# EBE-EFPIA Personalised Medicine Working Group Manifesto

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## Purpose and content of the Manifesto

The EBE-EFPIA Personalised Medicine Working Group Manifesto aims to highlight policy elements that are considered essential to ensure that personalised medicines and their paired diagnostic tests, also called companion diagnostics, successfully reach patients.

The Manifesto consists of three distinct parts, supported by a glossary, addressing the following policy needs:

- **A clear and coordinated process for the regulatory approval of personalised medicine (Part I)**
- **A clear and predictable process for the economic/value assessment of and access to personalised medicine (Part II)**
- **A European regulatory framework that is supportive of innovation – creating a flexible and "forward-looking" regulatory and reimbursement environment (Part III)** – which includes:
    - The use of multi-marker signatures
    - The use of electronic health record systems that facilitate clinical research, ease the collection and processing of real-world data and improve clinical practice
    - Data protection legislation that effectively facilitates the use of "big data" in healthcare research.

For each of the three parts above, barriers as well as related solutions are highlighted.

**This document constitutes Part III of the Manifesto:**

**A European regulatory framework that is supportive of innovation – creating a flexible and "forward-looking" regulatory and reimbursement environment**

# Part III: A European regulatory framework that is supportive of innovation – creating a flexible and "forward-looking" regulatory and reimbursement environment

The current regulatory and reimbursement systems that are in place were designed for medicinal products that are used in non-stratified patient populations. However, in "personalised medicine", a medicinal product is authorised for use in conjunction with a diagnostic test that allows the identification of likely responders to a medicinal product, thus stratifying the population for which a medicinal product is authorised. This brings opportunities for better patient care, but is also challenging when regulatory and reimbursement decisions need to take into account the evolving science linked to how the product is used or how it should be tested.

## 1 - The use of multi-marker signatures

**Barriers:**

- Current regulatory and reimbursement systems are not designed to assess multi-marker signatures, which can evolve over time and may help determine the use of multiple medicinal products.
- Diagnostics and multi-marker signatures developed by academic groups are not subject to regulatory reviews, and quality as well as validity are not often assessed formally.
- Patients, healthcare professionals and health systems are not currently well equipped to understand and explain the use, benefits and limitations of "omics" data in medicine.

The current regulatory environment is designed for a "one medicinal product – one test" paradigm. Biomarker development in many therapeutic areas is already moving in the direction of tests that are composed of multiple markers (often referred to as signatures) identified from multiple data sets from different platforms (genomic, proteomic, pharmaco-genomic, etc.), which are then combined using complex bio-informatics approaches.

Such signatures may inform an entire treatment pathway (i.e. a combination or sequence of treatments), not just one medicinal product. Furthermore, such signatures may evolve over time as more data is collected and analysed. These unique, new features will impact the making of regulatory assessments, in which the use and effectiveness of several therapies are linked to complex signatures. Keeping these indications up to date will be challenging in the current regulatory framework.

This challenge of signal evolution is analogous to the concept of "adaptive pathways". This is the idea that the evidence for a therapy and its related diagnostics evolve over time, thus regulatory assessments will also need to evolve over time.

Similarly, as signatures evolve, the definition of the treated patient population will change, as will the population's relevant clinical outcomes. How a therapy is used and its value determined in that particular setting will also need to evolve over time. Tracking this changing value and adjusting its reimbursement appropriately will represent a significant challenge. Thus, adaptive reimbursement mechanisms are an urgent requirement. If a signature (or evolution of a signature) defines a population with improved outcomes, the possibility to adapt reimbursement to reflect the increased value to patient and healthcare system must be available.

Scientists in industry and academia are already developing genetic (and other biomarker) signature approaches, and are testing these in clinical trial settings. As academic researchers often have access to large clinical and genomic research databases, they may develop their own signatures and place them into clinical practice where improvements in outcomes have been identified. There is currently no regulation related to this type of activity, and they become complex in-house developed tests. Careful thought needs to be given to ensure the quality and validity of these tests, as they will be used in direct treatment decisions for patients.

Implementing signature approaches into clinical practice presents challenges to healthcare systems, healthcare professionals and patients. Such approaches will place new demands on existing clinical information systems, and would ideally be introduced using integrated e-health records. Healthcare professionals will require training in these new approaches and systems to be able to use them in their daily practice.

Increasingly, patients are also seeking genomic sequencing directly from commercial organisations to identify their most suitable treatment options (e.g. Foundation Medicine's FoundationOne). When patients receive this type of personal genomic report, medical advice is often sought on the health implications of the information. Education for patients on the subject of "omics", signatures and the impact of this information on their own treatment options will also require new approaches.

Given these likely developments, the current process for the review of medicinal products and related diagnostic tests is unlikely to be fit for purpose in this new environment – it would represent a major change in regulatory philosophy. This evolution is already being considered in discussions and pilot-projects related to the adaptive pathways approach. Methods to repetitively evaluate the benefit-risk balance need to be considered – with a periodic review that reflects the benefit in relation to the risk and size of the population that is impacted.

Professionals, expert societies or clinical guideline committees, which can oversee evolution of signatures and their introduction into clinical practice, also have an important role to play. A process for EU-wide quality assurance systems for non-commercial diagnostics should be established.

**Solutions:**
- The EMA could convene a workshop on multi-marker signatures, to gather input from stakeholders (patients, academia, industry, regulators) as to what adequate assessment and regulation of these platforms should look like.
- European professional societies and regulators should discuss the potential for validation and quality assessments of signatures developed by academic groups, which are introduced into clinical practice.
- Member States should embark upon efforts to educate patients and healthcare professionals on the use, benefits and limitations of "omics" technologies in medicine.

## 2 - The use of electronic health record systems that facilitate clinical research, ease the collection and processing of real-world data and improve clinical practice

**Barriers:**
- A lack of integrated electronic patient health data systems, and defined inter-operability standards.
- Quality and validity of real-world data (RWD) to support regulatory submissions is often questioned by regulators and payers.

With the evolution of e-health records (eHR), healthcare systems are now able to electronically track patient data (diagnosis, treatment and outcomes) in an almost continuous way (RWD). Currently, RWD is considered different from clinical trial data and often deemed of a somewhat lower quality, as it is not subject to the same rigorous quality controls as data emerging from randomised clinical trials (RCT).

However, progress in informatics technology means that these two data approaches (RWD and RCT) are converging. It is possible to have a very high quality, audited eHR system, where data quality approaches that of randomised clinical trials. Thus, it is possible that in the near future there could be a single electronic clinical data source within a health system which would provide the "real-world" (and potentially "real-time") clinical data, but in a comprehensive and high-quality system that would make the data acceptable for regulatory purposes.

This convergence of eHR systems, RWD and RCT data platforms potentially has extremely significant implications for research, regulation and reimbursement. Currently, there is a separate collection of

overlapping data for different purposes (drug development and marketing authorisation, as opposed to reimbursement purposes) which could be substantially reduced because of this convergence. It is possible that new data generated in clinical trials could become part of the patients' eHR. For example, if multi-marker signatures are generated, these data might be captured in the eHR, so they would not need to be regenerated later. This would require significant new investments in expanded technical capabilities (genetic data handling, consent for the use of data, flagging clinical utility, genetic counselling, etc.).

This would allow new approaches to clinical trials (e.g. registry-based randomised clinical trials). Using an eHR, suitable patients could be identified, their consent randomised into appropriate treatment approaches within normal clinical care, and their trial data collected via normal clinical research practices. This could enable more patients to join clinical trials at a lower cost, and would result in quicker answers to clinical questions, thus contributing to better healthcare. The outlined approaches have the potential to be faster, less costly and more flexible – but they require investment in high-quality, validated eHR platforms within healthcare systems.

Such advances in clinical data collection would support adaptive pathways in regulatory approval. Furthermore, the ability to collect clinical data reliably in practice would also allow for both efficacy and safety data to be collected efficiently in support of post-marketing surveillance studies (i.e. pharmacovigilance).

This new approach to the collection of clinical data (RCT and RWD) would have a significant impact on reimbursement systems. The clinical value of medicinal products and diagnostics can be more readily tracked, as data on their utilisation, as well as other health resources and clinical outcomes, can be collected. Accordingly, innovative reimbursement models, such as pricing by indication or payment based on clinical outcomes, can be more easily implemented.

eHR systems can provide accurate and timely clinical information, allowing for the continued assessments of the benefit-risk balance and value of products in multiple, evolving, well-stratified patient populations. Gaining the most benefit from these systems will require the pooling and analysis of data across countries in order to collect enough data for the evaluation of less common sub-groups of patients. Such systems, therefore, need to be interoperable in the EU – this requires common data standards.

**Solutions:**

- Launch of an EU-wide clinical data project to define minimal standards and ensure inter-operability.
- The EMA should define quality standards for using electronic data from e-health records in post-marketing commitments (e. g. registry databases) and submissions of applications for marketing-authorisation.

## 3 - Data protection legislation that effectively facilitates the use of "big data" in healthcare research

**Barriers:**

- Regulations governing data privacy and informed consent have unintended, highly negative consequences for the use of electronic health records and "omic" data in clinical practice, clinical research, drug development and reimbursement.

The approach to "big data" in healthcare that is outlined in the previous section has large implications for patient consent and data privacy, and will require substantial educational efforts and discussions with stakeholders on the benefits, implications and limitations of such approaches to healthcare.

The European data protection and data consent frameworks must take into account the need to re-use and pool health data in order to allow its analysis for research, clinical care and reimbursement. This needs to occur on a European level to make the best use of these rich data sources, particularly as the application of personalised medicine defines smaller subgroups of patients using precisely identified diagnostic parameters. This has to be balanced with the need for data security, confidentiality and the individual's right to decide on the use of their data.

True anonymity is no longer a viable concept in the face of genomics and detailed clinical data, which implicitly identify an individual. Therefore, there is an urgent need to ensure data privacy and security measures that are appropriate for the genomic age. Educational initiatives and discussions with patients on the potential benefits, implications and limitations of these approaches for healthcare, and progress in health research, will be essential to move these types of initiatives forward.

Current requirements for informed consent lack flexibility and may restrict the re-use of data for further research. More consistent and flexible approaches should be sought. Furthermore, the concept of the "donation" of data to research should also be explored, with the goal to reduce the impact that withdrawn consent (or seeking consent from the family of deceased patients) has on current and future research projects. Dynamic consent platforms could serve a role and other forms of improved accountability to the providers of data should be considered, in cooperation with patients.

Given the need for healthcare systems, regulators, reimbursement agencies and payers as well as academia and industry to access such data, clear agreements are necessary regarding the acceptable use of data.

Finally, the complexity and interdependency of different data sources to provide personalised, data-driven healthcare requires improved collaboration between patients, academia, healthcare providers, regulators, payers and industry – all focused on solving the highlighted challenges.

**Solutions:**

- The European Commission should enter into a dialogue with all stakeholders about data privacy and informed consent issues to facilitate the use of electronic clinical records and "omics" data in healthcare and research, while balancing the rights and freedoms of the individual.