

VALUE OF COMPANION DIAGNOSTICS IN PERSONALISED MEDICINE

Stimulating innovation for improving health through companion diagnostics

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I. Introduction

Personalised healthcare provides targeted medical treatment to patients, allowing the right treatment to reach the right patient at the right time. This rapidly growing approach to health is stimulated by the possibilities arising from the use of companion diagnostics, which play an essential role in terms of assessing the appropriateness of a specific pharmacological intervention for an individual patient through prediction and monitoring of response or toxicity related to that pharmacological therapy. Personalised healthcare shifts health systems from being treatment-centred to being comprehensively patient-centred with a care management approach of cost-containment that has the potential to enhance efficacy and reduce adverse events.

As with other in vitro diagnostic medical devices, companion diagnostics do not provide treatment themselves nor do they come into direct contact with patients; they provide key information on a patient in relation to their eligibility for a targeted therapy based on specific biomarkers. This distinction has prompted the European Commission to acknowledge the specific attributes of companion diagnostics through the provision of a separate definition within the broader scope of in vitro diagnostics.

'Companion diagnostic' means a device specifically intended *for and essential to the selection of* patients with a previously diagnosed condition or predisposition as *suitable or unsuitable* for a *specific* therapy *with a medicinal product or a range of medicinal products*.

*Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices.
2012/0267 (COD). 26 September 2012.*

Companion diagnostics provide value by increasing information available to patients, health practitioners and payers. They are able to make informed decisions with less uncertainty about the value of a treatment, care pathway, and in the case of patients, lifestyle choices. For payers, this decrease in uncertainty results in improved efficiencies in selecting treatment, managing cost, and optimising patient outcomes as they are able to fund therapies targeted to subpopulations most likely to benefit. Providing access to companion diagnostics results in health gains and cost-offsets through the reduction or avoidance of adverse events associated with treatment, loss of quality of life, containment of cost increases of treating non-responder patients, and time delays in selecting appropriate interventions. Companion diagnostics increase effectiveness of treatment strategies by stratifying responder patients. They decrease patient uncertainty through their ability to 'rule out' response to one treatment, which allows fast initiation of a better suited option and diminishing the sense of 'ambiguity', increasing patient empowerment, improving adherence to therapy, and fostering a sense of well-being.

EDMA strongly believes in the value provided by such diagnostic information, which not only has an inherent value for patients, but it also goes beyond the health systems and reaches overall societal gains, like getting patients and carers back to work earlier. In order to fully utilise this potential, however, there are regulatory and structural needs that must

be put in place through the scope of the European Commission proposal for a Regulation on in vitro diagnostics, development funding, and value-acknowledging reimbursement structures.

II. Why action is needed

Acknowledging the unique role of companion diagnostics in personalised healthcare is a significant step toward developing a well-suited regulatory approval procedure that is coupled with more efficient pricing and reimbursement systems. Such a practical recognition of the value of diagnostic information is needed in Europe to secure patient access to these key diagnostic tools and foster innovation to fulfil unmet health needs in Europe. Yet the development and implementation of new companion diagnostic tools, which have the potential to personalise healthcare approaches, are still hampered.

Development and validation processes for new companion diagnostics have unique characteristics that necessitate more resource requirements than those for well-established biomarker tests. Additionally, unlike many approved personalised medicines, which are linked to an individual companion diagnostic test, companion diagnostics may target multiple therapeutic solutions, further contributing to the need for complex and resource intensive data gathering and production processes.

In addition to higher investments, development risks of the associated therapeutic agent have to be added to the IVD project risks and are hence higher than those for traditional diagnostic tools.

Stimulating further diagnostic development and overcoming high business risks are two critical factors that can only be achieved through the implementation of a multifaceted, multi-stakeholder and targeted approach that will cover the whole spectrum of development – from funding to regulatory aspects to reimbursement – all of which must be in place in order to achieve successful approaches to personalised medicine.

III. Incentivising innovation through development funding

In acknowledging that the resources required to develop companion diagnostics are high, incentives should be in place to foster innovation that is targeted specifically towards areas of unmet needs. The Strategic Industrial Innovation (ISI) programme in France promotes collaboration between industry and academia to help bring products and technological breakthroughs to the market through support from public funding. The financial aid ranges from 3 to 10€ million and comes in the form of grants and reimbursable advances, such as the development of companion diagnostic for measuring the response to the therapeutic vaccine (VAC-3S) to treat AIDS, as well as to identify an early marker of disease progression.

A positive national example of how funding can help innovate the healthcare sector to the advantage of patients, the ISI initiative can, and should, be supplemented by appropriate incentives for the development of companion diagnostics on a broader scale. Many such funding initiatives already exist for pharmaceutical products and could be adapted to the diagnostics, but it would require recognition of the inherent value of companion diagnostics. For example, the Supplementary Protection Certificates – which provides protection for a product while a patent is pending – could be expanded to companion diagnostics by providing protection for the developers of new diagnostic tools.

As it currently stands, the Supplementary Protection Certificate only applies to medicinal products and is intended to, “remedy the disparities and shortcoming in national patenting systems for pharmaceutical research (...) to guarantee sufficient protection for the development of medical products in the European Union.” Of course the adoption of the regulatory framework to companion diagnostics would have to be amended and appropriated for in vitro diagnostics, but the overarching principles of encouraging innovation, research, free movement of products in the EU, and avoiding vast differences between countries, may also incentivise IVD developers, particularly small- and medium-

enterprises (SMEs), to dedicate more of their limited resources to bringing new companion diagnostics to patients.

Beyond a fitting protection for new products coming onto the market to fulfil unmet needs, funding schemes for research, such as Horizon 2020 could provide new opportunities by helping to identify biomarkers that will serve as the basis for the next generation of companion diagnostics. While Horizon 2020 sets out clear objectives for its health-related calls that are aligned with the value that companion diagnostics bring – such as “improve our ability to monitor health and to prevent, detect, treat and manage disease” and “test and demonstrate new models and tools for health and care delivery” – it is now up to relevant stakeholders to engage in such initiatives. Without their participation, the funding schemes may not continue to be available in the future – a risk that should not be taken.

IV. Creating an appropriate regulatory framework

In the process of the revision of the legislation on in vitro diagnostic medical devices, the special characteristics of companion diagnostics have been noticed. While the text has not yet been finalised, as talks continue, there are several new and critical aspects introduced in the Draft proposal for a Regulation on in vitro diagnostics that will influence how companion diagnostics reach the market in the future.

- *Classification:* The overhaul in the classification of IVDs will impact companion diagnostics, which will be classified at least under class C, representing the highest risk class of an IVD to individual patients, in line with the proposal of the Global Harmonisation Task Force (GHTF) and acknowledging their role in the selection of patients for treatment eligibility. General principles of classification will also apply. This means that if a new companion diagnostic fulfils the criteria for a class D IVD – currently those that pose a possible risk to a wider population and could, for example, apply to a companion diagnostic for HIV – it would be classified as D, not C.
- *Conformity assessment:* The European Commission proposes a procedure for the assessment of companion diagnostics that involves the European Medicines Agency (EMA) in each individual review alongside the designated Notified Body. The involvement of EMA in such reviews would essentially create a duplicate assessment, as a second review would come after the new companion diagnostic data was already checked as part of the drug approval procedure. For second-generation companion diagnostics, this review would not provide any additional information. In both situations, such a move would lead to a significant additional regulatory and administrative burden with no evident safety gain. This could create a situation whereby a medicinal product is already available but cannot be used, if the supporting companion diagnostic would still be in the approval process. This carries a risk of delays in bringing needed medication to patients. The added hurdles associated with EMA involvement in each review process, both in terms of time and resources, could pose major challenges – especially for small-and-medium enterprises (SMEs) – when investing in second-generation, improved versions of already existing companion diagnostic tests.

Key concerns include:

- The degree of review by EMA is not defined, neither in timing nor desired outcomes;
- Interaction between EMA and notified bodies is not clear; and
- The level of expected evidence for demonstrating the ability of the companion diagnostic to appropriately select patients is not clarified.

EDMA does not support EMA involvement in batch release testing for IVDs, but sees a role for the agency, or national equivalents, among the stakeholders involved in the development of Common Technical Specifications for companion diagnostics, as proposed in the European Parliament.

The European Parliament has expanded the control of companion diagnostics compared to the Commission text, by including the mandatory development of CTS for

companion diagnostics, which would outline the prerequisite targets and expectations that these devices must satisfy. These CTS would be developed by regulators with input from EMA, physicians, patients, notified bodies and manufacturers and would provide a high level of detail and transparency of prerequisite safety and clinical requirements. These CTS would furthermore cut down on time and red tape by providing clear technical requirements that companion diagnostics need to meet whilst ensuring a high level of safety and performance.

- *In house exemption for companion diagnostics:* In order to encourage innovation, the majority of IVD tests that are developed and used within a single health institution currently do not have to fulfil the requirements of the proposed Regulation, provided that they do not fall into the highest risk-based classification category (class D). This, for example, allows laboratories to quickly create tests to react to outbreaks, new strains, or mutations without having to generate all of the clinical evidence requirements that are needed to place a test on the market. This approach is useful when there is an urgent need for a new diagnostic test and no commercially available alternative exists.

The European Commission proposal maintains that a so-called ‘in-house exemption’, which allows high-risk in vitro diagnostics – those falling into Class D according to the new classification system – to be developed and used within a single health institution. This indicates that tests manufactured and used under a single quality management system in an EN ISO 15189¹ health institution whose primary purpose is the promotion of healthcare or public health, do not have to provide the otherwise required clinical and performance studies, provided that no comparable test is commercially available yet.

However, in expanding the in-house exemption to all companion diagnostics some concern arises for these IVDs. Different to other tests, companion diagnostics are subject to specific requirements in order to demonstrate that patients are being appropriately selected for the use of targeted therapies. As such the clinical evidence requirements for companion diagnostics are substantially higher than those for most other IVD assays, thus explaining why companion diagnostics should only be permitted to benefit from the in-house exemption in instances when no equivalent test is available and no longer eligible once the equivalent test is CE-marked.

Such an approach is in line with the United States Food and Drug Administration (FDA) specific rules for the regulation of laboratory developed tests, which identify companion diagnostics as the first priority. In instances where a laboratory developed companion diagnostic fulfils an unmet need, the FDA will exercise enforcement discretion. When an approved test exists however, the laboratory developed tests will be subject to the registration and listing, reporting, and pre-market review requirements. As an added measure, laboratories will eventually be subject to quality management system requirements.

- *Clinical evidence* - It is important to understand that IVDs never interact directly with patients. Any risk to patients – as emphasised by the new risk-based classification system – would stem from the information that IVDs provide. Much of the clinical evidence that is required for other in vitro diagnostic devices can therefore usually be gathered in the developmental phase with samples obtained from biobanks. However, as companion diagnostics are linked to the choice of a specific therapy for a patient, they present a unique case and necessitate specific requirements, including more stringent oversight and extended scientific validity. The unique case of companion diagnostics must be acknowledged with an adapted and appropriate review process that accounts for their specificities.

This approach is already accounted for in the European Commission proposal and establishes the means for collecting clinical evidence and conducting performance studies that provide safe and streamlined processes, but this approach should not be

¹ EN ISO 15189 provides specific requirements for the quality management system of particular medical laboratories, including competences. Full text: http://www.iso.org/iso/catalogue_detail?csnumber=56115

mimicked for all in vitro diagnostics, as it would not be appropriate and, in some cases, may be not just impractical, but also impossible.

V. Reimbursement for companion diagnostics

The approaches to reimbursement for companion diagnostics vary widely across and within Member States, with uncertainties for manufacturers spanning the entire cycle – from the initial development through assessment and on to the market. Achieving appropriate reimbursement is a time consuming and, often, unfruitful process. In practical terms the complexity and unpredictability of reimbursement pathways poses a real challenge for diagnostic manufacturers, particularly due to significant variations in system design, cost, and coverage.

In the UK alone, there are more than 210 Clinical Commissioning Groups (health providers managing payment and assessment requirements for IVDs), each with slightly different processes, procedures, and requirements. This heterogeneity can impact the speed of adoption, while an uncertain and potentially fragmented entry point for IVD manufacturers add hurdles along the pathway. This highlights that in some instances, already approved and CE-marked companion diagnostics are still undergoing various appraisals due to the tendency of most Member States to review tests at the local level. This local approach to coverage and reimbursement assessment of diagnostic tests compared with national level reviews for most drugs, can present substantial barriers to consistent market access for diagnostic-medicine combinations.

The differences between, and within, countries are further illustrated by the fact that each country in Europe has country-specific technology evaluation and reimbursement systems. As a result, coverage for many personalised medicine technologies varies across Europe. For example, while trastuzumab – a drug used for the treatment of breast cancer where the HER-2 overexpression is present – is widely reimbursed across the EU, reimbursement for its HER-2 companion diagnostic test varies widely. In the UK, France, Germany, and Italy, HER-2 testing is publicly funded, but in Spain, the pharmaceutical manufacturer funds the majority of testing. This represents a real contributor to inequality, as patients do not have the same access across Europe, but it also creates a barrier for manufacturers, who have no predictability or clarity regarding the necessary steps for value demonstration leading to effective uptake of the diagnostic component.

Yet despite the fragmentation across the European Union, the fundamental and overarching obstacle for reimbursement and assessment in Europe is a lack of recognition as to the inherent value of the information the diagnostic component brings to personalised medicine. With no countries having an established value-based pricing pathway for novel diagnostics, prices are fixed based on use and competitive pricing. Companies 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 basis. This process delays access and could be avoided once diagnostics are recognised for their independent value in the provision of information in both pricing and reimbursement.

To avoid unequal access for patients, EDMA calls for economic evaluations that take into account the therapy and the diagnostic information independently, are fit-for-purpose, and consider the improved efficacies to healthcare systems offered by companion diagnostics through the avoidance of unnecessary therapy costs achieved through the targeted diagnosis.

VI. What can personalised medicine offer?

In vitro diagnostics, especially companion diagnostics, are essential for the advancement of personalised healthcare. These valuable tools are able to predict therapeutic effectiveness by ruling out patients that will be non-responders to a specific therapy. This is precisely the role of the BRAF V600 mutation analysis in patients with metastatic melanoma – selecting those individuals who would benefit from treatment with BRAF inhibitors therapy of dabrafenib. The use of this combination of diagnostic and targeted therapy delays progression of the disease and increases patient survival.

Companion diagnostics can also predict safe use by ruling out those at risk of serious adverse events. For example, KRAS mutation testing is able to exclude treating metastatic colorectal cancer patients with cetuximab, who are at higher risk of adverse events from the drug and are less likely to respond to treatment.

Even after the choice of therapy is made, companion diagnostics are of sustainable value thanks to their ability to continually monitor the safe and effective use of a therapy, adjusting treatment to improve safety and effectiveness through changes to dosage, schedule or discontinuation.

By selecting patients who are most likely to benefit from a treatment, isolating those who are susceptible to adverse events, or providing targeted treatment during the course of a therapy through monitoring, companion diagnostics provide intrinsic value and offer the opportunity to reduce overall healthcare costs. These costs may require an initial investment – e.g. a test – but contribute to the avoidance of unnecessary hospitalisation and inappropriate therapeutic treatment for a specific patient

VII. Conclusions

The future of personalised healthcare promises more sustainability for healthcare systems by offering solutions that are targeted for patients, optimising outcomes, and reducing overall burden of disease. To move forward and achieve access to innovative companion diagnostics and companion drugs, decision-makers at European level and Member State level must work together to ensure that an innovation-friendly environment exists, uptake is encouraged, and patient access is improved. In order to do so, concrete actions must be undertaken.

1. Collaboration with academia provides a unique opportunity for manufacturers to gather research and fuel the development of innovative products. Such initiatives should be supported by broader programmes like Horizon 2020 and a strong regulatory framework, including appropriate patent protections that take into account the sensitivity of the raw data produced by evidence generation for IVDs.
2. A stable regulatory environment that accounts for the unique role of companion diagnostics within the broader scope of IVDs and is reflected in the Draft proposal for a Regulation on in vitro diagnostic medical devices through:
 - a. Mandatory development of common technical specifications with the involvement of relevant stakeholders, including manufacturers, patients, European Medicines Agency, notified bodies and physicians, but not batch release testing for each individual assay;
 - b. An in-house exemption should only be available for those companion diagnostics, which do not have a commercially-available, CE-marked test already on the market; and
 - c. Clinical evidence for companion diagnostics should be more extensive and stringent than for other IVDs due to their relationship to the choice of therapy.
3. Clear, transparent and timely market access processes suitable for the specificities of companion diagnostics should be created. This can be achieved through:
 - a. The value of diagnostic information must be accounted for in pricing and reimbursement decisions;
 - b. Incentives that will further drive innovation and continuously improve patient care;

- c. Assessments should only be done to inform a decision point that has been reached through a fit-for-purpose approach, i.e. linked to coverage, reimbursement, funding, and/or use decision; and
- d. Adoption of assessment mechanisms to the specificities of companion diagnostics and using appropriate methodologies developed in cooperation with relevant stakeholders.

With these critical aspects in place and with continued on-going collaboration among stakeholders, personalised healthcare can bring the future of healthcare to the present.

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