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An Index of Barriers for the Implementation of Personalised Medicine and Pharmacogenomics in Europe

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Key Words

Europe · European Alliance for Personalised Medicine · Implementation · Index of barriers · Literature review · PerMed project · Personalised medicine · Pharmacogenomics · Stakeholders · Translation

Abstract

Background: Personalised medicine (PM) is an innovative way to produce better patient outcomes by using an individualised or stratified approach to disease and treatment rather than a collective treatment approach for patients. Despite its tangible advantages, the complex process to translate PM into the member states and European healthcare systems has delayed its uptake. The aim of this study is to identify relevant barriers represented by an index to summarise challenging areas for the implementation of PM in Europe. ***Methods:*** A systematic literature review was conducted, and a gaps-and-needs assessment together with a strengths-weaknesses-opportunities-and-threats analysis were applied to review strategic reports and conduct interviews with key stakeholders. Furthermore, surveys were sent out to representatives of stakeholder groups. The index was constructed based on the priorisation of relevant factors by stakeholders. ***Results:*** A need for stakeholder-agreed standards at all levels of implementation of PM exists, from validating biomarkers to definitions of 'informed consent'. The barriers to implement PM are identified in 7 areas, namely, stakeholder involvement, standardisation, interoperable infrastructure, European-level policy making, funding, data and research, and healthcare systems. ***Conclusions:*** Challenges in the above-mentioned areas can and must be successfully tackled if we are to create a healthier Europe through PM. In order to create an environment in which PM can thrive for the patients' best outcomes, there is an urgent need for systematic actions to remove as many barriers as possible.

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Preventive Rather than Reactive Healthcare

The emphasis in modern healthcare has shifted significantly in recent years. Prevention has become one of the hallmarks of healthcare, resulting in preventive rather than reactive healthcare [1–3]. This approach translates into primary prevention of disease, allowing a more accurate diagnosis and specific treatment but also preventing negative individual patient outcomes (e.g. adverse drug reactions) [4]. More attention is paid by pharmaceutical companies as well as healthcare policy makers to combine each person's unique clinical, molecular, and environmental information to adjust healthcare to the specific biology of a patient [2, 5]. Focussing on these individual patient outcomes results in more effective healthcare and greater precision, increasing the quality of care and decreasing healthcare costs [1, 6, 7]. The individualisation of healthcare delivery should be approached by personalised medicine (PM) methodology. PM is defined as a targeted approach to the prevention, diagnosis and treatment of disease based on an individual's specific profile [8].

One of the most common examples of PM is introducing genomics in healthcare, especially as pharmacogenomics (PGx). In PGx the focus is on the predictive outcome of drug interventions [9]. PGx are often companion diagnostics (CDx) for treatment: a molecular assay that, for instance, measures specific mutations to stratify subpopulations, select appropriate medication and tailor dosages to a patient's specific needs [7]. PGx have the potential to change healthcare significantly, since differences between patients' responses to treatment can be partially explained by the genotype (drug metabolism, transport and sensitivity) [10]. Using PGx can result in individualised and, consequently, sustainable healthcare, since PGx can increase an effective and safer use of drugs, decreasing costs resulting from drug toxicity and lack of efficacy by identifying patients with the highest probability of therapeutic efficacy [11–14].

CDx will enable PGx to make use of genomic biomarkers: 'a measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes and/or response to therapeutic or other interventions' [9]. The identification of biomarkers has significance for individualised intervention regimens, but the process of biomarker discovery, validation and clinical qualification is slow [15, 16]. The full advantages and the potential of PM can only be achieved when it is used in clinical decision making in an informational, structured framework, but the discrepancy between the ability to sequence a genome and to identify a small amount of relevant genes for translation into clinical practice is a major bottleneck [17–19].

The translation of biomarker research into clinical practice is also challenging, since it affects various areas of healthcare. It involves a wide range of stakeholders and entails tackling numerous barriers for implementation [4, 6, 10, 13, 20]. In order to integrate PM in clinical practice, these barriers must be lifted [1, 2]. Therefore, we must be able to identify existing barriers in Europe. Currently, the uptake of PM in Europe is stagnant, despite its increasingly abundant benefits [4].

To assess the most relevant barriers, an index will be developed. Different sources and viewpoints will be combined in a systematic literature review, strategic reports analysis, and a stakeholder analysis (surveys and interviews) across several European countries (fig. 1). This index will target patient access to PM and will focus on testing rather than disease prevention, as currently most developments warrant guidelines in the field of PM tests and treatment [15, 21, 22].

Literature Review of Barriers in PM Implementation

Methods

A systematic literature review was undertaken to develop an overview to contextualise the known barriers of access to PM; PubMed, Web of Science and Medline were searched. Search terms were based on terminology used by e.g. the European Alliance for Personalised Medicine and the authors' own experiences in the field and focussed on (synonyms of): 'barriers' and 'personalised medicine' combined with 'care', 'treatment', 'Europe', 'patient', 'ethics', 'biological', 'clinical', 'public health', 'regulatory', 'legislation', and 'commercial'. Only documents in English were included in the review.

Specific attention was given to European strategic reports in the context of a gaps-and-needs assessment and strengths, weaknesses, opportunities and threats (SWOT) analysis from the FP7-project PerMed [23]. The aim of gathering these results is to identify relevant fields, organisations, current initiatives, policies, and capacities related to PM, based on an inventory and synthesis of existing relevant information [24]. The data from PerMed were combined with the results from the review of scientific literature, since it offers a broader scope on the knowledge available. Furthermore, PerMed constitutes a network of national funding bodies and governments at the European level not only adding to the viewpoints in this research, but also ensuring impact on future strategic research approaches.

'Gaps' were defined as flaws in the status quo acting as barriers to PM, and 'needs' were considered to be the necessary initiatives to be able to bridge the gaps. A SWOT analysis identifies the factors that shape PM and its enabling characteristics. For the SWOT analysis, the following 4 factors were considered in the reports: (1) helpful to achieve objective, (2) harmful to achieve objective, (3) internal attributes, and (4) external attributes. The relations between these factors are summarised in figure 2.

Results

The systematic literature review resulted in 1,543 articles, which were filtered for reviews. Relevance was assessed based on the title and abstract, resulting in 81 articles that were included in the review. The search for strategic reports resulted in 17 papers, gathered from relevant European partners and initiatives in the PerMed network [24]. The strategic reports were assessed on the reported gaps-and-needs and analysed for SWOT aspects. The assessment and analysis resulted in an extensive list of gaps-and-needs (185 in total) and information on the SWOT aspects (146 in total) [23].

Striving for PM for patients with the help of healthcare professionals would bring about benefits: better individual patient outcomes, resulting in higher-quality healthcare, and a decrease in costs [3, 6, 7, 16]. To gain these benefits, the chain leading from research to PM care and treatment needs to overcome barriers. The barriers identified from the analysis were categorised and discussed from (1) scientific, (2) operational, (3) economic, and (4) European levels, as is shown in table 1.

Scientific Level

On a scientific level, barriers exist, since molecular data is complex to translate into information for clinical practice, for example, because of the heterogeneity of disease subtypes [25, 26]. In order to provide the information for a valuable implementation of CDx needed in clinical practice, researchers have to attempt to model and understand multiple, interacting and potentially conflicting predictors of risk by integrating several sources of health data [10, 13, 26, 27]. This data is structured in informational models, not only including information on biomarkers and CDx, but also other -omics profiles, clinical data, lifestyle and environmental data [5, 7, 10, 19, 28].

Within these models, CDx can be linked to therapeutics, but on research level, the drug-development process of therapeutics and CDx is not optimised, since several obstacles exist for pharmaceutical and biotechnological companies to develop them simultaneously [7, 29]. Examples that hamper the rapid development of relevant biomarkers are complex regulatory processes for coupled diagnostics, differences in business models, company cultures, and other organisational aspects [5–7, 10, 14, 30–32].

In summary, a lack of consistent evidence exists, which results in clinical uncertainty, for instance, by inadequate validation of biomarkers and inadequate evidence of clinical utility. Development strategies have to be adjusted to clinical needs, to decrease the difficulty to capture the full value of a test generated for clinical practice [2, 6, 16, 33–39]. For clinical practice a biomarker test is useful when it provides reliable, actionable and predictive information to imply an alternative drug or drug-dosage regimen

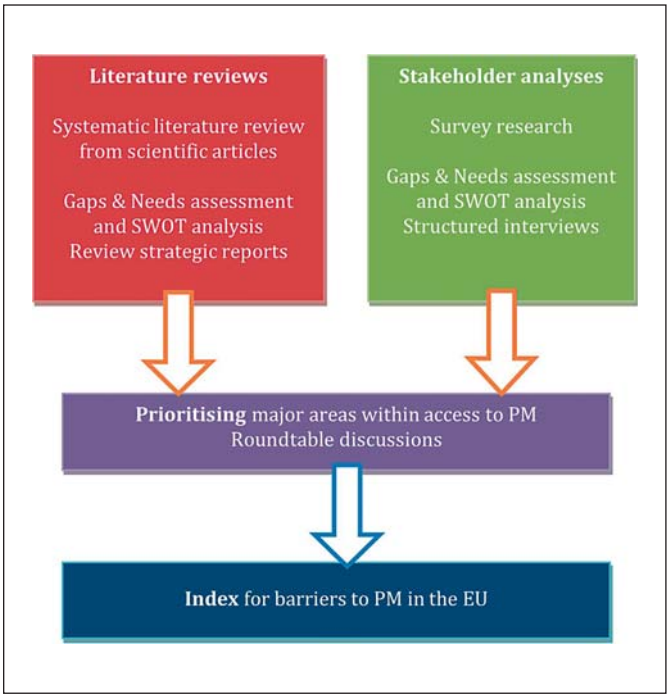

Fig. 1. Summary of research methods to develop the index with barriers in access to PM in Europe.

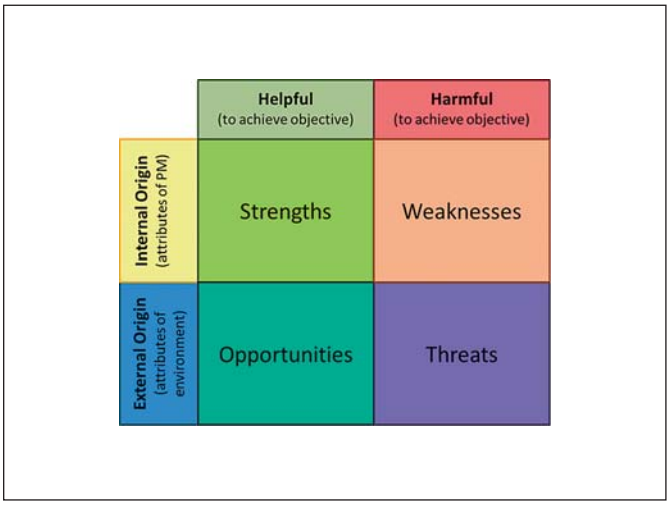

Fig. 2. Rationale behind the SWOT analysis [23].

Table 1. List of summary points from the literature review concerning PM and biomarker testing for CDx, grouped by sections within the levels

Level	Section	Summary points
Scientific	Systems biology and data	Integrated analyses, health data, biomarkers, informational structured model, drug development process, HTA framework
	Research	Different regulatory processes; business models; company cultures; clinical relevant information, CER, EMR; informed consent; interoperability
	Clinical study design	Standards, methodologies, harmonisation; guidelines
Operational	Information delivery	CDS, infrastructure, limited resources, databases, secure environment, turnaround time tests
	Education and training	Healthcare professionals, lack of knowledge, interpretation, sense of competence, communication, multidisciplinary team training, curricula medical schools
	Inform, educate, empower patients	Low awareness, health literacy, privacy regulations, reduce concerns
	Regulations	Guidelines, lack of consensus, outdated, adherence, standards for practice, clinical study design, infrastructure of biobanking, ethical and legal issues, automated CDS
Economic	Reimbursement	Lack of evidence, incentives, streamline, market-based approaches, HTA, approval process
European	Biobanks	Lack of standardisation, international interoperability, regulatory procedures, infrastructure, management, cost investment, EU-funding procedures
	Translation	Cross-border data collection and sharing, HTA framework
	Reimbursement	Reimbursement models, national healthcare systems, exchanging information, timely access (patients), market access
	Legal and ethical	Sharing confidential data, EU directive, legal framework tests and treatments, privacy, IP, researchers' accessibility, different legislations, ethics

CER = Comparative effectiveness research; EMR = electronic medical record.

based on health data in a cost-effective way, as summarized in health technology assessment (HTA) approaches [4, 12, 16, 35, 38, 40–43].

A clinical study design facilitating relevant information gathering for clinical practice is the comparative effectiveness research [2, 7, 44]. This research comprises a direct comparison between 2 approaches of care and their effectiveness in real-world settings, integrates biomarker studies into traditional care, and increases the number of participants in data collection [19]. A new approach to research, however, also implies new approaches to informed consent, data collection and storage, for instance, operating with electronic medical records [19, 37]. These new approaches will need to ensure uniform testing of parameters (including HTA factors), which calls for multidisciplinary guidelines on methodologies [2, 4, 13, 19, 20, 25, 43].

Operational Level

Not only the operational level within science needs progression to adjust to the PM approach, also other operational levels concerning the translation of PM into healthcare will need to be addressed, i.e. information delivery, education and training, empowering patients, and regulations (table 1).

Healthcare professionals should be supported by tailored information delivery. An option to facilitate such information delivery is the development of clinical decision support systems (CDSs). Automated CDSs address the lack of infrastructure for delivering treatment and care information and should include genomic and non-genomic health data in order to combine genotypes and standard clinical parameters in an interactive informatics portal, including electronic medical records [18, 25, 27, 30, 42]. Healthcare professionals can catch up with latest

scientific findings by continuous dissemination of study results on relevant biomarkers and incorporate risk assessment within disease prognosis and treatment prescription, while preventing an information overload [3, 44, 45]. The information delivery should also be in a timely fashion, i.e. the turnaround time for a biomarker test should be less than the time to make a decision about the course of treatment [10, 40, 41].

Developing and implementing such a system poses a great challenge, since healthcare has limited resources available for implementation, maintenance and sustainability [46]. Furthermore, including large patient information databases with electronic medical records requires complex infrastructure developments in a real-time and secure environment [19, 31, 47, 48].

Amongst healthcare professionals, overcoming the barrier of lack of knowledge and awareness about CDx would enhance the implementation of PM tests in clinical practice and help to realise the benefits of CDx [2, 5, 10, 11, 14, 17, 19, 30, 34, 35, 41, 42]. Education will need to be provided to healthcare professionals, so increasing their ability and sense of competence in interpreting PM tests and in communicating the results to the patient, since the current lack of knowledge and awareness results in uncertainty about how to interpret a biomarker test or in under-appreciation of the therapeutic benefit [4, 10, 19, 34, 49–52]. More awareness and knowledge can be gained by supporting healthcare professionals with the above-mentioned CDS but can also be aided by labelling drugs with relevant biomarkers, as already is the case for 121 pharmaceuticals by the Food and Drug Administration in the US [36, 38, 53, 54].

Next-generation healthcare professionals will also need to be educated according to an updated curriculum incorporating PM [1, 3, 12, 25, 55, 56]. The role of information delivery to patients is not limited to medical doctors but includes also practice nurses and pharmacists, so the education for several healthcare professions will need to incorporate PM using CDx [57–59]. Furthermore, it is important to incorporate education on PM tests in core medical education, since it also imposes challenging ethical implications [5]. Besides education, healthcare professionals should be aware of (genetic) counsellors and their expertise regarding genetic information, and multidisciplinary team training is suggested [4, 25, 39, 60].

Not only healthcare professionals, but certainly the public and patients have low awareness of the value and integration of biomarkers [2, 3, 38, 53]. In summary, health literacy needs to be increased by clear communication channels to adjust the public's expectations and information about biomarkers (including genomic assays). Besides the utility of CDx, concerns on privacy regulations and genetic discrimination that exist among the public should be reduced [3, 25, 61–65]. Within the communication to patients, the legislation for privacy concerning genomic information has to be stated clearly [2]. Attention should be paid to the relation between the social economic status and health literacy, alongside genomic factors that are specific to minorities and/or could be misused for discrimination between societies [5, 25].

In order to provide clear communication to the public and other stakeholders involved, several aspects were named that should be standardised and harmonised at regulatory level (table 1):

(1) infrastructure of biobanking (e.g. clinical study design, accessibility of researchers to data, and intellectual property) [2, 19, 41, 45, 66],

(2) legal and ethical issues (e.g. informed consent, reimbursement, data safety) [30, 38, 41, 45, 57], and

(3) automated CDS (e.g. dosing guidelines, interpretations resulting from testing) [2, 13, 19].

Barriers exist in part due to the lack of adequate application of current regulations but also because of a lack of consensus in guidelines on interpretation and use of PM tests [5, 35]. Drug administration authorities should update regulatory guidelines with several stakeholders involved in partnerships to provide guidance, clarity and predictability to research and clinical practice, and these should be enforced to increase adherence to guidelines [4, 6, 7, 19, 27, 67–69].

Economic Level

Besides the concerns raised on scientific and operational levels, barriers on the economic level are also entangled in the process from research to the implementation of PM. Currently, insurance companies are reluctant to reimburse biomarker tests and treatment because of the lack of evidence and incentives. As a consequence, reimbursement is nonexistent or insufficient, while it is stated that changing the reimbursement environment could be the most direct way to generate the desired evidence of effectiveness in biomarker research [2, 6, 7, 17, 36, 70].

Biomarker research should support HTA evidence needed for a streamlined reimbursement process by using a market-based approach. An HTA framework can separate useful from ambiguous CDx and support PM to reach patients in an equitable and transparent fashion [19, 30, 34, 57, 60, 71, 72].

European Level

As discussed above, barriers exist at the levels of science, operation and economics. These barriers are highly relevant at the European level. Europe has fragmented regulation and approval authorities, which poses problems in bridging the barriers mentioned above [73, 74]. Moreover, realising the promise of cost savings under the PM approach will first require investments at the European level, which is perceived as a considerable barrier [73].

Essentially, coordination and cooperation across Europe is needed on (1) biobanks, (2) translation, (3) reimbursement, and (4) legal and ethical issues (table 1). Several initiatives exist to overcome the gaps in a comprehensive inventory of biobanks and disease registries in Europe, e.g. by the European Medicines Agency, and the European Commission [73, 75]. Besides the general issues illustrated on scientific, operational and economic levels, barriers to harmonisation exist in Europe. Different national governments are involved facilitating healthcare to their citizens. This calls for international interoperability, e.g. managing data safety, standardised data collection, international trials, and European funding procedures [74, 76, 77].

Besides differences in the regulations on data collection, the evaluation and translation of biomarker research data varies in Europe across countries [73, 74]. Currently, different methodologies for HTA are used, and appropriate methods concerning comparators should be stated clearly across Europe [3, 74, 76]. Exchanging information between countries can support decision making on reimbursement across borders and ensure timely access for patients to effective PM treatment [3, 74, 76].

There are clear regulations for pharmaceuticals in the EU; however, there appears to be a lack of a framework for CDx [75]. A partial explanation can be found in the fact that pharmaceuticals and CDx fall under different legislation. These concerns are currently addressed by the European Federation of Pharmaceutical Industries and Associations and the European Medicines Agency [73, 75]. Legislation for medicines, diagnostic regulations, data protection, informed consent, specimens use, and medical devices need to be harmonised and must take into account international coherence, since European citizens and data move across borders [45, 77–79].

In short, harmonising data in biobanks together with the international interoperability between biobanks can aid research and translation towards effective PM. Such biobanks will offer standardised information on biomarkers for CDx, and by this contribute to the evidence base for HTA. This information will provide input for CDS for healthcare professionals and reimbursement across Europe, within legal frameworks, and will enable a patient-centered and timely implementation of PM.

Stakeholder's Views on Barriers in PM Implementation

Methods

Stakeholders were asked about their views on barriers in PM implementation via an online survey and structured interviews. The involved stakeholder groups represented basic science, translational research, the regulatory field, health systems, and patient perspectives.

The data for the online survey was collected by the European Alliance for Personalised Medicine between January and March 2014. Each survey was divided into sections, partially identical among groups and partially tailored to the stakeholder group. In the invitation e-mail, stakeholders received information about the study and the survey was briefly outlined, thus, fully informing the stakeholders.

Each survey consisted of close-ended questions to ensure comparability among the responses. For example, a section on general information included questions about current healthcare applications to facilitate PM. Other sections focussed on cross-border initiatives (e.g. if they are supported by the government). In summary, a range of variables was included to achieve a nuanced exploration of possible barriers.

Thirty-five structured interviews were conducted in February and March 2014 within the PerMed project [23]. Interviewees were selected from the stakeholder groups. Each interview took a maximum of 30 min, and several interviewers carried out the interviews. To ensure comparability, the interviewers were informed beforehand and received an interview guide.

Interviews were conducted and analysed according to statements on gaps-and-needs and SWOT factors. Within each group, statements were coded according to the level of stakeholder they represented. The coding was not limited to one viewpoint per statement; when stakeholders from different viewpoints made the same statement about a gap, need or SWOT factor, this statement was coded for multiple viewpoints.

Results

Surveys

The survey results showed that the majority of respondents were aware of the term PM. The definition differed somewhat; respondents from basic science (90%), translational research (90%), regulatory field (81%), and patient groups (73%) viewed PM as individualised care. Overall, respondents from health systems also defined PM as individualised care; however, specifically oncologists viewed it as a stratification of a certain subpopulation (50%). Looking at the current state of PM in healthcare, applications

are still in the test phase, such as ICT tools focussing on DNA sequencing, bioinformatics and statistical analyses.

Stakeholders were not sure if biobanks were used in their region, while they stated that their government predominantly does support sharing of anonymous data. However, current research activities do not focus on precompetitive biomarker research, since incentives for a PM approach to research were considered unavailable or limited.

This lack of streamlined research into PM also translates into the availability of PM in healthcare. Respondents from translational research and the regulatory field viewed PM to have limited availability in healthcare. Eighty percent of the general healthcare providers answered that there are no programmes in place for PM in healthcare, and also the majority of patient representatives agreed to this statement. If PM programmes were in place, patient representatives considered them to be in oncology.

Besides the limited availability of PM in healthcare, the state of best practice guidelines at different stakeholder levels also posed striking differences. Two-thirds of the respondents were not aware of any best practice guidelines. In the field of oncology, most healthcare professionals were aware of best practice guidelines.

Even though programmes to stimulate the application of PM are currently considered unavailable, responses from 'translational research' and 'regulatory field' showed that (national) ethics committees to evaluate molecular tests are in place, and new legal and/or regulatory frameworks are under preparation. These ideas found resonance in responses from 'healthcare', where plans to promote PM were considered to be at the horizon. Amongst patient representatives, the expectations were more divided; half of them thought PM will eventually be available, while half disagreed. Overall, respondents from patient groups were not sure whether health insurance covered PM, but felt it would boost its application. In 'basic science' and 'translational research', a boost is more expected from tools to share data according to centralised guidelines and legislation.

It may be expected, when the availability of best practice guidelines is increased, PM will develop at a higher pace. Only patients' representatives considered healthcare professionals to be not well equipped to implement PM applications. Respondents from translational research, the regulatory field and healthcare itself deemed healthcare professionals to be well equipped to implement PM applications.

Interviews – Gaps and Needs

In the interviews, a gaps-and-needs assessment and a SWOT analysis were conducted. The analysis of the interviews resulted in the identification of 63 gaps and 91 needs. Furthermore, 71 strengths, 73 weaknesses, 79 opportunities, and 73 threats were determined [23].

From the patient perspective, patients should be empowered, and it is advisable to look at complementary issues in stakeholder agendas. Early involvement of patient representatives, to allocate funding to their unmet needs and to ensure access to their own data are essential aspects to be tackled.

Basic science is too far apart from PM, limiting the evidence needed to implement PM. Long-term policies in order to integrate -omics will need to be developed to overcome this gap. A large part of preclinical trials is conducted in a commercial setting, hampering transparent knowledge transfer between basic research amongst companies and towards clinical research. More feedback should be communicated back and forth in order to close the circle of research and plan improvements.

Translational research should be more aware of multistakeholder needs and incorporate stakeholders in interdisciplinary research and translation centres (e.g. centres of excellence). The focus should be on sharing interpretations and knowledge management, for example, training healthcare professional in IT and interpretation, instead of focussing only on sharing data in research. New research should be conducted to improve clinical decisions, incorporating suggestions of different stakeholders into an implementation plan.

Regulatory speaking, approval of CDx should become a formal part of drug-approval regulations, so processes direct towards generating evidence to link specific tests and treatment outcomes, including regulation and legislation necessary to facilitate safe data storage and data ownership. These data will need to be shared, to sustain studies and ensure feasible and efficient studies that apply to daily practice and that use harmonised methodology for small populations.

The way healthcare decision making and healthcare delivery is currently facilitated should be reconsidered to allow a more effective, efficient and timely translation from science to healthcare. The inclusion of PM in the education of healthcare professionals is vital, and more refined information systems are required to support them in translating PM to their patients, hence increasing health literacy. Funding should be allocated to unsolved ethical and legal issues as well as developing an inventory in healthcare systems.

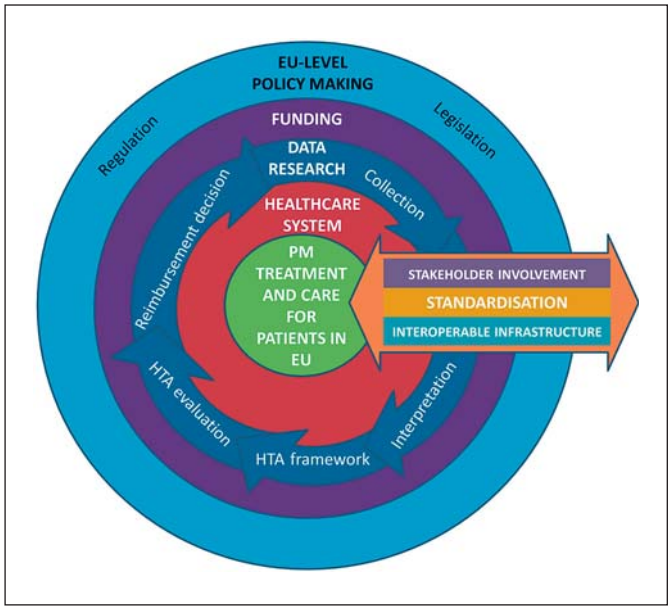

Fig. 3. Index of barriers to PM in Europe.

Interviews – SWOT

PM strengthens efficacy of healthcare by necessitating close collaboration between its stakeholders. These stakeholders will focus on an organised discussion to develop, for instance, guidelines, which will facilitate better rational treatment based on individual health data. Health data that are stored in large datasets directly impacting the interface of patient and healthcare professional will keep clinical practice up-to-speed with science.

'Weakness' can mainly be found in the evidence that is needed to facilitate PM. Not only are disease mechanisms highly complex, individual parameters do not reflect the full story; technologies to store and analyse big data and to try to model them are not fully developed yet. Furthermore, the illustrated change in healthcare delivery will be hard to realise in the current rigid system.

Especially in the field of drug development, PM offers opportunities. Cooperation between stakeholders will stimulate innovation, resulting in more successful implementation of CDx combined with a pharmaceutical product prescribed by informed healthcare professionals. Regulations facilitating such targeted treatment will also change the mind-set towards greater efficiency in healthcare, not only looking at disease definition critically but also towards innovations targeting public health.

Multi-stakeholder involvement indicated threats to the implementation process, e.g. in the duration of trials and long research processes resulting in patient groups becoming impatient. Not only are these research processes lengthy, they are also costly, and a worst-case scenario would be developing CDx that only increase costs of treatment, but not positive health outcomes.

Indexing Relevant Barriers in PM

Methods

After comparing the results from the 2 research arms (literature review and stakeholder analyses) an index was developed. The index consists of relevant barriers to improve access to PM for patients. In order to select relevant barriers, the barriers were scored by representatives of each stakeholder group.

The prioritisation of relevant barriers took place at the PerMed meeting in Berlin on March 28–29, 2014; 82 participants representing different organisations attended the meeting. After a presentation of the identified barriers, each stakeholder group had a session to prioritise the results, both from the strategic reports and the structured interviews.

Each group received the results from the analyses in paper form and was asked to rank 5 major areas to be prioritised regarding the implementation of PM in European health systems. Furthermore, within each of these areas the stakeholders were requested to pinpoint 3 specific areas needing attention. The results from these sessions were presented to all participants. The stakeholders' prioritisations in the PerMed meeting were combined with the results from the systematic literature review to select the relevant barriers summarised in the index.

Results

Comparing the stakeholders' prioritisations to the summary points from the systematic literature review resulted in the identification of 7 main areas (fig. 3). The barriers facilitating access to PM including to CDx lie mainly in the areas of (1) stakeholder involvement, (2) standardisation, (3) interoperable infrastructure, (4) healthcare system, (5) data and research, (6) funding, and (7) policy making. As an example, the development of 'data and research' is explained below.

In the systematic literature review within the section 'science', the main points concern 'systems biology', 'data and research', and 'clinical study design'. In the prioritisation from the stakeholder groups from the viewpoint of basic science, the 'access to data', 'measurable outcomes', and 'making sense of the data' are considered the most important factors. Furthermore, the stakeholders from translational research and the regulatory field prioritised 'data and research'. All aspects in the literature review and the prioritisation were compared using this approach to define the main areas.

Discussion

Focus on Harmonisation in Europe

The goal of this research was to develop an index that shows the most relevant barriers to the implementation of PM and PGx in Europe. In order to develop such an index, 5 approaches were used within 2 main research directions: literature review and stakeholder analysis.

The 5 approaches consisted of (1) a systematic literature review of scientific articles, (2) a gaps-and-needs assessment and SWOT analysis of strategic reports, (3) a survey study among several stakeholders, (4) structured interviews based on gaps-and-needs and SWOTs concerning PM, and (5) the prioritisation of the barriers according to groups of stakeholders. As mentioned above, comparing the results from these research arms provided an index with 7 main areas: (1) stakeholder involvement, (2) standardisation, (3) interoperable infrastructure, (4) healthcare system, (5) data and research, (6) funding, and (7) EU-level policy making (fig. 3). Different barriers exist in these fields that hamper the access to PM treatment and care for patients across the EU.

The findings from the different research approaches provided comparable data. In order to facilitate PM, the way research is approached and conducted, for example, in the field of drug development, needs revision, e.g. by cooperation between pharmaceutical and diagnostic companies. However, to be able to change research, the chain before and after it also needs to be adapted. The development of best practice guidelines is helpful to both direct research and to evaluate results from new research.

The harmonisation of gathered information from research to implement PM in healthcare is needed to ensure the interoperability between biobanks by providing the same type of data and interpretation. The evaluation and information availability will need to be translated into healthcare by ICT tools to support healthcare professionals in giving information to the patients and also to standardise reimbursement information across the EU. Stakeholder groups need to be involved more in the development and implementation of PM, not only through education and training but also for bottom-up policy making.

Since Europe consists of nearly 30 countries, some specific barriers could be pointed out. These barriers are also relevant in general, but for instance, the interoperability between biobanks is hampered in Europe, since different national frameworks exist, and this increases the complexity of merging datasets. The national differences in legislation and regulations not only impact on interoperability for biobanks but also financial issues such as reimbursement evaluation. Thus, standardised information requirements should be agreed upon.

When comparing the index to survey responses, the barriers that were analysed in this research occur internationally. Most of the stakeholders were not aware of, for example, best practice guidelines for the application of PM, be it on a national or European level. Even though ICT support tools are under development, they are not being adapted at a fast enough pace. However, stakeholders do feel healthcare professionals could be able to implement such care, and healthcare could become more individualised. To facilitate PM research, funding through reimbursement was considered a major boost.

Taking into account the different barriers from this research, the implementation of PM has numerous ones. At the EU level most of them exist on the harmonisation of approaches to research, reimbursement and information delivery. Facilitating such harmonisation, platforms bringing together the stakeholders, should focus on developing standardised legislation and best practice guidelines for those factors.

The beginning of PM currently seems to be evolving in the field of PGx, and the process of drug development and the study designs can be streamlined to be better adapted to biomarkers and CDx. Starting points to increase access lie in the 7 main areas of the index and the collaboration between different stakeholders to facilitate a safe and effective environment to implement PM.

The recommendations in table 2 are based on this study; however, to provide evidence-based strategies, more research is needed in feasible methods to increase the access to PM for patients, such as implementation and dissemination strategies how to design information delivery to patients in user-friendly methods. For instance, our study did not show results for the payment strategies if healthcare becomes more cross-border because of increased collaborations across the EU, or how patient support should be organised when patients use cross-border healthcare. Furthermore, the feasibility and the available resources to achieve the end goal of accessible PM and changing and applying new policies remain unclear and should be assessed in an overview. To facilitate efficient stakeholder involvement in order to harmonise practices throughout the different stakeholder sections within the index undertaking a mapping of the different stakeholders that engage in the process and the different ways that they interact is advisable. Realising the promise of cost savings under the PM approach will first require invest-

Table 2. Recommendations based on the barriers within the main areas of the index

	Barrier	Recommendations
Stakeholder involvement	• Mismatch in needs and provided information between clinical practice and research • Lack of awareness and knowledge on added value of CDx in clinical practice	Facilitate stakeholder involvement in policy making and research implementation by • Early dialogue • Public private partnerships • Public debate • Bottom-up policy making
Standardisation	• National focus for research grants • Lack of comparable data and information in databases • Differences in reimbursement decisions and implementation of CDx in healthcare systems	Standardisation of methods across the EU by • Evaluation research grants • Guidelines on data collection, interpretation, and quality assurance • Information on reimbursement decisions
Interoperable infrastructure	• Lack of ICT-support tools for data and information sharing • Lack of data and information across the EU to support research with PM approach	Develop ICT tools for data- and information sharing, which should include information on • Biobanks • Data accessibility • Information on best practice guidelines
Policy making	• Scattered policies and legislation across the EU	Update and/or develop regulations and legislation at EU level, such as • Best practice guidelines (research, reimbursement, implementation, CDS) • Harmonise legislation for diagnostics and treatment, development processes
Funding	• Lack of harmonised funding by limited reimbursement for biomarkers in CDx	Adjustment of funding models • Best practice guidelines • Conditional reimbursement • Adaptive licensing
Data and research	• Lack of relevant data: clinical practice, HTA indicators • Lack of information to interpret health data for clinical practice • Lack of information relevant for HTA evaluation • Lack of reimbursement • Lack of translation of CDx	Point-of-care research (CER) • Agreements on type of data, annotation and quality • Adjusted informed consent (EMR) Integrated informational models • Harmonisation of relevant data • Updated disease models Use HTA framework in CER: • Best practice guidelines
Healthcare system	• Lack of awareness and knowledge of CDx before starting treatment • Lack of support in clinical decision making • Lack of uptake of PM	Training and education • Workshops • Automated support tools • Curricula healthcare professionals
PM to patient	• Lack of awareness and knowledge value and integration of biomarkers	Information about PM to patients, e.g. by • Education programmes by government • Communication by healthcare professionals

ment costs at EU level. However, several initiatives exist on stakeholders working together to realise new research approaches in order to facilitate PM by CDx with relevant biomarkers.

Conclusion

PM is one of the most innovative areas in the future of health research. At present, its full potential for patients, citizens and the economy in Europe cannot be developed

due to fragmented activities, insufficient communication, and lack of generic solutions in the different areas of PM.

This study identified the relevant barriers and challenges for the implementation of PM into the health systems across Europe. The derived recommendations to overcome these stumbling blocks will aid policy makers and other key stakeholders to integrate PM into a European health strategy in a timely, effective and efficient manner.

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