

*Issue Brief*

Advancing Access to Personalized  
Medicine: A Comparative Assessment of  
European Reimbursement Systems

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## 1.0 Executive Summary

European reimbursement systems should reassess their evaluation and payment systems to accommodate the growing number of personalized medicine technologies that are being brought to market. Currently, all European countries' reimbursement infrastructures are limited in their ability to adequately evaluate and rapidly provide access to personalized medicine diagnostics or combined drug and diagnostic products. The goal of this white paper is to identify country-level reimbursement factors that support or inhibit market access to personalized medicine technologies, provide a ranking of the major markets in terms of their relative receptivity to these technologies, and recommend improvements in technology evaluation and reimbursement practice.

Today, many European reimbursement systems are not appropriately aligned to promote the development of companion drugs and diagnostics. For example, European payers consider drugs and diagnostics under separate evaluation and payment processes, which, in many settings put drugs through a more sophisticated appraisal process. Additionally, reimbursement, coding, health technology assessment (HTA), and pricing decisions are made at the country level (either nationally or regionally), while regulatory decisions are largely made for the entire European Union. This creates fragmentation in technology evaluation, evidence requirements, and market access for personalized medicine technologies across Europe. As a result, health systems in many countries are failing to appropriately evaluate and pay for personalized medicine technologies. Thus, patients are often deprived of the most advanced drug and diagnostic treatments while health systems bear the costs of outdated trial-and-error approaches to medicine.

This paper ranks European countries in terms of each reimbursement system's ability to effectively assess and provide access to novel personalized medicine technologies. This ranking considered each country's current reimbursement infrastructure, whether it supports or inhibits access to personalized technologies, and whether changes are being made to accommodate the evolving personalized medicine landscape. With this methodology, countries such as Germany, the UK, and France were ranked higher, due in large part to their current reimbursement pathways for combined diagnostics and therapeutics, previous support of other personalized medicine technologies, and their investments in personalized medicine research. Conversely, countries such as The Netherlands, Finland, and Norway were ranked lower due to their current reimbursement systems' lack of clear pathways for evaluation and funding for personalized technologies.

Despite advancements in certain countries, personalized medicine will not achieve its full potential without changes to health technology assessment methodologies, integrated and rational reimbursement pathways, and straightforward coding systems for both drugs and diagnostics. Personalized medicine innovators need clarity in these areas in order to speed the rate at which personalized medicine technologies are brought to market.

## 2.0 Introduction

*“Personalized medicine” refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.*

*-President’s Council of Advisors on Science and Technology (PCAST)  
September 2008*

The number of personalized medicine technologies being commercialized in Europe has quadrupled from 2006 to 2011.<sup>1</sup> With this growing trend, European payers are increasingly challenged to evaluate companion drug and diagnostic approaches and more advanced personalized medicine diagnostics. Current country specific systems largely consider drugs and diagnostics via separate evaluation and payment processes. Additionally, diagnostic reimbursement evaluation and payment systems are far less sophisticated than drug related systems in most countries.

### White Paper Objectives:

- To identify country-level reimbursement factors in Europe that support or inhibit widespread access to valuable personalized medicine diagnostics and therapies;
- To evaluate and rank each of the major markets on their relative receptivity to personalized medicine technologies from a reimbursement and market access standpoint; and
- To provide insights into current variability in reimbursement practice across countries and to suggest opportunities for improvement within and across markets.

Within the current health care delivery model, a more personalized approach to diagnosis and treatment is possible. Recent scientific advances have increased understanding of the physiological pathways for diseases and the responses to various treatments on a molecular level. Identifying the subset of patients for whom targeted therapies are most appropriate increases treatment success and limits exposure to potentially toxic treatments from which patients will not benefit. This has resulted in more specific diagnosis (i.e. EGFR-expressing metastatic colorectal cancer or Her-2/*neu*-positive breast cancer) and a more personalized treatment plan for many patients. As scientific understanding of disease at the molecular level becomes more prevalent, personalized medicine approaches to diagnosis and treatment will become more common.

However, for personalized medicine to continue its development, reimbursement pathways to support access to innovative technologies must be in place. Today, that is not yet the case in many European countries. Payers and health technology assessment (HTA) agencies need to be made aware of the financial implications of current diagnostic and treatment approaches, side effects associated with non-targeted treatments, and the costs associated with giving patients ineffective therapies. By providing *the right treatment, to the right patients, at the right time* not only do patient outcomes improve, but so does the efficiency of the health care system. As such, payers, clinicians, patients, and industry should work together to ensure that European health systems see the value in increasing the availability of

<sup>1</sup> Personalized Medicine Coalition, “Personalized Medicine by the Numbers”. To be released 2011.

personalized medicine technologies via rational reimbursement pathways and value-driven evidence development programs.

#### Reimbursement Challenges:

- While the field of personalized medicine is expanding rapidly, European reimbursement systems are not set up to adequately evaluate novel diagnostics and combination diagnostic/therapeutic products. This challenge is consistent with what is seen in the US and other markets.
- In Europe, reimbursement, coding, health technology assessment (HTA), and pricing decisions are made at the country level (either nationally or regionally) though regulatory decisions are made either centrally or nationally. This creates variability in the processes, evaluation methodologies, evidence requirements, and outcomes among the European countries.
- Variability impacts the relative ease with which personalized medicine technologies reach each market and how rapidly personalized medicine technologies are integrated into standard practice.

*Today there are no clear guidelines for both industry and reimbursement regulators when creating coverage and payment for personalized medicine technologies. We are spending millions of dollars to develop evidence to support regulatory approval and clinician adoption of our products, but it is unclear whether this same evidence will support the requirements of payers and HTAs across Europe.*

– Industry Executive

#### Ranking European Market Reimbursement Systems' Receptivity to Personalized Medicine Technologies

The ranking within this analysis considers how each country's system supports or inhibits access to personalized medicine products and identifies countries where opportunities for improvement remain. The ranking highlights the nuances of how each country's reimbursement infrastructure currently works, and the changes that are being made to accommodate the evolution of personalized medicine. Each country was graded and ranked based on performance against eight metrics, including:

- Reimbursement pathways available for combined therapeutic/diagnostic assessment
- Diagnostic value-based pricing opportunity
- Technology specific coding opportunities
- Health technology assessment processes developed to address the specific attributes of diagnostics
- Health technology assessment processes for personalized diagnostic/therapy combinations
- Speed of coverage and payment decision-making
- Track record of coverage and payment for currently available technologies
- Level of national funding/support for personalized medicine research

A more detailed review of the methodology can be found in Appendix A.

The country ranking builds on previous attempts to consider the cross-border variation in health care delivery costs and structures by the European Commission via their HealthBASKET project.<sup>2</sup> This comparative analysis will inform policymakers, manufacturers, and funding decision-makers of opportunities to improve current reimbursement systems and where investments should be made to optimize access to valuable personalized medicine technologies moving forward. Additionally, the analysis can begin to help sponsors of new personalized medicines navigate the reimbursement processes within each market.

<sup>2</sup> Reinhard Busse, Jonas Schreyo, Gga And Peter C. Smith. Variability In Healthcare Treatment Costs Amongst Nine EU Countries – Results From The HealthBASKET Project. Health Econ. 17: S1–S8 (2008).

While no simple solutions exist, identifying key aspects of the reimbursement system in each market that support or inhibit access to personalized medicine technologies provides guidance to decision-makers as to where future efforts and investment are likely to have significant impact.

**Proposed Solutions:**

- Improve coding systems and reimbursement processes across countries to facilitate more rapid access to personalized medicine technologies.
- Enhance diagnostic reimbursement processes that require greater sophistication in many countries, on par with drugs.
- Align reimbursement with demonstration of clinical and/or economic value to health systems in order to incentivize manufacturer investment in research and development programs aligned with market access requirements.
- Provide clearer guidance as to the evidence requirements to achieve widespread reimbursement within each European country to optimize the time from product development to patient access.

### **3.0 Country Investments in the Future of Personalized Medicine**

Several European countries are investing in the research and development of novel personalized medicine technologies. This funding underscores a commitment to the future growth of this area, which will likely lead to the availability of innovative and life-saving diagnostics and therapies in the near future.

For example, in Luxembourg, the government invested \$200 million to create a number of new research facilities including the Luxembourg Centre for Systems Biomedicine, which partners with American institutions such as Translational Genomics Research Institute (TGen), the Institute for Systems Biology, and the Partnership for Personalized Medicine from the US. A similar investment of \$45.6 million by the government of Sweden helped to establish the Science for Life Laboratory in that country.

Meanwhile, in the United Kingdom (UK), a group of scientific and academic organizations has invested £500m to establish the Francis Crick Institute. Set to open in 2015, this interdisciplinary institute will use research discoveries to aid in the development of clinical applications to fight cancer, heart disease, and neurodegenerative disorders.

Additionally, The UK's Technology Strategy Board (TSB) and the Medical Research Council (MRC) will jointly invest more than £3.7m in seven major personalized medicine research projects. The investment is the first to be made through the Technology Strategy Boardmanaged Stratified Medicine Innovation Platform (SMIP), an initiative that will oversee an investment of more than £50m of government funding across five years in innovative research and development. The platform covers areas including tumor profiling to improve cancer care and developing biomarkers for more effective drugs.

To develop the process for personalized medicine adoption, France has funded a program looking at new, targeted therapies.<sup>3</sup> The French National Cancer Institute (INCa) initiated the program for the prospective detection of emerging biomarkers in lung cancer, colorectal cancer and melanoma. The program will provide support for 28 hospital-based molecular genetics platforms with a budget of €3million. The aim is to enable hospitals to routinely detect a panel of biomarkers that will determine access to the targeted therapies that are near ready for use in the wider patient population. The program

<sup>3</sup> <http://www.europabio.org/Healthcare/documents/3%20-%20Access%20to%20molecular%20tests%20EuropaBio%20Pers%20Med%20Workshop%20090211.pdf> (accessed May 2011).



is being developed so that the biomarker tests are operational when the new therapeutics are approved. Additional program details from other countries can be found in Appendix B.

The following detailed description of reimbursement systems and country specific opportunities for personalized medicine provides more detailed context for the rankings.

## 4.0 European Reimbursement Systems

### Overview

In Europe, reimbursement and pricing is determined on a country by country basis, leading to significant variations in system design, cost, and coverage.

The European Medicines Agency (EMA) is responsible for reviewing all the medicinal products that are subjected to the centralized procedure, whilst the European Commission formally approves all such drugs. According to a recent presentation, the EMA has reviewed close to 600 products to date, with approximately 20% containing “genomics” information to “personalize” use of medicines.<sup>4</sup> There are currently 13 targeted or personalized medicines that require mandatory testing prior to treatment.<sup>5</sup> The European Commission is supporting research and development of a small (but steadily increasing) number of personalized/targeted medicines.

In contrast, diagnostics can be commercialized either as kits or as laboratory developed tests. If kits, commercialization is possible as soon as the manufacturer affixes the CE-mark confirming that the diagnostic fulfills all the essential requirements of the European directive, which are based on the classification of the test via Annex and List level.

*“Payers in Europe understand that you cannot isolate a diagnostic. They must be educated about the entire story. Industry must get involved with payers, though this is difficult because this decision-making happens at different points.”*  
- German Payer

Predominantly, diagnostics are paid for from hospital and/or laboratory budgets or in some cases based on code-specific fee schedules. Diagnostic reimbursement pathways in many European countries are not as clearly-defined or sophisticated as those for drugs. Most often drugs are reimbursed in whole or in part by the national payer directly to hospitals, pharmacies, clinicians, or to patients (if out of pocket spending for the drug has occurred). Patient cost-sharing exists in many markets, though the mechanism driving it is often different for drugs versus diagnostics.

Each country in Europe has country-specific technology evaluation and reimbursement systems. As a result, coverage for many personalized medicine technologies varies across Europe. For example, while Herceptin (trastuzumab) is widely reimbursed across the EU, reimbursement for the HER-2/*neu* companion diagnostic test (which detects the Her-2/*neu* amplification and protein over-expression in order to determine which patients might benefit from Herceptin) varies across Europe (see Table 1). In the UK, France (only since 2007), Germany, and Italy, HER-2 testing is publicly-funded, but in Spain, the pharmaceutical manufacturer funds the majority of testing. (European Diagnostic Manufacturers’ Association [EDMA] workshop, 2010).<sup>6</sup>

<sup>4</sup> Presentation by Marisa Papaluca Amati of the Human Medicines Development and Evaluation Unit Scientific Support and Projects -Section Head, “Union personalised medicine towards the market and patients: the approval process” May 2011.

<sup>5</sup> Ibid.

Table 1: Reimbursement for HER-2 and K-RAS Testing by Country

Country	Examples of reimbursement
UK	HER-2 and K-RAS tests are publicly-funded but because the treatments associated with them are so expensive, few tests are performed.
France	HER-2 test was authorized in 2000 but has only been reimbursed since 2007.
Germany	Innovative tests are introduced as Laboratory Developed Tests (LDTs). The HER-2 and K-RAS tests are performed using LDTs leveraging assembled RUO reagents and are reimbursed by a CPT code like a procedure.
Italy	HER-2 and K-RAS tests are publicly-funded and available from a network of public hospital laboratories.
Spain	HER-2 and K-RAS tests are often paid for by the pharmaceutical companies whose drugs they indicate.

Source: BioHealth EpiMed 2011 [http://www.business-meets-research.lu/fileadmin/user\\_upload/presentations\\_2011/BioHealth-EPEMED.pdf](http://www.business-meets-research.lu/fileadmin/user_upload/presentations_2011/BioHealth-EPEMED.pdf)

Pricing of personalized medicine products is also country dependent. Pricing for novel pharmaceutical products is largely based on benefit (or value) assessments by payers orbased on similar products and prices in other markets (international price referencing or IPR). Several countries, such as Italy and Spain, make national pricing decisions; however access is determined at the regional level.

Pricing decisions for therapies have historically been conducted separately from those related to diagnostics. Pricing for diagnostics may be related to fee schedules, tied to specific codes, or established at the hospital or laboratory level. In contrast, drug pricing is usually product specific and can have cross-border implications due to international referencing. Currently, no countries have an established value-based pricing pathway for novel diagnostics. Instead, companies with high-value products are attempting to work with payers and other decision makers to enable access on a country by country, region by region, and in some cases hospital by hospital level.

Countries with budget shortfalls have attempted to reduce health care costs by cutting drug expenditures. In 2010, Spain carried out pricing cuts and Germany passed a law changing their drug pricing and reimbursement system that will go into effect in 2012. While the UK continues to have free pricing, value-based pricing is being introduced and there has been a growth in risk-sharing agreements for high-cost products.

***The following is a general overview of how several European countries have structured their reimbursement systems:***

In the **United Kingdom**, the National Health Service (NHS) provides health care and coverage to all citizens.<sup>7</sup> Individuals can purchase private insurance to supplement NHS' services or to pay for non-covered treatments and services. In England, Primary Care Trusts (PCTs), which are responsible for providing health care and health improvements within a local area, report to Strategic Health Authorities, which manage performance by region. Currently, the NHS awards 85% of their budget to PCTs to pay for health care products and services. Payment by PCTs is made using one of three mechanisms, payment-by-results, block contracts, or global budgeting. This arrangement is set to change starting in 2012, when PCTs will be replaced by a GP Commissioning Consortia.

<sup>6</sup> Datamonitor Case Study Personalised Cancer Therapy March 2011.

<sup>7</sup> Scotland, Wales and Northern Ireland have separate systems for evaluation and payment for health services.

The vast majority of the **German** population is covered by a “Bismarck” Insurance Fund based system. Statutory Health Insurance Funds (SHIs) are responsible for the costs of providing health care to the insured population. Private insurance coverage can only be used in addition for improved services or if an individual’s yearly income exceeds a defined level (49,950 EUR in 2010). Traditionally, hospitals are publicly-funded institutions which provide only inpatient care. Ambulatory care is supplied by private practices, which are paid by SHIs and private insurance. Reimbursement for diagnostics and drugs depends on the site where care is provided. In the inpatient system, both drugs and diagnostics are predominantly covered by a DRG global payment. In the outpatient environment, reimbursement for drugs and diagnostics is provided based on contracted charges (drugs) and a code-based fee schedule (diagnostics).

In **Italy**, the National Healthcare System (Servizio Sanitario Nazionale - SSN) provides health care coverage to the population, via public financing and a mixture of public and private provision of care. The Italian system is largely decentralized and can be broken down into three levels: national, regional, and local. The responsibility for delivering hospital and community services falls to the local level. Local health units (Azienda Sanitaria Locale- ASL) coordinate all non-emergency care and are funded by the SSN through a per capita budget. Public and private health care providers (whether they provide in-patient and/or outpatient care) are remunerated through a fee-for-service system based on two Formulary Lists, with different tariff levels. Both lists are based on the ICD-10-CM WHO Classification of Diseases and Procedures. The Italian Medicines Agency (AIFA) is the national authority responsible for drug regulation, pricing, and evaluation in Italy. Medical devices in Italy are not subject to pricing and reimbursement negotiation at the central level, thus funding must be addressed at the local level.

The **French** population is almost universally covered (99% of the population) by statutory health insurance (Assurance-maladie), managed by the Haute Autorité de Santé (HAS). HAS is responsible for evaluating drugs, devices, diagnostics, and other products. The Commission d’Evaluation des Médicaments (Transparency Commission), within HAS, assesses the clinical value provided by a new product and the health improvement it will provide to patients. The opinion is based on a value analysis (SMR- that considers whether the product should be reimbursed and what the reimbursement rate could be), comparative assessment of clinical benefit assessment (ASMR- the grading that provides a basis for price fixing in comparison with alternatives), and who the target population eligible for treatment should be. AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) carries out scientific and medico-economic evaluation as part of this system. In most cases, patients share the cost of drugs used or provided in the outpatient setting. Since 2004, hospitals have been funded through DRGs, with most drugs and diagnostics included in the global payment system (although some high-priced drugs are funded separately).

The **Spanish** health care system (Sistema Nacional de la Salud (SNS)) is compulsory and publicly-funded, with administration performed at the regional level through regional health authorities (RHA). Roughly 15% of the population has supplemental private insurance to augment their statutory coverage. The RHAs fund hospitals within their regions through prospective budgets. The basis for budget allocation is largely derived from the population within the hospital area. Outpatient services are covered based on regional decision-making, largely through a fee-for-service mechanism. A national HTA agency (Instituto de Salud Carlos III-ISCIII) and several regional HTA organizations coexist in the country. Reimbursement is considered at the national level through the Spanish Ministry of Health (MSC), while pricing is determined by the Inter-Ministerial Pricing Commission CIPM (La Comisión Interministerial de Precios de los Medicamentos).

## 5.0 Key Issues for Personalized Medicine by Country

### 5.1 Personalized or “Stratified Medicines” in the UK

In the UK, personalized medicines are commonly, though not always, referred to as ‘stratified medicines’. There are several UK initiatives currently in place that are working together to support the increased use of stratified medicines. These include The Technology Strategy Board, Medical Research Council, Association of British Pharmaceutical Industries and Cancer Research UK.<sup>8</sup> These efforts are being augmented by improvements in health technology assessment processes at NICE, related to diagnostic evaluation through the Diagnostics Assessment Program which primarily looks at tests that have a CE mark. Currently, the majority of genetic testing is performed by laboratory-developed tests rather than by CE-marked tests.

Today, there are many tests that are provided within an NHS lab that are marketed and/or commercially produced but do not go through a formal evaluation process and are routinely paid. For example, the HER2 test is paid for but was not formally reviewed. NICE looked at the medicine (Herceptin) but did not formally appraise the test. The agency’s assessment report makes assumptions about the tests performance and cost but does not include test specifications. Moving forward, for companion diagnostic and therapy products, it is expected that if the medicine’s label requires a specific test to be used with the product, then the diagnostic and therapy will be evaluated together. However, if the diagnostic is marketed separately and has obtained a CE mark, then the drug and diagnostic could be reviewed separately.

In the next several years, diagnostics are likely to continue to make inroads without formal assessment unless they are specifically listed in drug labels. However, private companies, as well as laboratory managers and other stakeholder groups, are likely to advocate for more systematic evaluation and standardization of processes so that evidence development can be aligned with technology assessment requirements. Partner groups at the European level are struggling to establish a prescriptive registration process for diagnostics that will be applied across markets as there is so much variation within each country--including within the UK.

### 5.2 Personalized Medicine in Germany

The German health care system provides patients with access to technologically-advanced products, and is a high-focus market for most drug and diagnostic manufacturers.

German payers, policymakers, and clinicians are actively engaging the personalized medicine debate. Germany remains a complex market for personalized medicine products. Recent pricing reforms will impact how pharmaceutical products are priced in Germany, while IQWiG and DIMDi continue to evolve their role and methods for evaluating diagnostics and combination products.<sup>9</sup>

*“A lot of companies are producing personalized medicines and the regional governments are gaining power in negotiations. Every region will likely choose different strategies.”- Italian Payer*

<sup>8</sup> Greenberg, T. Conference Scene: Personalized Medicine in Europe. Personalized Medicine May 2011, Vol. 8, No. 3, 317.

<sup>9</sup> IQWiG and DIMDi are described within Appendix D.

Moving forward, in Germany, pricing must take overall value impact into account so that the emergence of personalized medicine has positive value to payers. Companies like Amgen, Roche and Pfizer have begun to account for this by incorporating companion diagnostics into their clinical trials to support HTA analysis. This type of evidence development helps payers understand the clinical utility of novel tests. Most payers in Germany and in other markets indicate that if the test only provides information for information's sake then there is little value from the payer perspective. Alternatively, if the test can direct care, then the test has inherent value and will likely be covered if priced appropriately.

## 5.3 Personalized Medicine in Italy

For personalized medicine products, the drugs have to be listed on the national drug list, managed by AIFA. If the regional government decides to reduce its expenditures, the region can limit access to expensive technologies that are centrally-approved with their own regional list. Limiting access to very expensive therapies is more likely to occur when authorities are not entirely sure of the value of the new products. This speaks to the necessity of having solid evidence to demonstrate the clinical and economic value of personalized medicine technologies.

*“First phase was general enthusiasm that personalized medicine will save money with more directed use of resources. This could be interesting for the industry, and provide rationale for getting higher prices in a limited population. In phase two there was realism/ disappointment because development has been slow and the promise has not been fully realized yet. There are now many trials incorporating this approach with companion diagnostics. We are now moving towards phase three where personalized medicine will be more actively realized, value will be seen, but we need clear evidence to support its expanded use and funding. We are several years out to fully realize phase three.”*

– German Payer

Today, there is significant variation among regions in terms of coverage and availability of personalized medicine products. Additionally, there are different systems of establishing prices for new products. For drugs, the pharmaceutical company negotiates with AIFA to establish a price for a new drug. However, for sophisticated medicines there are more complex systems for setting drug prices that can include risk sharing and payback systems (whereby a certain threshold of performance would have to be met for full reimbursement to occur and only partial payment would be initially granted). This creates an opportunity for coverage where payer uncertainty exists, but companies are confident in the likelihood of positive results. The approach leverages a highly sophisticated data monitoring system in the country that can track the utilization and clinical impact of new products.

Regions are exerting control over purchasing decisions by moving some drugs from the traditional pharmacy channel to the hospital channel. This type of change can limit overall budget exposure for expensive therapies. In the future, companies will likely need to direct efforts for coverage and payment at both the national and regional level to ensure coverage across channels and inclusion in both local and national positive lists.

*“HER2 was performed by hospitals for two to three years prior to the tariff being established. The hospitals used their own budgets to fund use of the test. The hospitals were choosing to do this for competitive purposes...there are private clinics and hospital they are competing with. With oncology, hematology, the hospital will use the advanced therapy and tests within the hospital budget. The budgets involved to date have not been that big. The public hospitals have several extra budgets to account for things like this that are not yet established within the reimbursement or within a research frame. They have the resources to do these types of tests; we'll see how it evolves.”* – French Payer

*“Italy will not change significantly as most things are pretty cheap and everyone has the right to seek assistance. We are likely to see more of the same. There is an opportunity for innovative contracting, as is already being done. Expensive medicines challenge the budgets...all markets here are difficult as the budgets are constrained and budgets are being cut.”*

*– Italian Payer*

For companion diagnostics, the national agencies are well-equipped to review products and are supported in their efforts by regional appointees. Even with this regional participation, it is possible for new products to end up on the national positive list but not make it onto the regional list. If adopted by the regions, utilization controls are possible to limit the region's budget exposure.

## 5.4 Personalized Medicine in France

From a coverage and payment perspective, there is no differentiation between how payers deal with personalized versus one-size-fits-all therapies. In general, personalized medicines have been received favorably within the French evaluation process. All hospitals use tenders for usual drug purchasing and have hospital groups that manage the tenders. France has a specific process for coverage and payment for costly hospital drugs that are paid for outside the DRG.

Coverage and reimbursement for diagnostic tests is much more complex. Biological laboratories are private and paid on a fee-for-service basis for ambulatory procedures. There is a list for tariffs for each test performed. The descriptions are long and the process for obtaining reimbursement for novel tests is bureaucratic. The negotiation for a new code and associated tariff must be presented by a clinical specialty society. As a result, there are many tests that are performed in hospitals prior to coverage being established and reimbursements set.

Although drugs are reviewed by the transparency committee, coverage pathways for diagnostics are far less standardized. The diagnostics committee is primarily focused on the quality of the test first and secondarily on determining the tariff and ultimate budget impact. The manufacturers can get involved, though usually indirectly. Clinical specialty societies or laboratories often lead the coverage discussions with the central agency. There is also an established pattern whereby novel tests can be used in public hospitals with research use first, then expanded into routine coverage and utilization. It is expected that moving forward this process will become more formal and systematic.

In private clinics, there is significant competition for patients; many clinics choose offerings to maximize innovative care within the clinic budget. This can provide an opportunity for the use of personalized medicine technologies that are not covered within the public system. However, practically, most diagnostics and treatments for serious conditions are covered within the public system.

## 6.0 Country Ratings Results

The results of the ranking analysis show that Germany (32/40), the UK (30/40), and France (27/40) are currently the most favorable markets for personalized medicine technologies from a reimbursement and market access perspective. Other countries have relatively consistent scores (in the 16-21/40 range), indicating general room for improvement (see Table 2).

Table 2: Results of country specific evaluation of reimbursement and market access support for novel personalized medicine diagnostics and therapies.

	Reimbursement pathways for combined diagnostic/therapeutic assessment	Diagnostic value based pricing opportunity	Technology specific coding opportunities	HTA process for diagnostics	HTA process for companion products	Speed of coverage and payment decisions	Track record related to other personalized medicine technologies	Level of investment in personalized medicine research	Total
Germany	4	4	5	4	3	4	4	4	32
UK	4	4	2	5	5	3	3	4	30
France	2	3	3	3	3	3	3	4	27
Italy	2	3	3	2	2	3	3	3	21
Sweden	3	2	2	2	2	3	3	4	21
Switzerland	2	3	3	2	2	3	3	3	21
Spain	2	3	3	2	2	3	3	2	20
Norway	2	2	2	2	2	3	2	2	17
Finland	2	2	2	2	2	3	2	2	17
Netherlands	2	1	2	2	2	3	2	2	16

Most of the variation in scoring was due to less sophisticated diagnostic reimbursement mechanisms in many countries. Additional drivers for score variation include the relative investment countries are putting into personalized medicine, having established pathways to review combination products and track record of coverage and payment for other technologies.

## 7.0 Future Developments in Personalized Medicine Reimbursement in Europe

*“The base frameworks for diagnostic regulation and reimbursement that will allow for personalized medicine to be realized are not yet developed or robust enough to sustain the personalized medicine approach. Specifically the IP protection and regulatory pathways are not currently set up to incentivize investment in developing highly validated diagnostics.”*  
 – Industry Executive

The country rankings indicate that while a few countries have made significant strides (Germany, UK), significant room for improvement exists across Europe. Moving forward, reimbursement agencies should evolve their current systems of technology evaluation and payment to better account for personalized medicine technologies.

This process will vary from country to country. Examples may include creating combined pathways for companion products or enabling special evaluation of diagnostic technologies that have implications for targeting treatments but are not developed in combination with a specific therapy.

Greater collaboration in review and analysis of personalized medicine products should occur between the agencies involved in coverage and payment. Additionally, appropriate reimbursement rates for personalized medicine diagnostics need to be established, where today many companion diagnostic costs

are subsidized by manufacturers.<sup>10</sup> Together these factors are likely to improve access to personalized medicine technologies and provide greater consistency across markets relating to coverage and payment decision-making and processes. However, there is a long way to go before this promise is realized.

To achieve this, health technology assessment methodologies will have to evolve to address the multiple components of value that a diagnostic and therapy can provide. It is likely that different mechanisms of evaluation will be developed that are appropriate to each scenario (i.e. drug/diagnostic combinations versus diagnostics that direct therapy or provide prognosis).

Additionally, in order to account for drug/diagnostic combinations that may currently exist within separate budget silos or cost-sharing mechanisms, funding pathways and patient costsharing need to be harmonized. This will enable more streamlined product access and simplify the reimbursement for patients. Today, patients are often forced to be their own advocates, demonstrating to providers or payers why they need a given treatment. As personalized medicine becomes more common and more products establish value to payers, access may improve for clinicians and patients if coverage hurdles are reduced.

Coverage and payment pathways must be developed to adequately capture the value of diagnostic and treatment combinations to incent future personalized medicine innovation. Evidence to support each product's value needs to be developed from both the clinical and economic point of view to help payers and HTA decision-makers evaluate new products and provide access to them. Helping manufacturers align evidence development pathways with reimbursement processes will ensure that health systems are investing in those products that have significant impact.

Many believe that in order to maximize the full value capture potential of personalized medicine a “vision of a unified system” for reimbursement, pricing as well as product registration needs to be considered within the context of the political process of unification of the European Union. Should stakeholders ultimately agree to move forward with this type of approach, it would likely take a decade or more to move from concept to reality. While the synergies and advantages for all stakeholders would be significant, others consider this type of unified approach unlikely given country-specific differences and desires to retain autonomous decision-making powers.

Significant debate continues around how to best regulate complex personalized medicine diagnostics. While many tests have historically been made available as laboratory-developed tests, performed by regulated laboratories, many companies are seeking regulatory review for the tests themselves. For example, in the US, many companies seek FDA approval for their tests, distinguishing them from laboratory-developed alternatives. Given the impact personalized medicine diagnostics have on clinical decision-making, some within industry and clinical communities are suggesting a need to further increase the quality standards and clinical validation requirements needed to get market approval and payment for them. Others consider laboratory developed tests an important part of delivering care and expanding access to patients who can benefit.

Reimbursement systems evolving to provide greater access to personalized medicine may also need to

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<sup>10</sup> For example, AstraZeneca paid for EGFR mutational analysis to be paired with lung cancer drug Iressa® and Merck Serono paid for KRAS testing for assessment of Erbitux® prior to NICE assessment in the UK.



consider how to support utilization of new approaches to care delivery. This may include providing access to services like genetic analysis and counseling associated with risk evaluation and treatment selection.

*“HTA frameworks are developing rapidly and will likely lead the way in demonstrating what evidence to develop and what should be required. NICE in the UK and Australia provide examples where the HTA groups are ahead in creating methodologies and pathways. I believe they will help both payers and industry to understand what is relevant and necessary evidence to facilitate approval, coverage, payment, and utilization.” - Industry Executive*

HTA groups are well underway in defining pathways and evidence criteria for personalized medicine technologies. As these programs evolve and findings are disseminated among other HTAs, to payers, clinical specialty groups and ultimately to regulators--more harmonization is possible. Greater consistency would allow industry to have a clearer picture of requirements, while investors would be able to see the rationale for high cost studies in terms of their direct impact to reimbursement outcomes.

## 8.0 Conclusion

The significant variation in reimbursement and market access systems across Europe creates differentially receptive environments for personalized medicine technologies. Countries like Germany, the UK, and France are currently better poised to take advantage of the benefits that these innovations provide by having evolved their reimbursement systems to assess and incorporate these technologies more efficiently. Other countries with less advanced reimbursement systems will need to adapt to the changing requirements of personalized medicine technologies.

More work is needed across all settings to improve pricing, reimbursement, and HTA methodologies to ensure they reflect the true value of diagnostics and therapies, thus facilitating the advancement of personalized medicine. Industry requires clearer guidance as to the evidence requirements across markets to achieve widespread coverage and payment. Additionally, countries that are making a significant investment into the research and development of personalized medicine technologies must ensure that their reimbursement systems are prepared to evaluate and pay for the resulting innovations once they are commercially available.

## 9.0 Appendix A: Methodology

This analysis is based on a systematic review of published information related to European health system reimbursement for personalized medicine products, review of health system policies and practices, and key informant interviews. Interviews were conducted with payer and industry decision-makers in the target markets to confirm current practice and expectations for future changes. Discussion guides were used to standardize interviews.

The information gathered through primary and secondary research was then analyzed and presented within this report. Topics addressed include background on personalized medicine technologies, overviews of health systems in major European markets, considerations for reimbursement of personalized medicine technologies in Europe, and key issues for the future.

### *Scoring Methodology*

Each country has been graded relative to their performance on each of eight metrics. The metrics were chosen to reflect attributes of reimbursement, regulatory, and HTA systems that enable access to personalized medicine technologies. Each country was scored on a one to five scale (one is least acceptable while five indicates the attribute is well-established) for each of the eight attributes. The scoring for each factor was based on published information about each country's system, experiences of other technologies going through each system reported during interviews and in the literature, and data received from key market access stakeholders contacted for this study. Each country was able to achieve a maximum score of 40 (five points for each of eight categories). A detailed description of each category and the scoring methodology is available in Appendix C.

All ratings are subjective, therefore each country's ratings are meant to provide directional information as to the relative receptivity of the reimbursement and market access infrastructure within that country to personalized medicine diagnostics and therapies. Opportunities for improvement are discussed when country scores on specific elements or overall are low in comparison to other countries.

## 10.0 Appendix B: Examples of Personalized Medicine Investments by Country

### *UK*

In 2010, Cancer Research UK, the Wellcome Trust, the Medical Research Council, and University College London agreed to develop a £500 million medical research institute. The focus of this institute will be to progress biomedical research with the goal of learning how to better prevent and treat certain diseases. The institute has since been renamed the Francis Crick Institute and will be completed in 2015.

- <http://www.crick.ac.uk/about-us/francis-crick>
- <http://crossborderbiotech.ca/2010/01/07/trends-update-personalized-medicine-a-big-market-if-we-can-just-figure-out-how-to-get-people-to-use-it/>

### *Luxemburg*

In 2008, Luxemburg invested \$200 million dollars in a personalized medicine initiative. The government entered into a partnership with three US-based research centers in order to create three major programs devoted to molecular medicine with a focus on molecular diagnosis. The partnership called for the creation of the Luxembourg Centre for Systems Biomedicine (LCSB), the Integrated Biobank of Luxembourg (IBBL), and the Lung Cancer Project. All projects carried out by the programs are being coordinated by the Personalized Medicine Consortium. The IBBL officially opened in February of 2010.

- <http://www.azcentral.com/arizonarepublic/news/articles/0606biz-tgen0606.html>
- <http://www.biomedicine.lu/luxembourg/personalized-medicine/>
- [http://www.business-meetsresearch.lu/fileadmin/user\\_upload/presentations\\_2011/BioHealth-Big\\_Science\\_Small\\_Country.pdf](http://www.business-meetsresearch.lu/fileadmin/user_upload/presentations_2011/BioHealth-Big_Science_Small_Country.pdf)

### *Sweden*

In 2010, the Science for Life Laboratory was created in Sweden. A partnership between four Swedish universities, it is aimed at large scale research of molecular biosciences and medicine. The SciLifeLab is being funded by the Swedish government, which is providing 100 million Swedish Kronor (approximately \$15.2 million) per year, over three years.

The SciLifeLab is split into two divisions. The Stockholm division looks at genome and proteome sequencing, bioimaging, and bioinformatics. The Uppsala division will focus on DNA sequencing technologies and protein analysis to improve human medicine.

- [http://ec.europa.eu/research/health/pdf/event06/12052011/mathias-uhlen\\_en.pdf -slide 18](http://ec.europa.eu/research/health/pdf/event06/12052011/mathias-uhlen_en.pdf-slide%2018)
- <http://www.scilifelab.se/en/scilifelab-stockholm/scilifelab-stockholm>
- <http://www.scilifelab.uu.se/About+SciLifeLab/>
- <http://www.ssci.se/en/Projects/Science-for-Life-Laboratory-SciLife-Lab/>

### *Germany*

In Germany, there is a recently-assembled group, made up of clinical research institutes, biotechnology companies, and pharmaceutical companies, called PerMed.NRW. The group focuses on new diagnostic, therapeutic and prevention opportunities for common diseases and aims to become an international center for personalized medicine. PerMed.NRW received 40 million Euros in funding after winning a research competition sponsored by the German government. This new alliance will complement the Institute of Medical Molecular Diagnostics in Berlin, which was founded in 1994.

- <http://www.gtai.com/homepage/info-service/publications/our-publications/germanyinvestment-magazine/vol-2011/vol-012011/top-science-and-research-location-2/print/>
- <http://www.immd.de/?ca=42.1>

### *Belgium*

Biomina is a new biomedical informatics research center that opened in June of 2011 in Antwerp, Belgium. This center was created by the University of Antwerp and Antwerp University Hospital. The center has a focus on data collection, research, and development of clinical applications.

- <http://www.bintangjayareload.com/2011/08antwerp-belgium-data-fusion-methods-for-personalized-medicine/>

### *Netherlands*

Started in 2009, the Sino-Dutch Centre for Preventive and Personalized Medicine is a joint research program aimed to improve current diagnostics and develop preventionbased approaches to medicine. This initiative was started by two Dutch research institutes and the Chinese Academy of Sciences/Dalian Institute of Chemical Physics to identify novel biomarkers that are specific to type 2 diabetes and arthritis. The SDPPM recently received a €1 million grant from the Netherlands Genomics Initiative.

- <http://www.metabolomicscentre.nl/page/sino-dutch-centre-preventive-and-personalized-medicine-sdppm>
- <http://www.sinodutchcentre.nl/index.php?parentContentID=&contentID=1724c6e2-02f0-449c-a694-42a8ccad19e7>

### *Norway*

Created in October of 2008, the Norwegian Center for Molecular Medicine has a goal of advancing basic medical research and applying new discoveries to clinical practice. As part of the Nordic EMBL partnership, the NCMM hopes to collaborate with similar centers in the region with the hope of developing and adapting technologies for personalized medicine.

- <http://www.ncmm.uio.no/about/>

### *Finland*

Developed in 2006, the Institute for Molecular Medicine Finland (FIMM) was created in order to conduct research on human genomics, medical systems biology, and translational research. In 2010, FIMM developed an internal team called the Personalized Cancer Medicine Group. This group was assembled to try and identify patient-specific biomarkers and develop.

## 11.0 Appendix C: Categories for Country Evaluation

- **Reimbursement pathways available for combined therapeutic/diagnostic assessment**
  - Scoring related to the extent central or regional payers have developed specific reimbursement pathways for companion personalized medicine technologies (diagnostic and therapeutic) that provide funding and payment for both the drugs and diagnostics enabling the personalized approach.
- **Diagnostic value-based pricing opportunity**
  - Scoring depends on there being an opportunity for diagnostic to achieve reimbursement/pricing that takes into account the value the test provides to the health system, over and above the payment based on the technology platform used to capture the result.
- **Technology-specific coding opportunities**
  - Scoring depends on there being a detailed coding infrastructure in place to accurately capture a specific technology, create new codes for personalized medicine innovations, or to distinguish innovations from products currently on the market from a coverage and payment standpoint.
- **Health technology assessment processes developed to address the specific attributes of diagnostics**
  - Scoring is based on the degree to which the health technology assessment authority within the country (if one exists) has created specific evaluation frameworks and methodologies for diagnostic products.
- **Health technology assessment processes for personalized diagnostic/therapy combinations**
  - Scoring is based on the degree to which the health technology assessment authority within the country (if one exists) has created specific evaluation frameworks and methodologies for personalized diagnostic/therapy combination products.
- **Speed of coverage and payment decision-making**
  - Scoring based on the relative speed from a technology gaining market authorization to the point of routine coverage and payment by health authorities or payer organizations.
- **Track record of coverage and payment for currently available technologies**
  - Scoring based on recent reimbursement decisions for personalized medicine products, considering whether they enhanced access and were timely.
- **Level of national funding/support for personalized medicine research**
  - Scoring based on the degree to which the national government in each country has prioritized research and funding for personalized medicine technology.

## 12.0 Appendix D: Country Specific Reimbursement System Overview

### 12.1 United Kingdom

The United Kingdom (UK) comprises England, Scotland, Wales and Northern Ireland. Since 1998, a process of devolution has given decision-making powers over health care provision and purchasing medical technologies to the devolved governments of Scotland, Wales and Northern Ireland. Hence the health care systems in these parts of the UK have developed differences over the past 10+ years. The description below principally covers the largest area, England with approximately 51 million people (~ 83.5% of the UK population), but where clear differences exist between the English system and that of Scotland, Wales, or Northern Ireland they are described.

The National Health Service (NHS) provides health care and coverage to all citizens in England. Individuals can purchase private insurance to supplement NHS care or for payment for non-covered treatments and services. Approximately 85% of the NHS budget is distributed to Primary Care Trusts (PCTs) that are responsible for providing health care and health improvements within a local area. PCTs report into regional Strategic Health Authorities (SHAs); these authorities help develop local NHS strategy and provide a link between PCTs and the national Department of Health (DoH).<sup>11</sup>

However, this system is set to change with the UK moving towards GP consortia replacing PCTs. The GP consortia will be responsible for commissioning health care services across a range of clinical or service areas, including: community health services, maternity services, elective hospital care, urgent and emergency care, ambulance, older people's and children's health care services, rehabilitation services, wheelchair services, health care services for people with mental health conditions, health care services for people with learning disabilities and continuing health care.<sup>12</sup> The actual date when these changes should occur remains somewhat unclear. The reforms are currently planned to take effect in 2012 may be passed back to the Parliament for further review.<sup>13</sup>

#### 12.1.1 Reimbursement Pathway for Diagnostics

There are three main mechanisms used by PCTs to pay for health care products and services:

- Payment-by Results (PBR) - essentially a DRG system, introduced to established fixed prices (prospective payments) for hundreds (approximately 1,400 at the end of 2010) of hospital procedures. Since its introduction the DoH has extended the PBR system to cover treatments and procedures provided to patients as day cases and outpatients. Certain services are funded as "unbundled" payments in the latest payments schedule (HRG4) in order to allow different payments for different parts of the care pathway, e.g. diagnosis, treatment, rehabilitation, etc. Hence the system of PBR, originally intended for paying for products and services used to treat inpatients, may eventually be extended to provide prospective payments for a range of out-of-hospital services.
- Block Contracts – agreements between care providers and PCTs to use and pay for a certain product or service.
- Global Budgeting – health care providers can purchase products or services from their own budgets.

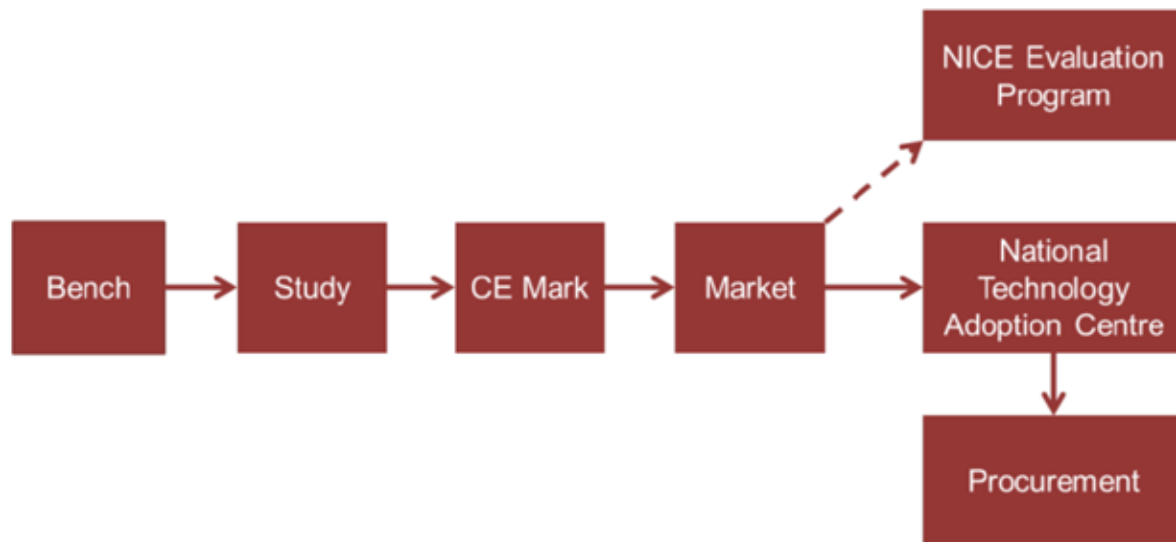
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<sup>11</sup> ISPOR

<sup>12</sup> [http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/documents/digitalasset/dh\\_125006.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_125006.pdf) (accessed May 2011).

<sup>13</sup> <http://www.bbc.co.uk/news/uk-politics-13557927> (accessed May 2011).

**Overview of pathway for diagnostic development** (developed from an interview with the Associate Director, Evaluation Pathway Program, NICE)



## 12.2 Pricing and Reimbursement Approval Process

The MHRA is the “competent authority” charged with translating the EU’s *In Vitro* Diagnostic Medical Devices (IVD) directive into UK law. If a companion diagnostic is to be commercialized, it must be CE marked as meeting all essential safety requirements. In the UK, companion diagnostics are evaluated alongside the medicines with which they are designed to be used, and the timescale for evaluating them is similar to that for medicines.

Manufacturers are free to set the price of their products in the UK, except for products classified as pharmaceuticals (e.g. diagnostic imaging contrast agents) which are subject to supply-side control by the DoH’s Pharmaceutical Price Regulatory Scheme (PPRS). However, funding is tightly controlled by the PCTs. Diagnostic manufacturers are therefore free to set price but have to negotiate funding with the providers or directly with the PCTs<sup>14</sup> or local hospital level.

To assist with decisions around the uptake of diagnostics, NICE has developed a Diagnostics Assessment Program (DAP) which, along with its Technology Evaluation Program, is designed to:

- Improve patient outcomes;
- Reduce costs; and
- Provide system benefits (e.g. facilitate service redesign).

<sup>14</sup> ISPOR.

The Medical Technologies Evaluation Program (MTEP) undertakes topic selection and routing for all Medical Technology products, including diagnostics and produces guidance on topics routed to it. MTEP can evaluate all types of diagnostics, from invasive ultrasound to labbased tests. The assessment of diagnostics within the program includes the evaluation of clinical effectiveness and budget impact, but not full cost-per-QALY analysis.

The program is a 38 week process from topic selection to guidance publication and the evaluation is limited to the specific technology notified to the program. For diagnostics the key criteria that are being evaluated are:

- Equivalent or superior clinical performance compared to current practice; and
- Potential for cost savings or no net increase to NHS costs.

The Diagnostics Assessment Program (DAP) is a specialist program for complex assessments of diagnostic technologies which can include single or multiple related diagnostic tests. Assessments include cost-effectiveness, which differentiates the assessments from those diagnostics evaluated through MTEP. Recommendations are devised by the Diagnostics Advisory Committee (DAC).

The challenges that are faced by diagnostic companies include a typically thin evidence base (compared to pharmaceutical assessments) which has increasingly been the case with medical technologies and lack of clinical utility data (patient outcomes not linked to the diagnostic used).

However, this program cannot at present evaluate all new technologies that are entering the market and is asking companies to notify NICE of new technologies that it should examine.<sup>15</sup>

The role of the National Technology Adoption Centre (NTAC) is to establish how best to implement new technologies with the NHS environment. The organization has worked with diagnostics companies that have required budget impact modeling and coding changing to allow increased uptake of their products.

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<sup>15</sup> Nick Crabb presentation – March 2011 Personalized Medicine Conference.



## 12.3 Germany

### 12.3.1 Reimbursement Overview

The population of Germany is approximately 82.5 million. The country is organized into 16 states (Laender). Germany utilizes a “Bismarck” Insurance Fund-based system of health care provision, which covers the vast majority of the population. Statutory Health Insurance Funds (SHIs) are responsible for the costs of health care provision to their insured population. Being insured is legally mandatory and 92% of the population is a member of a SHI. Private insurance coverage can only be used in addition for improved services or if the yearly income exceeds a defined level (49,950 EUR in 2010). Diagnostics are used both in the inpatient and the ambulatory sectors with markedly different reimbursement and funding mechanisms in each one.

Traditionally, hospitals are public institutions providing only inpatient care, while ambulatory care is supplied by private practices which are paid by SHIs and private insurances. Increasingly, hospitals are also providing ambulatory care which is regulated by a Committee for Ambulatory Care in the Hospital.

### 12.3.2 Reimbursement and Coverage/Payment Process

Reimbursement is dependent on the site of care, with inpatient care being largely reimbursed under a DRG global payment. Diagnostics and drugs used in the inpatient system are predominantly covered within the DRG payment.

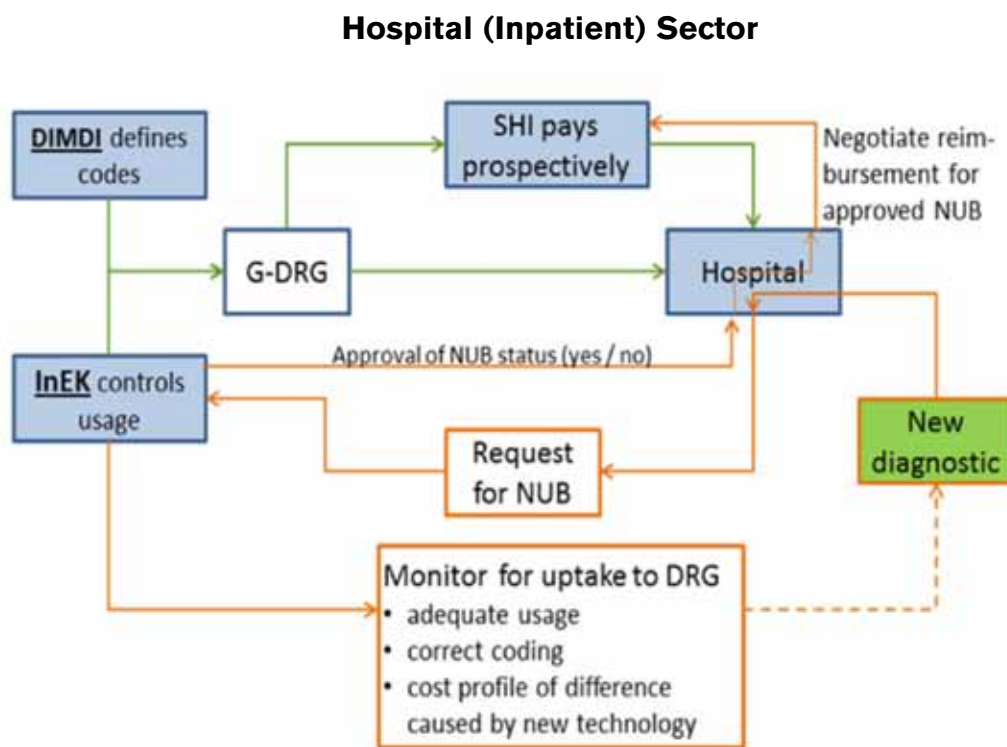
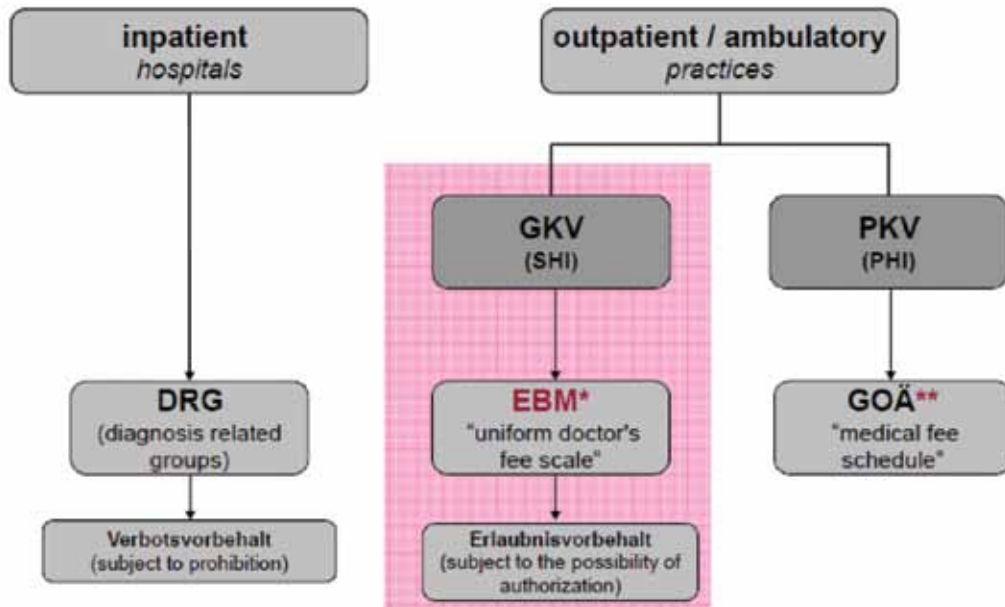


Figure 2: Reimbursement of Inpatient Hospital Products from ISPOR.org

In the outpatient environment, reimbursement for drugs and diagnostics is provided based on contracted charges (drugs) and a code-based fee schedule (diagnostics). Patients have little cost-sharing responsibility for covered services considered medically necessary. Doctors are paid via the physician's fee schedule, or EBM (Einheitlicher Bewertungsmaßstab) that has clearly delineated services and products associated with specific tariffs.



\* *Einheitlicher Bewertungsmaßstab* (EBM), also uniform value scale; \*\* *Gebührenordnung für Ärzte* (GOÄ)

Specific diagnostic and procedure codes are used for prospective (hospital) or retrospective (ambulant) reimbursement. However, coding does not directly and automatically lead to reimbursement.

### 12.3.3 German Institute of Medical Documentation and Information (DIMDI)

DIMDI is the publisher of official medical classifications such as OPS (German procedure classification) and maintains medical terminologies, thesauri, nomenclatures and catalogues (e.g. Medical Subject Headings (MeSH)) that are important for health telematics and other applications.

DIMDI develops and operates database-supported information systems for drugs and medical devices and is responsible for a program of health technology assessment (German Agency for Health Technology Assessment (DAHTA)). It also provides the market surveillance of medical devices and an up-to-date and central information system.

There are regulations provided publicly on the DIMDI website that detail construction, operation and application of medical devices, including *In Vitro* diagnostics although this has not been updated since 1998.

## 12.3.4 Institute for the Hospital Remuneration System (InEK GmbH)

InEK is responsible for the collection and processing of hospital costing data, the updating of the funding units associated with each funding code and the updating of the funding codes themselves. The institute is also responsible for certifying the logic system of various grouper software available to German hospitals. However, InEK maintains neither the diagnostic, nor the procedural codes employed by G-DRG, which are responsibilities of the “German Institute of Medical Documentation and Information” (Deutsches Institut für Medizinische Dokumentation und Information) or DIMDI.

Correct coding of a new technology will not necessarily lead to sufficient reimbursement immediately. Therefore, German hospitals (who are constantly under pressure to contain expenditure and improve efficiency) may have a counter-incentive against adopting potentially useful and cost-effective or cost-efficient technologies because of the possible negative initial budget impact.

There is also a time lag between the availability of a new procedure and correct coding. The update of the G-DRG by InEK is done yearly based on the data from the previous two years. If the cost of a new technology cannot be covered within the current DRG system the hospital can apply to InEK for additional funding via a Neue Untersuchungs- und Behandlungsmethoden (NUB). This can only be given if the costs are considered substantially higher than current methods and thus cannot be included into the current DRG system. It provides a “way in” for innovative treatments or procedures, but has to be applied for on a hospital-by-hospital basis. After approximately two years, by which time more data may be available for the new technology, a new DRG code may be established or the costs wrapped into an existing DRG.

## 12.3.5 IQWiG (Institute for Quality and Efficiency in Healthcare)

IQWiG may conduct health technology assessments if requested by the G-BA. There is no standardized health technology assessment procedure by IQWiG for (companion) diagnostics. IQWiG is increasingly focused on the review of diagnostic products, but has yet to publish a clear methodology for personalized medicine diagnostics and companion products.

Reviews of diagnostics are still relatively new at IQWiG but the agency has conducted them on various technologies, including:

- Screening for gestational diabetes
- PET in malignant lymphoma
- Screening for defined speech and language development disorders in children
- Ultrasound screening in pregnancy
- Neonatal screening for early detection of hearing impairment
- Screening for visual impairment in children

The health technology assessments conducted by IQWiG help inform the coverage policies by German payers, but there is no requirement from a statutory perspective to do so.

## 12.3.6 G-BA (Joint Federal Committee)

The G-BA is in charge of reviewing new technologies for coverage within the Statutory Health Insurance (SHI). If they determine there to be a significant clinical improvement from a novel approach, then coverage will be granted and patients will gain access. New technologies that will be used in the ambulatory sector must be listed on the EBM. This process requires physician support and “may involve a Health Technology Assessment (HTA) by IQWiG.” Determining the actual payment for an EBM-listed procedure is the responsibility of the Valuation Committee.

According to ISPOR, “ambulatory care procedures will need to be approved by the Ambulatory Care Committee and the Federal Joint Committee if they are to become listed on the EBM and offered to German patients through private physicians. This may involve an HTA by IQWiG which closely resembles the process used for the evaluation of pharmaceutical products. The IQWiG methodology has been recently updated.”

## 12.3.7 Budget Capitation

Despite the introduction of the G-DRG system, hospitals in Germany are not free to increase activity beyond pre-defined limits. Through G-DRG based calculations, German hospitals are still under a system of “global budget”. Therefore, all new technologies are essentially attempting to capture a share of a budget that remains largely stable throughout the years.

Successful market access is often based either on increases of this activity caps or on more efficient inpatient activity that will allow space for new procedures within current limits.

## 12.4 Italy

### 12.4.1 System Overview

Italy has a population of 60.3 million, residing in 20 Regions plus two Autonomous Provinces (Trento and Bolzano).

The National Healthcare System (Servizio Sanitario Nazionale - SSN) provides health care coverage to the population, combining public financing with a mixture of public and private provision. Legally placed under the central responsibility of the Ministry of Health, the system is largely decentralized resulting in three levels:

- National level: The Ministry of Health formulates every three years a health care plan PSN (Piano Sanitario Nazionale) which is set to determine general health care policies.
- Regional level: The Regions are due to implement the PSN with their own resources and can adjust to local needs or policies. As a consequence, some geographic disparity in terms of health care access or level of co-payments exists.
- Local level: Local health units ASL (Azienda Sanitaria Locale) provide health care services – e.g. primary medical services, specialist care, and coordination of all nonemergency admissions to public hospitals. The majority of outpatient care is provided via the ASL.

Responsibility for delivering hospital and community services rests with the ASLs, which are funded by the SSN through a per capita budget which is transferred from the centre to the regions and from these to the ASLs.

Since 1994 funding through DRGs was implemented and applied to both public and private hospitals, with different tariff levels. Public and private health care providers (whether they provide in-patient and/or outpatient care) are remunerated through a fee-for-service system based on two formulary lists, both based on the ICD-10-CM WHO Classification of Diseases and Procedures.

On the regulatory side, Italy has recently dedicated resources exclusively to improve medical vigilance of diagnostic products. Innovative tests such as HER2 and KRAS are publicly funded and available via a network of public hospital laboratories organized in a network comparable to France.<sup>16</sup>

## 12.4.2 National Bodies

### 12.4.2.1 Ministry of Health - General Directorate of Medicines and Medical Devices

Direttorato Generale Farmaci e Dispositivi medici – DGFDM, among other related areas, carries out reviews and supervision of pharmaceutical products (including advertising), collaborates with the Italian Drug Agency, reviews medical devices, including vigilance and evaluation of clinical trials, investigates *in vitro* diagnostics, including vigilance and supervision over blood products.

### 12.4.2.2 CUD (Commissione Unica Dispositivi Medici)

The CUD is in charge of “exerting a consulting role on any issue regarding medical devices for the Ministry and/or for the DGFDM”; though, the CUD represents the key consulting body of the Ministry for medical devices.

#### **The Italian Medicines Agency (AIFA)**

AIFA is the national authority responsible for drug regulation, pricing, and evaluation in Italy. AIFA is responsible for the evaluation of clinical benefit, pricing, and innovative contracting (i.e. risk sharing). The price of pharmaceutical reimbursements by the National Health Service is set through negotiation between AIFA and the pharmaceutical companies.

## 12.4.3 Reimbursement: Central Decision Makers

Medical devices, including diagnostics, in Italy are not subject to pricing and reimbursement negotiation at the central level, thus funding must be queried at the local level (see below).

### 12.4.3.1 Reimbursement: Regional and Hospital Bodies

- Agenzie Sanitarie Regionali (regional health agencies): their role is to plan hospital and ambulatory resources in the region according to the population needs, to implement national

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<sup>16</sup> Market access challenges in the EU for high medical value diagnostic tests. *Personalized Medicine* (2011) 8(2), 137-148.

health plans at regional level, to contract with hospitals for optimizing provision of health care and negotiate hospital budgets for the part not financed by the DRGs. Part of the contracts are related to appropriate utilization of costly drugs and medical devices.

- Commissioni Regionali Dispositivi Medici (Regional Medical Device Committees). According to local specificities, the Regions and the ASRs may envisage the need to set up technical committees with the aim to evaluate devices and issue recommendations on their use. Examples of this are found in EmiliaRomagna, with the institution in 2008 of the CRDM, in Veneto where the CTRDM (Commissione Tecnica Repertorio Unico Regionale Dispositivi Medici) and CTDM (Commissione Tecnica Dispositivi Medici di Area Vasta) were set up in 2009.
- Commissione Prontuario Terapeutico Ospedaliero (CPTOs): A hospital drug committee is empowered in all hospitals in Italy. Its role is to monitor drug prescription consumption and delivery, to decide for enlisting drugs on the hospital formulary, which is mainly based on national references and sometimes completed by economic assessments. Concerning MDs the situation is quite different as some, but not all, CPTOs monitor the use and decide on enlistment/purchase of medical devices: due to the fact that the cost of MDs falls into the hospital budget, and with the hospital being funded through DRG Tariffs, the responsibility of the local committees in the acquisition process, may be considerably larger for MDs, in comparison with drugs; again, this largely depends on regional legislation and organization.

## 12.4.4 Market Approval Process

The core legal framework consists of Directive 98/79/EC regarding *in vitro* diagnostic medical devices. The framework aims at ensuring a high level of protection of human health and safety and the good functioning of the Single Market. A CE mark does not guarantee any specific SSN' reimbursement, funding of diagnostics is basically related to the capability of local providers to effectively manage hospital admissions or out-patient treatments - that imply the use of one or more devices - within the pre-determined Tariffs.

## 12.4.5 Market Access Pathway

The approval for SSN funding for drugs follows a well-established pricing and reimbursement path. However, funding of devices appears largely unregulated and purchase decisions are in practice left to individual providers (hospital committees and managers).

## 12.4.6 Health Technology Assessments in Italy

HTAs are not systematic for IVDs and not required for diagnostics in Italy. The Ministry of Health will review cost effectiveness and budget impact analysis for new IVDs. NICE evaluations are highly thought of and can be leveraged in Italy. The ministry of Health and the National Agency for Regional Health Services developed the following HTAs for certain diagnostics and medical devices:

- Wireless Capsule Endoscopy in the diagnosis of small bowel disease (2008)
- Prostheses for primary total hip replacement in Italy (2008)
- Rapid (bed-side) tests for influenza (2008)
- Technologies for the identification of osteoporosis (2009)
- Prostheses for primary total knee replacement in Italy (2009)

## 12.5 France

### 12.5.1 Background

France has a population of approximately 63.9 million.

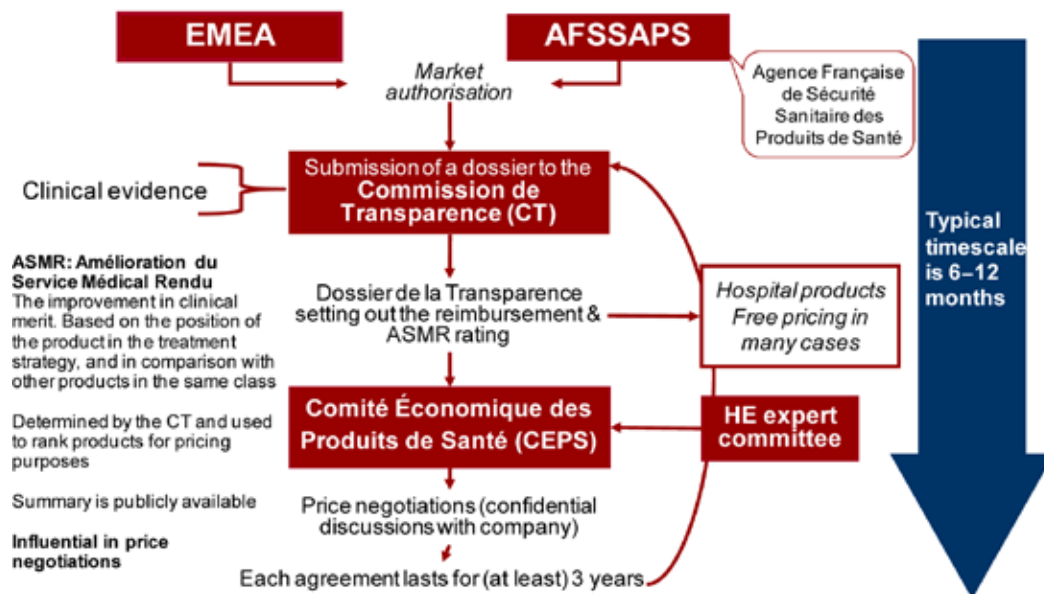
At the national level, the health care system is managed by government and Parliament with 22 regional health agencies (Agences régionales de Santé) in mainland and three in overseas departments in use since 2010. These are in charge of regulating hospital and ambulatory care and medico-social care, in coordination with the local sick funds.

**Outpatient Care:** Theoretically, patients are free to consult any healthcare provider, including specialists, without a referral. However, a gatekeeper system (médecin traitant) was introduced in 2004 and has been widely adopted. While it remains voluntary, patients not registered with a gatekeeper practitioner – normally a general practitioner (GP) – or who consult a specialist without a referral are reimbursed for the consultation fee at a lower rate. Office-based doctors are paid on a fee-for-service basis, which is fixed approved by the government.

Approximately 55% of hospitals work in the public sector (public establishments, plus privatenot-for-profit contracted establishments). The public sector amounts to 77% of the overall hospital expenditure. Since 2004 funding through DRGs (Tarification à l'activité) is implemented and now applied to both sectors, although tariffs still differ.

### 12.5.2 Health System Overview and Key Stakeholders

#### France: The Current System



## 12.5.2.1 Reimbursement decision makers

- **Health Ministry:** The Health Minister determines if a device will be admitted for reimbursement, based on the opinion emitted by the CNEMiDTS, the price or tariff is fixed by the CEPS, and the reimbursement rate is determined by the UNCAM.
- **CEPS (Comité Economique des Produits de Santé):** The Economic Committee on Health Care Products is composed of representatives of the concerned department in the Health Ministry (Department for Public Health Direction Générale de la Santé – Department for Social Security - Direction de la Sécurité Sociale), the Ministry of Industry, the Ministry of Finance and representatives of the statutory health insurances and the complementary insurances. It determines the price or the tariff after negotiation with the manufacturer.
- **UNCAM (Union Nationale des Caisses d'Assurance Maladie):** The UNCAM is a new public health care organizational system following reform law of 12 August 2004. Its first purpose is the coordination of the three mandatory sickness funds, links with complementary scheme and with health care professionals, to obtain a better health insurance management. Its second purpose is the intervention in negotiation of agreements with medical professionals in decisions concerning prescription drug, medical devices and medical or other professional procedures.
- **Agences Régionales de Santé (regional health agencies):** Plan hospital and ambulatory resources in the region according to the population needs, implement national health plans at regional level, contract with hospitals for optimizing the health care provision to the population and negotiate their budgets for the part not financed by the DRGs. Part of the contracts are related to appropriate utilization of costly drugs and medicals devices (Contrat de bon usage des soins).

## 12.5.3 DRG funding

In 2004, a DRG funding scheme in both the public and private sectors was implemented in France. Therefore, most diagnostics are included in the DRG tariff funded by the Health Insurance. In that case, hospitals are purchasers in the context of public tender regulation and there is no health technology assessment at the national level. It is the role of COMEDIMS (Comité des Médicaments et des Dispositifs Médicaux Stériles) to assess products for inclusion on the hospital formulary and decide on purchasing. Hospitals are increasingly grouping into procurement organizations to obtain lower prices. This practice is encouraged by the Ministry of Health.

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<sup>17</sup> Market access challenges in the EU for high medical value diagnostic tests. *Personalized Medicine* (2011) 8(2), 137–148.



## 12.6 Spain

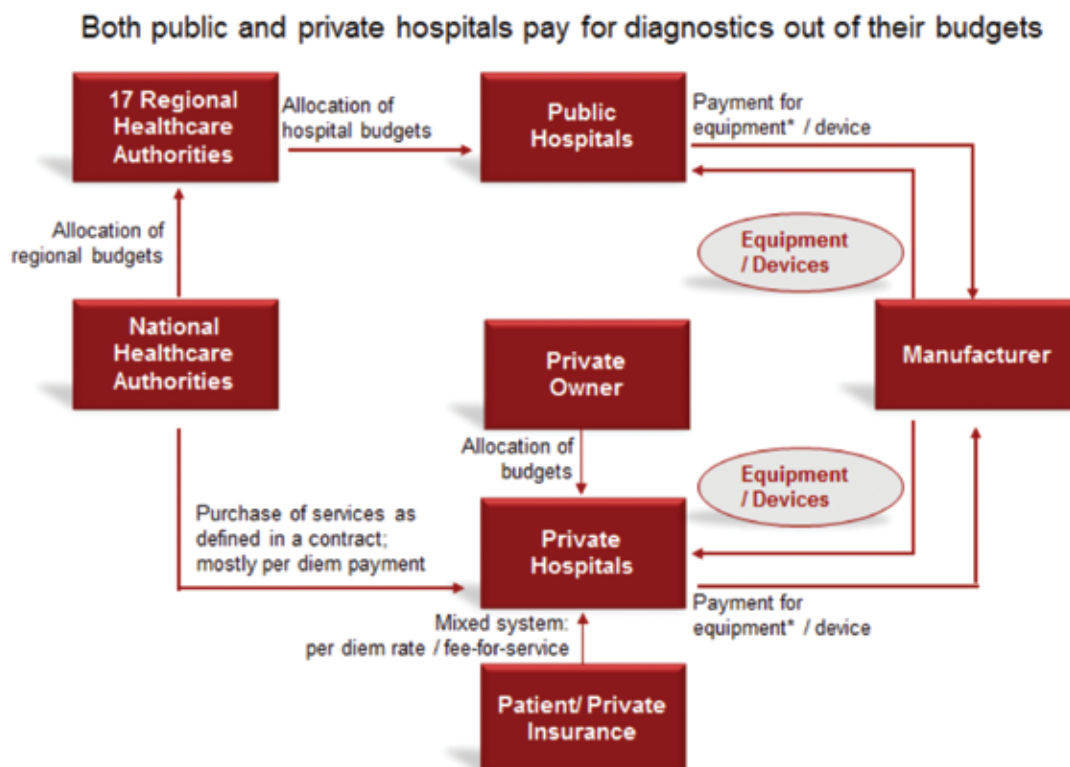
### 12.6.1 Background

Spain has a population of over 45 million people and contains 17 autonomous regions. National coordination amongst the regions is managed via the National Health System Interterritorial Council, chaired by the National Health Minister. In 2003, the Law of Cohesion and Quality of the National Health System was introduced which mandated the inclusion of new technologies in the national catalogue after a review of efficacy, cost, efficiency, effectiveness, safety and therapeutic utility of the different alternatives. The council makes decisions relating to inclusion of products and services, but the central government representatives are responsible for pricing decisions.<sup>17</sup>

### 12.6.2 Health System Overview

The Spanish health care system (Sistema Nacional de la Salud (SNS)) is compulsory and publicly funded, but the administration is done at the regional level through regional health authorities (RHA). Roughly 15% of the population has supplemental private insurance to augment the statutory coverage the entire population enjoys.

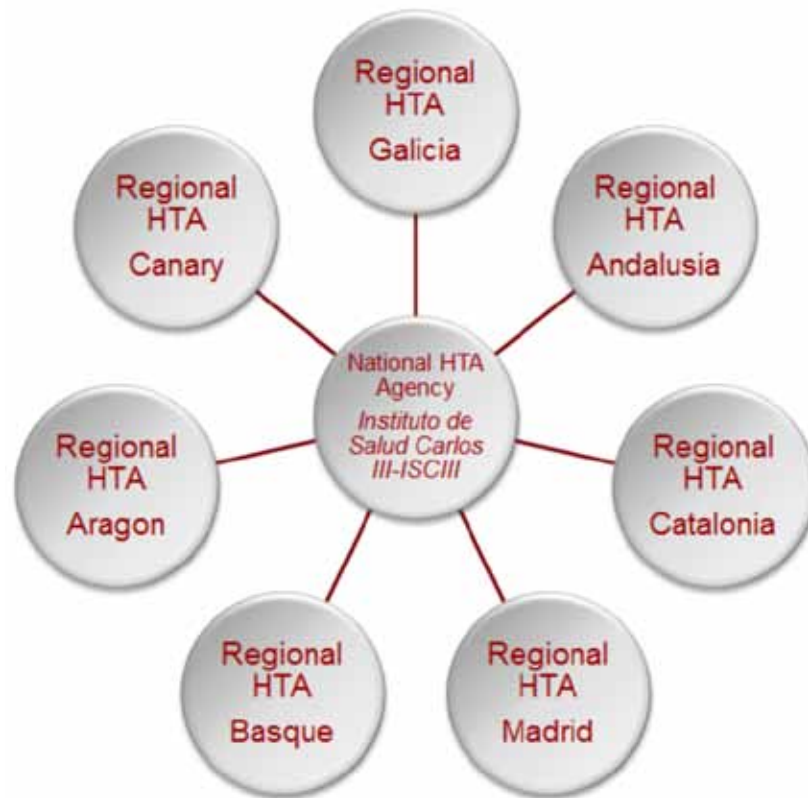
There is a blend of public and private hospitals but the majority are public. The RHAs fund hospitals within their regions through prospective budgets. The basis for budget allocation is largely derived from the population within the hospital area.



**\*\*Pay-per use where the hospitals pays for the disposables only is an established payment-model**

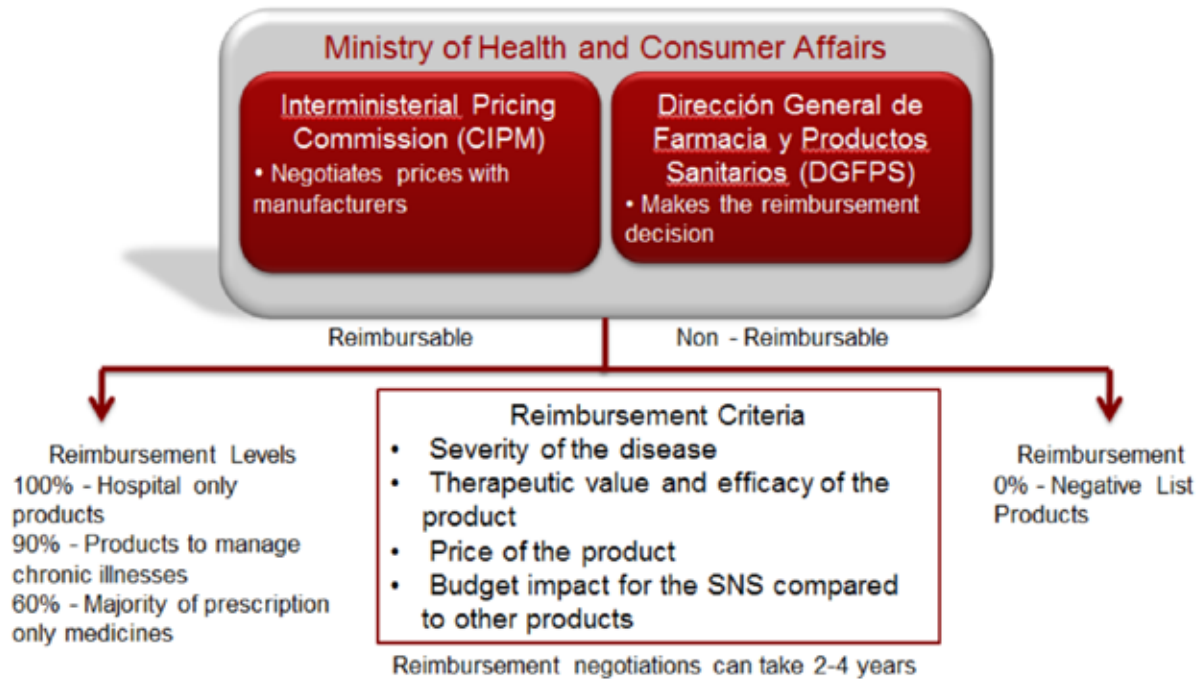
## 12.6.3 Health Technology Assessment

HTAs in Spain are performed at both the national and regional levels. There are seven regional HTAs that collaborate with the National HTA (AETS) as well as perform reviews individually. The methods employed for medical device and IVD assessments include both clinical evaluations and economic analyses (cost-effectiveness). Recommendations made by the HTAs can be used by the regional health authorities for purchasing decisions.



## 12.6.4 Market Access for Diagnostics

Once medical devices or IVDs have been reviewed by HTAs and approved by the Spanish Medicines Agency (AEMPS), public hospitals will purchase them using their allocation of the global hospital budget.



However, national review is not necessary for hospital adoption. Hospitals can use their discretion and purchase medical devices and IVDs from their own budgets and the prevalence of DRG-based hospital systems enable hospital-level decisions without national guidance.

