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# EBE
# White Paper on Personalised Medicine

EBE is a specialised group of European Federation of Pharmaceutical Industries and Associations, EFPIA

# Content

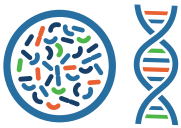
# Executive Summary

Personalised medicine aims to deliver the right medicine to the right patient at the right time.[1] It targets treatments to patients that are most likely to benefit from them, in contrast to the traditional "one size fits all" approach to medicine development and prescription. Personalised medicine leads to improved clinical outcomes and better quality of life for patients, and it offers tremendous potential savings to our struggling healthcare systems. But we are only at the beginning of this journey.

As EBE, the European trade association representing the voice of biopharmaceutical companies, we have developed this White Paper as a blueprint for transforming this promising future into a consistent medical reality for patients.

The White Paper describes the challenges in delivering personalised medicine, from the classification of disease, the need for greater investment in e-health and big data infrastructure, to calls for effective regulatory science and access mechanisms for the benefit of patients. We, at EBE, believe it is a top priority to establish data privacy and protection laws which effectively protect patients while at the same time making pan-European research initiatives possible. Likewise, appropriate regulation needs to ensure access to reliable methods for correct diagnosis.

Many of the components needed to make the personalised medicine approach a reality do not require a change in the law, so much as a change in mind-set. The implementation of personalised medicine requires an unprecedented level of collaboration between industry, patients, regulators, prescribers and payers to embrace innovation and support more flexibility in the way we develop, approve, prescribe and reimburse medicines. Together we must address the calls to action laid out in this White Paper to accelerate medical advancement in the EU and ensure sustainability in our healthcare systems whilst enhancing patient lives.



1 European Alliance for Personalised Medicine (2013) Report on Innovation and Patient Access to Personalised Medicine

# 1. The promise of personalised medicine

Personalised medicine[2] aims to deliver the right medicine to the right patient at the right time.

**TRADITIONAL MEDICINE often helps only 30 to 50% of patients.**

Personalised medicine is a therapeutic strategy that departs from the traditional "one-size-fits-all" approach. It is based on an increased understanding of the molecular mechanism of diseases, so we are now better able to sort patients into groups who benefit from a treatment. Personalised medicine starts to address the common observation that patients with apparently the same clinical diagnosis or symptoms often exhibit different responses to the same treatment. Therefore, personalised medicine has enormous potential to make treatments both more clinically and cost effective. This is especially the case in the area of complex diseases, such as cancer or inflammatory diseases, where even in the best examples a medicine often helps only 30-50% of patients given the treatment. By only treating those patients most likely to benefit, or identifying patients at higher risk of adverse reactions, personalised medicine also helps to reduce unnecessary safety risks. This improves safety and reduces the financial burden for health systems.

The ability to target therapies relies on patient characteristics called biomarkers, which are indicators of pathological processes or markers of response to a treatment. These are objectively measured biological traits, which can be of many different types e.g. genetic, levels of substances in blood, imaging.[3] A patient's biomarker status is determined with the aid of modern diagnostic tools, in particular with so-called companion diagnostic tests. These are used to identify patients who will either benefit from a specific medicine, or who may be at risk of particularly severe side effects. The ability to implement personalised treatment depends on three critical components: our understanding of the diseases and the significance of the biomarker, the accuracy and reliability of the associated diagnostic tool, and the targeted medicine.

Personalised medicine holds great promise. It offers the potential for more precise medical decisions. Thus, personalised medicine may help eliminate the trial-and-error inefficiencies which currently could undermine patient care and inflate healthcare costs.[4] Through personalised medicine, physicians can identify the patients who are most likely to benefit from a specific treatment, or those at high risk of severe side effects.

2 Also known as stratified medicine, personalised healthcare, precision medicine or targeted therapies.

3 WHO International Programme on Chemical Safety Biomarkers in Risk Assessment: Validity and Validation (2001) Retrieved from *http://www.inchem.org/documents/ehc/ehc/ehc222.htm*.

4 The Personalized Medicine Coalition (2014) The case for Personalized Medicine, 4th Ed.

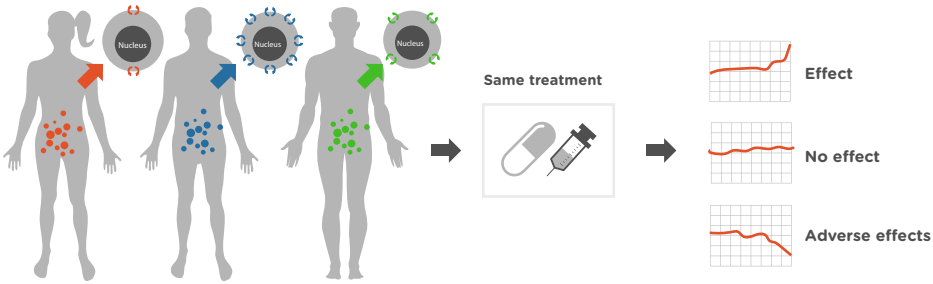
Targeted treatments aim to:

- Improve clinical outcomes and predictability;
- Avoid side effects caused by inappropriate treatment;
- Increase quality of life;
- Encourage patient compliance due to better results;
- Optimise use of healthcare resources.

Finally, it should not be forgotten that personalised medicine is also beneficial for Europe in terms of driving innovative science in both academic and industrial research centres, and in stimulating a healthy bio-pharma industrial sector for both medical therapies and diagnostics.

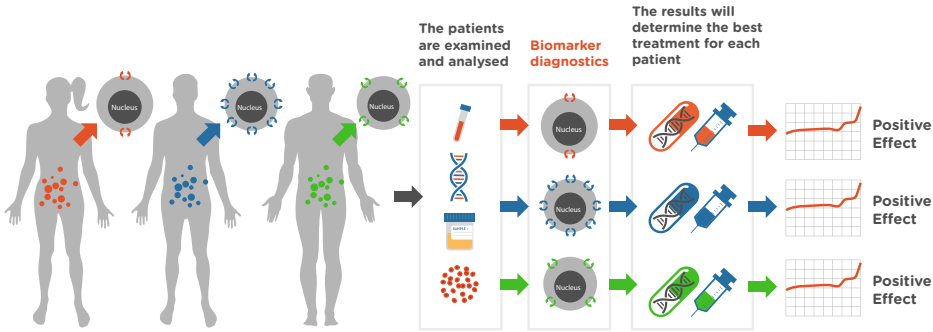
## TRADITIONAL MEDICINE: SAME TREATMENT FOR ALL

Cancer patients with e.g. colon cancer receive the same therapy even though they have different biomarkers




## INNOVATIVE MEDICINE: PERSONALISED MEDICINE

Cancer patients with e.g. colon cancer receive a personalised therapy based on their biomarkers



# 2. The challenges and needs to fulfil the promise of personalised medicine

Realising the promises of personalised medicine will require a paradigm shift on multiple levels. It includes modernising disease classification, modifying the conduct of clinical trials, instituting an appropriate framework for data privacy and protection, investing in bioinformatics infrastructure and expertise (including e-health records), establishing an infrastructure for companion diagnostic tests, adapting regulatory processes for personalised medicine, educating healthcare professionals and patients and ensuring that pricing and reimbursement structures are in place for both personalised medicines and associated tests. Only if those challenges are addressed will personalised medicine be able to deliver on its promise.

## a) New molecular understanding and classification of disease – the scientific basis of personalised medicine

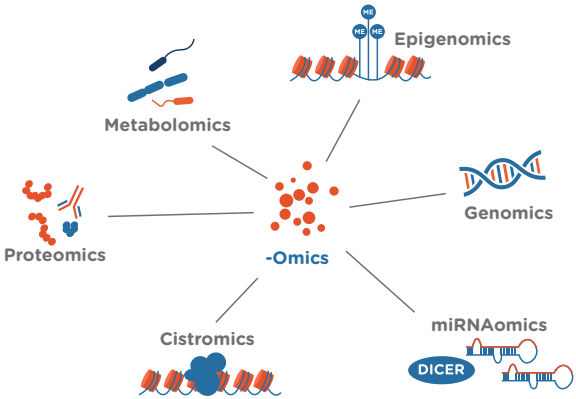
Historically, healthcare has been organised around organ- and system-based specialties that have, in turn, informed the classification of diseases. With the advances in science brought about by personalised medicine, these definitions of disease appear increasingly inadequate. For example, the diagnosis "breast cancer" merely describes the site of the disease, yet fails to address its molecular and genetic characteristics. There is not one breast cancer medicine which can effectively treat all patients; instead, classes of cancer medicines are tailored to specific underlying mechanisms and used to treat certain breast cancers, as well as other forms of cancer. It is clear that the situation is the same for many diseases such as diabetes, arthritis and schizophrenia, where there are many different causes of the same disease symptoms. Consequently, diagnosis of diseases needs to account for underlying characteristics or molecular markers in addition to the organ systems.[5]

**KEY MESSAGES:**

- Pan-European support for basic and translational medical research must continue to redefine the understanding and diagnosis of diseases at the molecular level and help identify biomarkers.
- The complexity of this endeavour demands collaboration across countries, and between academia and industry. Initiatives should be encouraged such as IMI, which catalyse the formation of consortia and provide some funding to address such endeavours.
- Undergraduate and postgraduate healthcare courses need to incorporate courses relevant to personalised medicine, e.g., genomic medicine and molecular diagnostics.
- The current healthcare workforce should be trained through suitable, continuous professional development programmes.
- Patients and the broader public are particularly important stakeholders and must be educated about personalised medicine.

5 National Academies Press (2011) Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease.

## b) Bioinformatics, e-health records, bio-banks and data sharing / protection - Essential resources for personalised medicine




Although 'omics' datasets have provided remarkable insights, it is by analysing, linking and comparing different large datasets (genomic, clinical outcomes, bio-banks, imaging etc.) that the greatest insights have been gained – so-called 'big data'. Continued progress in research and implementation of personalised medicine in national healthcare systems demand the collection, linkage and analysis of big datasets from patients in routine treatment and clinical trials. There will also be a continuing need for complex bioinformatics platforms and analytic expertise.

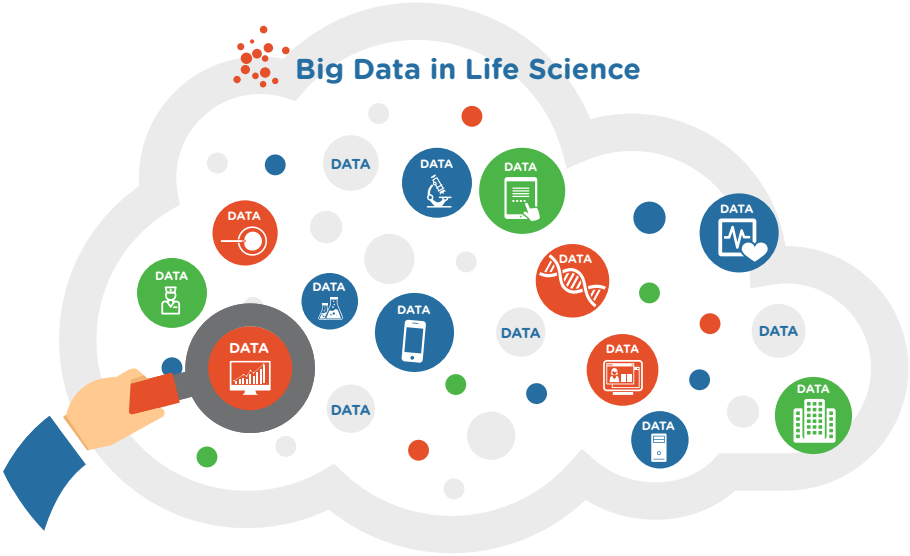
The existence of many bio-banks in individual academic institutions or at a national level represents a valuable resource for the EU. Research on personalised medicine is highly dependent on being able to look for potential biomarkers in tissue and blood samples from patients. As noted above, linkage of clinical data to bio-bank samples for the same patient is a particularly powerful approach. To facilitate progress in personalised medicine, collaboration between bio-banks (both within and across national borders) and linkage of bio-bank samples to clinical data should both be encouraged. Very often, new discoveries highlight potential biomarkers that were not known when patient consent had been originally given. The ability to conduct further research on such novel biomarkers in existing sample collections is important to maintain and accelerate progress in this area. Therefore, consistent research consent mechanisms to approve further research on existing bio-bank specimens should be implemented.

The quality of the preparation and storage of the samples in a bio-bank are critical. Standardised approaches and best practice-sharing between bio-banks are important in ensuring the high quality and reliability of research.

As highlighted earlier, many common diseases are now more accurately defined into smaller groups with similar underlying molecular defects. Therefore, the need to collect and analyse already existing clinical data / samples through different countries becomes a key issue. A single country will only have a limited number of patients with a given molecular diagnosis.

Given these challenges, in order to maximise patients' benefit and medical progress, pan-EU co-ordination for bio-banks, research consent and e-health records needs to be encouraged. The approach to e-health records should ensure consistent datasets are collected, with good quality, so

that they are compatible for analysis across countries. Patients' right to privacy and security must be guaranteed, but it is important that legislation around data protection does not unintentionally prevent the ability of medical research to gather and analyse patient data from several countries. Likewise, consent for research should be able to be broad enough to allow the pursuit of new research questions on existing datasets or samples without attempting to re-contact each and every patient. It is of paramount importance to strike a balance between protecting patients' rights to privacy while still allowing for research.




**KEY MESSAGES:**

- 'omics' generates large and complex datasets that require specialised bio-informatics platforms and expertise to implement and interpret them – increased investment in infrastructure and training is needed.
- It is a top priority to establish data privacy and protection laws which effectively protect patient privacy while simultaneously facilitating pan-European research initiatives.
- Consistent approaches to obtaining consent for further research on existing datasets and samples should be carefully considered, perhaps by closer co-ordination of national ethical approvals across the EU.
- If patients consent to the broad use of their data in clinical research, it should be possible to share anonymised protected data in a pan-European network without the need for re-consent each time.
- High-quality e-health record systems with consistent datasets and interoperability will be key to both continuing research and the implementation of personalised medicine in the EU.
- The EU has a rich resource of bio-banks – but standardisation in collection, preparation and storage of samples and the quality of the related clinical data is important to maintain high quality.
- Collaboration between bio-banks and improving research access to collections should be encouraged, together with increased efforts to link these bio-bank resources with clinical data.

## c) Improving speed and efficiency of clinical trials using personalised medicine

Currently, many clinical trials evaluate the efficacy and safety of a new medicine by analysing treatment effects in largely unselected (in terms of biomarkers) populations of patients. As a result, large trials are used to detect relatively small benefits. This approach to clinical trials is obviously inefficient, and is one of the factors for high failure rates in drug development. Such clinical trials may demonstrate no overall benefit of a drug, but 'miss' a substantial benefit for a small sub-group of patients within the trial. As noted in the introduction, even when these trials are successful, often only 30-50% of patients who are treated will benefit, and some patients will not gain any benefit but may still experience serious adverse events. Pre-selecting patients based on biomarkers, a personalised medicine approach, helps to identify those patients most likely to respond to the test treatment and allow for smaller, more targeted clinical trials.

However, difficulties can arise when biomarkers are identified retrospectively, after the conduct of a phase 3 clinical trial, or even after the approval of a medicine. In these cases, it is beneficial, if not essential, to be able to re-analyse the data in light of the newly discovered biomarker. The standardisation of approaches to consent and approval for additional and retrospective analyses (and use of tissue samples) would therefore be an important achievement. Clear regulatory guidance and pathways for using high quality retrospective bio-marker analyses to update product labelling would also facilitate the development of personalised medicine in Europe.

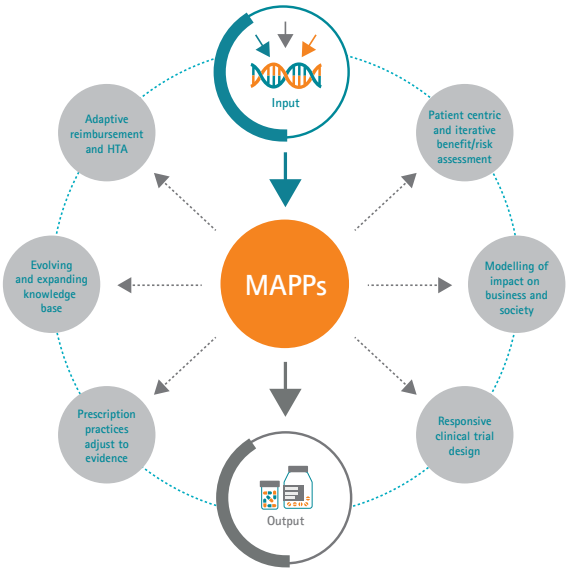
With genomic information becoming more routinely available for patients as part of standard clinical care, it should be possible to rapidly identify patients eligible for participating in trials of new treatments using electronic health information systems. As pointed out above, this requires consistent datasets and interoperability of e-health records across the EU, efficient and secure e-health data software / hardware and appropriately flexible privacy legislation to allow the health and research use of genomic, e-health and other clinical data.

**KEY MESSAGES:**

- Well-designed analysis of banked samples from previously conducted clinical trials, i.e. retrospective analyses of new biomarkers, should be accepted as a basis for regulatory submissions.
- Regulatory authorities should encourage and support more flexibility in alternative clinical trial designs and statistical analyses, including adaptive trial designs and greater use of observational studies. On-going discussions about adaptive licencing pathways are an opportunity to do this.
- Use of consistent datasets, interoperability of e-health record systems and appropriately flexible privacy legislation will be important to support future clinical trials and routine clinical care.

## d) Regulatory environment to encourage and sustain personalised medicine

**Medicines Adaptive Pathways to Patients***




There are several important differences between personalised medicine and traditional medicine development, not least because diagnostic tests need to identify patients with the required biomarker. The adaptive pathways approach[6] is potentially very suitable for personalised medicine therapies, as smaller, biomarker identifiable populations can be studied in smaller clinical studies and then used, after initial licensing approval, to identify patients for efficacy and safety surveillance in post-marketing surveillance. Once more, the collection of 'real world' data for ongoing efficacy and safety data analysis to support adaptive pathways has an important link with e-health records. The ability to efficiently collect high-quality, consistent e-health data would markedly simplify the task of on-going safety and efficacy monitoring for adaptive pathways.

To improve early patient access to personalised medicine, further development of adaptive pathways and the testing of these in pilot schemes should continue. Regulators should actively encourage the use of existing flexible licencing approaches – such as conditional marketing authorisation, accelerated assessment, marketing authorisations subject to conditions (such as post authorisation safety and efficacy studies)[7]. Biomarker driven 'orphan indications' in the orphan products regulation would be another potential approach that would be simple to implement.

6 "The concept of adaptive pathways foresees either an initial approval in a well-defined patient subgroup with a high medical need and subsequent widening of the indication to a larger patient population, or an early regulatory approval (e.g. conditional approval) which is prospectively planned, and where uncertainty is reduced through the collection of post-approval data on the medicine's use in patients." – European Medicines Agency, *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp (2015/03/02).*
**http://vitaltransformation.com/mapps/.*

7 European Science Foundation (2012) ESF Forward Look: Personalised medicine for the European citizen.

**KEY MESSAGES:**

- Adaptive pathway approaches are well suited to personalised medicine, and offer some opportunities for faster development of these products.
- 'Real world' data collection is a key aspect of adaptive pathways and could be far more efficient and become a routine part of clinical practice if consistent datasets and interoperable e-health record systems were available.
- Other incentives for personalised medicine should be developed, such as further guidance allowing biomarker defined orphan indications.
- As regulation of companion diagnostics evolves, there will need to be efficient co-ordination between the EMA and future diagnostics competent bodies, when therapies and diagnostics are co-developed.

## e) Developing diagnostic tests for personalised medicine – informing clinical decision making and patient care

An integral component in personalised medicine is the companion diagnostic test (CDx). Without accurate, reliable and timely diagnosis, the entire concept will fail.

In this context, the on-going revision of the regulatory framework for in-vitro diagnostics plays a key role (EBE position available at www.ebe-biopharma.eu). While a final text has yet (September 2015) to be negotiated between Commission, Parliament and Council, the proposed text constitutes a big step forward for personalised medicine by explicitly addressing CDx. It places them in risk class C – the second-highest category – and thus requires that manufacturers provide evidence that their CDx are able to meet the claims on the label, meaning that they appropriately select patients for targeted treatment with a medicine. The draft text also suggests a certain amount of coordination between the medicine regulatory authority and the bodies involved in certifying CDx. As long as this is organised in a clearly defined, efficient manner that does not unduly delay patient access to novel treatments, this is another step towards an environment to foster personalised medicine.

However, there is currently a gap where laboratories develop their own solutions to replace a CDx that has been certified by the regulatory process; these lab-developed 'in-house tests' are not regulated and therefore not subjected to the same kind of scrutiny as a commercial test. While innovation must not be stifled, adequate external control should be put in place to ensure that if a lab decides to replace an available, validated and certified CDx with a different procedure, this procedure delivers results that are no less reliable than the available CDx. Otherwise, patients may not receive the correct treatment.

The area of medical technology is evolving rapidly. This is both due to breakthroughs in molecular biology, and because new innovative technology platforms for tests are emerging, such as Next Generation Sequencing, which allows for the simultaneous analysis of many genetic biomarkers. This means that the 'one test-one medicine' paradigm is changing, and multiple markers (sometimes referred to as 'signatures') will determine how and when medicines are used. Regulating and reimbursing multiple test panels will increase the challenges posed by the diagnostic component of personalised medicine. It is also worth considering that with the rapid expansion of clinical, 'omics'

and e-health data there are efforts to integrate these datasets to provide clinical decision support to healthcare professionals. While not strictly 'diagnostics', this type of bio-informatics systems will increasingly guide clinical decision making and treatment pathways for patients. Developing, implementing and assessing the effectiveness of such systems will raise new challenges for regulators, payers and healthcare systems. Education of patients and healthcare professionals in this area of bio-informatics and decision support will be required.

To add further complexity: the ongoing process of innovation in this area will place increasing demands on labs carrying out such tests. Not only will they need to be equipped with modern diagnostic tools that deliver timely results; personnel must also be trained to carry out the tests and interpret the results.

On a last note, the market for diagnostics is characterised by weak protection of innovation. Appropriate incentives are needed to encourage development and marketing of CDx.

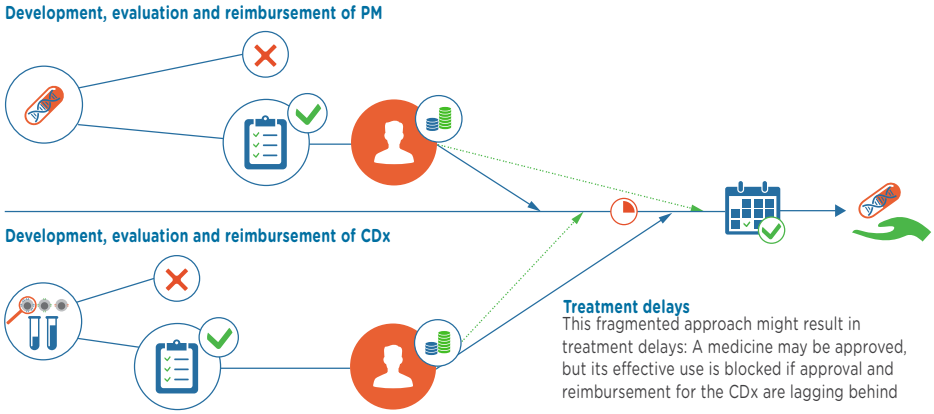
**KEY MESSAGES:**

- An adequate regulatory framework needs to guarantee the quality and reliability of test results, irrespective of who manufactures them.
- This framework must be able to handle panels which test for numerous biomarkers at once, ensuring their reliability and accuracy.
- A discussion about incentives for developing CDx should take place.
- Clinical decision support systems, based on the information in the large datasets related to personalised medicine, will likely play an increasing role in delivering personalised medicine. Developing, implementing and assessing such systems will require new approaches.

## f) Health technology assessment, pricing and reimbursement – an integrated approach for personalised medicine

Evaluating and comparing the value of new treatment options plays a crucial role in optimising healthcare spending. Current approaches used by Health Technology Assessment (HTA) bodies are generally not adequate to capture the true benefits offered by personalised medicines with companion diagnostic tests as a 'combined technology' – such as the benefits of non-treatment and an improved benefit-risk ratio for those treated.[8] These aspects should be reflected and rewarded, on par with the direct improvements they yield for patient care.

The current HTA framework in Europe considers medicines and companion diagnostic tests under separate evaluation and reimbursement processes. This fragmented approach might result in treatment delays; a medicine may be approved, but its effective use is blocked if approval and reimbursement for the companion diagnostic test are lagging behind. The existing reimbursement paradigm attributes value to medicines rather than diagnostics. Historically, diagnostic tests, e.g., blood cholesterol tests, were relatively simple, and the reimbursement system was based on a cost recovery basis. However, biomarker-based CDx are complex, and their future regulation is likely to require a level of evidence for CDx that goes beyond that of other tests of the same risk class. This extended evidence implies a higher value within the healthcare setting. By selecting patients for appropriate treatment with a medicine, CDx help save unnecessary healthcare expenses; their value must thus be considered in the context of the prescribed medicine. At present, uncertainties regarding reimbursement discourage investment into research and development by diagnostic companies, with most investment into CDx being funded by the company developing the medicine.




8 This is a key learning from the recently published Escher report - *http://escher.tipharma.com/fileadmin/media-archive/escher/Reports/Escher_report_IA.pdf* (2015/02/19).

Targeted medicines are frequently developed for multiple indications with common underlying biological mechanisms, e.g. different forms of cancer that share a genetic mutation. However, the value of the medicine can vary by therapeutic area – for example, a certain biomarker may occur more frequently in breast cancer than in stomach cancer. Today, the price of a medicine is usually the same across indications. Pricing that varies by indication would allow the value of a medicine to be better defined, improve patient access, and set incentives for patient-relevant innovation. Once again, effective and consistent e-health record systems would be essential in implementing such value-based reimbursement approaches.

**KEY MESSAGES:**

- To realise the true value of personalised medicine, the benefit to patient care both in terms of clinical and economic value to health systems must be consistently factored into pricing and reimbursement decisions, using robust methodology that is consistent across the EU. Projects like EUNetHTA should continue to be encouraged and funded.
- Timely and co-ordinated advice from regulators and payers should be easily available to companies.
- HTA processes within a country should result in a coordinated assessment of the medicine and the companion diagnostic test to ensure that patients have timely access to treatment.
- Approaches to value based pricing - both pricing by indication and outcomes-based payment need to be developed in collaboration between payers, industry and health systems. Implementing such approaches will require consistent and interoperable e-health data systems.

## g) Partnership and collaboration between stakeholders in the healthcare system

Because of the high level of complexity, implementing and progressing personalised medicine requires an unprecedented level of collaboration between the numerous stakeholders in the healthcare system. Effective public – private partnership will be an essential part of this collaborative approach.

Most molecular causes of diseases are not simply a single dysfunctional process in the cell, but often combinations of different defects that lead to diseases such as cancer, leukaemia, diabetes and inflammatory diseases. This understanding implies that the long-term treatment or cure of these diseases might require combinations of targeted therapies. This means that different pharmaceutical companies, academic groups and regulators will need to be able to work together on combinations of these agents in clinical trials.

The fact that personalised medicine can more accurately define molecular subtypes of diseases – leading to smaller sub-groups of patients with a specific molecular diagnosis – implies that to find the patients with the appropriate biomarkers for a clinical study, collaboration across many hospitals and even across countries is required. Working with these smaller sub-groups of patients raises challenges comparable to those of orphan diseases, where the traditional model of industry-sponsored clinical studies is often difficult to implement. Instead, collaboration with academic and patient groups will be necessary to identify suitable patients. E-health records would also help to identify patients with rare biomarkers more effectively for the recruitment to clinical trials.

Adaptive pathways, as discussed in a prior section, will require more real-world data collection to monitor efficacy and safety. This will require collaboration between regulators, industry, payers and hospitals to ensure that accurate and timely data are collected and available to all parties. Similarly, value based pricing, where a differential value may be given to different indications of use for a medicine and payment may be based on outcomes, will require consistent and interoperable e-health data systems to allow indication and outcome data to be reliably collected from clinical practice. Industry, payers and hospitals will need to collaborate to enable this significant change in medicine reimbursement.

**KEY MESSAGES:**

- Personalised medicine requires a more collaborative approach between industry, academia, patients, regulators, payers and health care systems. Incentives to encourage this approach, like IMI, should be continued and expanded.
- Effective personalised medicine for many diseases could require combinations of targeted therapies. Collaborative frameworks for clinical research between companies, academia and regulators should be developed to incentivise these interactions.
- E-health data will be critical to many aspects of developing personalised medicine: finding patients with the required biomarker for trials, monitoring efficacy and safety of targeted therapies that are marketed under adaptive licences, establishing the indication that a medicine is used for reimbursement by indication, paying for performance type agreements. Thus, collaboration across many parties will be required to ensure that e-health record systems are fit for all these purposes.

Personalised medicine requires a more collaborative approach between industry, academia, patients, prescribers, regulators, payers and health care systems.

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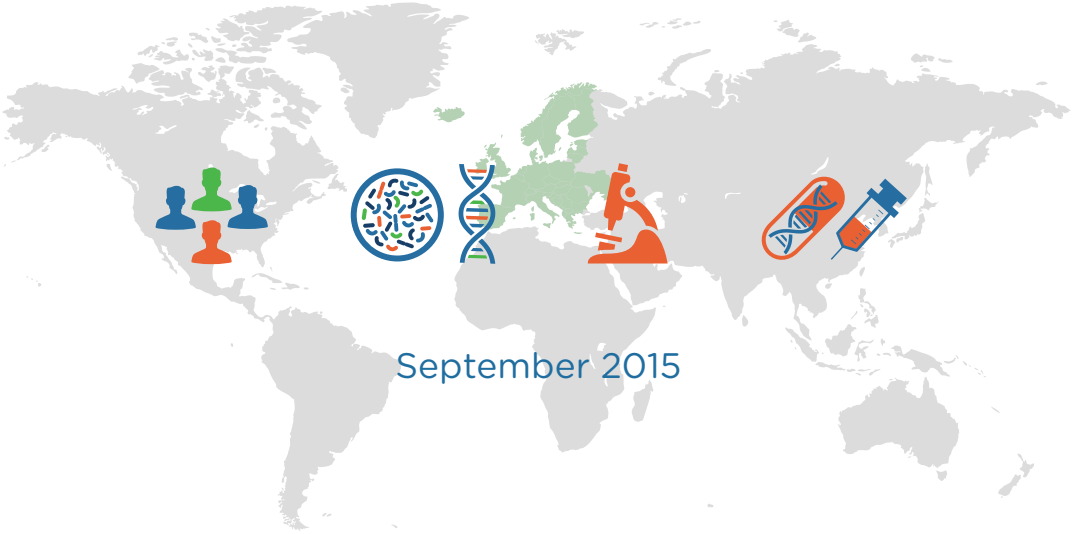

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