition to disease at the population level and to deliver timely and stratified prevention” (“Omics in personalised medicine, summary workshop report,” 2010).

The key concept in this definition is molecular profiling. Molecular profiling involves the use of a biomarker. A biomarker can be defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention”. (Trusheim, Berndt, & Douglas, 2007). Different types of biomarkers can be distinguished according to their purpose:

- predisposition biomarkers – to assess the risk of developing a disease (e.g. BRCA1 for breast cancer)
- diagnostic biomarkers – to identify a specific disease (e.g. HCV RNA after infection)
- prognostic biomarkers – to predict the course of disease (e.g. HER2 for breast cancer)
- monitoring biomarkers – to keep track of disease progression (e.g. BCR-abl for monitoring the treatment response in patients with chronic myeloid leukaemia)
- predictive biomarkers – to predict the response or reactions to a pharmaceutical drug (e.g. BRAF-V600 for melanoma patients)

This report will exclusively focus on predictive biomarkers. At standard doses, patients respond differently to the same pharmaceutical drug. A test for a predictive biomarker that is associated with a pharmaceutical drug (Rx) is called a companion diagnostic (CDx). Recently, a formal definition of companion diagnostics was proposed by the European Commission and further modified by the European Parliament. The current definition reads as follows and is subject to final approval by all EU institutions in the context of *in vitro* diagnostics regulation: “‘companion diagnostic’ means a device specifically intended for and essential to the selection of patients with a previously diagnosed condition or predisposition as suitable or unsuitable for a specific therapy with a medicinal product or a range of medicinal products.” (European Parliament, 2013a)

For a full understanding of the implications of pharmaceutical drugs associated with companion diagnostics, it is important to keep in mind that they are co-dependent: “Health technologies are co-dependent if their use needs to be combined (either sequentially or simultaneously) to achieve or enhance the intended clinical effect of either technology” (Australian Government, 2011)

The most important application of companion diagnostics is to support the choice of the most appropriate pharmaceutical drug for a given patient. It is well known that patients respond differently to the same pharmaceutical drug. One subgroup of patients may not respond at all, another subgroup may respond partially whereas a third subgroup may experience adverse drug reactions. One heuristic to find out which subgroup a patient belongs to is trial and error. A trial-and-error approach can be very time consuming, and patients with a life threatening disease may run out of time before the most appropriate pharmaceutical drug is identified. (Aspinall & Hamermesh, 2007). The promise of predictive biomarkers is the ability to identify patients who benefit or who are at risk of suffering harm from a pharmaceutical drug before treatment even starts, thereby improving patients’ health outcomes.

A second application of companion diagnostics is during pharmaceutical drug development (Evans & Relling, 2004). If the association between a predictive biomarker and a new pharmaceutical drug is discovered early enough, subgroup-specific drug development is possible. Such an enriched patient population is expected to yield higher efficacy rates with smaller sample sizes and, hence, may also lower trial costs. In theory, even development time could be shortened, leading to increased overall efficiency of the pharmaceutical drug development process (Deverka, Vernon, & McLeod, 2010).

However, in practice more often than not subgroup-specific development is initiated only after a phase III study has failed and a subgroup analysis has revealed the importance of stratifying patients. In such a scenario costs and development time would be increased. However, using a companion diagnostic may allow a comparatively small group of responders to gain access to an efficacious pharmaceutical drug that would otherwise never have received a marketing authorization.

1.1

COMPANION DIAGNOSTIC AND ONCOLOGY

As of December 2013, 35 substances associated with a companion diagnostic were approved in Germany, the largest pharmaceutical market in Europe. Remarkably, 27 of the 35 substances (77%) belong to the therapeutic area of oncology (Table 1).

Several reasons may explain the large proportion of cancer drugs. In recent years a lot of research has been aimed at understanding the molecular basis of cancer. An understanding of the molecular basis of pathogenesis is a prerequisite for targeted pharmaceutical drug development. Such research is supported by the availability of tissue samples in biobanks where excess tissue is stored. Furthermore, patients confronted with a life-threatening disease may be more willing to accept the risk associated with invasive diagnostic procedures and to participate in clinical trials which offer the benefit of early access to new treatment options.

In the field of oncology, one of the unsolved challenges is the heterogeneity of tumour cells. Tumours consist of several cell clones with different mutations. At metastatic sites additional cell clones may be present. Therefore, a tumour sample usually contains various – but rarely all – cell clones. If biomarker tests are applied to this mix of cell clones, the test result is likely to over-represent the more frequent clones. Targeting therapy to these clones reduces their number but allows treatment-refractory clones to persist and grow, leading to disease recurrence. In order to account for the extent of heterogeneity, a large fraction of single cells in a biopsy would need to be analysed. But even in an ideal world, where genomes were sequenced at a single cell level and biopsies contained all relevant cell clones, there would still be a problem of heterogeneity, because tumours change over time. In other words, the tumour characterized with a biomarker test may no longer be present *in vivo*.

SUBSTANCE	THERAPEUTIC AREAS	BIOMARKER	STATUS
ONCOLOGY			
Anastrozol	breast cancer	expression of oestrogen- and/or progesterone receptors	required
Arsentrioxid	acute promyelocytic leukemia	PML/RAR-alpha	required
Bosutinib	CML	Philadelphia-Chromosome	required
Brentuximab vedotin	certain lymphomas	CD30 overexpression	required
Cetuximab	colon cancer	KRAS wildtype	required
Crizotinib	lung cancer	EML4 ALK fusion gene	required
Dabrafenib	melanoma	BRAF-V600 Mutation	required
Dasatinib	acute lymphatic leukemia	Philadelphia chromosome	required
Erlotinib	lung cancer	activating mutations of EGFR-tyrosine kinase	required
Everolimus	breast cancer	no expression of HER2/neu, hormone-receptor expression	required
Exemestan	breast cancer	oestrogen receptor expression	required
Fulvestrant	breast cancer	expression of oestrogen and progesterone receptors	required
Gefitinib	lung cancer	activating mutations of EGFR-tyrosine kinase	required
Imatinib	ALL/CML	Philadelphia chromosome	required
Lapatinib	breast cancer	HER2-overexpression	required
Letrozol	breast cancer	expression of oestrogen and/or progesterons receptors	required
Mercaptopurine	oncology	TPMT deficiency	recommended
Nilotinib	CML	Philadelphia chromosome	required
Panitumumab	colon cancer	KRAS wildtype	required
Pertuzumab	breast cancer	HER2 overexpression	required
Ponatinib	acute lymphatic leukemia	Philadelphia chromosome	required
Tamoxifen	breast cancer	HOXB13:IL17BR ratio	recommended
Tamoxifen	breast cancer	hormone receptor expression	recommended
Toremifen	breast cancer	hormone receptor expression	required
Trastuzumab	breast cancer and gastric cancer	HER2-overexpression	required
Trastuzumab emtansine	breast cancer	HER2-overexpression	required
Vandetanib	cancer of thyroid gland	RET mutation	recommended
Vemurafenib	melanoma	BRAF-V600 mutation	required
OTHER THAN ONCOLOGY			
Abacavir	HIV/AIDS	HLA-B*5701	required
Azathioprin	immunosuppression	TPMT	recommended
Carbamazepin	epilepsy	HLA-B*3101	recommended
Carbamazepin	epilepsy	HLA-B*1502	recommended
Ivacaftor	cystic fibrosis	G551D-mutation	required
Lomitapid	familial hypercholesterolemia	homozygosity	recommended
Maraviroc	HIV/AIDS	CCR5-tropism	required
Natalizumab	multiple sclerosis	anti-JCV antibodies	recommended
Oxcarbazepin	epilepsy	HLA-B*3101	recommended

TABLE 1

Pharmaceuticals approved in Germany on 2 October 2013 for which testing is either required or recommended before use (Source: www.vfa.de/personali-siert, accessed on 13 December 2013, slightly modified)

In the future, other therapeutic fields than oncology may benefit more from stratifying the patient population. Such therapeutic fields include autoimmune, inflammatory and neurodegenerative diseases.

Today, most commonly one commercial test for one biomarker is associated with one pharmaceutical drug. With the development of the field alternative tests for the same biomarker will become available for an increasing number of biomarkers. For example, the National Institute for Health and Care Excellence (NICE) in the UK recently published a comparative evaluation of tests available for detection of mutations in the epidermal growth factor receptor tyrosine kinase (EGFR-TK) gene (NICE, 2013a). Conversely, there is a trend towards development of multiple pharmaceutical drugs associated with the same biomarker. For instance, Erlotinib and Gefitinib are associated with EGFR-TK mutations in the field of non-small-cell lung cancer (Table 1).

The number of diagnostic tests that can be performed with a single biopsy is limited. Therefore, developers aim to detect several biomarkers in a single test. Such multiplexed tests or test panels are already available for patients with breast cancer for prognostic purposes, e.g. EndoPredict (12 genes), OncotypeDX (21 genes) and MammaPrint (70 genes).

Developing indication-specific predictive biomarker panels will be an important intermediate step toward the ultimate goal of sequencing the whole genome. The technology for sequencing a whole genome in a reasonable time is already available. It is called next generation sequencing (NGS) or massive parallel DNA sequencing (Shendure & Ji, 2008).

As yet, costs and accuracy of NGS do not meet the requirements for routine diagnostic use. However, costs are plummeting at the same time as quality and speed of performing the test are increasing. (Crews, Hicks, Pui, Relling, & Evans, 2012). It is only a matter of time before NGS will be cost-effective compared to current biomarker tests.

Apart from technical and scientific challenges, NGS also poses serious ethical questions. For example, it might be contentious whether a germ line genome for every individual should be analysed and stored immediately after birth to be accessed by health care professionals whenever it is needed for treatment and prevention (Chiang & Million, 2011).

It must be noted that biomarkers do not only refer to variations in DNA. Other molecules interact with DNA and change gene expression processes. Therefore, it might be fruitful to study epigenetic modifications, the transcriptome, metabolome and proteome (Crews et al., 2012).

As the -omics technologies develop, discovery of combinations of biomarkers that together predict drug response becomes more likely. This would be a big step up from the highly penetrant monogenic variations in the genome that are exploited today. (Eichelbaum, Ingelman-Sundberg, & Evans, 2006; Evans & Relling, 2004). However, interpreting test results in such a complex scenario becomes more challenging.

A prerequisite for handling the massive volumes of data generated by applying -omics technologies is the availability of adequate information technology. Moreover, technologies have to be developed to detect patterns in the data that can be linked to clinical states. Therefore, progress in the field of personalised medicine depends on parallel development of bioinformatics and big data approaches to pattern recognition.

Apart from these medical scientific challenges, patient access to stratified pharmaceutical drug therapy faces a different, more structural challenge: *In vitro* diagnostics and pharmaceutical drugs traditionally follow separate routes to patient access at an institutional level. In contrast, pharmaceutical drugs conditional on a particular biomarker status can only be used after companion diagnostic testing, which inevitably links a pharmaceutical drug to a companion diagnostic.

AIM OF THIS STUDY

This study aims

- to identify factors impeding or facilitating patient access and
- to develop policy recommendations for improving patient access on the basis of the identified factors

in Europe analysing patient access pathways to pharmaceutical drug-diagnostic companion products from a patient's perspective.

Patient access was analysed following a framework that takes into account the sequence of stages a new pharmaceutical drug and/or the associated companion diagnostic have to pass before a patient gets access to them (Figure 1).

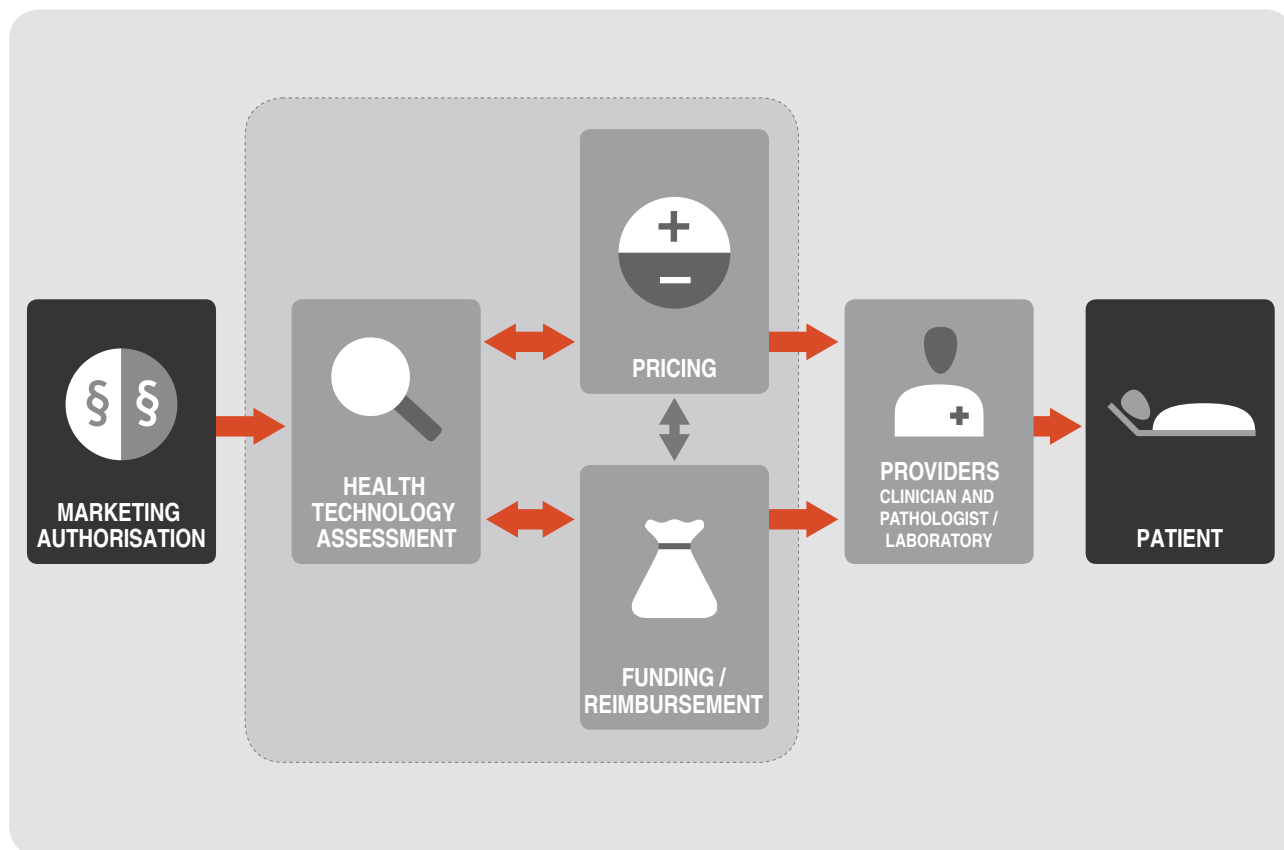


FIGURE 1

Patient access framework. Regulatory approval/certification includes a marketing authorization for the pharmaceutical drug issued by EMA and may require a CE marking of a commercial test kit for the companion diagnostic. In some countries health technology assessment methodologies will be used as solid evidence base for reimbursement and pricing decisions. Funding pathways then need to be found for companion diagnostics, as knowledge of a biomarker status is often mandatory prior to prescribing the pharmaceutical drug. At a provider level, the relationship between patient and clinician is paramount. Patients require access to trustworthy information in order to actively participate in the medical decision-making process.

The framework starts with regulatory approval of the pharmaceutical drug or certification of the associated companion diagnostic. This first stage is followed by assessment of value using health technology assessment (HTA) methods. Such evaluations are used to inform pricing and reimbursement/funding decisions. The next stage is provision of companion diagnostic testing and the pharmaceutical drug by pathologists/laboratories and clinicians. The endpoint of the framework is the patient, and considerations about the patient's role were briefly made at a European level. The interactions between patients, pathologists, and payers are more complex and therefore displayed in more detail (Figure 2).

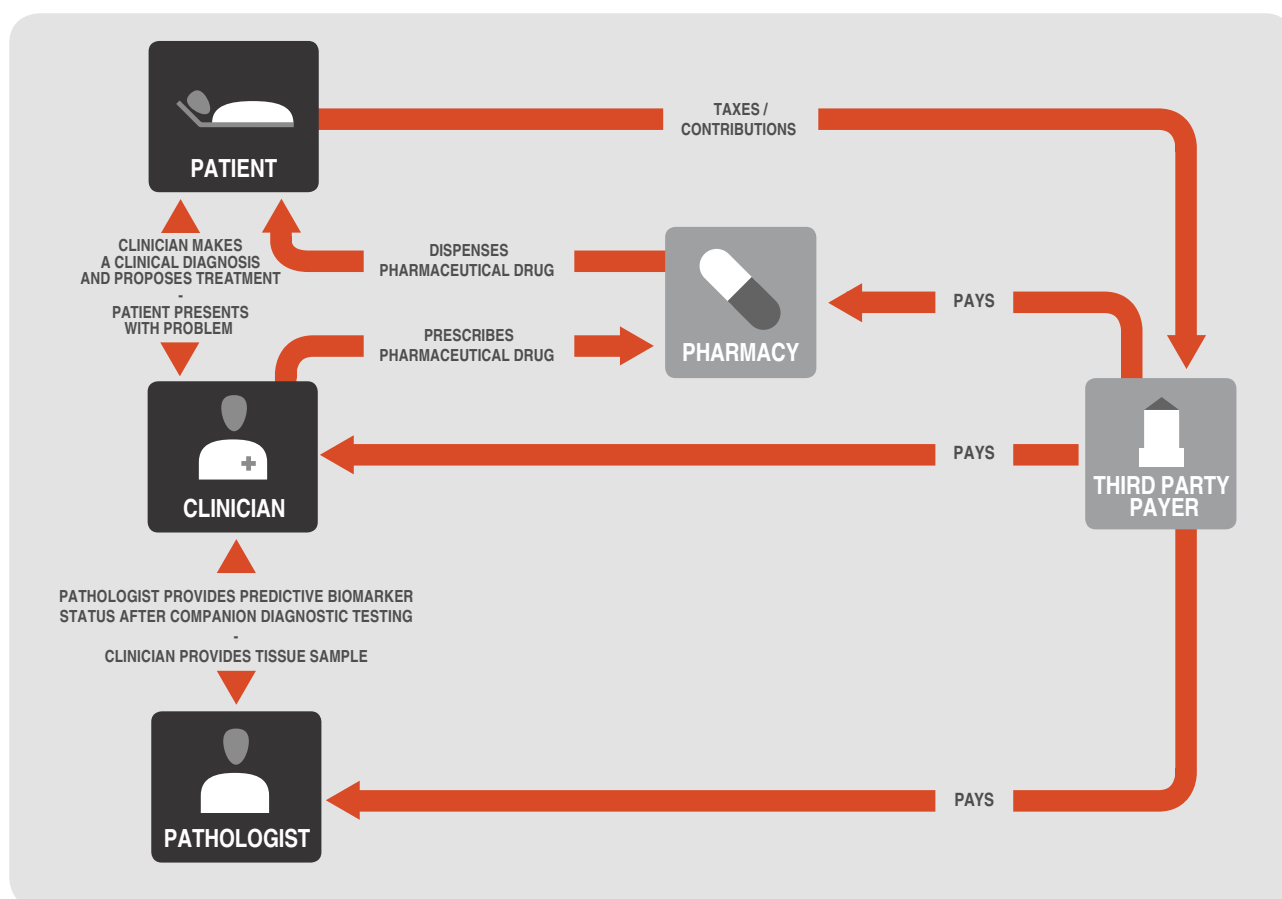


FIGURE 2

Patient access framework – key interactions at the provider level. Patients consult a clinician creating a relationship of trust and confidence. The clinician may take a biopsy and send it to the pathologist in order to get the right diagnosis. This process involves companion diagnostic testing to inform treatment decisions. Based on the result of the companion diagnostic test clinicians will prescribe the most appropriate drug which will be dispensed either by a hospital or ambulatory pharmacy. The whole process only works if clinicians and pathologists are compensated for their services, and costs for the pharmaceutical drug and companion diagnostic testing are funded.

For stages in the framework with large country-by-country differences the five most populated EU countries (EU-5) i.e. Germany (DE), United Kingdom (UK), France (FR), Italy (IT) and Spain (ES) – were used as examples as they represent more than 60 % of the EU-27 population (Eurostat, 2013).

Ideally, systematically collected data on actual patient access in terms of drug and companion diagnostic utilization would have formed the evidence base for this study. However, such data rarely exist in the EU-5. A narrative literature review was performed to identify relevant publications with a focus on peer-reviewed articles. Company reports, presentations, abstracts and institutional websites were also considered. The literature review was guided and supplemented by 30 exploratory interviews with expert stakeholders (mostly suggested by the advisory committee) to ensure that the description and analysis reflected current practices. Expert stakeholders came from various groups, i.e. academia, regulators including EMA, health technology assessment, industry (diagnostic and pharmaceutical), laboratories, hospitals, patients' organizations and consultants. The majority of expert stakeholders were based in the United Kingdom, France and Germany. Several facets of patient access were considered including scope of access, time to access, equality of access and performance of the patient selection method.

3.1

REGULATORY APPROVAL AND CERTIFICATION

In Europe regulatory pathways for pharmaceutical drugs and associated companion diagnostics are separated.

Marketing authorization applications for pharmaceutical drugs have to be submitted to the Committee for Medicinal Products for Humans Use (CHMP) within the European Medicines Agency (EMA). Based on the assessment and recommendation of EMA, the European Commission then grants a single marketing authorization valid in every member state of the European Union. The association with a companion diagnostic test is stipulated in the pharmaceutical drug label. It is important to note that EMA recommendations on the pharmaceutical drug label do not specify a particular test and therefore any validated test can be used.

A pre-marketing approval is not necessary for companion diagnostics. Commercial companion diagnostics are classified as *in vitro* diagnostics (IVDs) in Europe and therefore have to be in compliance with the respective 'IVD directive' ("Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices," 1998). Compliance with the IVD directive is indicated by a CE marking. Today, self-certification by the manufacturer is sufficient in most cases to acquire a CE marking. Laboratories which develop their own biomarker tests for in-house use – so called in-house tests or laboratory developed tests – are exempted from CE marking requirements.

The IVD directive is currently under revision. The European Commission's proposal for a Regulation on IVDs (expected to apply between 2015 and 2019) introduces a risk classification that classifies companion diagnostics as Class C (high individual risk and/or moderate public health risk). Class C *in vitro* diagnostics require a compulsory review by a notified body. "Notified Bodies are the only recognized third party bodies that can carry out a conformity assessments laid down in the relevant harmonized European standards or European Technical Assessment" (European Commission, 2013). Manufacturers will have to submit a clinical evidence report to a notified body that demonstrates scientific validity, analytical performance and, where applicable, clinical performance. The review process of the clinical evidence report involves consultation with a national competent authority or EMA. The competent authority or EMA then have 60 days to give their opinion which may be extended once by further 60 days on scientifically valid grounds according to the proposal issued in September 2012 (European Commission, 2012). Notified Bodies have to consider EMA's opinion and justify any deviations (European Parliament, 2013b). In order to ensure quality of testing, laboratories developing in-house tests are required to be compliant with accreditation standard EN ISO 15189 or any other equivalent recognized standard.

3.1.1

FACTORS FACILITATING AND IMPEDING PATIENT ACCESS

Regulatory approval has an impact on the performance of patient selection. EMA does not specify a particular test that has to be used to inform treatment decision making. Any validated test can be used as long as the manufacturer certifies conformity with the European IVD-directive. Alternative tests may differ with regard to their methodology, validation criteria used and the targeted mutations. Therefore, the patient populations selected by alternative tests may be different from the patient population selected by the test used in regulatory studies. Different populations taking the same pharmaceutical drug may experience different health outcomes, thus leading to a change in the benefit/risk ratio of being treated.

RECOMMENDATIONS

It is recommended that EMA specifies minimum requirements for diagnostic tests that are used with pharmaceutical drugs, e.g. validation criteria.

Reason: Currently, no specifications regarding the companion diagnostic test to be used with a pharmaceutical drug are made and hence, many alternative tests for the same biomarker may become available. However, data linking the population selected by a test to health outcomes may only be available for the test used in regulatory trials.

HTA, PRICING AND REIMBURSEMENT/FUNDING

Country-to-country variations are largest at this level, therefore, pathways were analyzed country-by-country. An overview of the health care system of each country is given at the beginning of each chapter to provide context.

GERMANY**Overview of the health care system**

About 90% of Germany's population (81.8 million in 2012) are covered by a statutory health insurance (SHI) which is provided by 134 statutory health insurance funds (as of 1st Jan 2013). About 10% of the population is covered by private insurance. Statutory health insurance is funded by contributions from employers, employees and taxation.

German federal law sets the framework for providing and financing health care but leaves details to delegated decision-making bodies. The central decision-making body is the Federal Joint Committee (Gemeinsamer Bundesausschuss – G-BA). The G-BA consists of physicians, dentists, hospital representatives, representatives of the SHIs and patient representatives. The tasks conferred on the G-BA include regulation of reimbursement, assessment of new methods of medical examination and treatment, evaluation and classification of new pharmaceutical drugs on the German market and publication of treatment guidelines.

In-patient care in Germany is provided by public and private hospitals. They are reimbursed by the SHI on the basis of an adaptation of the Australian diagnosis-related group system (G-DRG). The G-DRG system is updated yearly by the Institute for the Hospital Remuneration System (Institut für das Entgeltsystem im Krankenhaus). Patients are generally free to seek treatment in a hospital of their choice.

The majority of ambulatory services are provided by community-based practitioners. The German system is unique in its structure because the ambulatory and hospital sector are strictly separated. Patients are free to choose their community-based practitioner – including specialists – among the members of the association of statutory health insurance physicians (Kassenärztliche Vereinigung – KV). The KV guarantees the provision of ambulatory services and receives a fixed annual remuneration from the SHIs in return. The fixed annual remuneration is then distributed among the physicians in the KV in accordance with the uniform value scale catalogue (Einheitlicher Bewertungsmaßstab - EBM). In contrast to in-patient care principles, in an ambulatory setting, clinicians are not allowed to offer new diagnostic and therapeutic procedures at the expense of the SHIs unless they are listed in the uniform value scale. The uniform value scale is maintained by the evaluation committee (Bewertungsausschuss) which is a part of the G-BA.

Health Technology Assessment

Since 2011, the Act on the Reform of the market for Medicinal Products (Gesetz zur Neuordnung des Arzneimittelmarktes – AMNOG) has been in effect. AMNOG introduced a relative benefit assessment for new drugs. The aim of the AMNOG was to keep costs under control by linking the price of new pharmaceutical drugs to the added benefit for patients.

The process is clearly defined and follows a strict timeline. Manufacturers are obliged to

submit a dossier on benefit assessment to the G-BA when a new product is launched. Within 3 months, the G-BA compares the additional benefit of a new pharmaceutical with the appropriate comparator as defined by the G-BA. Typically, the G-BA commissions the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen – IQWiG) to assess the added benefit of a new therapy. The added benefit assessment will be published on the internet and is open for comments by pharmaceutical companies, associations and experts. Three months after publishing the added benefit assessment the G-BA passes a resolution considering the added benefit assessment and the comments received.

AMNOG ensures that approved orphan drugs are treated as if they had proven added benefit provided that their sales during the past 12 months do not exceed EUR 50 million.

Applications for admission of new diagnostic procedures to the uniform value scale are reviewed by the laboratory working group (AG Labor). The laboratory working group makes recommendations to the evaluation committee on the basis of HTA reports of the competence centre for laboratory related issues and the medical review board of SHI funds. The review process takes about six months.

PRICING, REIMBURSEMENT AND FUNDING

Ambulatory setting

Each prescription drug approved by an appropriate regulatory authority is automatically reimbursed by SHIs from the time of launch without further assessment. Initially, i.e. at launch, the manufacturer of a new pharmaceutical drug can set a price freely. In the months after launch, the G-BA evaluates the added therapeutic benefit in relation to the appropriate comparator. If, according to the G-BA, there is an additional benefit, the reimbursement price is negotiated between the manufacturer and the umbrella organization for the statutory health insurance funds (GKV-Spitzenverband) as a rebate on the initial price. The amount of the rebate is often dependent on the level of uncertainty associated with a product.

If, according to the G-BA, there is no additional benefit, the new pharmaceutical will be included in the internal reference price system. If assignment to any reference price group is not feasible, a reimbursement price will be agreed such that annual therapeutic expenses will not exceed those of the appropriate comparator.

CDx are only reimbursed by an SHI if they are listed in the uniform value scale. If the pharmaceutical drug label requires companion diagnostic testing, reimbursement is mandatory but still requires a code in the uniform value scale. Codes for molecular diagnostics could either be generic, i.e. referring to the method used (e.g. hybridization, amplification, sequencing, polymerase chain reaction) or specific, i.e. referring to the biomarker tested. If a code is available, companion diagnostic testing can be immediately reimbursed. Otherwise, a new code needs to be generated by the evaluation committee.

There is no legal provision that regulates the maximum time period for code generation. Therefore, in theory there may be a gap between pharmaceutical drug launch and companion diagnostic reimbursement of up to a few years and hence, a delay in patient access. However, there is a temporary fix in the uniform value scale for laboratory tests that are not listed. “Similar examinations” can be reimbursed if justified by the clinician on grounds of medical necessity. Another possibility to bridge such a gap is via a selective reimbursement contract between the pharmaceutical drug/diagnostic manufacturer and the SHI funds.

Hospital setting

Reimbursement in a hospital setting is based on a DRG system. Companion diagnostics can be considered in a DRG if a procedure code is available. Procedure codes in the G-DRG are listed in the operation and procedure code (Operationen- und Prozedurenschlüssel). The operation and procedure code is updated on an annual basis by the German Institute of Medical Documentation and Information (Deutsches Institut für medizinische Dokumentation und Information). For a new companion diagnostic to be reflected by the DRG system a

procedure code has to be generated, used and usage statistics of select hospitals have to be calculated. The whole updating process can take several years. Such delays are inevitable and potentially delay patient access to innovations. Therefore a temporary funding process for innovative products has been created to bridge the gap called “new diagnostic and therapeutic procedures” (Neue Untersuchungs- und Behandlungsmethoden – NUB). NUB is only applicable for technologies that have just been introduced in Germany. Every hospital will need to apply separately and funding will be available only to the applicant and not to every hospital in Germany. NUB applications for companion diagnostics have been rejected in the past, supposedly because of the low cost impact of testing.

Facilitating and impeding factors for patient access

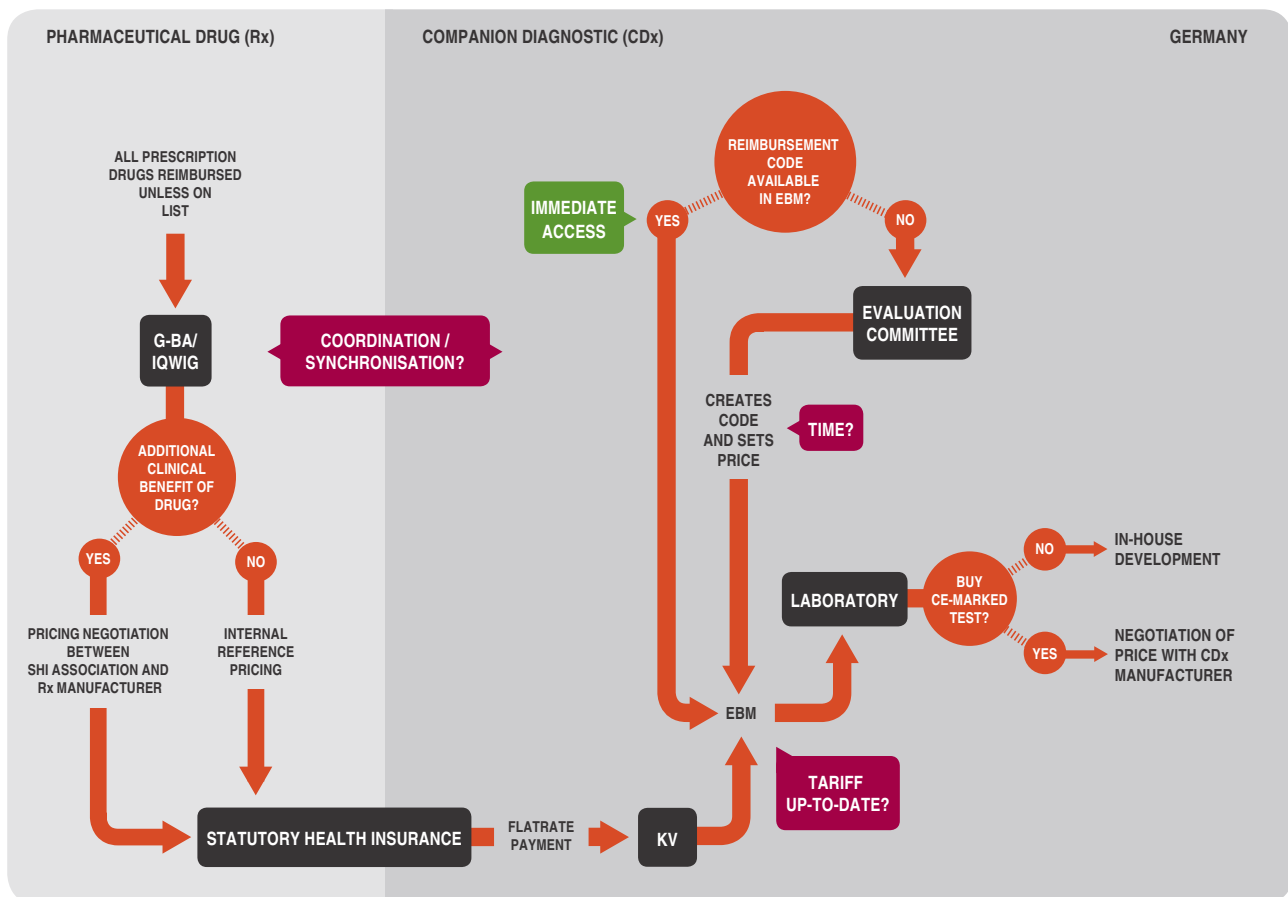


FIGURE 3

Impeding and facilitating factors in Germany. Health technology assessment processes for pharmaceutical drugs (G-BA: Gemeinsamer Bundesausschuss (Federal Joint Committee) and IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) and companion diagnostics (evaluation committee (Bewertungsausschuss) within the G-BA) are separated. Laboratory services are reimbursed by the Statutory Health Insurance (SHI) via the associations of statutory health insurance physicians (Kassenärztliche Vereinigungen – KV) according

Facilitating factors

HTA for pharmaceutical drugs is transparent with a fixed maximum timeline attached to it. Approved pharmaceutical drugs are automatically reimbursed by the system, thus, providing for immediate access. Reimbursement of companion diagnostic testing is mandatory if testing is required according to the drug label of the associated pharmaceutical drug. If generic codes are available in the uniform value scale, patients have access to companion diagnostic testing at drug launch provided that tariffs associated with reimbursement codes sufficiently reflect current testing costs of laboratories. Otherwise, if justified by the clinician on the grounds of medical necessity, laboratory tests not listed in the uniform value scale can be reimbursed as similar examinations (Figure 3).

In a hospital setting DRGs allow for immediate coverage of a new method.

to the Uniform Value Scale (Einheitlicher Bewertungsmaßstab – EBM). There is no time limit for the process of reimbursement code generation. Actual testing costs of laboratories are not always reflected by the tariffs associated with reimbursement codes.

Impeding factors

Health technology assessment processes for pharmaceutical drugs and companion diagnostics are separated, which is relevant whenever companion diagnostic reimbursement is not mandatory or new codes have to be generated. There is no formal HTA process dedicated to a comparative evaluation of multiple test kits for the same biomarker (Figure 3).

Recommendations

An HTA programme dedicated to the comparison of different companion diagnostics for the same biomarker should be established.

A general reimbursement code for temporary funding of companion diagnostics should be generated that can be used for companion diagnostics for which generic codes do not apply without justification of medical necessity by a clinician.

3.2.2

UNITED KINGDOM

Overview of the health care system

The UK has a tax funded universal health care system called the National Health Service (NHS). The NHS provides a comprehensive service available to all with access based on clinical need, not an individual's ability to pay. Responsibility for NHS services in Scotland, Wales and Northern Ireland is respectively devolved to the Scottish Parliament and the National Assemblies for Wales and for Northern Ireland. This outline will focus on NHS England because it is the largest country within the UK (covering 53m people, 84% of the UK population).

As a taxpayer-funded service, government is accountable to the Parliaments/Assemblies for the outcomes and spending of the NHS (although the primary tax-raising authority rests with the UK Government, sanctioned by the Parliament at Westminster). The Secretary of State retains ministerial responsibility to Parliament for the provision of the health service in England

Elective access to health care is regulated by a gatekeeper – the general practitioner (GP). If patients need secondary or tertiary care they are referred by their GP. GPs are organized in small groups known as general practices which also frequently provide the services of other primary care professionals including nurses and allied health professionals (such as physiotherapists). Almost all funding for primary care services is practice-based, which means that it is a payment to the practice rather than individual GPs. Funding is allocated based on weighted patient populations rather than number of doctors.

April 1st 2013 saw the implementation of the Health and Social Care Act 2012 revisions, which further develop the commissioning role of GPs in Clinical Commissioning Groups (CCGs) determining priorities for expenditure of approximately £65 billion in 2013/14 to commission health care for their local populations. The CCGs replace Primary Care Trusts.

The Department of Health is responsible for strategic leadership and allocation of funding to both the health and social care systems, but will no longer be the headquarters of the NHS, nor will it directly manage any NHS organizations.

The responsibilities of NHS England formally established as the NHS Commissioning Board include resource allocation to clinical commissioning groups and oversight of their operations, along with commissioning development, primary care and 'prescribed' specialized services, 'Prescribed' specialized services are those 'tested' against the four factors in the Health and Social Care Act 2012 as suitable for commissioning by NHS England. The four factors are:

- the number of individuals who require the provision of the service or facility
- the cost of providing the service or facility
- the number of people able to provide the service or facility
- the financial implications for Clinical Commissioning Groups (CCGs) if they were required to arrange for the provision of the service or facility

Health Technology Assessment

The most relevant HTA body for England and Wales is the National Institute for Health and Care Excellence (NICE). NICE provides national guidance and advice to improve health and social care. The evidence-based guidance and advice includes technology appraisals to assess the clinical- and cost-effectiveness of health technologies, including pharmaceutical drugs associated with companion diagnostics. Interestingly, Scotland and Wales have their own HTA agencies, the Scottish Medicines Consortium and the All Wales Medicines Strategy Group.

NICE does not evaluate all technologies. Technologies not evaluated by NICE, are evaluated at a local level by local budget holders. Local budget holders may differ considerably with regard to their criteria and decision processes, and these potentially lack transparency.

Pharmaceutical drugs associated with companion diagnostics that have been co-developed are likely to be evaluated in tandem within the NICE Technology Appraisals programme.

Two programmes were set up by NICE to evaluate innovative diagnostics: the Diagnostic Assessment Programme (DAP) and the Medical Technologies Evaluation Programme (MTEP) (Crabb, Marlow, Bell, & Newland, 2012).

Topics for evaluation by NICE are selected by the Medical Technologies Advisory Committee typically after notification from a product sponsor and routed to either DAP or MTEP based on the complexity of the evaluation and the value claim of the product (see Table 2 for the differences between DAP and MTEP).

	DAP	MTEP
Timeline	Around 60 weeks from topic referral to guidance publication	48 weeks from notification to guidance publication
Methodology	Clinical effectiveness and cost-effectiveness analysis	Clinical effectiveness and cost savings, no cost-effectiveness analysis
Complexity	Complex assessments, involving modelling	Gold standard or well-established diagnostic pathway already available
Value claim	Higher	Lower

TABLE 2

Comparison of NICE's Diagnostic Assessment Programme (DAP) and the Medical Technologies Evaluation Programme (MTEP) Source: (Crabb et al., 2012)

Companion diagnostics developed for existing pharmaceutical drugs or multiple companion diagnostic tests for the same target, are likely to be evaluated within the DAP (Crabb et al., 2012).

Pricing, reimbursement and funding

Depending on the guidance issued by NICE, either the NHS or the Cancer Drugs Fund are potential sources of funding for pharmaceutical drugs associated with companion diagnostics. The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals.

Prices for prescription drugs are currently determined by the Pharmaceutical Price Regulation Scheme (PPRS), a voluntary agreement between the Department of Health and the branded pharmaceutical industry. Pharmaceutical companies are free to set the price of a newly launched product (assuming it is accepted for use by NICE). PPRS reviews the prices applying profit caps. For high-cost drugs, pharmaceutical companies may negotiate risk-sharing agreements with the Department of Health to improve cost-effectiveness – so-called patient access schemes (PAS). A simple example of improving cost-effectiveness is to offer discounts on the price of the pharmaceutical drug. The Government announced in 2010 that it planned to introduce a new system of value-based pricing from 2014 which links the price of a health technology to its health benefits.

In the NHS, the funding stream starts with the NHS Commissioning board, which allocates resources to CCGs. CCGs typically pay for services offered by secondary health care providers using the Payment-by Results (PbR) system. PbR involves national tariffs for admitted patients and out-patients. Admitted and emergency patients are classified based on the health care resource group system which is essentially a DRG-type system. The tariff for out-patients is based on attendance, i.e. initial and follow-on attendances.

Some high-cost pharmaceutical drugs and devices are excluded from the PbR scheme. In the majority of cases, funding for laboratories associated with hospitals is based on global annual budgets. However, some molecular pathology tests are paid on a fee-for-service basis.

The Cancer Drugs Fund (CDF) was originally established in 2011 as an interim measure before value-based pricing, which was to be introduced in 2014. The CDF has since been extended until March 2016. The fund receives 200 million GBP/year from Government to pay for cancer drugs that are not routinely funded by local budget holders, e.g. those that have been rejected or not (yet) appraised by NICE. Pharmaceutical drugs eligible for CDF funding are listed on the national CDF list. Access to the fund is via cancer specialists who apply for funding on behalf of patients.

In the NHS, laboratories operate with global annual budgets. Therefore, provided there are no budget constraints, the system is able to fund companion diagnostics at the time of launch of the associated pharmaceutical drug. Furthermore, it can be assumed by implication that mandatory funding for NICE-recommended pharmaceutical drugs extends to funding of the associated companion diagnostics. However, interviewed stakeholders held different views on this topic. Some stakeholders confirmed this assumption; others reported funding for companion diagnostics being inconsistent and currently under debate.

Stakeholders expressed varying opinions regarding pharmaceutical drugs associated with companion diagnostics listed on the national CDF list. Again it seems to be contentious whether such companion diagnostics are eligible for funding by the CDF.

If funding for companion diagnostic testing is contentious at a local level, inequalities in patient access may result.

In the light of the aforementioned uncertainties about companion diagnostic funding, and to facilitate the introduction phase pharmaceutical companies often provide temporary funding for companion diagnostic testing. A current example is BRAF testing of patients with melanoma. The pharmaceutical company has contracted with three reference laboratories and pays for testing in patients who are potentially eligible for treatment.

Facilitating and impeding factors for patient access

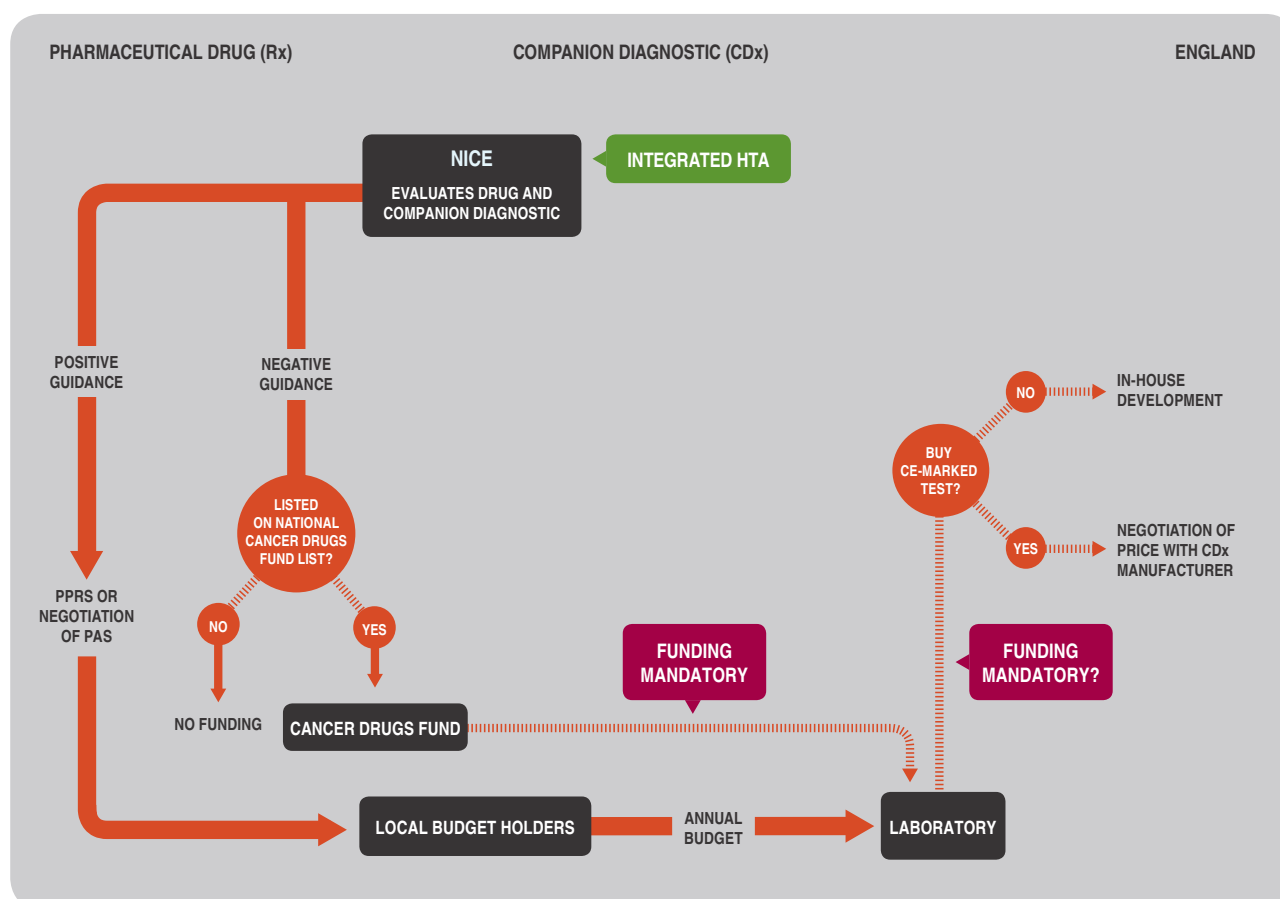


FIGURE 4

Impeding and facilitating factors in the UK (England). The National Institute for Health and Care Excellence (NICE) is the health technology assessment (HTA) authority which evaluates co-developed drug-diagnostic companion products in tandem within the technology appraisals programme. Funding for NICE-recommended pharmaceutical drugs is mandatory for local budget holders. Pricing for newly launched products is free according to the Pharmaceutical Price Regulation Scheme (PPRS). Patient access schemes (PAS) may be involved to meet cost-effectiveness expectations of NICE. Pharmaceutical drugs that have been rejected or not (yet) appraised by NICE may be listed on the national Cancer Drugs Fund list. Companion diagnostic testing is funded out of global annual laboratory budgets. It can be assumed by implication that funding for pharmaceutical drugs extends to the associated companion diagnostics. However, interviewed stakeholders held different views on this topic.

Facilitating factors

NICE has established specific health technology assessment programmes for *in vitro* diagnostics and is able to handle different assessment scenarios either in the technology appraisal programme alongside drug evaluation or in the diagnostic assessment programme. If a drug associated with a companion diagnostic is recommended by NICE, the global budget system in principle allows for immediate access to reimbursed and funded companion diagnostics, as no codes have to be generated for reimbursement. If NICE considers a drug associated with a companion diagnostic to not be cost-effective, the drug may still be listed on the national cancer drugs fund list and thus be eligible for temporary funding. However, as yet, pharmaceutical companies at least temporarily pay for a considerable proportion of companion diagnostic tests due to uncertainty about funding of companion diagnostics by the NHS (Figure 4).

Impeding factors

The major barrier to access in England is uncertainty about funding of companion diagnostics by NHS England. According to expert stakeholders it is contentious whether the obligation to provide funding for NICE-recommended pharmaceutical drugs extends to associated companion diagnostics. In addition, although positive NICE recommendations imply mandatory funding by local budget holders they are not provided with additional funding. Therefore, annual budget restraints potentially limit or delay patient access even to pharmaceutical drugs recommended by NICE and inequalities in patient access may be the result (Figure 4).

Recommendations

It is recommended that NICE evaluates all pharmaceutical drugs requiring companion diagnostic testing. Furthermore, mandatory funding for NICE-recommended pharmaceutical drugs should explicitly be extended to associated companion diagnostic tests and it should be ensured that sufficient funding is available to implement NICE recommendations.

THE NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

In the UK decisions about reimbursement of pharmaceutical drugs are made on a regional level. The HTA agency that evaluates new pharmaceutical drugs in England – NICE – is one of the leading HTA agencies in Europe. The responsibilities of NICE go beyond pure HTA because positive guidance means an obligation for the NHS to make funding for the respective pharmaceutical drug available. The Guide to the methods of technology appraisal 2013 explicitly addresses companion diagnostics and, for co-developed drugs, require to incorporate companion diagnostics in the technology assessment of the drug (NICE, 2013b). In this respect, NICE implemented the ideal scenario of evaluating pharmaceutical drugs and companion diagnostics in a coordinated and synchronized way that results in a single HTA report. NICE further acknowledges other assessment scenarios, like e.g. the comparison of several tests for the same biomarker. Such a scenario is covered by the diagnostics assessment program. Under this program available tests for EGFR-TK were assessed and guidance has been issued. (NICE, 2013a) NICE implements a value based evaluation approach, which is well documented on its webpage, thus providing a high level of transparency with regard to the decision making process.

3.2.3

FRANCE

Overview of the health care system

The health care system in France is a mandatory health insurance system that covers the entire population (65.4 million) and is managed at the national level by the government and the parliament. The national health insurance is funded through contributions from employers, employees and taxation. Every year the parliament adopts an indicative (non-binding) national health spending objective.

90% of the population is covered by complementary health insurance which is provided by a network of non-profit providers (so-called *mutuelles*) and private insurers.

The national association of health insurances (Nationale des Caisses d'Assurance Maladie - UNCAM) defines common policies for the three principal health insurance funds.

Since 2010, 25 regional health agencies (Agences régionales de Santé), 22 in mainland France and 3 in overseas departments, are in charge of regulating hospital, ambulatory and medico-social care, in coordination with regional and local health insurances.

Funding in a hospital setting is based on a DRG system (groups homogènes de séjour – GHS). In order to adopt innovative and/or costly medicines more quickly, separate reimbursement for such medicines is possible provided they are listed on the 'liste en sus'.

Office-based doctors are paid on a fee-for-service basis, which is fixed through an agreement between physicians' trade unions and UNCAM and approved by the government. A voluntary gatekeeper system was introduced in 2004 and has been widely adopted. Patients not registered with a gatekeeper practitioner – or who consult a specialist without referral – are reimbursed for the consultation fee at a lower rate.

In 2004 the National Institute of Cancer (Institut National du Cancer – INCa) was created. It is a national health and science agency dedicated to cancer. Its responsibilities include providing early nationwide access to innovative molecular testing in the field of oncology.

Health Technology Assessment

The French National Authority for Health (Haute Autorité de Santé- HAS) is responsible for conducting HTAs, in particular three specialist committees:

- The transparency committee (Commission de la Transparence): assesses the clinical effectiveness (service medical rendu – SMR) and relative effectiveness (amélioration du service medical rendu – ASMR) of pharmaceutical drugs. There are currently (03/2013) discussions whether to merge the assessment of SMR and ASMR into one procedure called the relative therapeutic index (index thérapeutique relative), similar to the German early-benefit assessment system.
- The Economic and Public Health evaluation committee (Commission d'évaluation économique et de santé publique) will evaluate pharmaceutical drugs on an economic basis from the End of 2013. For pharmaceutical drugs with ASMR scores between I (major) and III (modest) the analysis will be transmitted to the Economic Committee on Health Care Products (Comité Economique des Produits de Santé – CEPS) to better inform the pricing process.
- The Assessment committee for medical devices, procedures and technologies (Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé - CNEDiMTS). One of the responsibilities of CNEDiMTS is evaluation of CDx. Criteria are expected service (service attendu – SA) based on risk/benefit ratio, the role of CDx within the therapeutic strategy and its benefit to public health and assessment of improvements to expected service (amélioration du service attendu – ASA) comparing the CDx to the current gold standard in order to classify the added clinical value as major, substantial, moderate, minor or absent.

Pharmaceutical drugs and the associated companion diagnostics are evaluated separately by different committees. Pharmaceutical drugs are evaluated by the transparency committee (HAS) and the economic and public health evaluation committee (CEPS). Companion diagnostics are evaluated by CNEDiMTS (HAS) and price setting and enlistment are made by UNCAM. Assessment requests for pharmaceutical drugs can be directly made by pharmaceutical companies. However, some expert stakeholders pointed out that diagnostics manufacturers cannot directly apply for assessment. Assessment requests for diagnostics have to be made by external bodies like UNCAM, or less frequently by scholarly societies, the Ministry of health or INCa. There is no fixed assessment timeline attached to the evaluation. For example, when Vemurafenib was launched, evaluation of the associated BRAF test by CNEDiMTS was still ongoing.

Pricing, reimbursement and funding

PHARMACEUTICAL DRUG

Out-patient setting

For a pharmaceutical drug to be reimbursed by the national health insurance in an out-patient setting, it has to be listed on the refundable medicines list – a decision made by the Ministry of Health. Reassessment of the decision is mandatory after 2-5 years. Pricing is dependent on the ASMR determined in the HTA. Depending on the ASMR one of three pricing mechanisms applies:

- Major to moderate added clinical value (ASMR I-III) – international reference pricing: The pharmaceutical drug or device is eligible for faster access at a European price (price notification instead of negotiation)
- Minor added clinical value (ASMR IV) – pricing based on clinical effectiveness: Negotiation of pharmaceutical drug price between CEPS and the manufacturer employing price-volume and risk-sharing agreements
- No added clinical value (ASMR V) – internal reference pricing: The price of the pharmaceutical drug or device must by law be lower than that of the comparators.

Hospital setting

Funding in a hospital setting is based on the French DRG system. Generally, pharmaceutical drugs have to be covered by DRGs. Hospitals are responsible for procuring their own pharmaceutical drugs. Therefore, pharmaceutical drug prices can be freely negotiated between manufacturers and the hospitals. In order to gain leverage in such negotiations, hospitals associate to form purchasing groups.

The impact of newly launched innovative and/or expensive pharmaceutical drugs on hospital budgets cannot be adequately reflected, as DRGs are determined retrospectively. Therefore, hospitals may be reluctant to introduce innovative and/or costly pharmaceutical drugs if they put more pressure on the budget. In order to counteract this disincentive to adopt innovations, innovative and/or costly pharmaceutical drugs can be reimbursed separately until the DRG system has been updated to reflect these pharmaceutical drugs. Pharmaceutical drugs eligible for separate reimbursement in addition to DRG rates are listed in the *liste en sus*. The prices for pharmaceutical drugs listed on the *liste en sus* are negotiated at a national level between CEPS and the manufacturer.

COMPANION DIAGNOSTIC

Out-patient setting

In order to obtain reimbursement for a companion diagnostic in an out-patient setting, the test must be listed on the joint classification of medical procedures (*classification commune des actes médicaux - CCAM*), or the nomenclature of procedures in laboratory medicine (*Nomenclature des actes de biologie médicale - NABM*). After a positive assessment of the companion diagnostic by the CNEDiMTS, UNCAM will include it in the CCAM/NABM and set a reimbursement price (no negotiation with the diagnostic manufacturer). The price has to be finally agreed and published by the Ministry of Health.

Hospital setting

Reimbursement for an in-patient stay is determined according to the DRG system GHS. As described in the pharmaceutical drug section the added costs of new tests may not be properly reflected in the existing GHS. If companion diagnostic tests are registered on the *Nomenclature de Montpellier*, payment can be made by MIGAC (*missions d'intérêt général et à l'aide à la contractualisation*) funds.

COMPANION DIAGNOSTICS IN ONCOLOGY

In oncology, predictive biomarker testing is temporarily provided and supported by INCa at 28 designated molecular testing centres. INCa is funded by the Ministry of Health and private companies. Irrespective of the time needed to update permanent funding mechanisms, INCa support for companion diagnostics ensures availability of companion diagnostic testing at pharmaceutical drug launch.

Pathologists are reimbursed by INCa for sending samples to the molecular testing centres, these centres receive funds directly from INCa.

Currently, funding for some companion diagnostic testing in a hospital setting is shifting from INCa to the Ministry of Health (MIGAC funds). In an out-patient setting, discussions are ongoing to potentially get more tests reimbursed through CCAM/NABM. Some of the tests available in the marketplace already have dedicated CCAM codes (e.g. regular immunohistochemistry tests for ALK and cMet or in situ hybridization for HER2). With pharmaceutical companies having an increasing number of pharmaceutical drugs associated with companion diagnostics in the pipeline, it is foreseeable that INCa will not be able to support all companion diagnostic testing activities. Therefore, managing the transition from INCa support to regular funding mechanisms and providers for older companion diagnostics will become a key issue. According to expert stakeholders, there is currently no standard transition process available. A crucial part of managing the transition is to expedite the process of updating DRGs and CCAM/NABM codes.

Currently, due to the support and promotion of INCa, French cancer patients have excellent access to companion diagnostic testing.

The flowchart illustrates the process of pharmaceutical reimbursement in France, starting from the drug launch and moving through various committees and pricing mechanisms to the final reimbursement decision by the Ministry of Health.

PHARMACEUTICAL DRUG (Rx)

COMPANION DIAGNOSTIC (CDx)

FRANCE

INCA
ONLY ONCOLOGY

IMMEDIATE ACCESS AT DRUG LAUNCH

INCREASE CLINICIAN AWARENESS

28 MOLECULAR TESTING CENTRES

SEEKS TO PROVIDE TEST AT THE TIME OF DRUG LAUNCH

TRANSITION?

TEMPORARY ONLY

TRANSPARENCY COMMITTEE EVALUATES IMPROVEMENT OF MEDICAL BENEFIT

COORDINATION / SYNCHRONISATION?

CNEDIMTS

MAJOR / MODERATE

MINOR

NONE

EUROPEAN PRICE (INTERNATIONAL REFERENCE PRICING)

PRICING NEGOTIATION BETWEEN CEPS AND Rx MANUFACTURER

INTERNAL REFERENCE PRICING

REIMBURSEMENT DECIDED BY MINISTRY OF HEALTH

TARIFF UP-TO-DATE?

STATUTORY HEALTH INSURANCE

UNCAM

CREATES CODE PRICE

CCAM/NABM

LABORATORY

TIME?

Impeding and facilitating factors in France. Different specialist committees within the French National Authority for Health (Haute Autorité de Santé – HAS) are responsible for conducting health technology assessments: The transparency committee for pharmaceutical drugs and the Assessment Committee for Medical Devices, Procedures and Technologies (Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé – CNEDIMTS) for companion diagnostics. Assessment processes are separated without coordination or synchronization. Pricing for pharmaceutical drugs depends on the improvement of medical benefit involving negotiations between the Economic Committee on Health Care Products (Comité Economique des Produits de Santé – CEPS) and the Rx manufacturer. Laboratory services are reimbursed according to the Joint Classification of Medical Procedures (classification commune des actes médicaux – CCAM) or the Nomenclature of Procedures in Laboratory Medicine (Nomenclature des actes de

France has a committee within its HTA agency (HAS) that systematically evaluates diagnostic tests. In the therapeutic area of oncology, the National Institute of Cancer actively promotes patient access to companion diagnostic testing at launch of the associated pharmaceutical drug. In this way it plays the role of a temporary funding source before the system takes over. The established testing infrastructure and the awareness among clinicians that has been generated also benefits other therapeutic areas. Besides INCa, the *liste en sus* (for pharmaceutical drugs) and the *Nomenclature de Montpellier* (for companion diagnostics) provide extra funding sources in a hospital setting (Figure 5).

Although France has incorporated HTA processes for pharmaceutical drugs and diagnostics within its HTA agency, both evaluation processes are strictly separated and not synchronized or coordinated. Therefore, evaluation for a pharmaceutical drug may be completed while the evaluation for the associated companion diagnostic is still ongoing. Another factor that potentially delays patient access is the time needed for generation of new reimbursement codes because there is no binding assessment timeline. In oncology, INCa bridges such gaps. However, promotion by INCa is temporary and managing the transfer of molecular testing to the institutions of the health care system remains a challenge yet to be addressed. Furthermore, promotion of companion diagnostic testing in France is limited to oncology and does not comprise other therapeutic areas (Figure 5).

Coordination and synchronization of HTA and pricing and reimbursement processes would help to enable patient access to pharmaceutical drugs associated with companion diagnostics in all therapeutic areas (not just oncology) and ensure consistent reimbursement

biologie médicale – NABM). The National Association of Health Insurances (Nationale des Caisses d'Assurance Maladie – UN-CAM) creates codes and sets the associated prices. There is no time limit for the process of code generation and actual testing costs of laboratories are not always reflected by the associated tariffs. The National Institute of Cancer (INCa) facilitates access to pharmaceutical drug-diagnostic companion products in oncology by providing molecular testing free of charge at the time of drug launch. However, promotion by INCa is temporary, and managing the transfer of molecular testing to the institutions of the health care system remains a challenge yet to be addressed. Furthermore, promotion of companion diagnostic testing in France is limited to oncology and does not comprise other therapeutic areas

decisions. Furthermore, expediting the NABM/CCAM code generation and DRG updating process will ensure that INCa funds are sufficient to promote access to an increasing number of new pharmaceutical drugs associated with companion diagnostics. Finally, extending temporary funding to other therapeutic areas would ensure that updating NABM/CCAM lists and DRG systems will not delay patient access to pharmaceutical drugs associated with companion diagnostics.

THE NATIONAL INSTITUTE OF CANCER (INCA)

The National Institute of Cancer (INCa) was founded in 2004. Its creation was one of the objectives of the 2003-2007 national cancer plan. It has an operating budget of about €120 million per annum.

It promotes molecular testing through a national network of 28 molecular genetics centres (one per two million inhabitants on average). Each molecular genetics centre is a partnership between several university hospital and cancer centre laboratories with complementary expertise. Together, these laboratories master all the DNA- and RNA-based techniques required for molecular testing of both haematological and solid tumours. Testing is provided to patients regardless of the institution where they are treated. Less common molecular tests are centralized in specialized centres. Molecular tests are free of charge for patients or health institutions, and the centres compensate local pathologists for tumour block shipment.

In 2011 median turnaround time for an EGFR or KRAS mutational status was about 8 days. The centres coordinate their activities at the regional level and are responsible for optimizing logistics for the circulation of prescriptions, tumour samples and molecular reports in order to minimize test result delivery times. They are also responsible for distributing molecular testing, tumour sampling and tumour tissue fixation guidelines to local clinicians and pathologists.

INCa set up a programme of prospective detection of emerging biomarkers in order to facilitate immediate patient access to relevant testing at the time of pharmaceutical drug launch. It monitors ongoing clinical trials in order to identify biomarkers which will become relevant in the near future.

INCa monitors the activity of the centres using annual reports. The number of tests actually performed match estimations of the molecular tests required. Therefore, the programme is successful in enabling equal nationwide patient access to molecular testing. (Nowak, Soria, & Calvo, 2012)

Overview of the health care system

The National Health Care System (Servizio Sanitario Nazionale -SSN) is funded by general taxation. It provides health care coverage to the entire population (60 million in 2012). It is organized on three levels. At the national level, the Ministry of Health formulates a health care plan every three years and determines general health care policies. At the regional level, 21 regional health agencies (Agenzia Sanitaria Regionale) ensure that the essential levels of care defined by the Ministry of Health are fulfilled. Beyond that they have the authority to adjust for region-specific needs, e.g. they might charge additional co-payments. Regional health agencies sign contracts with hospitals and negotiate hospital budgets for services not covered by DRGs. These contracts contain regulations about the appropriate use of expensive pharmaceutical drugs and medical devices. At the local level, local health authorities (Azienda Sanitaria Locale) and hospital units are responsible for delivering hospital and community services. Local health authorities receive a per capita budget which is transferred via regional health authorities. The local level also includes large teaching and/or research hospitals.

Italian residents are assigned a General Practitioner who acts as gatekeeper to the system, thus allowing access to specialist care, hospital visits or admission, or other types of medical care (under SSN coverage). GPs and paediatricians are paid through a national collective contract which is negotiated centrally and adapted by local health authorities.

Public and private health care providers are remunerated based on two formulary lists: Out-patient services are paid according to a fee-for-service system called the Nomenclature Tariffario delle Prestazioni Ambulatoriali (NTPA). Since the health care system was regionalized in 2005, regions have developed their own versions of the NTPA. The regions are free to add services if they cover the costs. The result is an extreme variability in codes and tariffs between regions.

In-patient services are paid based on the Nomenclature Tariffario delle Prestazioni Ospedaliere a DRG-based system that covers all hospital activity from acute or day-hospital admissions to long-term care and nursing home assistance. It is important to note that the regions have the authority to issue their own DRG system based on a local analysis of the hospital resources used. The regionalization of the DRG system may lead to the use of different codes for the same procedure and to a different level of funding for the same code.

Health Technology Assessment

Innovative pharmaceutical drugs are assessed centrally by the Italian medicines agency (Agenzia Italiana del Farmaco - AIFA) to inform the pricing and reimbursement process on a national level. Based on the major criteria (seriousness of the disease, availability of existing products and extent of therapeutic benefit) AIFA assesses whether the pharmaceutical drug is an important, moderate or modest innovation. A new method for evaluating innovation is currently under review.

However, there is no common path for HTA of companion diagnostics. Formal HTA evaluation on the regional level is so far limited to a few individual excellence centres, e.g. the HTA programme of Lombardia (still in a run-in phase), the HTA programme of the Unità di Valutazione dell'Efficacia del Farmaco in Veneto, the experience of the Laboratorio SIFO in Toscana, or the PRIER programme in Emilia Romagna. At a national level the National Agency for Regional Health Services (Agenzia Nazionale per i Servizi Sanitari Regionali – AGENAS) is responsible for coordinating HTA experiences across the regions. Interactions between AGENAS and regional HTA agencies are not public.

If there is no formal HTA programme on a regional or local level, companion diagnostics may be informally evaluated by hospital therapeutic committees. Stakeholders reported that budget impact is the major criterion applied in such informal evaluation.

Pricing, reimbursement and funding

PHARMACEUTICAL DRUGS

For a pharmaceutical drug, the manufacturer will apply for reimbursement from the National Pharmaceutical Formulary (Prontuario Farmaceutico Nazionale - PFN). Listing on regional hospital formularies is mandatory for innovations that are considered important as a result of AIFA's evaluation; listing of moderate or modest innovations is optional.

After AIFA's assessment the price of the product will be negotiated between the manufacturer and the Pricing and Reimbursement Committee (Comitato Prezzi e Rimborso) within AIFA using several criteria including cost-effectiveness, relative risk-benefit ratio, therapeutic cost/day and budget impact on the SSN.

Despite decentralization pricing and reimbursement decisions for pharmaceutical drugs are mainly made at a national level. Regions may exert their authority by applying co-payments in out-patient settings (2-4 EUR per prescription) or by delaying or excluding some pharmaceutical drugs that are classified as moderate or modest innovation from their regional formularies.

In an in-patient setting, the cost of pharmaceutical drugs is covered by DRGs with few exceptions (e.g. life-savers, some oncological drugs, very high cost, orphan drugs). For the exceptions not covered by the DRG system many regions have activated programmes to share the cost between the hospital and the local health authorities.

In order to ensure reimbursement of costly pharmaceuticals while adhering to the pharmaceutical budget, AIFA introduced risk sharing schemes in 2006. The rationale behind such schemes is that the full price has to be paid only for responders. The type of scheme (e.g. payment by results, cost-sharing and risk-sharing) is proposed by AIFA on a case-by-case basis. Examples for which risk-sharing agreements have been negotiated include Dasatinib, Erlotinib, Nilotinib and Lapatinib (Adamski et al., 2010).

COMPANION DIAGNOSTIC

There is no formal reimbursement process in place for companion diagnostics. The companion diagnostic will become an issue only after the corresponding pharmaceutical drug is included in regional formularies. The trigger for review/adoption of a companion diagnostic will be a specific request from the specialist, who will ask the local pathologist to provide the test. The likelihood of local access to the companion diagnostic is higher if the pharmaceutical drug label requires testing.

In a hospital setting, companion diagnostics are typically included in the DRG tariffs as part of an existing procedure and, therefore, fully covered by the SSN. If the DRG tariff is not sufficient to compensate hospitals, extra funding may be provided from a regional budget or the pharmaceutical company who offers the pharmaceutical drug.

In an outpatient setting, generic codes on the local version of the fee-for-service formulary (NTPA) may cover the test. However, codes and tariffs are often not modified with the progress of medical science. According to expert stakeholders, update of the NTPA at the regional level is often difficult and slow, in part because of the lack of a formal update process. In some regions tariff codes have stayed the same for more than 10 years. Update is often initiated by a clinician request and decided on a case-by-case basis. If a service is not covered by the local NTPA version, it can still be funded by regional or local health authorities or pharmaceutical companies.

Facilitating and impeding factors for patient access

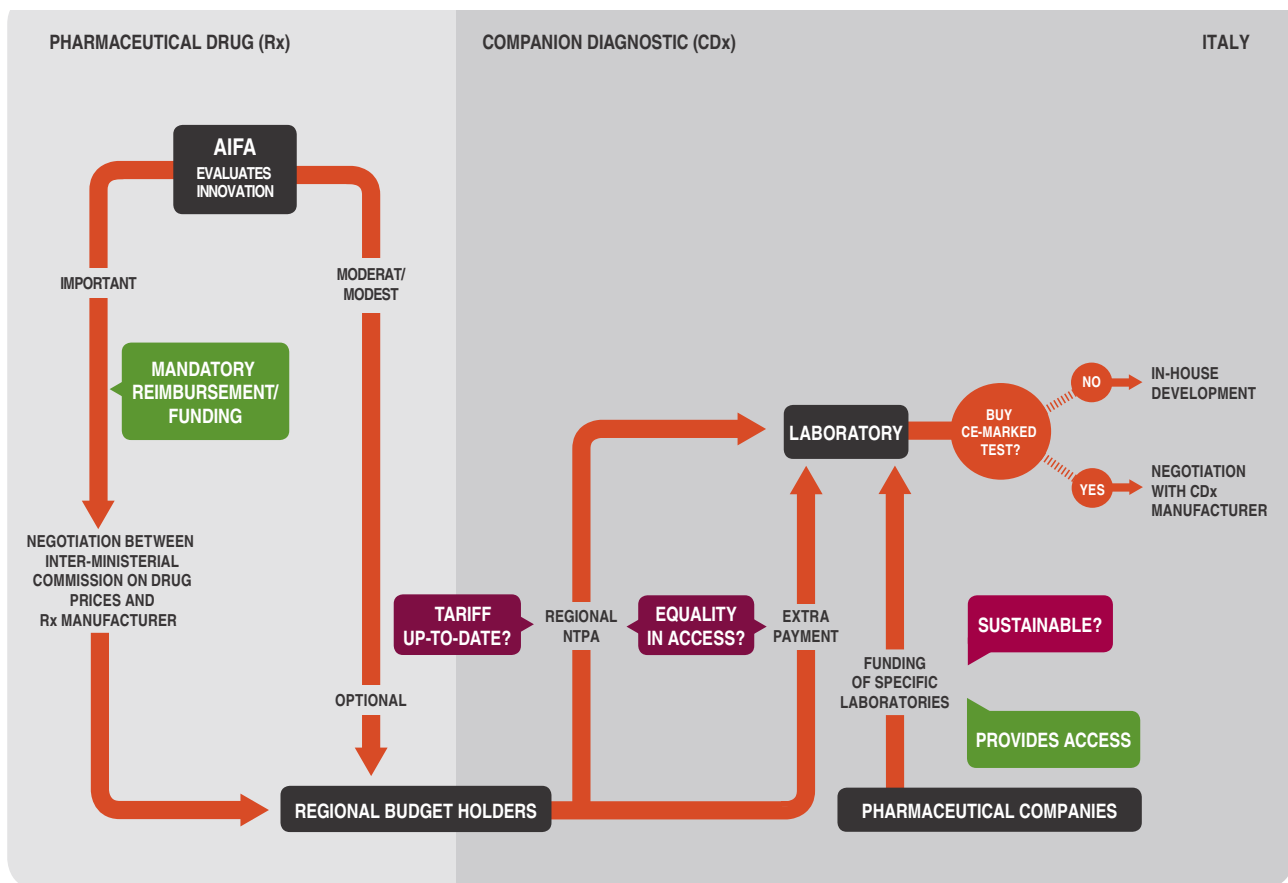


FIGURE 6

Impeding and facilitating factors in Italy. The Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA) assesses whether pharmaceutical drugs are important, moderate or modest innovations at a national level. For important drugs funding by regional budget holders is mandatory. Companion diagnostics are assessed separately at a regional or local level in a non-standardized way and reimbursement decision-making is not linked to reimbursement decisions for the corresponding pharmaceutical drug. Regional decision-making implies the risk of inequalities in patient access. Laboratories are reimbursed according to regional versions of the tariff of ambulatory prices (Tariffario delle Prestazioni Ambulatoriali – NTPA). Extra funding may be provided by regional budget holders. Because NTPA codes are infrequently updated, the tariffs associated with codes might not always be sufficient to cover laboratory costs. Pharmaceutical companies may contract with specific laboratories to fund companion diagnostic testing which enables patient access in the short term but may not be sustainable.

Facilitating factors

Patient access to new companion diagnostics is immediately possible in an ambulatory setting if generic codes in the local version of the NTPA apply. Regional health authorities also have the possibility to provide separate funding for companion diagnostics.

Risk-sharing agreements for several pharmaceutical drugs associated with companion diagnostics have been applied to enable patient access despite uncertainties about patient benefit, and an infrastructure to record utilization data has been built. Alternatively, pharmaceutical companies may pay for testing (Figure 6).

Impeding factors

Health technology assessment processes for companion diagnostics and pharmaceutical drugs are separated. Whereas decisions about reimbursement of pharmaceutical drugs are made centrally, coverage of companion diagnostics is based on regional or local decision-making. Furthermore, only a few regions have established HTA agencies to support the decision-making process. Coverage of companion diagnostic tests is not linked to reimbursement decisions for the corresponding pharmaceutical drug. Different decision criteria and processes used by local health authorities are potential sources of patient access inequalities. Because NTPA codes are infrequently updated, the tariffs associated with codes might not always be sufficient to cover laboratory costs for a given predictive biomarker test (Figure 6).

Recommendations

Assessment processes for co-developed drug-diagnostic companion products should be integrated on a national level and programmes for other assessment scenarios should be established. A positive coverage decision for a pharmaceutical drug that requires companion diagnostic testing should imply mandatory funding of testing. A formal update process for the NTPA should be generated to guarantee regular update of the codes with medical progress.

Overview of the health care system

The National Health Service (Sistema Nacional de la Salud - SNS) is funded by general taxation and covers 99.5% of the population (46 million in 2011). Provision is free of charge at the point of access, except for pharmaceutical orthopaedic and prosthetic products which usually entail a co-payment. The central government provides financial support to each region based on population and demographic criteria.

The regional health ministries in the 17 autonomous communities (Comunidades Autónomas) are responsible for delivery and organization of health services. National coordination is provided by the inter-territorial Board of the National Health System (Consejo Interterritorial del Sistema Nacional de Salud), comprising the 17 regional ministers of health, chaired by the national Minister of Health and Social Policy. The inter-territorial board approves the national catalogue of services that must be provided by all regional health services (cartera de servicios comunes). The catalogue contains services in primary care, specialized care, supplemental care and pharmacy. However, regional health ministries are able to provide health care services outside the national catalogue as long as they cover the costs.

On the regional level, the organizational structure is based on health areas, covering a population of 200,000-250,000. Each area is assigned a general hospital and several primary care centres staffed by multidisciplinary teams (e.g. general practitioners, paediatricians, nurses). Access to specialist care, which is provided either in specialist care centres or hospitals, requires referral from a GP.

Being a decentralized system, patient access to health technologies is virtually exclusively determined by decisions at regional and local levels.

Spain has been particularly affected by the global financial crisis. Therefore, economic measures designed to rationalize costs have been implemented, which also impact on the health care budget. The Rajoy health reform (RD Ley 16/2012) redefined the SNS benefits package by increasing existing co-payments by income group and introducing new co-payments for pensioners (also by income group).

Health Technology Assessment

Before June 2013, pharmaceutical drugs were evaluated on the national level by the SNS Advisory Committee of Pharmaceutical Benefits (Comité Asesor de la Prestación Farmacéutica del Sistema Nacional de Salud), which supported the decisions of the inter-ministerial Commission on Drug Prices (Comisión Interministerial de Precios de los Medicamentos). Recently, the Spanish Government launched an initiative for a new national system of pharmaceutical drug review. Central to the new process is the national therapeutic positioning report (informe de posicionamiento terapéutico – IPT), which will be provided by a new commission (Grupo de Coordinación de Posicionamiento Terapéutico – GCPT). Criteria for evaluation are clinical benefit, innovation and position in therapy of a pharmaceutical drug. The IPT will be a key document for the inter-ministerial Commission when making decisions on drug prices.

For other health technologies the national HTA agency Agencia de Evaluación de Tecnologías Sanitarias – AETS) which is part of the national public research and scientific support organization Instituto de Salud Carlos III provides HTA reports to the inter-territorial board of the SNS.

Some regions have created HTA agencies. Regions with HTA agencies include: Basque country, Catalonia, Andalusia, Galicia, Madrid and Aragon. Regions without an HTA agency rely on recommendations issued by other regional or national HTA agencies. In the absence of national guidelines, data requirements, processes and assessment criteria vary. For manufacturers such variance translates into uncertainties which may act as disincentives. A web-based platform has been developed for improved coordination between the national (AETS) and regional levels (<http://aunets.isciii.es>).

Instead of improving coordination, the Spanish Health Economics Association recommends setting up a national HTA agency following the example of NICE in England in order to inform reimbursement/funding decisions. (Asociación de Economía de la Salud (AES), 2012)

Pricing, reimbursement and funding

PHARMACEUTICAL DRUGS

In order to launch a new pharmaceutical drug in Spain the manufacturer first has to apply for a national product code at the AEMPS. The application will include information on cost per day compared with equivalent products in Spain, price of the product in other EU countries, sales forecast, overall cost of research and development, production costs, etc.

The Directorate of Pharmaceutical and Health Products (Dirección General de Farmacia y Productos Sanitarios) is responsible for reimbursement decisions. Reimbursement is ruled by negative lists excluding pharmaceutical drugs considered of low therapeutic benefit. For pharmaceutical drugs excluded from public financing there is free pricing; however, manufacturers must report the price to the Ministry of Health, which reserves the right to challenge prices in the public interest.

If a reimbursement state is granted, pricing will be decided simultaneously. The Inter-Ministerial Commission on Drug Prices negotiates prices with manufacturers. The agreed prices are subject to a profit cap, i.e. if actual sales exceed the predicted volume, prices are lowered to adjust profits. Regions have a certain degree of freedom to impose their own pharmaceutical price caps or cost-containment targets. According to some stakeholders, the whole pricing and reimbursement process used to take 6 months, but this has since increased to 15 months, which may delay patient access markedly.

The final responsibility for setting pharmaceutical prices rests with the national government cabinet. They publish new product prices in the Official journal (Boletín Oficial del Estado).

So far, hospital pharmaceuticals have been covered 100% by the global hospital budget, whereas the majority of prescription-only pharmaceuticals outside of hospital were subject to income dependent co-payments of between 10% and 60%. However, overall pharmaceutical drug expenditure is under a lot of pressure due to the financial crisis, with repeated budget cuts in recent years. Pharmaceutical drug payment by regional health authorities is delayed (in some autonomous communities for longer than a year). In addition, regional health authorities are seeking new funding initiatives, like risk-sharing models in the case of Catalonia.

Due to the enormous cost pressure, the key factor for patient access to any innovative pharmaceutical drug in Spain is budget impact.

COMPANION DIAGNOSTICS

The majority of diagnostic procedures, including CDx testing, are performed in a hospital out-patient setting. There is neither a national price reference list nor reimbursement coding for diagnostics. The Spanish hospital funding system is based on a global budget. For a CE marked diagnostic to be funded by a hospital budget, a clinician has to propose its use, providing scientific evidence of therapeutic efficiency. The hospital's evaluation commission rules on the proposal, considering at least budget impact and clinical evidence. In most autonomous regions HTA is beginning to be introduced at the hospital level to support decision-making. Finally, the hospital manager is responsible for adopting diagnostics. Hospitals commission diagnostic tests through public tendering. For small hospitals tenders are organized on the regional level whereas large hospitals usually organize their own tenders. In cases where there is only one test manufacturer, there is direct negotiation with the manufacturer.

Diagnostics can also be included in the national benefit basket. Typically, this happens after they have already been introduced at the local or regional level and the autonomous region proposes the diagnostic for inclusion in the common benefit basket.

Although in theory these funding pathways for diagnostics would be applicable to companion diagnostics, this is not normally the case. Several expert stakeholders agreed that regional and national administrations refuse funding of companion diagnostic testing. Consequently, they remain largely funded by pharmaceutical manufacturers.

Facilitating and impeding factors for patient access

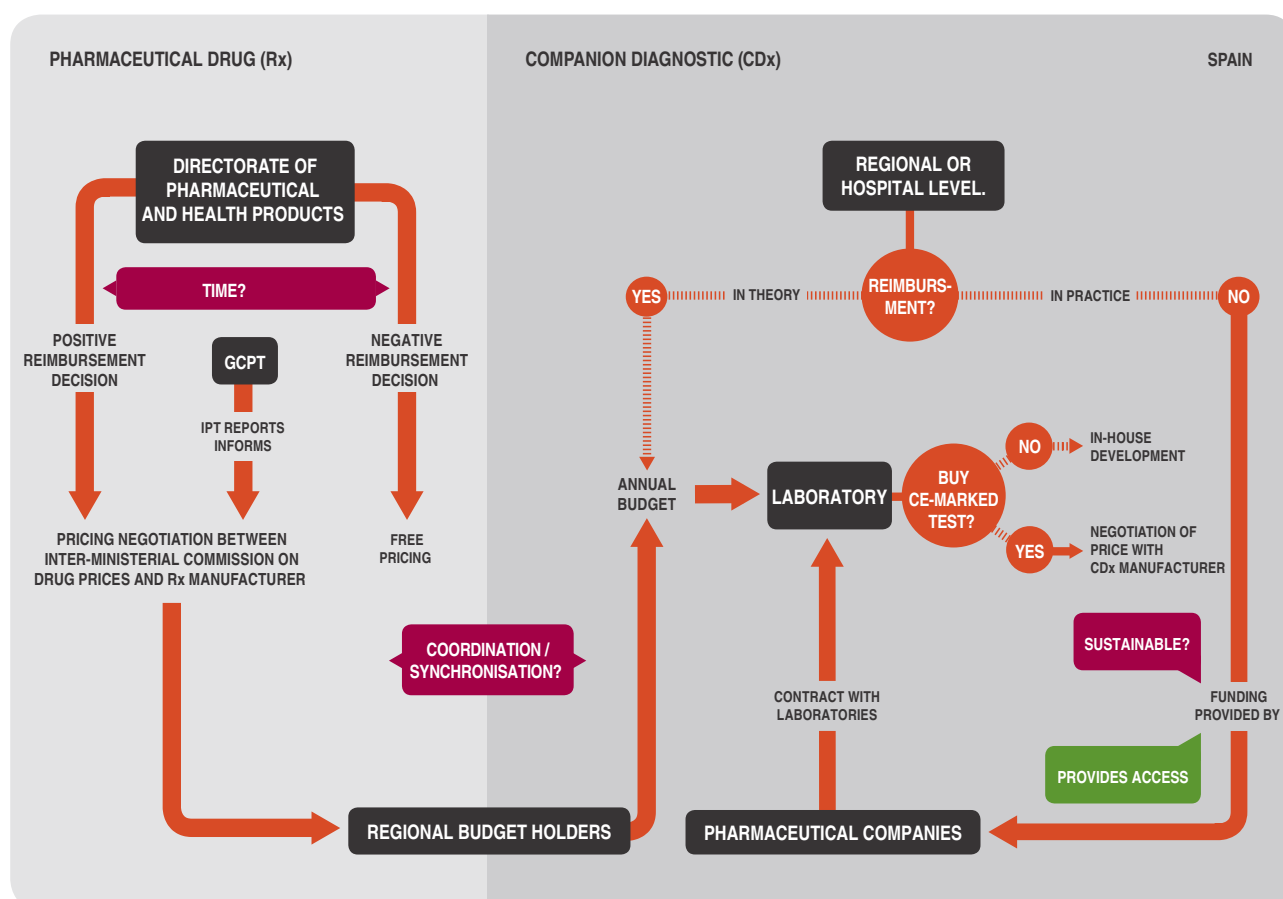


FIGURE 7

Impeding and facilitating factors in Spain. Assessment processes for pharmaceutical drugs and associated companion diagnostics are separated. The Grupo de Coordinación de Posicionamiento Terapéutico (GCPT) evaluates pharmaceutical drugs and provides the national therapeutic positioning report (Informe de posicionamiento terapéutico – IPT) to inform pricing. Funding decisions for pharmaceutical drugs are made centrally but take considerable time, leading to delays in patient access. In practice companion diagnostic testing is in most cases funded by pharmaceutical

Facilitating factors

Companion diagnostic testing is in most cases funded by pharmaceutical companies thereby currently enabling patient access. Catalonia has begun to introduce risk-sharing models for pharmaceutical drugs associated with companion diagnostics. Such models may be adopted by other regions and may be a way to facilitate patient access (Figure 7).

Impeding factors

Currently the economic measures to cope with the financial crisis put a lot of pressure on pharmaceutical drug expenditure. Funding decisions for pharmaceutical drugs are made centrally but take considerable time, leading to delays in patient access. Companion diagnostic testing is typically funded by pharmaceutical companies, which is a facilitating factor for now but may be difficult to sustain when several pharmaceutical drugs are available for the same test or testing panels become widely adopted (Figure 7).

companies thereby currently enabling patient access which may be difficult to sustain when several pharmaceutical drugs are available for the same test or testing panels become widely adopted.

Recommendations

It is recommended to continue with the establishment of HTA structures – either by fostering the existing HTA network or by establishing a national Spanish HTA agency – because they provide an evidence basis for rational decisions on budget cuts. Coverage decisions for a pharmaceutical drugs and companion diagnostic testing should be consistent.

3.2.6

SUMMARY AND DISCUSSION OF FINDINGS

Health Technology Assessment

Health technology assessment (HTA) seeks to determine the value of pharmaceutical drugs associated with companion diagnostics in order to provide a solid evidence base to decision-makers. The result of the assessment depends on the perspective taken (e.g. patient, manufacturer, payer). From a patient or clinician's perspective, the value of any health technology is in the improvement of health outcomes under routine care conditions, irrespective of the associated costs. Manufacturers seek adequate rewards for innovation and incentives to invest in future research (M. Drummond, Tarricone, & Torbica, 2013).

Payers represent those who fund the public health care systems, e.g. taxpayers or those who pay insurance contributions. They have only limited financial resources and therefore apply HTA methodologies to assess whether new health technologies improve health outcomes in a routine care setting when compared to currently available treatment options and whether the improved outcomes justify additional costs (M. Drummond et al., 2013). Therefore, a positive evaluation by payers is essential for patient access but the value concept differs between payers and patients.

METHODOLOGICAL CONSIDERATIONS

Among experts there is broad agreement that the toolbox of HTA is – with minor modifications and adjustments – generally suitable for the evaluation of pharmaceutical drugs associated with companion diagnostics (Postma et al., 2011).

Among the HTA agencies of the EU-5, NICE is the one that most systematically addresses the different assessment scenarios that arise in the context of pharmaceutical drugs associated with companion diagnostics: For companion diagnostics that have been co-developed with the associated pharmaceutical drug, NICE in its technology appraisal guide suggested incorporating the costs and, when appropriate, the accuracy of companion diagnostic testing into the evaluation of the pharmaceutical drug (NICE, 2013b). Other assessment scenarios may arise if companion diagnostics are developed for established pharmaceutical drugs or if several alternative tests for the same biomarker (either in-house or CE marked) are used in practice. Crabb et al. point out that “[I]n such cases, the evaluation of the various alternative tests and understanding the links between diagnostic test performance, the patient group selected for treatment and the subsequent outcomes may add considerable complexity to the evaluation.” (Crabb et al., 2012). NICE recently published such a comparison of alternative assays designed to detect mutations in the epidermal growth factor receptor tyrosine kinase (EGFR-TK) gene. The assays differed by detection method and the number of targeted mutations. NICE recommended five testing strategies, provided they were used in accredited laboratories participating in an external quality assessment scheme. Furthermore, minimum requirements for in-house tests were recommended. For five testing methods (including one CE marked kit), no recommendation was made because the evidence was considered insufficient (NICE, 2013a).

A common approach to measuring value for money is the incremental cost-effectiveness ratio (ICER). ICER is determined by the ratio of the additional health costs to the additional health gains when comparing two technologies with an explicit or implicit acceptance threshold. However, cost-effectiveness evaluations can be subject to considerable variability. For example, NICE and the Scottish Medicines Consortium (SMC) assessed the cost-effectiveness of EGFR-TK testing associated with gefitinib in patients with non-small-cell lung cancer in the UK. Interestingly, the resulting estimations of cost per quality adjusted life year differed by a factor greater than four (Faulkner et al., 2012) despite the fact that both authorities use similar guidelines for cost-effectiveness evaluations of pharmaceutical drugs (Postma et al., 2011).

When combined with a fixed cost-effectiveness threshold, the variability within cost-effectiveness evaluations may lead to an erroneous rejection of a truly cost-effective technology. NICE adopted a willingness to pay threshold of about £20,000 - £30,000 per quality adjusted life year gained. However, even in the UK, the threshold is flexible under certain circumstances, e.g. in case of end-of-life drugs. Most other EU countries choose incremental approaches for determining clinical value ahead of value for money to inform pricing negotiations between payers and the drug manufacturer (Giuseppe Carone, 2012).

INSTITUTIONAL IMPLEMENTATION

Traditionally, in the EU-5, separate committees are responsible for evaluating pharmaceutical drugs and diagnostics. The country-by-country analysis in this study revealed that companion diagnostics are often no exception to that rule. Different approaches are in place. In the EU-5 countries pharmaceutical drugs are typically evaluated centrally. The associated companion diagnostic may be assessed centrally together with the pharmaceutical drug (UK), centrally but independently of the pharmaceutical drug (FR, DE) or regionally or even locally (ES, IT).

Like all diagnostics, companion diagnostics have no direct health improvement effect but potentially generate downstream health effects.(Garau, 2013). Therefore, companion diagnostics should be incorporated into the evaluation of their associated pharmaceutical drug.

Such an integrated evaluation requires a coordination and synchronization between the committees who are engaged in the evaluation process. In countries with centralized evaluation processes for pharmaceutical drugs and companion diagnostics such coordination should be achievable with relative ease. In countries with decentralized evaluation processes for companion diagnostics coordination is more challenging and may involve alternate assignment of regional agencies or a committee consisting of members from each regional HTA agency.

Such collaboration between institutions applying HTA-like processes requires a common methodological framework. In order to improve coordination among HTA agencies, in 2004 the European network for HTA (EUnetHTA) was established (EUnetHTA, 2013). EUnetHTA developed a standardized methodological framework for producing and presenting HTAs (HTA Core Model®) which can be easily adapted locally (Kristensen et al., 2009). This model may be used to support the aforementioned collaboration of HTA agencies within a country.

Facilitating and impeding factors

Companion diagnostics and the associated pharmaceutical drugs form a compound product and therefore should be evaluated together when they are brought to the market. In practice evaluations often follow separate pathways – sometimes even at different organizational levels. In some countries HTA processes are even applied in a decentralized way. If the evaluation of pharmaceutical drugs and companion diagnostics are not coordinated and synchronized inconsistent recommendations or delayed access may result. Therefore, patient access could be facilitated by evaluating pharmaceutical drugs and the associated companion diagnostics in a single HTA report.

Recommendation

HTA processes within a country should be coordinated in a way that results in a single integrated HTA report for pharmaceutical drug-diagnostic companion products. Reason: Companion diagnostics have no direct health improvement effect but potentially generate downstream health effects when used as indicated with therapeutics.

Pricing & Reimbursement/Funding

Mechanisms for pricing and reimbursement/funding of pharmaceutical drugs and companion diagnostics are different. In the case of pharmaceutical drugs, reimbursed/funded refers to the actual product, whereas companion diagnostic testing is reimbursed/funded as a service. In order to provide this service, laboratories may either develop an appropriate test in-house or buy a CE marked companion diagnostic. In the latter case, procurement prices are negotiated between laboratories and diagnostic test manufacturers.

Pricing

From a health care system point of view, in the short-term the price of a given health technology should be as low as possible. However, prices in the long term also serve to reward and encourage manufacturers of technologies to invest in research and development. Therefore, from a societal perspective it is important to find a good balance between short-term and long-term effects of pricing.

Due to resource constraints payers have to make decisions on how to efficiently allocate resources. Such allocation decisions will exclude some technologies from reimbursement, impeding patient access. A rational heuristic to guide allocation decisions is to maximize value for money. Two policies for achieving this goal have become more popular: External reference pricing and value-based pricing (M. Drummond, Jonsson, Rutten, & Stargardt, 2011; M. F. Drummond & Mason, 2007).

EXTERNAL REFERENCE PRICING

External reference pricing determines a price by referring to prices in other countries (the reference countries). It guarantees that a country will not pay more for new pharmaceutical drugs than comparable countries without a formal assessment of the value of a new pharmaceutical drug. Therefore, it is a particularly interesting mechanism for countries that lack the resources to set up their own regulatory and HTA agencies.

External reference pricing is very common in the EU – 24 out of 27 countries used it in 2010. Among the EU-5, the UK is the only country not using external reference pricing. The price determined by external reference pricing depends on the reference countries chosen and the calculation method (e.g. calculating the average or taking the lowest price). The most frequently referenced countries are Germany, Spain, France and the UK, with calculation of the average being the most common method. According to several studies external reference pricing seems to be an effective policy for reducing pharmaceutical prices (Leopold et al., 2012). However, if high income countries reference lower income countries pharmaceutical companies may be less willing to offer differential prices and hence, patient access in the referenced lower income countries may be impeded by comparatively high pharmaceutical drug prices.

The method is suitable for pharmaceutical drugs and the associated companion diagnostics. However, external reference pricing only works if there is at least one country that determines the value of a new health technology independently.

VALUE-BASED PRICING

The concept of value-based pricing (VBP) links the price of a health technology to the value it offers to the health care system. The value of health technologies is determined by employing HTA methodologies. the new technology will only be funded by the system if the determined value is above the willingness to pay.

The VBP approach can also be applied to pharmaceutical drugs associated with companion diagnostics. The result of such an approach is a compound value for the pharmaceutical drug and the associated companion diagnostic. The key challenge of the VBP approach is attributing proportions of the compound value to the components as any given proportion is essentially arbitrary (Garau, 2013). Currently, the pharmaceutical drug represents most of the compound value of pharmaceutical drug-diagnostic companion products. Negotiation between pharmaceutical drug and diagnostics manufacturers may be the most pragmatic way to split the compound value of pharmaceutical drugs associated with companion diagnostics. This approach works as long as each pharmaceutical drug is only associated with one test. If several companion diagnostics are combined in a “multiplex”, this approach becomes more complicated and other solutions for value allocation may be needed.

Reimbursement/Funding

Reimbursement/funding mechanisms for prescription pharmaceutical drugs are in place in all of the EU-5 health care systems. In contrast, companion diagnostic funding sources and mechanisms have not been established to the same extent.

Generally, funding can either be provided by the health care system, a pharmaceutical company or patients (Figure 8).

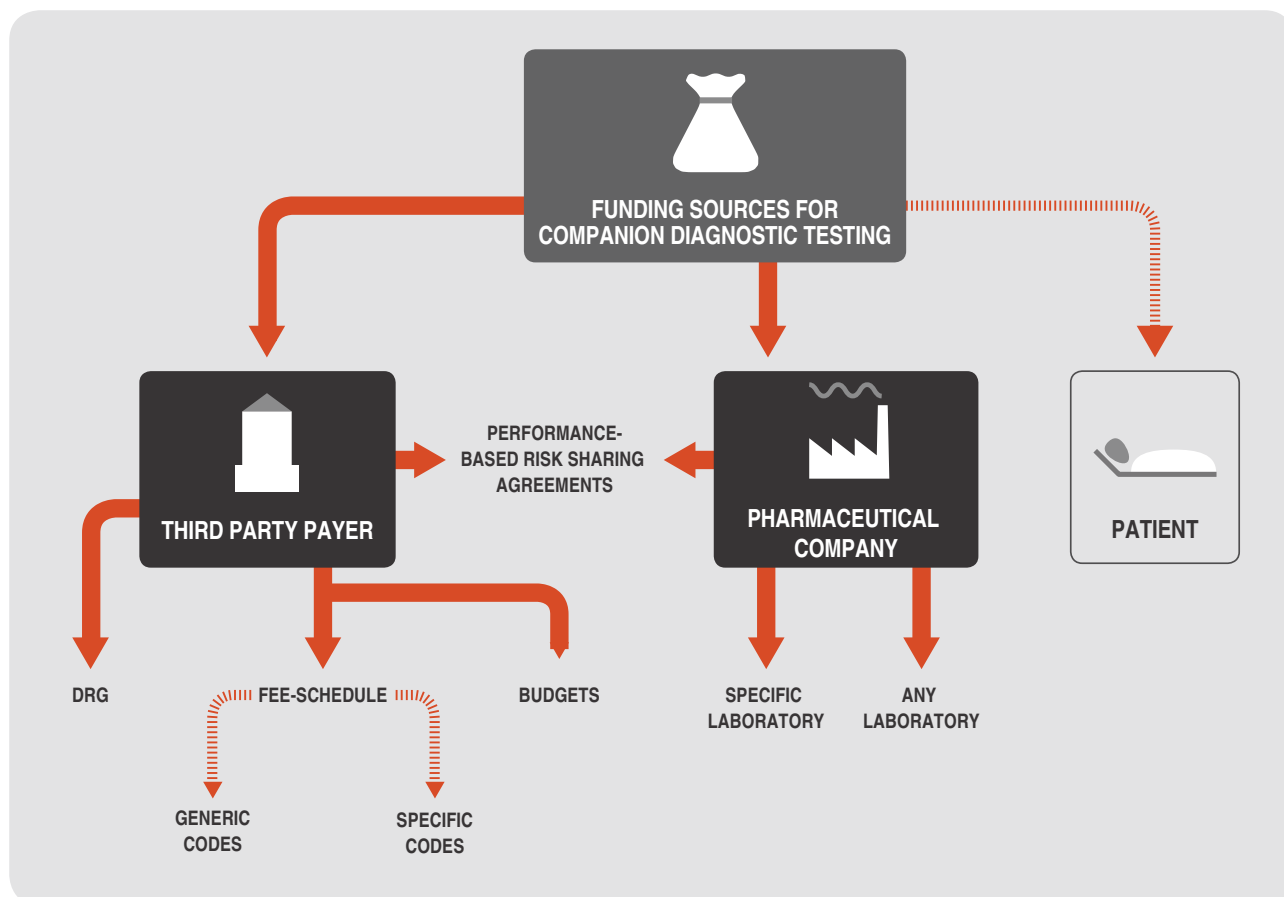


FIGURE 8

Potential funding sources and mechanisms for companion diagnostics

PATIENT FUNDING

Although costs for biomarker testing are low compared to pharmaceutical drug prices, in absolute terms they are still too high to be paid out of most patients' pockets. Therefore, patient funding of companion diagnostics would be a big barrier for patient access and would particularly disadvantage patients with limited financial resources. In the EU-5, either the health care system or pharmaceutical drug manufacturers pay for testing. Depending on the health system, reimbursement/funding mechanisms differ.

HEALTH CARE SYSTEM

In a hospital setting, the most common model is the DRG system. Each patient is assigned to a DRG. The DRG determines a flat rate fee that is paid to the hospital for the case irrespective of the actual costs, including expenses for pharmaceutical drugs and companion diagnostic testing.

In an ambulatory setting countries differ with regard to the reimbursement/funding system.

Fee-schedule based systems

In Germany, France and Italy fee-schedules with procedure codes and associated tariffs are used to reimburse testing services for each patient. Codes can either be specific (i.e. referring to a specific testing method for detecting a particular analyte) or generic (i.e. referring to a method only without specifying the analyte, e.g. FISH). Frequently, reimbursement of testing for a given predictive biomarker involves a combination of generic codes – so-called code stacking. The major advantage of generic codes is immediate coverage and hence patient access to companion diagnostics. However, stakeholders often noted that tariff levels do not adequately reflect current testing costs, particularly if the reimbursement codes are not updated on a regular basis. In a worst case scenario, if the proportion of predictive biomarker tests for which tariff levels do not reflect testing costs is high, laboratories may be tempted to save costs by sacrificing quality.

Even if a system decided to generate new specific codes, the process often takes years. If there are no temporary funding streams to bridge such a reimbursement gap, patients might not have access to pharmaceutical drugs requiring companion diagnostics despite a positive reimbursement decision.

Budget-based systems

The funding mechanism in the United Kingdom and Spain is based on global annual budgets allocated to local budget holders. Local budget holders decide how to spend their budget based on the health care needs of the local population. Funding of laboratory services is also based on global annual budgets. In such systems funding decisions for pharmaceutical drugs are made centrally, but often funding decisions for companion diagnostics are made at the regional or local level. If companion diagnostic testing is required and not paid for locally, patients will not have access to the pharmaceutical drug.

Global annual laboratory budgets may also lead to delayed patient access if new tests become available during the year. Expert stakeholders reported that local authorities have sometimes delayed implementation of central guidance decisions regarding pharmaceutical drugs leading to inequality in patient access.

PHARMACEUTICAL COMPANIES

In some systems, pharmaceutical companies are allowed to pay for companion diagnostic testing. This model may be interesting from a pharmaceutical companies' point of view to initially promote the introduction of a pharmaceutical drug. Having pharmaceutical companies pay is also of interest to the health care system to bridge reimbursement gaps within a system (e.g. in the UK) or even to fund companion diagnostic testing in the long term (e.g. in Spain).

Commonly, pharmaceutical companies contract with specific laboratories that are able to guarantee a high quality standard. For example, the NICE guidance issued for Vemurafenib states: "The manufacturer of vemurafenib is currently making BRAFV600 mutation testing free of charge by funding 3 BRAF reference testing centres in the UK." (NICE, 2012)

The current "pharma-pays" model works well as long as only one pharmaceutical company benefits from a given test. In the future, more pharmaceutical drugs may be associated with the same test – because multiple pharmaceutical drugs are associated with the same biomarker, or because one test would provide information on different biomarkers or because generic pharmaceutical drugs are brought to the market. In such situations, various pharmaceutical companies would benefit from testing. The benefitting companies would then have to agree on the proportion each company has to contribute to test funding. Although not impossible in theory, such a process takes time and potentially delays patient access. In such a situation, health care systems may take over the funding role in order to ensure patient access.

PERFORMANCE-BASED RISK-SHARING ARRANGEMENTS

Performance-based risk-sharing arrangements "(...) involve a plan by which the performance of the product is tracked in a defined patient population over a specified period of time and the level or continuation of reimbursement is based on the health and economic outcomes

achieved.” (Garrison et al., 2013). To reach their full potential they need an infrastructure to systematically study the use of pharmaceutical drugs, health care services and related outcomes.

Risk-sharing arrangements have successfully been used by all EU-5 countries to enable patient access to pharmaceutical drugs despite uncertainties about their value. Most performance-based risk-sharing arrangements are in place in Italy, followed by the patient access schemes in the UK. Such arrangements also exist in France Germany and Spain, albeit to a lesser extent.

Facilitating factors

In fee-schedule systems immediate access to companion diagnostic testing is often ensured through generic codes. Systems based on global annual laboratory budgets allow for immediate access to companion diagnostic testing irrespective of the availability of a reimbursement code. Regarding pricing, value-based pricing approaches are useful to reconcile interests of society and manufacturers by linking prices to the value pharmaceutical drugs associated with companion diagnostics offer to the health care system. Active promotion of molecular diagnostics helps to facilitate patient access, which is demonstrated by the example of INCa in France. However, it has to be pointed out that INCa only promotes molecular testing in the therapeutic field of oncology and this promotion is temporary in nature. Linking the reimbursement decision for a companion diagnostic to the requirements of the drug label (e.g. in Germany and in theory in the UK) is another practice that facilitates patient access. Furthermore, if pharmaceutical companies are allowed to pay for testing, it facilitates patient access in two situations: when a gap exists due to the time needed for updating the funding/reimbursement system and when a system is reluctant to pay for companion diagnostic testing in general (like in Spain). A further way to facilitate patient access, especially if uncertainties about the value of effective utilization in a routine-care setting are present, is via performance-based and other risk-sharing agreements.

Impeding factors

The first impeding factor for patient access is inconsistent reimbursement/funding decisions. These occur when there is no coordination between evaluation of pharmaceutical drugs and the associated companion diagnostics. Access is delayed when the decisions are consistent but reimbursement/funding for companion diagnostic testing is made available later than for the drug patient. If new codes need to be generated to enable reimbursement for companion diagnostic testing or global annual laboratory budgets do not sufficiently cover the costs for a new test, patient access is delayed due to the time needed for the update of the reimbursement/funding systems. Furthermore, updating tariff levels in existing fee-schedule systems takes considerable time and effort. Therefore, it may take years before tariff levels are reviewed and updated. If tariff levels do not reflect current laboratory costs to perform a particular test and predictive biomarker testing represents a larger percentage of overall testing for a laboratory, quality of testing may be jeopardized.

There is no doubt that DRG, fee-schedule and annual budget systems cannot be changed immediately. The resulting reimbursement gaps could be bridged by providing temporary funding for companion diagnostic testing. The French Institute of Cancer (INCa) is an example of companion diagnostic test promotion in the field of oncology that has the same effect as a temporary funding mechanism. INCa was mentioned by the majority of stakeholders as a best practice example for patient access to companion diagnostic testing.

Recommendations

- If a health system decides to fund a pharmaceutical drug, companion diagnostic testing should also be funded.
Reason: Patient access to a pharmaceutical drug associated with a companion diagnostic is dependent on the actual availability of both the pharmaceutical drug and the associated companion diagnostic which requires reimbursement and funding.
- Health systems should implement a temporary reimbursement/funding pathway that guarantees funding of companion diagnostic testing at the time of pharmaceutical

drug launch, e.g. a generic reimbursement code for companion diagnostic testing.
Reason: Even if there is a positive reimbursement/funding decision for a pharmaceutical drug and associated companion diagnostic testing, implementation of such a decision, i.e. updating existing reimbursement/funding systems, may take 2-3 years. Without a temporary reimbursement/funding mechanism, patient access is likely to be delayed. Temporary reimbursement in a fee-schedule system could, for example, be implemented by a generic code for companion diagnostic testing.

- Reimbursement tariffs/codes for companion diagnostic testing should be updated on a regular basis.

Reason: If reimbursement tariffs do not cover the current costs for testing and predictive biomarker testing represents an important percentage of overall testing in a laboratory, quality of testing may be jeopardized.

ALK-TESTING FOR NON-SMALL-CELL LUNG CANCER PATIENTS

In its guidelines on non-small-cell lung cancer, the European Society for Medical Oncology recommends: “ALK activity can be efficiently targeted by the tyrosine kinase inhibitor Crizotinib, and routine testing for ALK rearrangements should be discussed where this pharmaceutical drug is available.” In Germany, Crizotinib is available on the market and ALK testing has been available at drug launch. In an ambulatory setting, reimbursement is assured through generic codes in the uniform value scale. In a hospital setting, ALK testing is covered by the DRG system. Some hospitals in Germany intended to obtain separate funding by applying for new diagnostic and therapeutic procedures (NUB) innovation coverage for ALK FISH testing. However, the application was rejected, presumably because testing costs account only for a small proportion of total DRG cost. Italy had a similar situation, as testing was reimbursed through generic codes at drug launch in an ambulatory setting. In a hospital setting, DRGs cover ALK testing. In France, ALK testing is funded by the Institute of Cancer (INCa). In the field of oncology, INCa enables access to companion diagnostic testing at the time of drug launch by providing a temporary funding mechanism until the permanent funding system has been updated.

In the UK, NICE acknowledged that ALK-positive non-small-cell lung cancer patients would benefit from treatment with Crizotinib when compared with chemotherapy. However, Crizotinib was not considered a cost-effective use of NHS resources and therefore not recommended by NICE guidance. Nevertheless, Crizotinib is available in the UK because funding is provided by the Cancer Drugs Fund. Patients have access to companion diagnostic testing, which is almost completely funded out of laboratories' global budgets.

In Spain, Crizotinib has not been formally approved yet. Therefore, it remains to be seen whether companion diagnostic testing will be paid by the health system. Based on previous experience, it can be assumed that budget holders in Spain expect the pharmaceutical manufacturer to pay for companion diagnostic testing.

3.3

PROVIDERS

3.3.1

PATHOLOGISTS/LABORATORIES

Predictive biomarker tests are generally offered by laboratories associated with hospitals or commercial laboratories. According to expert stakeholders, the capacity for molecular testing and the distribution of laboratories in the EU-5 is satisfactory. There might even be a consolidation trend.

In addition to testing capacity, quality of testing is an important aspect of patient access because lower quality means an increased risk of errors and errors may result in misclassifications (false-positive or false-negative test results). Misclassified patients may erroneously be denied access to the most appropriate pharmaceutical drug or patient access may be delayed.

When thinking about laboratory quality it is useful to divide the testing process into three stages: pre-analytical, analytical and post-analytical. Each of the stages can be a source of variability and error. The pre- and post-analytical processes include procedures in the laboratory but to a large extent occur outside the laboratory (Figure 9). It has been repeatedly shown that the majority of errors occur in the pre-analytical phase. (Bonini, Plebani, Ceriotti, & Rubboli, 2002). Therefore, any attempt to improve the overall quality of the testing process has to account for procedures outside the laboratory.

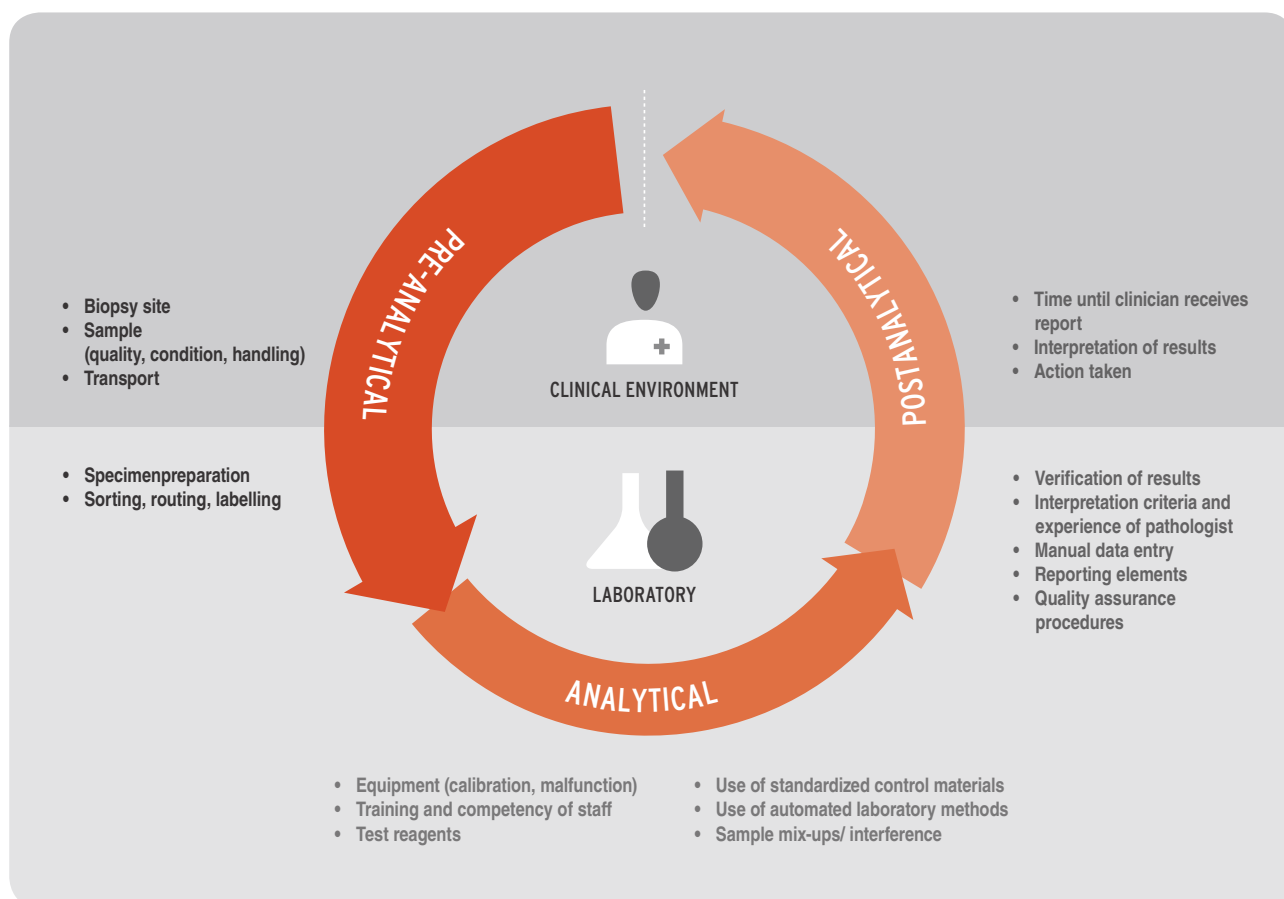


FIGURE 9

Stages of the testing process and sources of variability in and outside the laboratory

Quality can be improved by employing quality assurance (QA) measures. The meaning of different quality endorsements is often confused (Berwouts, Fanning, Morris, Barton, & Dequeker, 2012; Berwouts, Morris, & Dequeker, 2010):

- Accreditation formally recognizes adherence to a quality management system plus technical competence and requires participation in EQA schemes
- Certification formally recognizes adherence to a quality management system, often ISO 9001
- Licensing refers to a permission to operate a laboratory issued by a government agency
- External quality assessment (EQA) is defined by the World Health Organization “as a system for objectively checking the laboratory’s performance using an external agency or facility” (WHO/CDC/CLSI, 2009)

National level findings

Germany

Biomarker testing services are provided primarily by pathologists in an ambulatory setting. According to stakeholders, laboratory capacity for molecular testing is sufficient. The national accreditation body in Germany is “Deutsche Akkreditierungsstelle GmbH”. The German Pathologic Society (Deutsche Gesellschaft für Pathologie – DGP) launched a quality assurance initiative (Qualitätssicherungs-Initiative – QulP) in order to offer EQA schemes (Ringversuche) in molecular pathology. On their Website DGP points out that in order to guarantee reproducible results laboratories should use positive and negative controls internally and participate in EQA on a regular basis. QulP states that there is currently a lack of infrastructure to allow for regular conduct of EQA and aims to institutionalize EQA. Currently, EQA is offered for a whole range of biomarkers including EGFR, KRAS, B-RAF, HER2 but the number of participants is often limited.

United Kingdom

Generally, companion diagnostic tests are provided in a secondary care setting. Laboratories often operate within hospitals but there are also independent private laboratory services which are used by the NHS. Specialist and infrequent tests may not be available at a local level but be provided on a regional or nationwide basis. Due to cost pressures, a consolidation of the pathology service market is currently underway which is expected to result in fewer laboratories, mostly attached to research and teaching hospitals.

Regulation in England requires medical laboratories to enrol in an accreditation programme. The Clinical Pathology Accreditation (CPA) – a wholly-owned subsidiary of the United Kingdom Accreditation Service (UKAS) – is responsible for accrediting medical laboratories and external quality assessment schemes. A transition to the internationally recognized standard ISO 15189 is currently underway, and since October 2013 assessment of CPA-accredited laboratories has been based on this standard. NICE guidance often requires companion diagnostic tests to be carried out in accredited laboratories regularly participating in EQA schemes. CPA-accreditation includes a requirement to participate in EQA schemes. The choice of the particular EQA scheme is open (not limited to CPA-accredited schemes). A fully CPA-accredited example of an EQA scheme is the National External Quality Assurance Scheme (NEQUAS) for molecular genetics.

France

In order to enable rapid implementation of innovative molecular tests nationwide, a national network of 28 molecular genetics centres has been built by INCa. On average there is one centre per administrative region. Each molecular centre is basically collaboration between university hospitals and cancer centre laboratories with complementary expertise. The molecular genetics centres perform companion diagnostic testing for all patients in the respective region. As most companion diagnostics have so far been developed in the field of oncology, and INCa is responsible for providing equal access to molecular testing in oncology, INCa plays an important role for access to molecular testing in France.

Quality of testing is addressed by a regulation that requires all medical laboratories to become accredited (ISO 15189 standard) before 2016. Otherwise, they will not be allowed to offer their services any longer. Therefore, INCa guides the laboratories within its network to become accredited as soon as possible. (Nowak et al., 2012)

Italy

Outpatient testing can be done by laboratories based within hospitals or private accredited structures. Laboratories are accredited by ACCREDIA. EQA schemes have been organized by the Italian Association of Medical Oncology and the Italian Society of Pathology and Cytopathology, e.g. for EGFR (Normanno et al., 2013) and KRAS (Normanno et al., 2011). However, EQA for molecular pathology has not been established on a regular basis yet.

Spain

Almost all public sector laboratories are hospital-based. Most of the regions have reference laboratories for molecular diagnostic techniques in larger hospitals. Sometimes such regional reference centres even serve as national reference centres. Private clinical laboratories are generally much smaller and offer a more limited range of tests.

From accreditation to central testing

Accreditation is the most comprehensive statement of quality. In the EU, there is one national accreditation body in each country. According to a survey among the personnel of 291 laboratories in 29 European countries, accredited laboratories actually perform better on quality indicators than certified or non-certified laboratories. However, only 23% of the participating laboratories were found to be accredited. (Berwouts et al., 2012). Therefore, one way of improving quality is to increase the number of accredited laboratories through appropriate laws and regulations. For example, from 2016 in France, only medical laboratories accredited according to EN ISO 15189 are allowed to continue offering their services.

The European Commission's proposal for a Regulation on IVDs (European Commission, 2012) requires laboratories that develop in-house tests to be compliant with the EN ISO 15189 accreditation standard or any other equivalent recognized standard. The requirements of this standard include regular meetings with clinical staff regarding services and clinical interpretations, annual internal quality audits, usually biannual external audits and participation in EQA schemes. However, the scope of the future IVD Regulation is unlikely to cover laboratories using CE-marked companion diagnostics.

Raising quality standards above the level required for accreditation limits the number of eligible laboratories, ultimately leading to the central testing approach. Testing sites are limited to only a few large reference laboratories with a correspondingly high throughput. Pharmaceutical companies often choose this model if they pay for companion diagnostic testing. At the far end of the scale, only one central laboratory processes all samples worldwide (e.g. Oncotype DX® test, with one central laboratory in the USA).

The advantages of a central testing approach include more standardization of the process, higher testing quality and potentially lower costs per test through economies of scale. The disadvantages include time and effort for shipping tissue specimens, increased turnaround times, longer communication channels and a tendency to higher costs. Therefore, setting high quality standards may involve a trade-off between timely patient access and increased quality of testing.

External quality assessment schemes

Overall laboratory performance (excluding stages outside the laboratory) can be assessed by sending tissue samples to different laboratories and comparing their test results with the result of reference laboratories. Such inter-laboratory comparisons are called External Quality Assessment (EQA) schemes.

Some results have been published for EQA schemes on frequently tested predictive biomarkers. A recent report about EGFR-TK testing in non-small-cell lung cancer patients in the UK concluded that there was an unacceptably high incidence of genotyping errors. The

genotyping errors were not correlated to any particular method used. Throughout the three round scheme the genotyping error rate dropped from 24% in the first run to 6.4% in the last run (Deans et al., 2013), demonstrating the educational effect of EQA schemes.

In a large EQA scheme for KRAS testing with 59 participating laboratories in 8 European countries about 30% of laboratories did not correctly identify KRAS mutational status in all samples. Even if the test results were correct, report quality of diagnostic test reports was generally rated as poor. Mistakes (mostly false-positive or false-negative test results) occurred both with commercial kits and in-house tests. However, data were not sufficient to conclude whether mistakes happened more frequently with commercial kits or in-house tests. (Bellon et al., 2011).

The guideline recommendations for HER2 testing issued by the American Society of Clinical Oncology, together with the College of American Pathologists, state that about 20% of HER2 test results are inaccurate (Wolff et al., 2007).

These examples demonstrate the need for continuous quality assurance measures in laboratories. In both the KRAS and EGFR-TK EQA schemes, data was not sufficient to draw conclusions about quality differences between laboratories using commercial kits and laboratories using in-house tests. Further research should be carried out to study the impact of the testing methodology on the quality of the overall testing process.

Recommendations

- All laboratories performing companion diagnostic tests should be required to be accredited and existing external quality assessment schemes should be extended both on a National and European level

Reason: Improving testing quality reduces the number of misclassifications. Misclassifications lead to patients being treated who do not benefit from a pharmaceutical drug or may even be harmed. Accreditation is the most extensive quality endorsement covering the quality inside the laboratory and at the interface to clinicians. Accreditation standards include an obligation to participate in external quality assessment schemes. External quality assessment schemes have been shown to increase the accuracy of companion diagnostic testing.

3.3.2

CLINICIANS

Clinicians are important gatekeepers to patient access. According to a nationwide survey among US physicians, only about 10% of US physicians felt adequately informed about pharmacogenomics testing. The survey revealed that knowledge about pharmacogenomic testing is a predictor for early adoption by physicians. Knowledge in this context does not refer to the content of textbooks (Stanek et al., 2012); instead, “the gap is more pragmatic and clinical – what tests are available, how to procure them, when to use them, how to interpret the results, and how to apply them in an individual patient.”(Stanek et al., 2012). The same survey also revealed uncertainties about the clinical value of pharmacogenomics as a reason for not using them (Stanek et al., 2012).

Most pharmaceutical drugs associated with companion diagnostics are approved in the field of oncology. Therefore, the adoption of the technology by oncologists is most relevant for patient access. It turned out that the practice field of oncology was strongly associated with early adoption. In fact 68.8% of oncologists reported ordering a pharmacogenomics test in the previous 6 months (Stanek et al., 2012).

It would be desirable to conduct a similar survey among European clinicians to understand if there are any concerns with regard to drug-diagnostic companion products. This is further highlighted by the fact that many interviewed expert stakeholders disagreed about the role of clinicians. Some stakeholders reported that clinicians are very reluctant to adopt companion diagnostics even when funding is guaranteed, whereas others reported that clinicians' adoption is not a barrier to access at all.

In any case, close links between pathologists and clinicians help to increase clinicians' awareness about the kind of tests available and how they are appropriately used and

interpreted. Furthermore, clinicians have an important impact on testing quality during the pre-analytical stage. Finally, close links are helpful when informal advice for patients is needed.

Recommendations

- Further research should investigate the knowledge and attitude of European clinicians towards pharmaceutical drugs associated with companion diagnostics. Reason: Clinicians are gatekeepers for patient access to drug-diagnostic companion products. In sharp contrast to their importance for patient access comparatively little is known about attitudes and behaviours of European physicians.
- Collaboration between clinicians and pathologists in the area of personalised medicine should be intensified. Reason: A survey among US clinicians revealed that one reason for not using pharmacogenomics is a lack of knowledge about what tests are available, how to procure them, when to use them, how to interpret the results and how to apply them in an individual patient. Furthermore, it has been shown that the pre-analytical stage outside the laboratory is crucial for obtaining accurate test results. Intensified collaboration leads to an exchange of knowledge, lowers the threshold to ask for advice and generates awareness about the available testing options.

3.4

PATIENTS

Being confronted with a serious – often life-threatening – disease, patients suddenly need to make a series of difficult decisions. Traditionally, the clinician-patient relationship could be described as paternalistic. Patients relied on their doctors' professional opinion and followed their advice. In recent decades, the clinician-patient relationship has evolved into a partnership model. In a recent survey, roughly 75% of European patients, particularly those of younger age, wished to play a more active role in healthcare decision-making. (Coulter & Jenkinson, 2005). For these patients, it is crucial to have easy access to reliable information about their disease and treatment options in clear and non-technical language. This applies in particular to the complex field of personalised medicine. Ideally, the provider of such information has no vested interest in a particular treatment path. Health technology assessment agencies could be potential providers of such information. For example, IQWiG in Germany summarizes the advantages and disadvantages of Crizotinib on their patient information platform (IQWiG, 2013). Irrespective of who makes these information centres available, it is necessary to ensure that patients are aware of their existence and can easily find them on the internet.

4.1

REGULATORY APPROVAL/CERTIFICATION

It is recommended that EMA specifies minimum requirements for diagnostic tests that are used with pharmaceutical drugs, e.g. validation criteria.

Reason: Currently, no specification regarding the companion diagnostic test to be used with a pharmaceutical drug are made and hence, many alternative tests for the same biomarker may become available. However, data linking the population selected by a test to health outcomes may only be available for the test used in regulatory trials.

4.2

HTA, PRICING AND REIMBURSEMENT/FUNDING

4.2.1

NATIONAL RECOMMENDATIONS

Germany

An HTA programme dedicated to the comparison of different companion diagnostics for the same biomarker should be established.

A general reimbursement code for temporary funding of companion diagnostics should be generated that can be used for companion diagnostics for which generic codes do not apply without justification of medical necessity by a clinician.

United Kingdom (England)

It is recommended that NICE evaluates all pharmaceutical drugs requiring companion diagnostic testing. Furthermore, mandatory funding for NICE-recommended pharmaceutical drugs should explicitly be extended to associated companion diagnostic tests and it should be ensured that sufficient funding is available to implement NICE recommendations.

France

Coordination and synchronization of HTA and pricing and reimbursement processes would help to enable patient access to pharmaceutical drugs associated with companion diagnostics in all therapeutic areas (not just oncology) and ensure consistent reimbursement decisions. Furthermore, expediting the NABM/CCAM code generation and DRG updating process will ensure that INCa funds are sufficient to promote access to an increasing number of new pharmaceutical drugs associated with companion diagnostics. Finally, extending temporary funding to other therapeutic areas would ensure that updating NABM/CCAM lists and DRG systems will not delay patient access to pharmaceutical drugs associated with companion diagnostics.

Italy

Assessment processes for co-developed drug-diagnostic companion products should be integrated at a national level and programmes for other assessment scenarios should be established. A positive coverage decision for a pharmaceutical drug that requires companion diagnostic testing should imply mandatory funding of testing. A formal update process for the NTPA should be generated to guarantee regular update of the codes with medical progress.

Spain

It is recommended to continue with the establishment of HTA structures – either by fostering the existing HTA network or by establishing a national Spanish HTA agency – because they provide an evidence basis for rational decisions on budget cuts. Coverage decisions for a pharmaceutical drugs and companion diagnostic testing should be consistent.

- HTA processes within a country should be coordinated in a way that results in a single integrated HTA report for pharmaceutical drug diagnostic companion products.
Reason: Pharmaceutical drugs associated with companion diagnostics cannot be used according to the drug label without prior predictive biomarker testing which is not reflected if separate evaluation processes are used.
- If a health system decides to fund a pharmaceutical drug, companion diagnostic testing should also be funded.
Reason: Patient access to a pharmaceutical drug associated with a companion diagnostic is conditional on reimbursement/funding for both the drug and the associated companion diagnostic.
- Health systems should implement a temporary reimbursement/funding pathway that guarantees funding of companion diagnostic testing at the time of pharmaceutical drug launch
Reason: Even if there is a positive reimbursement/funding decision for a pharmaceutical drug and associated companion diagnostic testing, implementation of such a decision, i.e. updating existing reimbursement/funding systems, may take 2-3 years. Without a temporary reimbursement/funding mechanism, patient access is likely to be delayed.
- In fee-schedule systems, reimbursement tariffs/codes for companion diagnostic testing should be updated on a regular basis.
Reason: If reimbursement tariffs do not cover the current costs of testing and predictive biomarker testing represents an important percentage of overall testing in a laboratory, quality of testing may be jeopardized.

4.3

PROVIDERS

- All laboratories performing companion diagnostic tests should be required to be accredited and existing external quality assessment schemes should be extended both on a National and European level
Reason: Improving testing quality reduces the number of misclassifications. Misclassifications lead to patients being treated who do not benefit from a pharmaceutical drug or may even be harmed. Accreditation is the most extensive quality endorsement covering the quality inside the laboratory and at the interface to clinicians. Accreditation standards include an obligation to participate in external quality assessment schemes. External quality assessment schemes have been shown to increase the accuracy of companion diagnostic testing.
- Further research should investigate the attitudes and behaviours of European clinicians towards pharmaceutical drugs associated with companion diagnostics.
Reason: Clinicians are gatekeepers for patient access to drug-diagnostic companion products. In sharp contrast to their importance for patient access comparatively little is known about attitudes and behaviours of European physicians.
- Collaboration between clinicians and pathologists in the area of personalised medicine should be intensified.
Reason: A survey among US clinicians revealed that one reason for not using pharmacogenomics is a lack of knowledge about what tests are available, how to procure them, when to use them, how to interpret the results and how to apply them for an individual patient. Furthermore, it has been shown that the pre-analytical stage outside the laboratory is crucial for obtaining accurate test results. Intensified collaboration leads to an exchange of knowledge, lowers the threshold to ask for advice and generates awareness about the available testing options.

There are considerable differences in patient access with regards to the timing and scope of patient access in the EU-5. Several factors facilitating patient access have been identified: Integrated health technology assessment of pharmaceutical drugs and the associated companion diagnostics avoids inconsistent reimbursement decisions and delays caused by unsynchronized assessment processes. Mandatory reimbursement/funding of companion diagnostic testing if the drug labels of associated pharmaceutical drugs require testing reflects the co-dependency of drug-diagnostic companion products. In fee-schedule systems availability of generic codes allows for access to companion diagnostic testing at the time of drug launch. Risk-sharing agreements are useful to enable patient access despite uncertainties with regard to patient benefit. Quality assurance measures like accreditation and regular participation in external quality assessment schemes ensure that the risk of misclassification is reduced considerably. Linking performance in external quality assessment schemes to reimbursement of companion diagnostic testing would incentivize high quality of testing. Another way to contribute to testing quality is by comparative assessment of alternative tests for the same predictive marker by health technology assessment agencies.

Some countries have established temporary measures to facilitate patient access. In France, the National Institute of Cancer promotes access to companion diagnostic testing in the field of oncology. In Spain, and to a lesser extent in other countries, pharmaceutical companies pay for companion diagnostic testing and, hence, enable or facilitate patient access. Although these measures currently work well it is questionable whether they are sustainable in the long run.

This report is based on expert opinions and published literature. In some areas there is a lack of data. Further research should include the impact of testing methodology on the overall quality of the testing process and the role of clinicians for patient access. Beyond specific studies, it would be desirable to have systematic data reflecting utilization of pharmaceutical drugs, companion diagnostics and clinical outcomes available in a routine care setting, in order to guide decisions for better patient access to personalised medicine.

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ABBREVIATIONS

AETS	Agencia de Evaluación de Tecnologías Sanitarias
AGENAS	Agenzia Nazionale per i Servizi Sanitari Regionali
AIFA	Agenzia Italiana del Farmaco
ALK	Anaplastic Lymphoma Kinase
AMNOG	Gesetz zur Neuordnung des Arzneimittelmarktes
ASA	Amélioration du Service Attendu
ASL	Azienda Sanitaria Locale
ASMR	Amélioration du Service Medical Rendu
ASR	Agenzia Sanitaria Regionale
BCR-ABL	Breakpoint Cluster Region-Abelson
BRAF B	Rapidly Accelerated Fibrosarcoma
BRCA1	Breast Cancer 1 Gene
CA	Comunidades Autónomas
CCAM	Classification Commune des Actes Médicaux
CCR5	Chemokine Receptor
CDF	Cancer Drugs Fund
CDx	Companion Diagnostic
CE	Conformité Européene
CEPS	Comité Economique des Produits de Santé
CISNS	Consejo Interterritorial del Sistema Nacional de Salud
CNEDiMTS	Commission Nationale d'Évaluation des Dispositifs Médicaux et des Technologies de Santé
CPA	Clinical Pathology Accreditation
CPR	Comitato Prezzi e Rimborso
DAP	Diagnostic Assessment Programme
DE	Germany
DGP	Deutsche Gesellschaft für Pathologie
EBM	Einheitlicher Bewertungsmaßstab
EGFR-TK	Epidermal Growth Factor Receptor - Tyrosine Kinase
EMA	European Medicines Agency
EML4	Echinoderm Microtubule-associated Protein like 4
EQA	External Quality Assessment
ES	Spain
ESMO	European Society for Medical Oncology
EU	European Union
EU-5	France, Germany, Italy, Spain and the United Kingdom
EUnetHTA	European Network for Health Technology Assessment
FR	France
G-BA	Gemeinsamer Bundesausschuss
GHS	Groups Homogènes de Séjour

GP	General Practitioner
HAS	Haute Autorité de Santé
HCV	hepatitis C virus
HER2	Human Epidermal Growth Factor 2
HLA	Human Leukocyte Antigen
HOXB13	Homeobox B13
HRG	Health care Resource Group
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IL17BR	Interleukin-17B receptor
INCa	Institute National du Cancer
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISCI	Instituto de Salud Carlos III
IT	Italy
IVD	In-Vitro Diagnostics
JCV	John Cunningham Virus, a type of human polyomavirus
KV	Kassenärztliche Vereinigung
LDT	Laboratory Developed Tests
MIGAC	Missions d'Intérêt Général et à l'Aide à la Contractualisation
MTEP	Medical Technologies Evaluation Programme
NABM	Nomenclature des Actes de Biologie Médicale
NEQUAS	National External Quality Assurance System
NGS	Next Generation Sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence, National Institute for Health and Care Excellence
NTPA	Tariffario delle Prestazioni Ambulatoriali
NTPO	Nomenclatore Tariffario delle Prestazioni Ospedaliere
NUB	Neue Untersuchungs- und Behandlungsmethoden
PAS	Patient Access Scheme
PbR	Payment by Results
PFN	Prontuario Farmaceutico Nazionale
PM	Personalized Medicine
PML	Promyelocytic Leukemia
PPRS	Pharmaceutical Price Regulation Scheme
QA	Quality Assurance
QuIP	Qualitätssicherungs-Initiative
RAR-alpha	Retinoic Acid Receptor alpha
RNA	Ribonucleic Acid
Rx	pharmaceutical drug
SA	Service Attendu
SMC	Scottish Medicines Consortium
SMR	Service Medical Rendu
SNS	Sistema Nacional de la Salud
SSN	Servizio Sanitario Nazionale
TPMT	Thiopurine Methyltransferase
UK	United Kingdom
UNCAM	Nationale des Caisses d'Assurance Maladie
UVEF	Unità di Valutazione dell'Efficacia del Farmaco
VBP	Value-based Pricing