











Financial incentives to promote personalized medicine in Europe: an overview and guidance for implementation

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The implementation of adequate financing and reimbursement of personalized medicine (PM) in Europe is still turbulent. The views and experience of stakeholders about barriers in financing and reimbursing PM and potential solutions were elicited and supplemented with literature findings to draft a set of recommendations. Key recommendations to overcome the barriers for adequately financing and reimbursing PM in different healthcare systems in Europe included the provision of legal foundations and establishment of large pan-European databases, use of financial-based agreements and regulation of transparency of prices and reimbursement, and creating a business-friendly environment and attractive market for innovation. The recommendations could be used by health authorities for designing a sequence of policy steps to ensure the timely access to beneficial PM.

First draft submitted: 21 December 2022; Accepted for publication: 22 June 2023; Published online: 30 August 2023

There is a bulk of literature highlighting how conceptually and empirically the potential benefits of personalized medicine [1–6]. However, concerns have been raised that patients and the general population might not achieve the maximum benefit of promising personalized medicine interventions or even gain access to them due to issues with their financing and reimbursement [7]. Public–private financing agreements [8,9] and performance-based reimbursement models [10–18] have been identified as appropriate financing and reimbursement models, respectively, for the development and uptake of effective and cost-effective personalized medicine innovations [7]. This is because they aim to reward manufacturers for the value of the personalized medicine innovation and share the risk between manufacturers and payers, and are considered adequate for personalized medicine [7]. Appropriate models in the context of financing and reimbursement of personalized medicine interventions are models that provide the adequate financial incentives to achieve widespread adoption of personalized medicine with proven benefit [7]. However, several barriers have been identified when implementing these models [7]. With regards to financing research and development of personalized medicine, the lack of strong links between academic and private partners [19], discordance between research priorities on a national and regional level [20] and legal/ethical issues related to data sharing and generation of evidence [19,21] are the most important issues hampering these public–private partnerships [7].

There are several barriers to applying reimbursement models that are adequate for personalized medicine [7]. In particular, the lack of clear evidence and easily demonstrated value and benefit [22–24] coupled with the lack of or inability to obtain credible data to measure outcomes [25] have been identified as barriers with implementing performance-based models [7]. With respect to sharing financial risk, affordability issues resulting from the high costs of personalized medicine, especially for gene and cell therapies (even those with proven value and benefit) [26–30] have hampered reimbursement [7]. In the area of health technology assessment and regulatory frameworks,

there have been particular challenges to implementing risk-sharing agreements in different healthcare systems [7,31]. These include practical challenges such as negotiating and administering rebates over long time periods [14] as well as regulations related to data privacy and information disclosure [7,25]. Furthermore, existing health technology assessment frameworks that have struggled to assess the lifetime value of one-off potentially curative treatments (e.g., gene and cell therapies) [32] or attribute the added benefit of targeted therapies [33], and often did not jointly evaluate diagnostics and medicines as a personalized medicine intervention package [34] could also hamper the implementation of reimbursement models that reward value and innovation [7].

Following initiatives in the USA, the EU is increasingly investing in personalized medicine research and has launched several initiatives to support the development and implementation of personalized medicine at European and national level [35,36]. These initiatives include the European Partnership for Personalised Medicine, European Alliance for Personalised Medicine [37] and International Consortium for Personalised Medicine (ICPerMed) [38]. However, there is no coordination in the implementation of appropriate financing and reimbursement models for personalized medicine between European countries. This highlights the need for a roadmap for designing the adoption of such models based on the individualities of different types of healthcare systems in Europe. Given the significant potential benefit to patients and general population health from the use of personalized medicine, in this paper we report our efforts to construct a roadmap with recommendations for actions that need to be made to facilitate the adoption of appropriate financing and reimbursement models for personalized medicine in different types of healthcare systems across different European countries.

Materials & methods

This study was part of the work conducted by the EU-funded Healthcare- and Pharma-economics in Support of the International Consortium for Personalised Medicine – ICPerMed (HEcoPerMed) [39].

Workshop

In order to tackle some of the considerable barriers for financing and reimbursing personalized medicine interventions, we organized a workshop to elicit the opinions of relevant stakeholders involved in personalized medicine financing and reimbursement. The intention of the workshop was to try and identify possible ways to overcome the barriers to financing and reimbursement of personalized medicine in Europe.

Participants & preparation

Potential participants in the virtual 1 day workshop were identified through the scientific and grey literature selected in a relevant literature review [7], Google searching and the professional networks of the HEcoPerMed consortium and ICPerMed. Selection criteria included familiarity and experience with financing and reimbursing of personalized medicine. We tried to balance the representation of different stakeholders' groups (e.g., academia, industry, payers and insurers, research funding organizations, reimbursement and regulatory bodies) as well as country (limited to European countries due to time zone differences) and gender distribution. A total of 155 experts were invited in three subsequent invitation rounds from December 2020 to April 2021. Experts who confirmed participation were sent prereading materials prior to the workshop that included the planned agenda, a presentation of findings from a literature review of financing and reimbursement of personalized medicine [7] and the presentations containing the questions for the group discussions in the afternoon. The questions were based on the literature review on financing and reimbursement of personalized medicine and the barriers to financing and reimbursement identified in it [7]. The final version of the questions was derived through an iterative process of discussions between the HEcoPerMed partners.

Workshop structure

The one-day online workshop took place on 20 April 2021 and was divided into morning and afternoon sessions. A detailed program of the workshop is included in [Appendix 1](#) (Supplementary Material). The morning session involved an introduction to the HEcoPerMed consortium and the workshop, a keynote talk and a presentation of ICPerMed and the findings from the literature review of financing and reimbursement of personalized medicine [7].

In the afternoon session, the participants were split into three discussion groups. Each group was first given a reminder of the working definitions of concepts related to financing and reimbursement of personalized medicine followed by slides being presented with information on the main financing and reimbursement models for personalized medicine identified in the literature review [7]. In each session, experts were presented with a set of

Single payer/non-competitive environment	Single payer/competitive environment
Examples: Iceland, Nordic countries, Portugal, Spain, UK	Example: Italy
Multiple payers/non-competitive environment	Multiple payers/competitive environment
Examples: Austria, Germany, Luxemburg, Switzerland	Examples: Belgium, Central and Eastern European countries, The Netherlands

Figure 1. Classification of healthcare systems.

multiple-choice and open-ended questions and asked to choose their answers using the Mentimeter online polling software. Experts had the opportunity to elaborate on their responses at the end of each polling question. The group discussions were as follows.

Group 1 discussed financing research and development of personalized medicine, and the discussion was based on eight multiple-choice questions and four open-ended questions. Group 2 discussed performance-based reimbursement for personalized medicine and the discussion was based on 12 multiple-choice questions and three open-ended questions. Group 3 discussed financial arrangements for the reimbursement of personalized medicine and the discussion was based on ten multiple-choice questions and three open-ended questions. The working definitions used in the workshop are presented in [Appendix 1](#) and the template with questions used in the workshop is presented in [Appendix 2](#).

Transcripts & analysis

All group sessions of the workshops were recorded *via* Microsoft Teams with participants' consent. Captions and transcripts of the recordings were auto-generated, and transferred to a notepad to be reviewed and anonymized; analyses of poll answers and open text were performed.

Grouping of EU healthcare systems

We adapted the classification of healthcare systems developed by Böhm and colleagues to distinguish between healthcare systems in the EU depending on whether there are single (e.g., National Health Service) or multiple payers (e.g., social health insurers) for healthcare, and whether the 'market' environment (i.e., the interaction of health payers and health providers) has elements of competition or not ([Figure 1](#)) [40]. This four-way classification was chosen as these two dimensions are related to the level of complexity when regulatory, financing and provision aspects have to be reformed and agreed between stakeholders. For example, achieving adequate data sharing between multiple payers and providers under competition would be more difficult than in a healthcare system with a single healthcare payer and provider. In other words, the classification is useful to indicate the different levels of effort required to overcome the barriers and disincentives in the successful implementation of suitable financing and payment models for personalized medicine in different healthcare systems in Europe.

Identifying potential solutions for barriers & disincentives for personalized medicine financing & reimbursement

We mapped appropriate financing and reimbursement models, identified in the literature review, onto the four types of healthcare systems based on existing country-specific examples of their application. For each one of them, we selected and reported on the barriers and disincentives impacting on the financing and reimbursement of personalized medicine in Europe.

Table 1. Workshop participants' characteristics.	
Participants (28)	n (%)
Female	9 (32)
Male	19 (68)
Public sector	21 (75)
Academia	4 (19)
Health technology assessment/reimbursement agency	9 (42)
European Commission/ministries	4 (19)
Patient representative	2 (10)
Funding agency	2 (10)
Private sector	7 (25)
Industry/consultancy	7 (100)

To do that, we used data from the workshop regarding various factors, including appropriateness and feasibility of financing and reimbursement models, novel ways of collaboration between public and private financing entities, data, expertise, investment-risk and revenue sharing, measuring and rewarding value of personalized medicine, unit of payment, services and timeframe of reimbursement arrangements.

Drafting a roadmap with recommendations for Europe

We synthesized the data gathered through the review of the literature and the workshop with experts to draft a set of recommendations for financing and reimbursement of personalized medicine pertinent to the four types of healthcare systems in Europe. The proposed recommendations were stratified based on the period they could be aimed at being achieved within – short term (1–2 years), medium term (3–4 years) and long term (more than 4 years, i.e., longer than a mature electoral cycle). The recommendations were grouped into general and more specific that related to addressing the barriers and issues to financing and reimbursement of personalized medicine identified.

With respect to the financing of personalized medicine, recommendations were aimed at resolving the barriers around the lack of strong links between public and private partners, maintaining and upscaling current financing, resolving discordance between research priorities on the local and national level, issues related to legal matters, privacy/ethics, data sharing and generation of evidence [7,19–21]. For the reimbursement of personalized medicine, recommendations were aimed at resolving the barriers around evidence generation, sharing financial risk, use of reimbursement models and health technology assessment and other regulatory frameworks [7,22–34].

Results

Workshop participants

A total of 28 experts participated in the online workshop. The participants' characteristics are summarized in Table 1. The public sector was represented by 75% of the participants, including academia, health technology assessment and reimbursement agencies, the European Commission and ministries, funding agencies and patient representatives. The private sector, including industry and consultancies, was represented by 25% of the participants.

Financing of research & development of personalized medicine

This section summarizes the results of the discussion with experts during the Group 1 session of the workshop.

Current landscape of financing research & development of personalized medicine

All experts agreed that creating a favorable landscape for investors in financing research and development for personalized medicine was needed to encourage and support universities and small and medium enterprises to invest in personalized medicine innovation. However, less than a third of them thought that the current landscape of financing encourages the research and development of personalized medicine. Specifically, the experts suggested to expand approaches and arrangements that have worked in rare diseases to the personalized medicine domain, as rare diseases was the area of the most innovative financial arrangements in healthcare. They also recommended raising public or philanthropic investment to boost the development of advanced personalized medicine therapies and to have explicit reimbursement schemes for these therapies and overcome current capacity challenges by

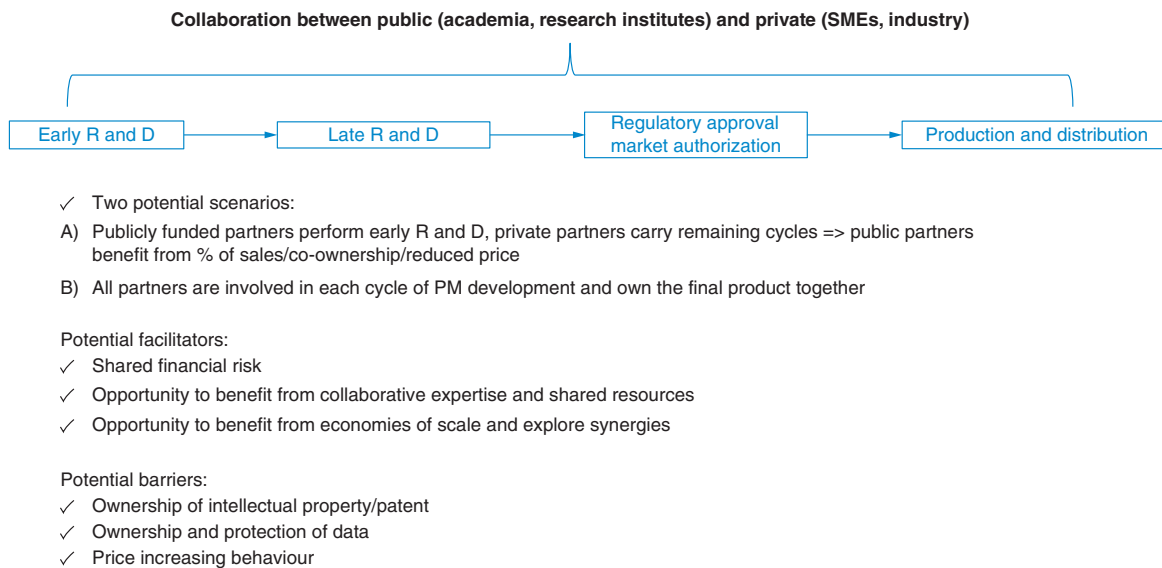


Figure 2. Proposed models for public/private financing of PM.

PM: Personalized medicine; R and D: Research and development; SME: Small and medium enterprise.

investing public funds in production infrastructure and workforce training. It was recognized that while there are currently financial resources for upstream basic and applied research in personalized medicine, there needs to be international coordination and discussion to enhance cooperation, especially to involve regional and local levels, and improve their understanding on funding for research and development of personalized medicine.

Models for financing research & development of personalized medicine

Experts unanimously considered a public–private mix of funding to be the most appropriate model for financing research and development for personalized medicine. According to them, the two models presented were equally feasible for achieving public–private agreements in financing personalized medicine (Figure 2). In the first model, public partners invest in early-phase research and development and hand over the commercialization of promising innovations to private partners. In that model, public partners would realize the return of their investment by either getting a share of the revenues, co-ownership or reduced prices. In the second public–private financing model, public and private partners are jointly involved in all phases of personalized medicine development under a coproduction and co-ownership agreement.

Most of the experts (75%) believed that that publicly funded research institutions and small and medium enterprises can become equal partners with development companies instead of their suppliers of innovation by providing funding as well as in-kind contributions such as sharing data and resources. With regards to funding, there was a strong belief that public authorities can justify the investment of public funds in high-risk research and development projects of personalized medicine by steering innovation where innovation, and its expected benefits for patients and society, is most needed.

Data sharing

Regarding data sharing, the experts added that it can be shared without giving away the ownership, but also stated that sometimes data sharing can be viewed as problematic, as generating data is considered an investment. Moreover, specific ethical aspects should be considered in data sharing to avoid the marginalization of specific population groups and increase in health disparities. In any case, all experts indicated that empowerment of patients and the citizens' trust in data are important elements of data sharing as well as the availability of specific legislation and policies.

Involvement of partners in sharing risks & benefits

Public partners could also contribute to the agreements with the private partners by funding education related to personalized medicine to meet the job market needs in this area. In addition, they could invest more in research

across the whole value chain (i.e., from biomedical and clinical research to economics, ethics and translational research); enhance collaboration between research centers (similar to the European reference networks in rare diseases); consider open science (the movement to make scientific research, including publications, data, physical samples and software, and its dissemination accessible to all); and apply the findable, accessible, interoperable and reusable (FAIR) principle in sharing research findings.

Furthermore, the experts thought that sharing risks and benefits between stakeholders can be achieved by considering the concept of open innovation, having clear and fair contractual agreements from the very start of the collaboration, involving payers/insurers early in the developmental phase of personalized medicine to discuss potential reimbursement agreements, and having properly designed incentives and (novel) structures that align stakeholders' interests. Regional initiatives within the ICPeMed family were given as an example of helping less economically strong countries and regions in Europe to apply for funding for personalized-medicine-related activities.

Performance-based reimbursement for personalized medicine

This section is based on the discussions with experts in the Group 2 session of the workshop.

Feasibility of performance-based reimbursement for personalized medicine

The experts considered performance-based models to be somewhat (30%) to very (70%) appropriate and feasible for reimbursing personalized medicine as they may facilitate financial risk sharing between health providers and manufacturers (44%), improve access for patients (22%) and enhance affordability (11%). They all agreed that a time horizon of up to 5 years for contracts was appropriate for performance-based models. Performance-based models may be more appropriate for personalized medicine interventions with accrued benefits in the short/medium term (e.g., acute therapies), as the measurement of their outcomes is simple (e.g., overall survival in cancer), and there is high uncertainty in their clinical outcomes and budget implications resulting from high costs. When asked about prerequisites that should be in place for performance-based models to be implemented, most experts (80%) highlighted the need for postmarketing activities, legislative actions and arrangements related to health technology assessment (including agreements about outcome measures and required healthcare infrastructure to monitor outcomes). The experts suggested that the EU and other international bodies should take more initiatives to support low- and middle-income countries in implementing performance-based models, which could be applicable to these countries by price discrimination or small-scale piloting before applying them on a national level.

Units & coverage of performance-based reimbursement

Most experts (67%) considered a subgroup of patients/population with a course of therapy being the smallest unit for reimbursement of personalized medicine through performance-based models. However, they all agreed that data collection should be done at the individual level. A justification of using subgroups as a unit of payment was the different efficacy and different value of the same personalized medicine intervention in different population subgroups. Different levels of efficacy could also merit indication-based pricing on the subgroup level. There was not a clear agreement among experts on the scope of the payment but a slight majority (56%) favored the reimbursement for the personalized medicine and the companion test/drug through performance-based reimbursement models, arguing that it would be too challenging (if feasible) to reimburse the personalized medicine and all related treatments/diagnostics as a bundle.

Outcomes & value in performance-based reimbursement

The views of experts on what outcomes should be used and measured in performance-based models were divided. Some experts expressed their preference in rigid clinical outcomes over patient-reported outcomes due to the variation of quality of life among different patients. Others suggested the use of value assessment frameworks that include patient preferences and quality adjustment life-years to be consistent with the evaluation of all innovations in healthcare. Other experts were inclined to expanding the current value framework even more by adding additional elements of value if there is evidence that these elements hold a certain value to people. Whose value to reward was also a divisive topic among the experts, as they could not agree whether to reward value only to current patients, current and future members of society, or current and future patients and their families.

However, all experts agreed that it is not feasible to include all value components in the reimbursement agreement and therefore, value of treatments, especially the ones in which the benefits are accrued in the long term and payments

are made in the short term, can be rewarded by paying in the long term or by applying adaptive payments in case they are acceptable in combination with risk management and performance measurement. In any case, the value elements included in performance-based models should be specific, measurable, achievable and realistic, and the key point is the timing at which the outcomes are expected to occur and the timing at which reimbursement is provided. The majority of experts (56%) thought that the payments in performance-based models should be initiated in installments after milestones are achieved, while 22% of them thought that payments should start at the time of treatment delivery with rebates if treatment fails.

Financial-based agreements for the reimbursement of personalized medicine

This section summarizes the discussions with experts during the Group 3 session of the workshop.

Feasibility of financial-based agreements for reimbursing personalized medicine

The majority of the experts (71%) considered financial-based reimbursement models to be somewhat appropriate and feasible for reimbursing personalized medicine because they are relatively easy to implement but they cannot overcome all challenges related to personalized medicine reimbursement. Experts thought that financial-based agreements could decrease financial risk for payers and providers, and increase cost-effectiveness and affordability by achieving cheaper prices, especially if negotiations take place at the EU level. At the same time, concerns were raised about limited patient access along with limited utilization of personalized medicine due to volume/budget caps. The experts agreed that financial-based agreements could provide earlier access to effective medicines and reduce unmet medical needs but also expressed cautiousness related to ethical considerations in cases when withdrawing reimbursement is considered due to large clinical uncertainty, and inability to establish effectiveness and cost-effectiveness. In any case, the experts thought that financial-based agreements models should have a time horizon of up to 5 years (71%) and that these models are not an intermediate step to performance-based models as these two types of reimbursement models served different purposes.

Moreover, financial-based agreements reimbursement models were considered more appropriate when there were uncertainties surrounding the price or the cost of personalized medicine, the dose and the length of the treatment period as well as in cases where the therapeutic outcomes could not be determined. Experts suggested that financial-based agreements could help overcome cost-effectiveness and value concerns by achieving lower price, or putting caps on volumes. Budget caps or volume caps could also be applied when there was uncertainty around the number of patients and the amount of the product they would utilise. According to the experts, the prerequisites for successfully implementing financial-based agreements included postmarketing activities, legislative actions and arrangements related to health technology assessment; horizon scanning or the preapproval initiatives to ensure that health technology assessment was performed and access to personalized medicine was not delayed; data access in the setting of interest; and integration of systems for pricing and reimbursement.

Units & coverage of financial-based arrangements

The views of experts on the units for reimbursement of personalized medicine through financial-based models varied from the individual (44%) to subgroup of patients/population (33%) and flexible depending on the product (33%). Similarly, there was no agreement among experts about the health services to be covered by the financial-based arrangements, but experts commented that reimbursing tests and drugs separately could potentially ensure that the best diagnostic and treatment options were provided for patients. It was also noted that given the emergence of 'big data' in personalized medicine, it was expected that the reimbursement coverage would be expanded in the future to include more than a test and drug combination.

Transferability of financial-based arrangements

The experts did not agree that the main criticism of financial-based arrangements was the lack of transparency (e.g., due to undisclosed rebates) as this allowed access to personalized medicine in smaller countries with fewer resources. Other experts expressed the view that the transparency should be regulated at the EU level to enable the disclosure of rebates after a certain time period. It was suggested that financial-based agreements could be made applicable to low- and middle-income countries and transferable across different EU countries by ensuring more collaboration between countries and increasing transparency related to these models. A suggestion was made to create registries (with the support of industry) that help with tracking patients where there were limited resources, in order to support utilization caps that would allow European-aligned list prices. Another suggestion was to make

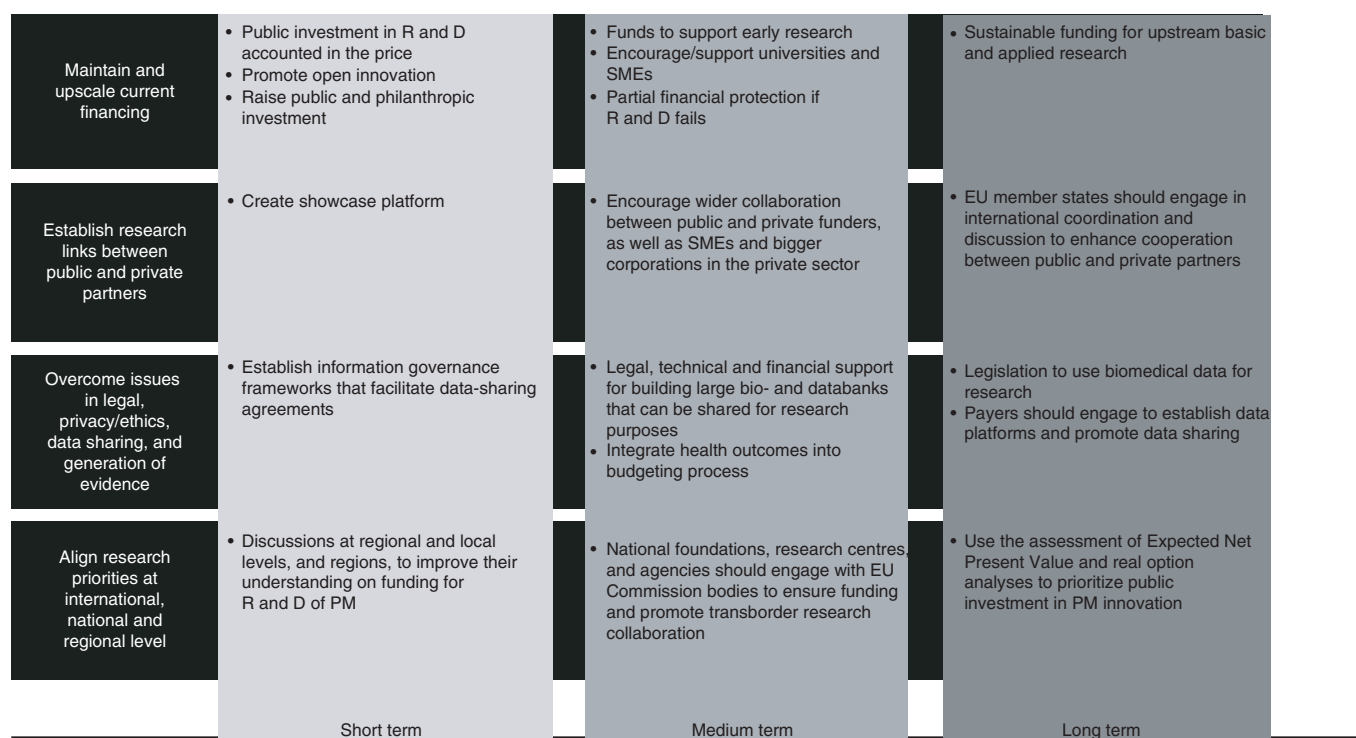


Figure 3. Recommendations and timeframe for application for financing R and D for PM.
PM: Personalized medicine; R and D: Research and development; SME: Small and medium enterprise.

financial-based agreements tailored to low- and middle-income countries rather than having just one model for all EU countries.

Recommendations for financing research & development for personalized medicine across European countries

The recommendations for adopting relevant actions for financing personalized medicine research and development and the timeframe for their application are listed in Figure 3. We have divided the recommendations into four groups: 1) maintain and upscale current financing; 2) establish research links between public and private partners; 3) overcome issues in legal, privacy/ethics, data sharing and generation of evidence and 4) align research priorities at international, national and regional level.

Maintain & upscale current financing

Actions aimed at maintaining and upscaling current financing for personalized medicine research and development involve in the short term sustaining and potentially increasing public investment in research and development, and also attracting philanthropic investment. European countries could engage with such initiatives through local and national authorities and involve research partners and manufacturers early in the discussion to ensure that any public investment in research is later accounted for in the price of the new personalized medicine. In health systems with single payers (either through taxation or insurance; i.e., Type A or B countries in Figure 1) it could be easier to factor public investment into the price of the personalized medicine. Also, the concept and practice of open innovation could be considered through dedicated platforms for sharing knowledge between governments, academics and innovators and developing evidence-led policy ideas at the local, national and European level.

In the mid-term, funds including both public and private sources to support early research and small and medium enterprises, and ensuring partial protection in case of unsuccessful ventures, should be ensured. These could be achieved at the EU level, as calls supported by the European Commission (Innovative Medicines Initiative, for example), or by dedicating national or local funding to regions in different countries that already have experience with personalized medicine research. In the long term, ensuring collaboration on the EU-level funding to upstream basic and applied research should be supported and maintained. Health systems where there is relative independence of

regions could implement and engage in research and development funding activities more easily than in centralized systems that are likely to be less nimble and flexible.

Establish research links between public & private partners

Actions aimed at establishing research links between public and private partners in the short term involve creating a platform (based on the FAIR principle), where public and private stakeholders could demonstrate and share their work. In the mid-term, encouraging wider collaboration between public and private funders, as well as small and medium enterprises and bigger corporations in the private sector, could be aimed for by all EU member states irrespective of the type of healthcare system.

In the long term, EU member states should engage in international coordination and discussion to enhance cooperation between public and private partners by engaging with large markets and players (e.g., USA and China) to facilitate large consortia investment and collaboration.

Overcome issues in legal, privacy/ethics, data sharing & generation of evidence

In an effort to overcome issues in legal, privacy/ethics, data sharing and generation of evidence, governments could establish information governance frameworks that facilitate data-sharing agreements in the short term. Similar actions in the medium term include providing legal, technical and financial support for building large bio- and databanks that can be shared for research purposes, and integrating health outcomes into the budgeting process. These actions mentioned could be implemented easily in the short to mid-term in healthcare systems (usually Type A: single payer, noncompetitive systems), with well-developed electronic health records that could be shared and used for research purposes provided that the legal framework is ensured (e.g., national General Data Protection Regulation). Such actions would be more challenging to implement in healthcare systems that need more investment into developing such patient databases. In the long term, legislation that relates to the use of biomedical data for research and engaging payers in the establishment of platforms for data sharing should be aimed at on the EU level.

Align research priorities at international, national & regional level

Actions related to aligning research priorities at the international, national and regional level in the short term require engaging regions in discussions to improve their understanding on funding for research and development of personalized medicine. In the mid-term, national foundations, research centers and reimbursement agencies should engage with European Commission bodies to ensure funding and promote *trans*-border research collaboration, as well the partnerships among research consortia internationally. Moreover, it would be beneficial to establish centers of financial expertise to incorporate risk into the financial viability of a personalized medicine innovations at a very early stage. These centers could use financial economic methods such as evaluating the expected net present value and real options analyses to help prioritize research and development investment decisions [41–43].

Recommendations for reimbursing of personalized medicine across EU countries

The recommendations for adopting relevant actions for reimbursing personalized medicine and the timeframe for their application are presented in [Figure 4](#). We have divided the recommendations into four groups: 1) evidence generation, 2) type of reimbursement model, 3) sharing financial risk and 4) health technology assessment and other regulatory frameworks.

Evidence generation

In the short term, actions related to generating evidence for reimbursement involve establishing agreements between payers and manufacturers about what outcomes and measures are relevant for different types of personalized medicine. In health systems where multiple payers are involved in paying health services (Type C and D countries in [Figure 1](#)), this might be difficult to coordinate between the payers and manufacturers, and confidentiality agreements and nondisclosed payments could result in distrust (especially in Type D countries because of the competition element). In such scenarios, collective agreements between payers and the manufacturer could be used to overcome difficulties and enable agreements based on effectiveness rather than price.

In addition, adapting and developing relevant health technology assessment processes and procedures could facilitate the generation of evidence for reimbursement. However, such action might require a mid- or most likely a long-term time horizon in countries where a health technology assessment (HTA) process is not yet established.

Evidence generation	<ul style="list-style-type: none"> • Agreement between payers and manufacturers about relevant outcomes and measures • Adapting or developing relevant HTA processes and procedures 	<ul style="list-style-type: none"> • Collect clinical/health outcomes for all PM treatments or test–treatment combinations • Patient involvement in monitoring and reporting the outcomes 	<ul style="list-style-type: none"> • Public investment in creating databases that include clinical, patient outcomes, as well as accidental findings.
Type of reimbursement model	<ul style="list-style-type: none"> • Consider financial-based models in case of budget constraints in the short-term • Consider performance-based models when clinical uncertainty is high • Apply the relevant units of payment that are different for the different type of PM 	<ul style="list-style-type: none"> • Establish dedicated reimbursement pathway for PM • Bundle the reimbursement of companion diagnostics and drugs 	<ul style="list-style-type: none"> • In the long run adaptive payments or switching models of reimbursement could be considered
Sharing financial risks	<ul style="list-style-type: none"> • Couple financial- and performance-based models with an evidence generation scheme with clear criteria for reimbursement coverage 	<ul style="list-style-type: none"> • Early access to new promising treatments 	<ul style="list-style-type: none"> • Apply frameworks that capture the long-term effects
HTA and other regulatory frameworks	<ul style="list-style-type: none"> • Outline the requirements for coverage with evidence development and clear stop/continue criteria to inform evidence generation • Adapt or develop relevant HTA processes and procedures 	<ul style="list-style-type: none"> • Dedicated pathway for evaluating different types of PM and subsequent value-based reimbursement • Apply horizon scanning and the pre-approval initiatives supported by HTA to ensure timely access to PM with proven benefit 	<ul style="list-style-type: none"> • Reassess benefit, value and budget impact when competitors appear or when patents expire
	Short term	Medium term	Long term

Figure 4. Recommendations and timeframe for the application to reimburse PM.
HTA: Health technology assessment; PM: Personalized medicine.

In the mid-term, establishing systems at the local and national level to collect clinical as well as health outcomes for all personalized medicine treatments or test–treatment combinations, and patient involvement in monitoring and reporting the outcomes, could facilitate the generation of evidence. On the EU level, establishing systems that collect such outcomes, especially in rare diseases (where individual countries have fewer patients, but many when countries are combined), would be beneficial, as well as establishing a shared pan-European system for all personalized medicine, although such venture would require substantial investment and change in legal regulations.

Type of reimbursement model

With regards to choosing a type of reimbursement, in the short term, financial-based models could help overcome budget constraints while performance-based models could facilitate access to personalized medicine for which clinical uncertainty is high, giving time to generate additional evidence. Applying performance-based models would be easier in countries with well-established health technology assessment processes and electronic patient databases with plenty of high-quality data. For both types of models, applying the relevant units of payment is crucial and this would be more easily achieved in health systems where activity-based costing has already been used. In the mid-term, European countries could aim to establish dedicated reimbursement pathways for personalized medicine, both at the local and national level, as well as consider pairing the reimbursement of companion diagnostics and resulting medicines, although that might be more challenging to achieve in systems with multiple payers. In the long term, payers could consider adaptive payments or switching models of reimbursement to ensure access to personalized medicine with proven clinical benefit.

Sharing financial risk

With regards to sharing financial risk, in the short and mid-term in order to provide early access to novel personalized medicine, both financial- and performance-based models could be used; however, clear criteria should be established on the evidence needed to reassess the reimbursement decisions and provide further coverage. These need to be agreed by all payers to avoid inequality of access and might be challenging to achieve in systems with multiple payers (i.e., Type C and D countries). In the long term, establishing frameworks and systems that capture the

long-term effects of personalized medicine could facilitate future reimbursed decisions. In systems with multiple payers this would require collaboration and agreements for sharing transparently negotiated prices and coverage. This would be more challenging for Type D countries than in Type C countries as transparency could be hampered by competition.

Health technology assessment & other regulatory frameworks

Actions aimed at overcoming barriers related to health technology assessment and other regulatory frameworks, in the short term, involve outlining the requirements for coverage with evidence development and clear stop/continue criteria to inform evidence generation, and adapting or developing relevant health technology assessment processes and procedures. These actions would require agreements between payers that might be more difficult to achieve in multiple payer systems (i.e., Type C and D countries). In the medium term, establishing a dedicated pathway for evaluating different types of personalized medicine and subsequent value-based reimbursement, as well as applying horizon scanning and preapproval initiatives supported by HTA to ensure timely access to personalized medicine with proven benefits, would facilitate personalized medicine coverage. These actions would require collaboration between payers and HTA and health authorities on local and national levels, and in the case of rare diseases potential involvement on the EU level. In the long term, in order to ensure payers cover personalized medicine interventions with proven benefit, reassessing benefit, value and budget impact is very important, especially when competitor personalized medicine interventions appear or when patents expire.

Discussion

In the financing of research and development for personalized medicine, European authorities and the European Commission could help facilitate the implementation of the roadmap drafted in this report by establishing platforms where research partners and investors could engage in discussions and potentially form new collaborations and enhance existing collaborations. In addition, facilitating or passing the legislation that would allow the creation and establishment of large pan-European databases that would include clinical and health outcomes and could be used to enhance investment in basic and applied research as well as future coverage of personalized medicine would further support the financing and reimbursement of personalized medicine.

However, funding recommendations feature the extensive involvement of public authorities. This could generate discussions about whether the public has not already invested enough. Public stakeholders could prioritize innovation by supporting research and development projects where innovation is most needed, and where private partners have been most reluctant to invest. Particularly, public investments could be steered toward those types of personalized medicines for which the industry cannot build a viable business case. The distinction between development of tests and algorithms, and treatments is important. For example, small and medium enterprises offering means of remote patient monitoring and risk-prediction algorithms face different barriers as compared with large pharmaceutical companies. For small and medium enterprises the period between seed funding to achieve a cost-effectiveness mark and (not) getting funds to do large scale randomized controlled trial is a hurdle to overcome, while this is much less of an issue for large manufacturers that develop drugs.

Expected net present value and real options analyses could be used to prioritize investment into personalized medicine innovations [41–43]. In addition, public authorities could support areas of unmet need requiring substantial early research that are expected to have potentially life-altering effects on patients. An explicit framework that allows for the evaluation of trade-offs between efficiency and equity in developing personalized medicine should be developed that could facilitate decisions of potential investment in costly innovations expected to benefit only a small number of people.

Public investment in personalized medicine research and development could also be justified by the possibility of creating databases that would benefit and empower patients, and allow for the findings from underrepresented groups to be more easily factored into the decisions made in this area. Such large databases can further enhance basic discovery research and allow manufacturers to further pursue their niche as well as encourage manufacturers to share data collected from clinical trials in exchange for access to the database or reimbursement agreements prior to official approval and market-access authorization.

While it could be beneficial to apply approaches and arrangements for research and development innovation of rare diseases to the broader area of personalized medicine, it is worth acknowledging that financing and advancing research in personalized medicine of common diseases can be complex in nature. The complexity stems from funding research that takes multiple variables into account, especially when there are multiple biomarkers defining

the personalized medicine approach, and investing into more complex strategies to identify subgroups of patients who are likely to benefit more from a certain course of therapy.

With regards to reimbursement, European authorities and the European Commission could facilitate the implementation of the roadmap drafted in this report by supporting legislative and regulatory changes relating to data sharing and collective health technology assessment. It should be noted that in case of affordability issues and considerable budget impact, generating more clinical evidence may not solve these issues [44]. In that case, especially for rare diseases for which expensive gene therapies have come to the market, it might be worth considering establishing EU-level financial-based agreements that could potentially lower the price and achieve an ‘acceptable’ cost–effectiveness level, as well as providing a larger pool for risk sharing and evidence generation. However, such agreements at the EU level should be carefully drafted not to impede the opportunity for each member state to negotiate their agreements for other types of personalized medicine that are different from one-off treatments with curative intent. In addition, transparency of personalized medicine prices and reimbursement models used could be regulated on an EU level by introducing a system for prices and rebates disclosure after a time period. It should be noted that performance-based agreements might be more challenging to implement in systems (particularly some in eastern Europe) where payers and health providers do not have the experience or the resources needed to establish and maintain a database of relevant outcomes. Therefore, these countries may need extra financial and technical support from the EU to implement risk-sharing agreements. Alternatively, payers may engage in agreements with manufacturers so that the latter might directly pay the cost of the establishment of databases in countries where such databases do not exist. For example, platforms for easy sharing of test results between caregivers is an important approach to improve access to personalized medicine as professionals involved in treating a particular group of patients could have instant access to results from previous tests and readily determine if patients are good candidates for a certain treatment, or prescribe additional testing. Furthermore, performing and reimbursing duplicate tests will be avoided.

It is also worth noting that what is acceptable in terms of cost–effectiveness still varies widely among European countries with western and northern counterparts having higher established ratios as compared with their eastern and southern counterparts; therefore, careful consideration of this variety should be given when implementing financial-based agreements on the EU level.

Moreover, establishing a common health technology assessment framework for personalized medicine in the EU could be beneficial in terms of saving resources and avoiding having to perform similar analyses multiple times. However, it should be noted that transferability issues, especially those related to the availability [45] of the personalized medicine technology, might prove challenging when trying to implement such a framework. The European Commission could also set the innovation agenda and prioritize areas for personalized medicine innovation by steering EU funds for research and development, and coordinating member states’ funding as well. In addition, European efforts could speed up the diffusion of technological innovation by supporting financially and technologically ‘early adopter’ member states and try to remove skepticism for adopting the innovations in other member states. Finally, the EU’s role could go beyond that of the regulator and facilitator, and could adopt an outward entrepreneurial profile to lead innovation by creating a business-friendly environment for innovation, attractive market, and strong competitor or collaborator with other large markets (i.e., USA and China).

The consensus approach we have utilized has strengths and limitations. In particular, it summarizes the view points and opinions of different stakeholders. In order to ensure representativeness we invited a large number of stakeholders who are experienced in the field of financing and reimbursement of personalized medicine. In addition, we reported observed agreements and disagreement, and the answers of open-ended questions. However, it is worth acknowledging that the views of stakeholders might be limited or prone to bias by their own experiences.

Conclusion

We have drafted a roadmap of actions to overcome the barriers in providing financial incentives for the development and adoption of personalized medicine in Europe. This roadmap could be used by European health authorities for designing a sequence of policy steps that would ensure the timely access of all Europeans in need of effective and cost-effective personalized medicine innovations.

Executive summary

Background

- Issues with financing and reimbursement of personalized medicine might prevent patients and the general population from achieving the maximum benefit of promising personalized medicine interventions or even gaining access to them.
- We constructed a roadmap with recommendations for actions to facilitate the adoption of appropriate financing and reimbursement models for personalized medicine in different types of healthcare systems across different European countries.

Methods

- We elicited the views and experience of stakeholders about barriers in financing and reimbursing personalized medicine and potential solutions, and supplemented with literature findings to draft a set of recommendations.

Results

- Key recommendations to overcome the barriers for adequately financing and reimbursing personalized medicine in different healthcare systems in Europe include:
 - Provision of legal foundations and establishment of large pan-European databases;
 - Use of financial-based agreements and regulation of transparency of prices and reimbursement;
 - Establishment of business-friendly environment and attractive market for innovation.

Conclusion

- The recommendations in the roadmap could be used by health authorities for designing a sequence of policy steps to ensure the timely access to personalized medicine with proven clinical benefit.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pme-2022-0145

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Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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