WHITE PAPER

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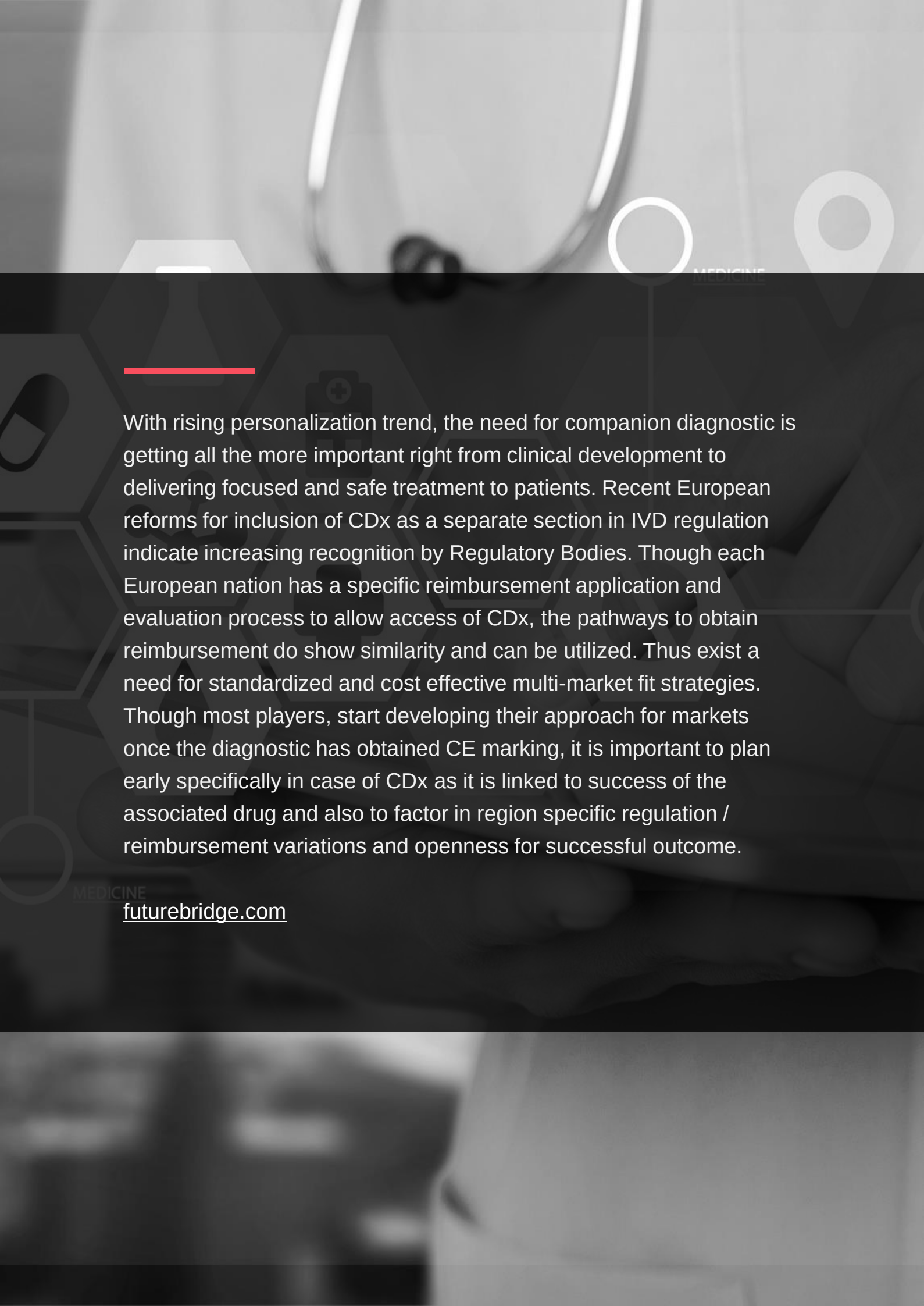
European Regulatory & Reimbursement Dynamics – Companion Diagnostic Access

FutureBridge



With rising personalization trend, the need for companion diagnostic is getting all the more important right from clinical development to delivering focused and safe treatment to patients. Recent European reforms for inclusion of CDx as a separate section in IVD regulation indicate increasing recognition by Regulatory Bodies. Though each European nation has a specific reimbursement application and evaluation process to allow access of CDx, the pathways to obtain reimbursement do show similarity and can be utilized. Thus exist a need for standardized and cost effective multi-market fit strategies. Though most players, start developing their approach for markets once the diagnostic has obtained CE marking, it is important to plan early specifically in case of CDx as it is linked to success of the associated drug and also to factor in region specific regulation / reimbursement variations and openness for successful outcome.

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Key Messages

1. CDx products are powerful tools in precision medicine which come with some unique regulatory challenges because they are considered to be on the cusp of pharmaceuticals and medical devices.
2. The co-development of a therapeutic agent and a companion diagnostic has tremendous impact on the business value proposition and paving the way to overall commercial success.
3. Presently, there is no coordinated mechanism to assess drug-diagnostic companion products in Europe, because of differences both at policy and implementation level for different regions. This has lead to inconsistency and delay in decision making with respect to market access for CDx.
4. The new IVD reform marks a significant change in the regulation of CDx devices in the European Union, not the least the requirements for a performance evaluation that includes significant evidence of clinical performance. It also marks a change in classification for CDx assays from a General IVD to a Class C device. All the evidence point towards growing recognition by the regulatory bodies and things getting mainstream for CDx.
5. In many countries, market access frameworks for diagnostic tests are fragmented and not aligned with generic funding and reimbursement mechanisms, discouraging the use of these tests. This has lead to patients missing out on the appropriate tests and treatments.

A Dynamic Shift from “One-size-fits-all” Towards “Personalized” Approach

The industry is in a transformative phase where one-size-fits-all or blockbuster model of drugs is getting replaced with more informed and personalized treatments offering higher safety and efficacy for that particular subpopulation.

While Companion diagnostics (CDx) are critical tools for precision medicine, there are many challenges in its implementation in Europe. These challenges are associated with regulatory pathways. Since they differ for medicines and associated companion diagnostics, their approval timelines are hampered. Also, the reimbursement process is different for each of the individual countries in Europe.

CDx provides highly valuable information, which helps the healthcare professional (HCP) in decision making with an increased level of certainty on potential benefits of

a particular treatment or care pathway, thus increasing treatment efficiency. IVD accounts for less than 1% of total health care expenditure, and CDx holds a minimal share, though it optimizes the patient outcome.

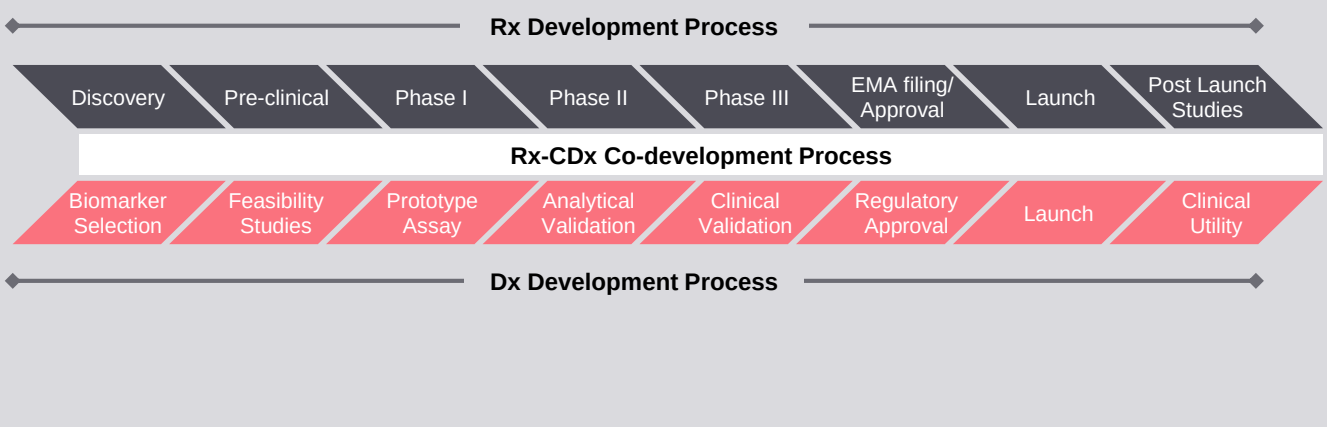
Investing in CDx can prove to be fruitful and provide long-term value for patients and health care systems.

Co-Development Framework for defining CDx success in Europe

For the first time, a definition for CDx is provided in the 2017 EU Regulation in-vitro diagnostic medical devices, defining it as *"a device which is essential for the safe and effective use of the corresponding medicinal product."* CDx can identify, before and/or during treatment, patients who are most likely to benefit from a particular therapeutic product, or patients expected to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.

The primary market access strategies adopted by pharma companies are a "therapy-test" co-development process that guides investment decisions. Ensuring the optimum use of time it makes sure that there is no delay or failure in market entry of the product. This also has a huge impact on the robustness of value proposition, thus facilitating success to any market access strategy. A well-managed co-development program has the potential to optimize costs and accelerate the trial completion by leveraging patient selection strategies to reduce clinical study size; enhance the safety profile; improve efficacy and fast-track the regulatory approval process.

EXHIBIT 1: Rx-CDx Co-development Framework



Industry example portraying the importance of Rx-CDx Co-Development

Scholars suggest that the use of biomarkers reduces the overall development time, attrition rate, and success.

- **A Non-Small-Cell Lung Cancer trial based on data from 676 trials** showed only 11% success rate for medicines receiving marketing authorization by routine method, while the success rate in biomarker targeted therapies was 69%.
- Roche, in partnership with Plexxikon, developed a biomarker-based **Cobas 4800 BRAF V600 Mutation Test**, which enabled the marketing authorization of Zelboraf in less than six years from the discovery time of vemurafenib, while ideally, it would have taken 10–15 years.

Challenges and success factors in CDx Adoption

Although the value of CDx is recognized, there are some challenges concerning their development and implementation/ adoption in clinical practice.

Sample Importance: Access to real-time samples is crucial to develop and validate complex biomarkers and require coordination among the academia and industry.

Identifying Immunotherapy efficacy biomarkers: Even though immunotherapy works very well, unfortunately, only a minority of cancer patients respond to it. Immunotherapy is based on the right biomarker identification, making it vital for effective patient treatment.

State-of-the-art Infrastructure: Testing with very high-quality standards is always recommended. However, at the country level, not all countries might have the capacity to create the required infrastructures. EU government should collaborate more closely and develop regional solutions that would allow resources to be pooled together in a cost-effective manner.

Investment in clinical utility studies: Incentivizing the process of investigating clinical utility is as important as medicines' discovery. Sufficient evidence to justify modification of medical practice is available only for a minority of medicines.

Involvement of patient in the full research lifecycle of CDx: Across all the innovation stages such as research and development, pricing, and reimbursement, evidence collection, etc., it is important to involve patients and focus innovation on satisfying their unmet needs.

Training for General Practitioners (GP): GPs act as "mediators" between patients and specialist doctors. But to fulfill this role at best, GPs need to be trained to be able to provide the necessary explanations on CDx and other technologies available.

Equality in access: Variability in access to medicines and related CDx exist not only among European countries but also regions within the same country. This should be minimized to increase the adoption of CDx.

From R&D to access: Realistic regulatory systems, as well as supportive reimbursement environment, are required to accelerate the development and uptake of approved targeted therapies and linked diagnostics.

Increasing use of Companion Diagnostics in different therapy areas: Unmet medical needs in therapeutic areas such as asthma and COPD are enormous, for which only a few new medicines have been made available to patients in the recent years. The biology of these diseases in contrast to Oncology is less understood, and shared efforts among industry and academic communities are needed in order to gain access to the right samples and cohorts available to validate biomarkers.

EU Regulatory Scenario and New Reform impact

EU is steering its directional focus in a way to align it with internationally agreed standards for not only CDx but also for overall diagnostics segment. Currently, the authorization process for drugs and diagnostics is different, even though the use of companion diagnostics (CDx) is considered to be crucial to the performance of the drug

In 2017, two new regulations - (EU) 2017/745 for medical devices and (EU) 2017/746 for the in-vitro diagnostic device - were adopted. These covered both pre and post-market regulatory scrutiny, especially of high-risk devices. It also focuses on additional requirements of transparency, traceability, and CDx as a separately defined category. This new regulation also acts as a consultative backbone to EMA for CDx certifications.

The Role of Notified Bodies (NB) & European Medicines Agency

Both Notified Bodies and the European Medicine Agency (EMA) have a distinct role in the authorization of CDx. At one end where the Notified Bodies will have to consult their national competent authorities regarding the suitability of the device to its associated drug, the EMA on another end will provide scientific advice to medicine developers, recommending appropriate tests and studies required for development and/or quality assurance.

As per the new legislation, the notified bodies under close scrutiny from the national competent authorities within the member states would be the decision makers in

case of the certifications of all IVDs, including the CDx products. The NB's will also be required to audit and inspect the sites of IVD manufacturers.

The NB will also be consulting EMA or a national medicines licensing agency if any scientific opinion is required before issuing an EU compliance certificate for a CDx. In this case, EMA is expected to provide an opinion under 60 days. While EMA cannot veto the NB's assessment, NB, however, has to give "due consideration" to EMA's or other agency's opinion, in case they have any negative opinion about the benefit/risk balance.

The new regulation (introduced in 2017) will come in complete effect in 2022. During this transition period, EMA will have plenty of opportunities to lay down requirements in guidelines, thus limiting the freedom of NB's to certify CDx products.

While the NB's are responsible for evaluating the technical features and qualities of a CDx, the EMA has to evaluate the benefit-risk balance between the drug and CDx. Both bodies need to consider the impact of the CDx on the treatment of patients. Health technology assessment (HTA) will play a pivotal role in understanding the cost-effectiveness of drug and CDx.

NB's are free to accept the parallel or alternative different diagnostic methods for the selection of patients as long as the benefit-risk balance is positive. Since the EMAs regulatory mandate is for medicine and not IVD, NB's will be held responsible for approving any inferior CDx that causes harm to patients. Even if the patient is treated with CDx with inferior accuracy, EMA cannot limit the use of the medicine, as long as the benefit-risk balance for the medicine remains positive.

Just the benefit-risk balance being positive is not sufficient for HTA, a more exact quantification of the benefit with regards to size (e.g., increase in time of survival or without symptoms) and frequency (effective in how many of treated patients) will be required.

Emphasis on improving links between CDx and medicines

Targeted medicines are supposed to be less toxic than chemotherapy and be used in conjunction with a CDx. As per new reforms, regulatory bodies are emphasizing on the extensive use of biomarkers and advanced technologies for personalization:

Identification of Novel biomarkers: Need to identify biomarkers for patients effective treatments and financial health.

Identification of resistance biomarkers for targeted therapies: Drug resistance is a major problem in the treatment of cancer patients. Possible solutions to advance

research and care for these patients are represented by sequential analyses of tumor DNA.

The Democratization of high throughput technologies to identify targets: Making high throughput technologies more widely available and easily accessible will advance diagnostic linkage to medicine.

New regulation affects Laboratory Developed Tests (LDTs) and license status of medicines

Nearly 50–60% of testing in the EU is still conducted through LDTs, while the rest of the markets have adopted commercial in-vitro kits. In updated regulations, regulatory bodies are supporting the usage of IVD kits over laboratories.

The EU's new legislation retains its existing regulatory system under which IVD manufacturers are able to self-certify the quality and safety of their diagnostic kits. It also states that public health institutes have the freedom "of manufacturing, modifying, and using devices in-house," although they may still be subject to national quality rules. However, manufacturers will need certifications from the NB for high-risk tests.

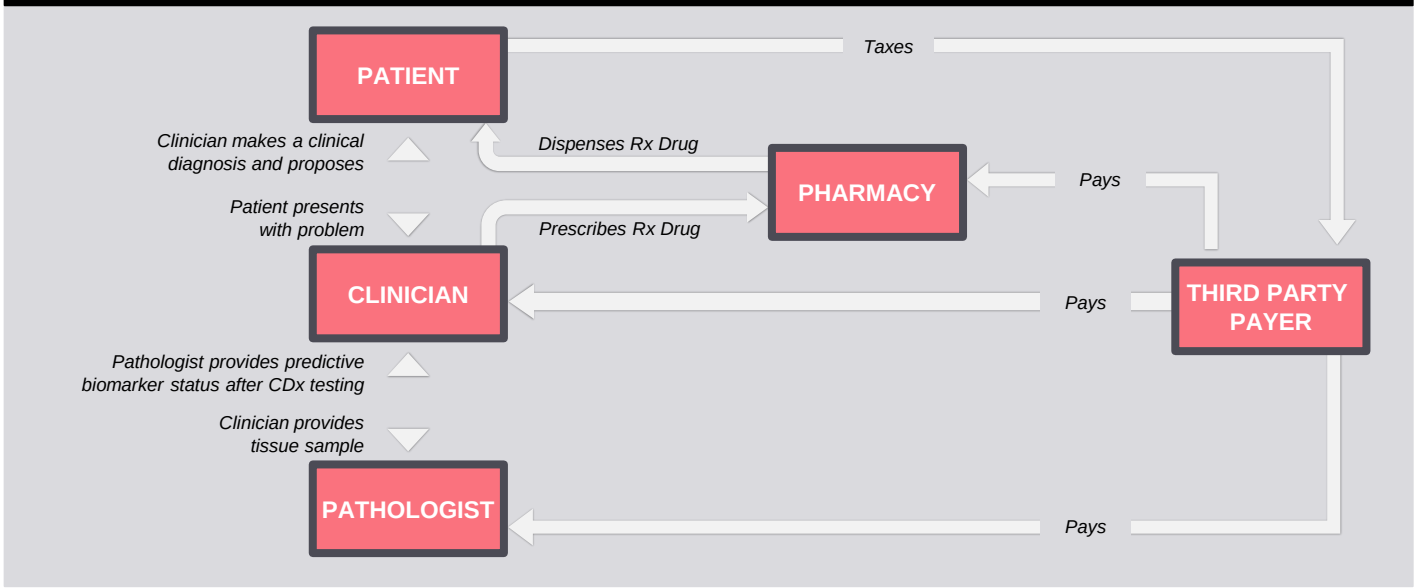
The marketing authorization, "CE Mark" for the CDx can be obtained from any NB and EMA. One medicine can have multiple certified CDx; however, the benefit-risk balance of the medicine may depend on the performance of a CDx such as sensitivity and specificity.

EU Reimbursement – Process, Regional Variations, and Adoption

The reimbursement process starts with regulatory approval of the drug and associated Companion Diagnostics. The value assessment is done using Heath Technology Assessment (HTA) methods for determining pricing and reimbursement decisions. Once approved, the provision of Rx-CDx tests to pathologist/laboratories is carried out. The interaction between patients, pathologists, and payers are complex; a simplified broad level view is shown in *Exhibit 2*:

Based on the results of the companion diagnostics tests, 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.

EXHIBIT 2: EU Reimbursement Pathway



Variations across EU Regions

In many European countries, reimbursement systems currently are not appropriately aligned to promote the development of companion drugs and diagnostics. For example, many European payers consider drugs and diagnostics under separate evaluation and payment processes. In Europe, reimbursement, coding, health technology assessment (HTA), and pricing decisions are made at the country level (either nationally or regionally), even 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.

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. 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.

Some of the country-specific variations at different stages are highlighted below:

Health Technology Assessment Evaluations

Drugs and companion diagnostic are evaluated separately in France, Germany, Italy, and Spain. In the UK, CDx evaluation is integrated into the technology appraisal of associated drug helping in decision consistency and avoiding delays.

Pricing

In most countries, value-based and external reference pricing is followed. In a fee-schedule system like Germany, France, and Italy, the availability of generic codes is important. To facilitate access to CDx at drug launch, new codes need to be generated, causing a delay in patient access. In the UK and Spain, code generation is not necessary.

Funding

Across all the EU-5 countries, companion diagnostic funding is based on Diagnostic Related Group (DRG) system in a hospital setting. Per case, basis evaluation is done. In Spain, CDx testing is reimbursed by the pharma companies, unlike other countries where it's covered at a national level.

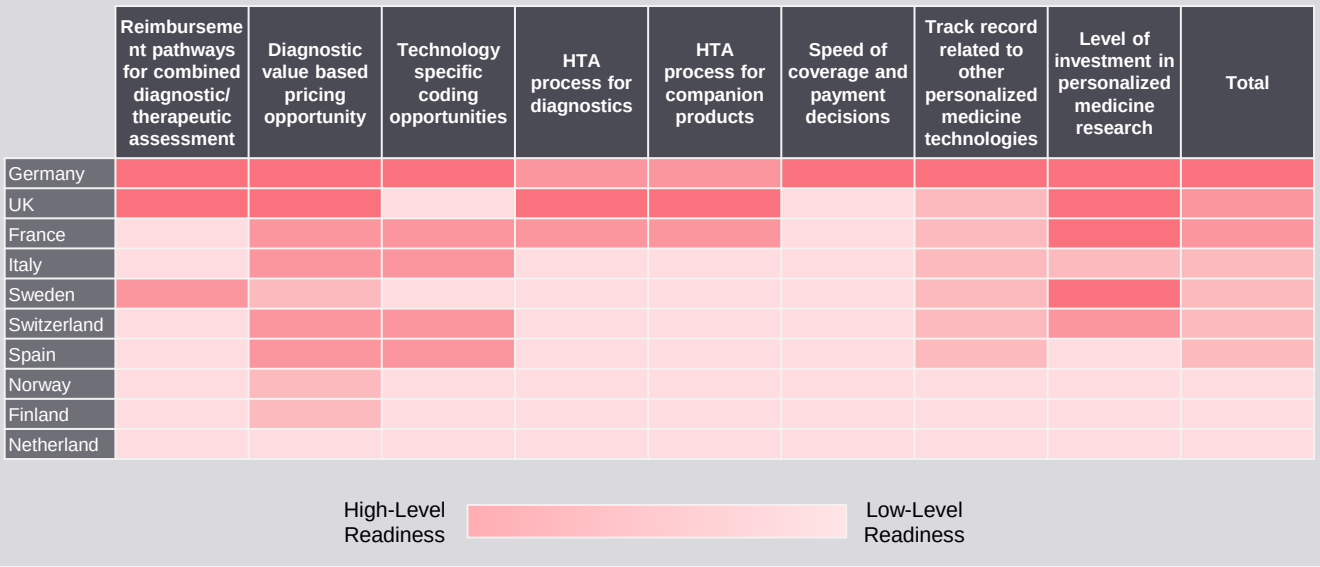
LDT Linked Reimbursement

Laboratory performance varies across countries, which might lead to misclassification of patients. A standard accreditation needs to be established, and testing quality can be incentivized to result in consistent reimbursement.

Adaptive Environment across EU Regions

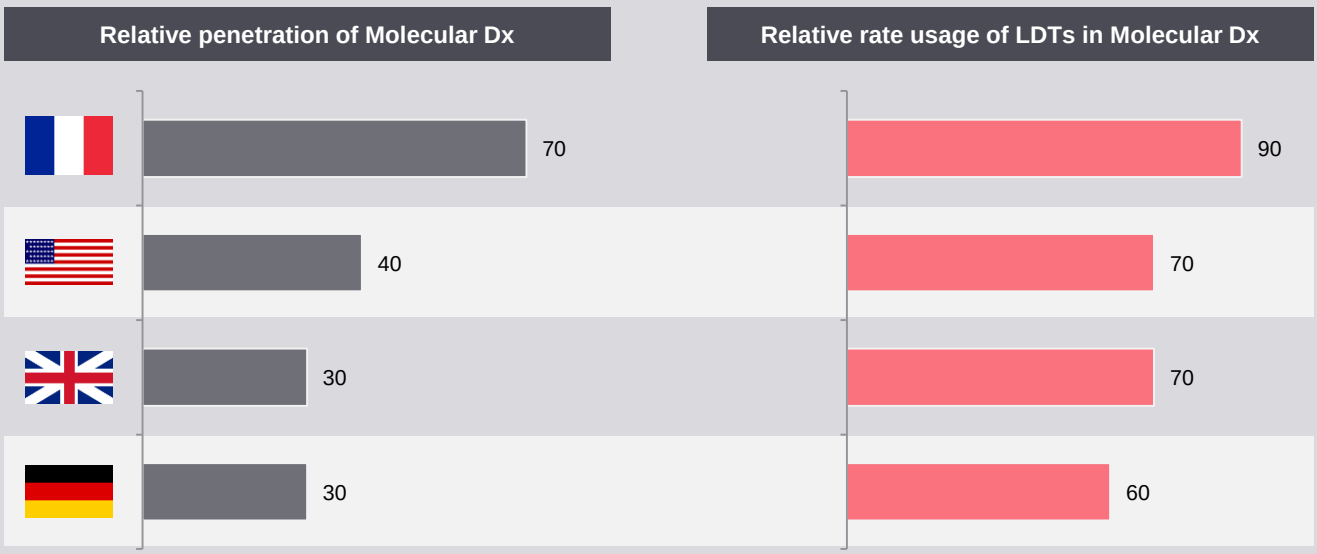
The Personalized Medicine Coalition (PMC), representing innovators, scientists, patients, providers, and payers, promotes the understanding and adoption of personalized medicine concepts, services, and products to benefit patients and the health system. As per the eight key metrics published by PMC, European countries' support readiness for adoption of personalized diagnostic linked treatment is shown in the heat map in *Exhibit 3*. Germany, UK, and France were found to be highly rated.

EXHIBIT 3: EU Regional Adaptive Index



Government-based funding support can be the most critical driver for adoption, as evident from high penetration and usage of MDx-based companion diagnostic tests in France.

EXHIBIT 4: Relative Penetration and usage comparison (based on customer survey for 3 CDx tests)



In conclusion, it can be stated that key regions in the EU do have access to companion diagnostic testing. However, variations with respect to access and time exist. By identifying the parallels in each country-specific process for reimbursement and market access, market players can look at building a standardized process that fits multiple European markets, saving both time and money. Considering a centralized approach and examining strategies to develop it in the most efficient manner will help in accessing more markets in less time.

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