HEcoPerMed

Health Economics for Personalised Medicine

Deliverable

5.1

Report Information	
Title:	Synthesis Report of HEcoPerMed Virtual Workshops
Authors:	
Version:	1
Work package:	2 and 3
Dissemination level:	Public

Project Information	
Project acronym:	HEcoPerMed
Project full title:	Health Economic Models for Personalised Medicine
Starting date:	01.01.2019
Duration:	42 months
Coordinator:	Doris Schartinger

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

History of changes			
Version	Date	Changes	Author

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

SUMMARY

Reimbursement agencies increasingly make decisions about which health care interventions to fund on the basis of the perceived clinical benefits and the results of the health economic evaluations. Therefore, it is key that these economic evaluations should be of high quality. It has been claimed that personalised medicine (PM) is different than non-PM, and should be assessed bearing in mind these differences, thus the HEcoPerMed consortium developed a Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine. In order to demonstrate the practical application of the guidance, three case studies were selected: Tumour Agnostic Treatments, DPYD Genotyping and Maturity Onset Diabetes of the Young. A virtual workshop was organised in September 2020 with experts in the area of health economics, health technology assessment and health economic modelling to present how the guidance was worded and applied to the three case studies and get their feedback. A second workshop with experts in payment and reimbursement followed in April 2021, then, to discuss how to finance and reimburse PM, what the feasible and appropriate models were, the value incorporation, the units of payment, and other issues. The two workshops successfully supported the overall aims of HEcoPerMed and expert insights provided valuable input to WP1, WP2 and WP3.

Chapter 1 discusses the rationale and the aim of organising the virtual workshops.

Chapter 2 presents the methodology, e.g. expert selection, discussed topics, polling methods.

Chapter 3 presents the results from the virtual workshops clustered in themes, and **Chapter 4** includes discussion of the workshop results and conclusions.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
PM	Personalised medicine
R&D	Research and development
HEcoPerMed	Health economics for personalised medicine
HTA	Health technology assessment
HERC	Health Economics Research Centre
DPYD	Dihydropyrimidine dehydrogenase deficiency encoding gene
ICPerMed	International Consortium for Personalised Medicine
MODY	Maturity-Onset Diabetes of the Young
ISPOR	The Professional Society for Health Economics and Outcomes Research
PD-L1	Programmed death-ligand 1
NTRK	Neurotrophic tyrosine receptor kinase
PB	Performance-based
FB	Financial-based
PFS	Progression-free survival
OS	Overall survival
PROMS	Patient-reported outcomes

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1 INTRODUCTION

Reimbursement of personalized medicine (PM) innovations is largely based on their expected clinical benefits, cost-effectiveness and budget impact. Therefore, high quality economic evaluations that are well-suited to personalized medicine are crucial in diffusing PM innovation to healthcare systems. There are currently many voices arguing that PM is different than non-PM and delivers benefits not captured in conventional evaluation frameworks [1], and its cost-effectiveness should be assessed bearing in mind these differences. However, there are no (inter)national guidances or scientific consensus on how to assess PM which leads to large variation in the methodology and reporting of economic evaluations of PM [2, 3]. Therefore, the Health Economic Models for Personalised Medicine (HEcoPerMed) consortium developed a Guidance for the Harmonisation and Improvement of Economic Evaluations of PM [4]. The consortium has demonstrated the practical application of the guidance using three different PM innovations as case studies, including Tumour Agnostic genetic Treatments, DPYD Genotyping for fluoropyrimidine chemotherapy, and gene screening of Maturity Onset Diabetes of the Young.

On behalf of the HEcoPerMed consortium, Syreon Research Institute organised a one-day virtual workshop with international experts including representatives of healthcare payers, test technology developers/manufacturers and health economic professionals. The modelling guidance for personalised medicine (PM) that was developed in Work Package 1 was presented, as well as preliminary findings from its application in three case studies (Work Package 2). The original plan was to organise a face-to-face workshop. However, due to the COVID-19 outbreak the face-to-face meeting was converted to a virtual one. The **aim** of the workshop was to solicit expert opinion that will be used to refine and validate the guidance and discuss the appropriateness of the modelling methods of the selected case studies. Results of the workshop are planned to be used to fine-tune the guidance development and to support modelling activities of the selected case studies.

Furthermore, the way that research and development (R&D) of PM is funded and manufacturers of PM innovations are reimbursed by healthcare payers impacts the availability, diffusion, and access to PM innovations [5, 6]. Currently, the vast majority of PM interventions that have been approved by regulatory agencies and marketed are reimbursed through traditional reimbursement models that include fees, bundled payments and diagnostic related groups. The risk-sharing agreements used to pay for PM are mostly purely financial and involve partial rebates, free cycles of treatment and discounted schemes. Several risk-sharing reimbursement models that take into account the performance of the drug have been identified in the literature and they are mainly applied to pay for gene and targeted therapies and companion diagnostics. The main barriers and disincentives to PM financing and reimbursement are the lack of strong links between stakeholders and the lack of demonstrable benefit and value of PM. Public-private financing agreements and performance-based reimbursement models could help facilitate the development and uptake of PM interventions with proven clinical benefit.

In order to elicit the opinion of experts on how to overcome the barriers to PM financing and reimbursement, identified in the literature, the Health Economics Research Centre at the University of Oxford (HERC) organised a one-day virtual workshop on behalf of the HEcoPerMed consortium on 20th April 2021. The workshop was part of Work Package 3 of the HECOPERMED project that focuses on suitable financing and payment models for personalised medicine (PM) and follows a systematic literature review of such models. The **aim** of this workshop was to bring together experts and stakeholders from academia, industry,

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payers and insurers, funding organisations, health technology assessment and regulatory bodies, as well as patient representatives, to discuss about models for financing and reimbursement that would ensure clinical translation and adoption, and patient access to PM with proven benefit.

The workshop was virtual, via Microsoft Teams as an in-person meeting was not possible as had been originally planned due to the ongoing COVID-19 pandemic and travel and social distancing restrictions. The workshop participants included international experts in the field of PM with experience and expertise in research financing, reimbursement, health economics and health technology assessment from academia, industry, payers and insurers, funding organisations, health technology assessment and regulatory bodies, and patient representatives.

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2 METHODS

2.1 Participants and preparation

Participants in virtual **workshop one** were identified from relevant literature and through the professional network of the HEcoPerMed members. The main selection criteria were familiarity and experience with personalized medicine modelling and knowledge of (at least) one of the case study topics, with efforts toward a balanced geographical and gender distribution of participants. Participants were sent pre-reading materials one week before the meeting, which contained the workshop agenda, information about the consortium, a description of the case studies and the draft paper on the guidance for the harmonization and improvement of economic evaluations of personalised medicine.

Participants in virtual **workshop two** were identified through relevant publications and Google searching, as well as the professional networks of the HEcoPerMed consortium and ICPerMed. Selection criteria included familiarity and experience with financing and reimbursing of PM and efforts were made to balance the representation of different stakeholders' groups, e.g. academia, industry, payers and insurers, funding organisations, health technology assessment 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 invitation rounds from December 2020 – April 2021. Participants were sent pre-reading materials the week prior to the workshop that included the workshop agenda, the presentation of findings from a literature review of financing and reimbursement of PM, 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 PM and the barriers to financing and reimbursement identified in it. The final version of the questions was derived through an iterative process involving discussion and feedback from HEcoPerMed partners.

2.2 Workshop structure

2.2.1 Virtual workshop 1

The workshop took place on the 24th of September 2020. The morning session started with a keynote speech by prof. Sarah Wordsworth, who presented the "Opportunities and challenges for health economics of personalised medicine". Subsequently, Wolfgang Ballensiefen introduced the International Consortium for Personalised Medicine (ICPerMed) network and the HEcoPerMed consortium. After a short break, Simone Huygens gave a detailed introduction to the "Guidance for the harmonization and improvement of economic evaluations of personalised medicine" (developed in Work Package 1). After the presentation the participants were invited to ask questions for clarification. The morning session ended with a brief overview by Balázs Nagy on the "Case study selection rationale".

During the afternoon session, the participants were separated into three groups according to the case studies:

- Testing for NTRK fusions and starting tumour-agnostic treatment with TRK inhibitors
- Upfront DPYD (dihydropyrimidine dehydrogenase deficiency encoding gene) testing (ToxNav) to personalise chemotherapy treatment for metastatic breast cancer

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- Adjusting insulin treatment after genetic testing in Maturity-Onset Diabetes of the Young (MODY)

Each session started with an introduction to the selected case study and the planned modelling methodology. After the overview the participants were invited to ask questions for clarification.

In the next phase, a structured discussion was held regarding the application of the guidance for economic evaluations of personalised medicine to each case study, which was guided by pre-selected guidance items. The relevant items for each case study had been selected by the HEcoPerMed researchers prior to the workshop and were allocated based on each team's priorities and aimed to ensure wide coverage of the guidance items. In the structured discussion, two questions were raised for each guidance item:

1. Given the context of this case study, does the recommendation seem complete and well-phrased?

2. Do you have any comments on the modelling approach we propose?

For question 1, the participants were asked to choose from three options: "Yes", "No, not complete" and "No, not well-phrased". Answers were managed with Mentimeter polling application, where each participant answered without knowing others' answers. Nonetheless, the answers of each participant were seen by the moderator of the sessions, which enabled the moderator to inquire for the rationale behind the chosen answer when necessary. The first question – which aimed to gather participants' reflections on the comprehensiveness and wording of the recommendations included in the guidance – was only opened for discussion in case of disagreement, where disagreeing participants were asked one-by-one to share their opinion. This method was used to avoid any peer pressure and to save time for meaningful discussion only in case of disagreements. The second question – which aimed to have participants' reflections on the (planned) modelling approach in the case studies – was opened for discussion in case of comments. In this case, participants were simply asked to provide their comments. These reflections were only used to facilitate and adjust the model development process and did not provide direct feedback on the applicability of the recommendations, therefore these are only briefly summarized in this report. The poll results and the comments of the participants are presented anonymously in the results section of this report.

2.2.2 Virtual workshop 2

The one-day workshop took place on 20 April 2021 and was divided into morning and afternoon sessions. The morning session started with an introduction to HEcoPerMed consortium and the workshop by assoc. prof. Apostolos Tsiachristas from HERC. A keynote talk was given by Dr Richard Charter, Vice President MedTech Market Access, Europe & Asia Pacific at AliraHealth and Co-Chair of ISPOR Special Interest Group on Medical Devices and Diagnostics, who presented the "Personalised Reimbursement for Personalised Medicine? A Tour of Innovative Funding Pathways in Europe". This was followed by a presentation of "ICPerMed and the PerMed family" by prof. Ejner Moltzen, Chair of ICPerMed and Director of Innovation Fund Denmark. After a short break, Dr Rositsa Koleva-Kolarova from HERC presented the findings from a literature review of financing and reimbursement of PM (performed in Work Package 3).

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In the afternoon sessions, the participants were split into three groups to discuss:

- Group 1: Financing of research and development (R&D) for personalised medicine, structured discussion led by Prof. Sarah Wordsworth from HERC;
- Group 2: Performance-based reimbursement models for PM led by Assoc. Prof. Apostolos Tsiachristas from HERC;
- Group 3: Financial-based reimbursement models for PM led By Dr Rositsa Koleva-Kolarova from HERC

Each session started with a brief reminder of the definitions, based on the performed literature review, which would be used during the structured discussions. These definitions related to:

- Personalised medicine – "a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention."
- Financing model – a mechanism to fund research and development (R&D).
- Appropriate model – a model that provides adequate financial incentives to achieve widespread adoption of PM with proven benefit.
- Facilitators and barriers – enablers or obstacles of the adoption of suitable financing/reimbursement models (i.e. models that could stimulate the development and uptake of PM).
- Incentives and disincentives – factors that could motivate or discourage the adoption of suitable financing/reimbursement models (i.e. models that could stimulate the development and uptake of PM).

In addition, reminder slides containing a brief overview of financing models, financial-based and performance-based reimbursement models for PM identified in the literature review were presented.

In each session, experts were presented with a set of 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. Group 1 discussed financing and reimbursement of PM and the discussion was based on 8 multiple choice questions and 4 open ended questions. Group 2 discussed performance-based reimbursement for PM and the discussion was based on 12 multiple choice questions and 3 open ended questions. Group 3 discussed performance-based reimbursement for PM and the discussion was based on 10 multiple choice questions and 3 open ended questions.

2.3 Transcripts and analysis

All group sessions of the workshops were recorded via MS Teams with the consent of the participants. Captions and transcripts of the recordings were auto generated, and transferred to a notepad to be reviewed and anonymised; analysis of poll answers and open text were performed.

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3 RESULTS

3.1 Participants and preparation

Of the 155 experts invited for workshop 2, 44 indicated availability and 35 attended the workshop, 5 declined and 106 did not respond (response rate 32%).

3.2 General recommendations related to the guidance

This section presents the general recommendations by experts which emerged in the discussion that followed the presentation of the guidance for the harmonisation and improvement of economic evaluations of personalised medicine.

Early HTA

Expert: We often build early economic models when PM is first developed. Have you thought about which of these recommendations are needed in an early economic analysis (as a minimum)?

Structure of guidance

Expert: In the final guidance/document, it might be helpful to consider grouping and ordering the individual recommendations in the same order/categories as the CHEERS checklist.

Model type

Expert: Some PM issues are difficult to incorporate in the often-used Markov models. Would you propose different modelling techniques, such as patient-level modelling?

Consortium member: There is no single model most appropriate for PM modelling, as the usefulness of a model type depends on the specific decision problem. We therefore don't prescribe any single modelling technique.

Relationship between surrogate and final outcome

Expert: It is potentially a waste of information if only premature survival data from the trial is used (e.g. in cancer), while data on surrogate outcomes (e.g. tumour response) is disregarded.

It might be worth adding a recommendation stating that if surrogate modelling is used, the strength of the relationship between surrogate and final outcome should be made explicit.

Consortium member: Agreed, the surrogate-final outcome relationship is important to consider. Another aspect to consider in addition to this is the genotype-phenotype relationship (e.g. how the level of PD-L1 expression relates to tumour response).

Expert: Agreed that it is worth exploring how we can make better use of trial data on surrogate outcomes.

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Treatment effectiveness data

Expert: Are there modelling solutions to address limited data availability (such as in the small single-arm trials for TRK-inhibitors larotrectinib and entrectinib)?

Consortium member: While modelling can be used to address some of the challenges, the main solution to insufficient/inadequate data may be increased communication between regulators and national HTA agencies about what kind of data is needed.

Allocating testing costs to subsequent treatments

Expert: Currently we have a black-and-white situation where treatments either get allocated 100% of testing costs (if a test is to be newly introduced) or 0% of testing costs (if the test is already part of standard care). Practice might be more nuanced, as multiple treatments may be given after a test that is to be newly introduced. The argument is being made by industry that assigning 100% of testing costs to the first treatment to come onto the market, punishes the “first mover”. Perhaps we need a better way of assigning cost.

Consortium member: An economic evaluation should reflect the decision problem at hand for decision-makers, which often requires allocating 100% of the costs of a newly introduced test to the treatment that requires its introduction. However, the effect of alternative ratios for the cost allocation can be investigated in sensitivity analysis.

Consortium member: Innovation can be rewarded using alternative governmental instruments (potentially not through the healthcare budget).

The issue of cost allocation may be temporary and may disappear once broad gene testing is common practice.

What to include in calculation of testing costs?

Expert: Is there a recommendation concerning the costs of the test/intervention and what should be considered/included, e.g. equipment, expected number of individuals using it, etc.?

Perspective

Expert: You could consider recommending taking a societal perspective in sensitivity analysis, if the base case perspective is not societal (to be in line with Neumann et al.).

Consortium member: This recommendation would potentially not be specific enough to PM. If we believe that a sensitivity analysis with a societal perspective should always be included, this PM-specific guidance is maybe not the place to discuss that.

Expert: I think it's always important to remember how the decision threshold should be adjusted (downward) if the scope of the analysis is broadened. I think Neumann et al. did not recognise this. Conducting multiple scenario analyses can result in multiple estimates without any clear decision emerging.

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3.3 Reflections and recommendations on specific guidance items

This section summarises the results of the Mentimeter polling on each guidance item presented and respective comments by experts.

#3 Item: "Ensure that the position of the modelled testing and treatment options accurately reflect clinical practice."

Mentimeter poll result:

	MODY	NTRK	TOXNAV	**SUM**
Yes	4	5	4	**13**
No, not complete	2	2	2	**6**
No, not well-phrased	0	1	0	**1**

Comments: Modellers should make clear

(1) how well included tests reflect all available options and

(2) where included tests fit in the testing pathway.

The word "modelled" should maybe be replaced, as this doesn't capture the key issue, i.e. to what extent what is "modelled" is relevant to the decision problem. Modellers should try to justify not only what they have done but also what they haven't done.
Clinical practice versus guidelines

- There are clinical guidelines but for certain reasons modellers may not choose to follow these guidelines because of what they want to model and the outcome they are interested in. The suggestion by experts is to differentiate between current practice and clinical guidelines.

When modelling screening interventions, modellers should take care of all relevant strategies for all patient subgroups, as otherwise (cost-)effective strategies might not be included in the model and consequently not identified by decision-makers.
Consider using the term "diagnostic strategy" instead of "testing".
Consider adding "in the relevant study population and/or subpopulation" after "reflect clinical practice".

#4 Item: "Ensure that the data on the predictive accuracy of a test is the latest available and obtained in a population that matches the modelled population."

Mentimeter poll result:

	MODY	NTRK	TOXNAV	**SUM**
Yes	3	3	3	**9**
No, not complete	3	2	0	**5**
No, not well-phrased	0	2	1	**1**

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Comments: Consider changing “latest” to “best” available, as latest might not be equal to best available data.

The uncertainty (resulting for example from variation in testing practice between labs) in the accuracy of tests should be considered.
Consider adding examples to “predictive accuracy of a test” in brackets, like: (i.e. positive predictive value, negative predictive value, sensitivity, specificity)
“Predictive accuracy” is affected not only by sensitivity and specificity of the test itself but also by human error and environmental factors.

#5 Item: “When different cut-off values are in use to determine test results, clearly define the cut-off value assumed in the base case. Investigate the effect of alternative cut-off values using sensitivity analysis.”

Mentimeter poll result:

	MODY
Yes	2
No, not complete	3
No, not well-phrased	1

Comments: According to expert suggestions the second sentence should state explicitly that we are interested in the effect of alternative cut-off values on cost-effectiveness outcomes.

The suggestion by experts is to use threshold analysis for cut-off values of test results.

#7 Item: “Confirm that the assumed cost and predictive accuracy of the test are accurate in the setting of interest and consider possible variation in cost and predictive accuracy of testing across laboratories.”

Mentimeter poll result:

	TOXNAV
Yes	5
No, not complete	0
No, not well-phrased	0

No comments

#8 Item: “If there is a risk of increased morbidity or mortality during waiting periods, incorporate relevant waiting periods in the model.”

Mentimeter poll result:

	NTRK	TOXNAV	**SUM**
Yes	6	3	9

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No, not complete	1	0	1
No, not well-phrased	1	2	3

Comment: Consider adding “a known and quantifiable risk” instead of just “risk”.

#9 Item: “When a treatment requires the use of a test to stratify patients, include the (downstream) costs and health outcomes of testing for both individuals who test positive and individuals who test negative in the model.”

Mentimeter poll result:

	MODY
Yes	4
No, not complete	2
No, not well-phrased	1

Comments: Although including downstream costs and health outcomes of testing seemed too obvious to be included to some experts, other experts were in favour of keeping this recommendation in the guidance.

According to experts the recommendation should explicitly point on the true and false negative and positive cases, e.g. include into brackets.

#10 Item: “Include the costs and health outcomes of testing relatives of index patients with inheritable genetic mutations in the model.”

Mentimeter poll result:

	MODY
Yes	1
No, not complete	2
No, not well-phrased	3

Comment: Consider adding “where possible” at the beginning to make it less strict

#13 Item: “When effectiveness of a treatment for a patient population with a specific gene mutation is estimated using historical data, account for the prognostic value of the gene mutation and its distribution in the historical cohort.”

Mentimeter poll result:

	NTRK
Yes	6
No, not complete	0
No, not well-phrased	1

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Comment: The experts suggested changing “historical” to “external” as the issue of unknown prognostic value is not only relevant to historical data, this is a relevant issue when using any kind of “external data” to estimate effectiveness in the control group.

#16 Item: “Do not include additional elements of value in the base-case analysis. When additional elements of value are included in scenario analyses, ensure possible elements of negative value have been equally considered and are included in the analysis of both intervention and comparator if relevant.”

Mentimeter poll result:

	TOXNAV
Yes	5
No, not complete	0
No, not well-phrased	0

No comments

#17 Item: “Include parameters reflecting patient and clinician compliance in economic evaluations for decision-makers who require cost-effectiveness results under realistic circumstances.”

Mentimeter poll result:

	MODY	TOXNAV	SUM
Yes	5	5	10
No, not complete	1	0	1
No, not well-phrased	0	0	0

Comments: It was found that there might be uncertainty around the applicability of this recommendation for all PM cases. It is still important to include it but with possible remarks/reflection on the context of decision making

The experts suggested to include **uptake** and compliance as in some evaluations this could make a difference. Expert elicitation may be used to obtain estimates of uptake and compliance.

#18 Item: “Confirm that the assumed compliance is accurate in the setting of interest and consider possible variation in compliance across societal groups.”

Mentimeter poll result:

	MODY
Yes	5
No, not complete	1
No, not well-phrased	0

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Comment: There could be variation of compliance between, for example some trial data and real setting, e.g. in many drug clinical trials it could be as high as 95% while in real clinical practice it could be 80% so this might also be included.

#19 Item: "When expert opinion is used to estimate quantitative model parameters, synthesise the opinions of the experts into a probability distribution to be included in sensitivity analysis."

Mentimeter poll result:

	NTRK
Yes	5
No, not complete	0
No, not well-phrased	2

Comment: Be careful with language around expert "opinions". The overarching term is expert judgement, with qualitative judgements called expert "opinion" and quantitative judgements called expert "values". Perhaps say something like "When experts are used to value input parameters …"

#20 Item: "Identify uncertainties in structural assumptions and decisions and investigate their impact on cost-effectiveness results through sensitivity analysis. Parameterise structural aspects where possible."

Mentimeter poll result:

	NTRK
Yes	7
No, not complete	0
No, not well-phrased	0

No comments

3.4 Case study specific recommendations in relations to the guidance or Reflections on the selected modelling methodologies

MODY

It was suggested to consider every diabetic patient below 35 years of age to be able reach more GCK MODY patients. Regarding the MODY calculator cut-off point, next to using the clinically recommended one, the "cost-effective" cut-off point could as well be determined as a result of the modelling process. Testing relatives of patients highly depends on MODY type however modelling these additional patients were not recommended for the base case. It was suggested to investigate several scenarios on screening strategies and respective clinical pathways, to make sure that finally the optimal strategy is adopted to the jurisdiction of interest.

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NTRK

It was mentioned that, when weighting studies that estimate diagnostic sensitivity and specificity, we should ensure to weight according to the number of samples tested positive, not the total number of samples tested. In estimating sensitivity and specificity for a test (e.g. IHC), we were encouraged to be specific about the technology used (e.g. Abcam or Cell Sign Tech). While the experts generally agreed with our proposed method for modelling the testing phase, it was mentioned that we might want to account for the fact that NTRK testing may happen a long time before TRK inhibitors are given to the patient. E.g. lung cancer patients might receive NGS early in their treatment process and test positive for NTRK but receive other, earlier-line treatments first. We were also encouraged to consider more explicitly how to account for heterogeneity in treatment effect across tumour locations.

TOXNAV

With regards to placement of the ToxNav test in the clinical pathway, the experts thought that the place of the test was reasonable and clinically justifiable. It was suggested that we could consider extrapolating the follow-up in the model to 5/10 years, or lifetime, which we have previously also considered. It was also advised to try and validate the predictive accuracy of the ToxNav test in another cohort/setting. Another suggestion was to compare the 19 variant ToxNav test to a test with less variants, e.g. 4, in terms of time to obtain the results from the test and cost which we have planned to do by comparing data of DPYD genetic testing from 2019 to 2020 that we obtained from local oncology directorates. Experts also advised to consider patients' compliance as well as clinicians', which we will incorporate in the model using hospital data.

3.5 Financing of R&D of PM

This section summarises the responses to the Mentimeter polling (details presented in Appendix 3) and discussion with the 9 experts during the Group1 session.

3.5.1 Changing landscape

Two (29%) experts thought that the current landscape of R&D financing encourages PM, while 3 (43%) considered current landscape to be hampering PM development (question 1, Table 1, Appendix 3). One expert (14%) thought that current landscape of R&D financing neither enables nor hampers PM development, and another (14%) had other opinion. Experts added that creating a favourable landscape for investors in financing R&D for PM is needed that will encourage and support universities and small and medium enterprises (SMEs) to invest in PM innovation. For example, applying approaches and arrangements that have worked in rare diseases to the whole area of PM could create better opportunities for PM investment. Another example is targeted public or philanthropic investment to boost the development of PM, and advanced therapies in particular, as these therapies currently face a huge uncertainty related to return on investment due to reimbursement challenges and require specific manufacturing capacity available at specific times. Overcoming the reimbursement challenges for advanced therapies include manufacturers and developers having a clear idea of which reimbursement schemes will be applicable to their products, something which is currently unclear, and hampers the investment in advanced therapies. In addition, public investment in developing technologies and facilities to produce advanced therapies and training healthcare professionals to deliver them could help overcome the manufacturing capacity challenge.

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Experts which found the current landscape facilitating stated that currently there are financial resources for upstream basic and applied research in PM, however, there needs to be international coordination and discussion to enhance cooperation, especially to involve regional and local levels, and regions, and improve their understanding on funding for R&D of PM. In addition, there are already well developed research institutes in different disease areas, for example cancer and cardiovascular, that can potentially collaborate on joint projects in PM (as there are no dedicated institutes for PM).

3.5.2 Public-private partnerships

Wider collaboration between public and private funders, as well as SMEs and bigger corporations in the private sector can help to close the gap between innovation and access to it, as well incentivise funding by involving multiple stakeholders in the discussions, data sharing, and integrating patient outcomes perspective and budget perspective in the health systems. Better involvement of regulatory bodies, the European Commission, and relevant stakeholders, including the patients, into the implementation of PM into healthcare systems could also improve the access to PM.

Experts were presented with the current state of financing R&D of PM, depicted in Figure 1 and Figure 2, and were asked which of the models used, e.g. public, private or public-private mix of financing, is appropriate for PM (question 2, Table 1, Appendix 3). Experts unanimously considered public-private mix of funding to be the most appropriate model for financing R&D for PM. One argument in favour of this model is that universities, academic hospitals, and SMEs can drive innovation development while private sector can drive the implementation of innovations into practice, e.g. they can make better use of their combined competencies. A specific example, where the mix of public and private investment could be beneficial is the development of gene therapies in the USA where the National Institute of Health engaged with industry to develop together with academic partners all the pipeline from the production to the regulatory approaches. This collaboration involved not only sharing of the funding, but also sharing expertise and open science at the precompetitive stage which then allows each company to go into their own competitive development niche subsequently.

An example of appropriate financing of R&D for PM (question 3, Table 1, Appendix 3) is the ERA PerMed collaboration which not only provides funding but is also dedicated to enhancing transborder cooperation, especially in fields such as data sharing where there are challenges also on national level, and has attracted international collaboration from countries outside Europe (Canada, Brazil and Egypt). Another example is the Innovative Medicine Initiative that is a programme funded by the European Commission and the pharmaceutical industry which have funded a lot of personalised medicine collaborative research projects.

Figure 1. Financing of PM

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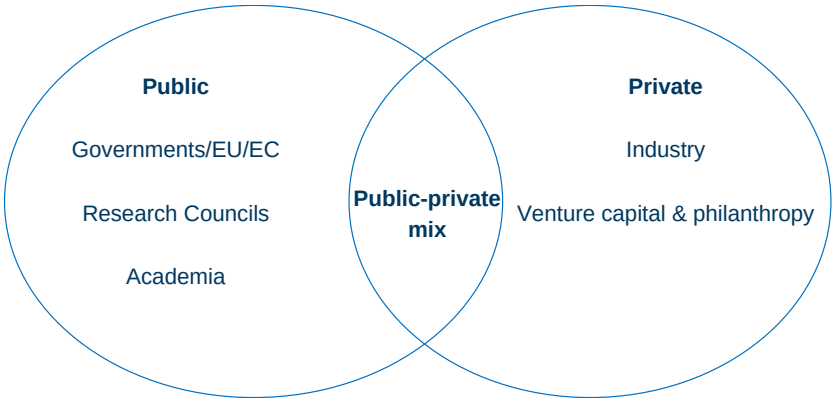
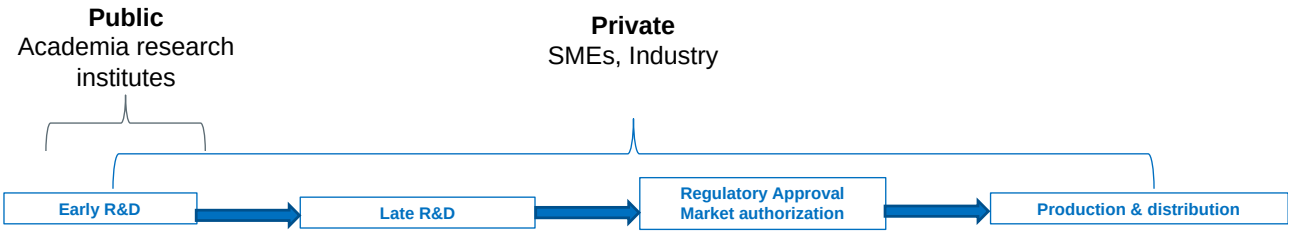


Figure 2.



- ✓ Experience & expertise in early R&D
- ✓ Profit from selling the patent/spin-off
- ✓ Reinvestment into other early R&D

- ✓ Experience & expertise in conducting large international RCTs
- ✓ Decreased financial risk from further developing a product already tested in early stages
- ✓ Experience & expertise with regulatory approval and market authorization processes
- ✓ Capacity to do large scale production & distribution
- ✓ Marketing and pricing strategies that reflect all potential benefits of the product
- ✓ Generating capital to buy another patent/spin-off

3.5.3 Ways of public sector involvement in partnerships

Figure 3. Proposed model for financing of PM

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✓ Two potential scenarios:
A) Publicly funded partners perform early R&D, private partners carry remaining cycles => public partners benefit from % of sales/co-ownership/reduced price
B) All partners are involved in each cycle of PM development and own the final product together

Potential facilitators:
✓ Shared financial risk
✓ Opportunity to benefit from collaborative expertise & shared resources
✓ Opportunity to benefit from economies of scale and explore synergies

Potential barriers:
✓ Ownership of intellectual property/patent
✓ Ownership & protection of data
✓ Price increasing behaviour

Experts were presented with two potential scenarios of future development of financing R&D for PM, presented in Figure 3, and were asked which of these scenarios was more feasible (question 4, Table 1, Appendix 3). Three experts (38%) considered both scenarios feasible, while scenario A or scenario B, separately, were supported by equal number of experts (2 votes (25%) for each), and one expert (12%) had other views. Experts noted that a potential challenge in scenario B is that not all stakeholder may have an interest in participating in all stages of the R&D. In addition, experts expressed views that the whole value chain should be considered, along with various needs for research, e.g. including not only biomedical and clinical research, but also research into the economic evaluation and ethics of PM, for example, as well as research into implementation of PM in health systems. Other examples of scenarios, involving health apps and telemedicine, were pointed where the roles of public and private partners are reversed, e.g. private companies develop the product while public partners take over the implementation in practice. It was also pointed that the feasibility of the scenarios would depend on what programmes for financing of PM research (Innovative Medicine Initiative, One million genome project, Europe beating cancer initiative) are already available and whether these are able to accelerate implementation.

Two experts (22%) considered that research partners should not benefit from data exclusivity and data produced should be owned by all partners, while 7 (78%) had other views (question 6, Table 1, Appendix 3). Experts also shared views that in addition to the fair principle in data sharing the care principle that relates to control over data sharing, the collective benefits and responsibility in the specific ethical aspects should also be followed, in order, not to allow for certain already marginalised groups of the society to be excluded, thus, increasing further already existing health disparities. It was pointed that empowerment of patients and the citizens' trust in data are important elements of data sharing. Experts added that data 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 (by industry, for example). A specific example of how industry can be encouraged to share data was given about a gene therapy that is in the last phase of development and the developing company were willing to share the data generated in a real world setting in exchange of the public payer providing early access of patients to the therapy and a price for the therapy before and after approval based of clear performance elements.

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Six experts (75%) thought that publicly funded research institutions and SMEs can become equal partners with development companies instead of their suppliers of innovation by providing funding, as well as in kind contributions, and sharing public resources while two (25%) had other views (question 7, Table 1, Appendix 3). A specific example was given which involved a large neurology hospital in Canada that implemented open science and consented their patients for research thus attracting investments from pharmaceutical companies.

Six experts (75%) thought that public authorities can justify the investment of public funds in high risk R&D projects of PM by steering innovation where innovation is most needed, and the expected benefits for patients and society (question 8, Table 1, Appendix 3) while two (25%) had other views. It was pointed that when a therapy that is still in development (e.g., in stage 3 clinical trial, for example) is given to patients (e.g., compassionate use), then there are already clear justifiable benefits for meeting an unmet need. It was also pointed out that if justifying public funding has to always take into account patient and societal benefit, then that might risk the investment in basic research that doesn't always have an identifiable benefit.

Experts thought that sharing risks and benefits between stakeholders can be done by further enhancing the concept of open innovation; by clear and fair contract from the very start of the collaboration, and by properly designed incentives and (novel) structures that align stakeholders' interests (question 9, Table 1, Appendix 3). With regards to funding education related to PM (question 10, Table 1, Appendix 3), an example was given about universities organising dedicated services to help researchers in their grant application which involves educational activities. In addition, an example of educating patients to be partners in research in the field of rare diseases was provided. Regional initiatives within the ICPerMed family were given as an example of helping less developed countries and regions in Europe to apply for funding for PM related activities (question 11, Table 1, Appendix 3).

3.5.4 Barriers and facilitators for public-private partnerships

Regarding facilitators and barriers to financing PM research (question 5, Table 1, Appendix 3), experts pointed open science and the application of the fair principle in sharing research findings as facilitators to promoting public and private research. Collaboration between research centres can further facilitate research (e.g., European reference centres for rare disease as well as collaboration between hospitals that have facilitated the diagnosis of some rare disease). In addition, involving payers/insurers early in the development of PM can also serve as a facilitator. Barriers to financing R&D of PM, that experts identified, were the availability of specific legislation and policies for data sharing. For example, Finland and Estonia passed the legislation necessary to use biomedical data for research but this has not been done in other countries mainly due to ethical issues and it serves as a bottleneck for research.

3.6 Performance-based reimbursement for PM

This section summarises the responses to the Mentimeter polling (details presented in Appendix 3) and discussion with the 10 experts during the Group 2 session.

3.6.1 Feasibility of performance-based reimbursement for PM

Seven experts (70%) considered performance-based (PB) models to be very appropriate and feasible for reimbursing PM, while three experts found them to be somewhat appropriate and

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feasible (10%), not appropriate and feasible (10%), and not appropriate and feasible at all (10%), respectively (question 1, Table 2, Appendix 3). It was noted that some PB models may be appropriate for reimbursing PM but there might be barriers to these models which actually make them less feasible in practice. In addition, it was pointed that the feasibility and appropriateness of PB models might depend on the perspective (e.g., patient, healthcare system, etc.), as well as on the setting, e.g. different countries and jurisdictions, and the opportunity costs related to introducing PB models for one type of treatment (e.g., PM) but not for others, and also costs related to gathering outcomes data.

The majority of experts (78%) considered PB models to be appropriate for some types of PM, while one (11%) thought PB models were appropriate for all types of PM, and one (11%) had other views (question 2, Table 2, Appendix 3). Experts thought that PB models may be more appropriate for PM interventions in which the time horizon for observing whether outcomes are actually achieved is short (for example, treatments for severe or recurrent cancers) than for interventions for which outcomes are expected to be observed in a longer time horizon (e.g., gene therapies for children). It was pointed that PB models may be more feasible in situations where agreements can be made around simple data points to measure outcomes, such as overall survival in cancer, and less feasible for diseases which face the burden of collecting complicated measurements. In addition, the feasibility of PB models may vary depending on the specific uncertainty that is present, e.g. related to budget or clinical outcomes. In situations where the clinical trials about certain drugs are not convincing for payers, the PB models might be the only way to convince payers to reimburse these drugs. It was noted that if patients themselves were monitoring and reporting the outcomes, then that might make PB models easier and feasible to implement. It was also stated that reimbursing PM by PB models and non-PM through models that are not based on outcomes might create imbalance and incentives for using the non-PM therapy because the reimbursement would be easier.

Most experts (80%) thought that post-marketing, legislative and HTA (10%) related arrangements are amongst the prerequisites that need to be in place for PB models to be implemented while one expert (10%) had other views (question 3, Table 2, Appendix 3). In addition, getting into early interactions with payers to discuss on what the relevant outcomes should be and agreeing on these outcome measures as well as on the healthcare infrastructure to be used for the provision of the PM technology would be crucial for successfully implementing PB models. In addition, it was noted that PB models can be challenging to implement, especially in some types of PM such as gene and cell therapies, and therefore, should be considered worthwhile when the value of information is positive. PM, especially the more costly one-off potentially curative treatments, face budget and clinical uncertainty barriers and PB models can create incentives to adopt these PM in clinical practice, as the payment will be maintained as long as the outcomes are maintained, e.g., the payment barriers would be overcome by spreading the payments in the future, and thus there is the necessity for agreeing (surrogate) endpoints which would be collected for measurement.

3.6.2 Units and coverage of performance-based reimbursement

The majority of experts (67%) considered sub-group of patients/population with a course of therapy being the smallest unit to be the units that should be used for reimbursement of PM through PB models, while two experts (22%) considered the individual unit to be more appropriate and one (11%) had another opinion (question 4, Table 2, Appendix 3). However, experts agreed that collecting data should be done on the individual level. One justification of using sub-groups as a unit of payment is the different efficacy as well as the different value of the same drugs in different population sub-groups. Different level of efficacy could also merit from indication-based pricing on the sub-group level.

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A different view was noted as well, e.g. that PB models can be considered as a tailored approach and therefore all units can be potentially used for reimbursement depending on the disease type.

One expert (11%) thought that only the PM should be covered for reimbursement, five experts (56%) considered reimbursement being offered for the PM and the companion test/drug, and three (22%) supported reimbursement of all related treatments/diagnostics, and one had another view (11%) (question 5, Table 2, Appendix 3). Practicality and the available healthcare infrastructure were named as justifications for offering reimbursement for PM and the companion test/drug, however, some experts noted that ideally all related treatments/diagnostics should be covered but that might be challenging in a real world setting due to HTA and price related considerations. A challenge that was noted to applying reimbursement for test and treatments, specifically for cases where one test can be indicative for assigning patients to more than one treatment, is the difficulty of splitting the cost of testing between these treatments. There were other views, however, according to which only the PM, e.g. the drug cost, should be covered as the cost of the companion diagnostic was considered small. It was noted by another expert with an opposite view that not reimbursing the companion diagnostic may in some cases lead to the drug not being offered to patients, and especially for drugs that are licensed together with the companion diagnostic, the reimbursement of the two as a package can be viewed as practically feasible. A specific example was provided for Belgium where after legislative changes currently tests have to be evaluated and considered on the basis of their value (expressed as positive and negative predictive value, also called prescription value which is something that is also currently being considered but not implemented in practice in the Netherlands).

3.6.3 Outcomes and value in performance-based reimbursement

The views of experts on what outcomes should be used and measured in PB models were quite split with clinical outcomes (e.g., specific clinical indicators, PFS, OS, etc.), both clinical and quality of life outcomes (PROMS), overall value and other outcomes gaining almost equal number of votes (question 6, Table 2, Appendix 3). Some experts mentioned that they would prefer rigid clinical outcomes to PROMS due to the variation of quality of life among different patients. Other experts preferred an overall value outcome that can be measured by a single or several components, e.g. progression-free and overall survival in cancer.

Experts thought that outcomes (including patient reported outcomes) and clinical benefits can be translated into value by applying value assessment frameworks including patient preferences, or QALYs, and has to be consistent with the objectives of the entire healthcare system (question 7, Table 2, Appendix 3).

Experts thought that it is not feasible to include all value components in the reimbursement agreement, but value of treatments, especially the ones in which the benefits accrue 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 caption for performance (question 8, Table 2, Appendix 3). A specific example was pointed about gene therapies for haemophilia where annuities can serve as means of solving the direct affordability issue, and not managing the risk in the long run. Some experts argued that a more realistic approach would be to consider only the value of PM from healthcare perspective and not include additional elements of value. Other experts were inclined to expanding the current value framework of overall survival gain, quality of life gain and cost offsets by adding some more elements, but only if these is (scientific) evidence that these elements hold a certain value to people. Experts pointed that values should be SMART, e.g. specific, measurable, achievable, realistic, and the key point is the timing at which the outcomes are expected to occur and the timing at which reimbursement is

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provided. In addition, experts pointed that we might start thinking about defining value beyond health, by using the approach of patients' willingness to forego certain amount of health benefits to achieve additional value such as reduction of uncertainty, for example.

Equal number of experts thought that the value to be rewarded in PB models was the one of the patient/s (3 votes, 33,5%) or the one of current and future members of society (3 votes, 33,5%); and the remaining three answers were also equally split between rewarding the value of patients and close family (1 vote, 11%), value of current and future patients, and their families (1 vote, 11%), and the value of current members of society (1 vote, 11%) (question 9, Table 2, Appendix 3).

The majority of experts (56%) thought that the payments in PB models should be initiated in instalments after milestones are achieved, two experts (22%) thought that payments should start at the time of treatment delivery with rebates if treatment fails and two (22%) had other views (question 10, Table 2, Appendix 3).

3.6.4 Facilitators and incentives of performance-based reimbursement

Experts considered that the facilitators and incentives that may result from the implementation of PB models related mainly to shared financial risk between health providers and manufacturers (4 votes, 44%); followed by improved access for patients (2 votes, 22%), coupled with greater affordability (1 vote, 11%) and other views (2 votes, 22%), (question 11, Table 2, Appendix 3). With regards to barriers and disincentives resulting from PB models experts found that shifting of payments towards the future among other barriers play a role (question 11, Table 2, Appendix 3).

3.6.5 Time horizon; applicability and transferability of performance-based reimbursement

The appropriate contract time horizon for PB models according to experts was considered to be the mid-term that was up to 5 years (question 13, Table 2, Appendix 3).

Experts thought that PB models could be made applicable to Low and Middle Income countries (LMIC) in Europe and transferable across different EU countries by applying price discrimination; or by firstly piloting them on a smaller scale (e.g., hospital level, small insurance-based levels) before applying them on a national level (question 15, Table 2, Appendix 3). Experts agreed that EU and other international bodies should take more initiative to support LMIC European countries in the implementation of PB models.

Specific examples on PB reimbursement provided by experts included the off-label reimbursement of PM, as well as the subscription model, that is used in Denmark for patients with cystic fibrosis. The subscription model addresses the budget and affordability issues as the manufacturer gets payments on a monthly lump sum irrespective of the number of usages. This model could be potentially used to also tackle the uncertainty in the number of patients (e.g., in gene therapies) (question 14, Table 2, Appendix 3).

3.7 Financial-based reimbursement for PM

This section summarises the responses to the Mentimeter polling (details presented in Appendix 3) and discussion with the 9 experts during the Group3 session.

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3.7.1 Feasibility of financial-based reimbursement for PM

Five experts (71%) considered financial-based (FB) models to be somewhat appropriate and feasible for reimbursing PM, while two experts (29%) had other views (question 1, Table 3, Appendix 3). Experts with other views considered FB models feasible as they were easy for implementing and providing financial options for PM but no really appropriate because they wouldn't be a solution to PM reimbursement challenges. In addition, experts suggested that the appropriateness of FB models depends on the uncertainties that were present, e.g. FB models were considered more appropriate when there were uncertainties surrounding the price or the cost of PM, the dose and the length of the treatment period, assuming that the therapeutic value has already been proven. Experts who considered FB models somewhat feasible and appropriate clarified that these models were deemed feasible and were used in the cases where the therapeutic outcomes could not be determined. In case the therapeutic outcomes were determined outcome-based models were considered more feasible. Experts suggested that FB models 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.

The majority of experts (71%) considered FB models to be appropriate for some types of PM, while one (14,5%) thought FB models were appropriate for all types of PM, and one (14,5%) had other views (question 2, Table 3, Appendix 3). A specific example was pointed involving immunotherapies where 10 to 30% of patients would be expected to benefit but these patients could not be identified upfront and therefore FB models could be applied to ensure the therapies meet the cost-effectiveness threshold and were reimbursed. Experts added that the appropriateness of FB models for PM would depend on how uncertain cost-effectiveness and budget impact were, and how important the use in subgroups was.

Four experts (50%) thought that post-marketing, legislative and HTA related arrangements are amongst the prerequisites that need to be in place for FB models to be implemented while only legislative or only HTA prerequisites were pointed as necessary by two experts (1 vote, 12,5%), respectively, and two (25%) had other views (question 3, Table 3, Appendix 3). Experts with other views pointed out that product differed in terms of prerequisites they had before they could enter a financial agreement. Other prerequisites that need to be in place for FB models were horizon scanning or the pre-approval initiatives to ensure that HTA was performed and access to PM was not delayed, in addition to data access in the setting of interest and other institutional arrangements (including the issues between having separate systems for pricing and reimbursement).

3.7.2 Units and coverage of financial-based reimbursement

Experts had differing views on the units for reimbursement of PM through FB models with four experts (44%) considering the individual unit to be most appropriate, three (33%) giving preference to sub-group of patients/population with a course of therapy being the smallest unit, while two (23%) had another opinion (question 4, Table 3, Appendix 3). Experts with other views pointed out that all units could be applied and considered appropriate depending on the product.

Experts had varied opinions related to the health services to be covered by reimbursement with FB models with one expert (12,5%) pointing out that only the drug should be covered, four (50%) considered reimbursement being offered for the PM and the companion test/drug, and three (37,5%) thought that all related treatments and diagnostics should covered

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(question 5, Table 3, Appendix 3). In Germany, for example, the tests were reimbursed in the outpatient settings by direct payment and in the inpatient settings by DRGs. In Sweden, for example, the cost of the companion diagnostic is included in the HTA evaluation but usually not reimbursed. In Belgium, tests were reimbursed separately and were not bundled up in the reimbursement with the PM or with the therapy that followed. Experts added 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 as the PM landscape was changing due to incorporating big data, we could expect that the reimbursement would be expanded in the future to include more than a test and drug combination. A specific example was mentioned about small cell lung cancer in which multipanel gene testing had to be applied and then a specific treatment assigned based on the results so dedicated reimbursement through a separate budget for test only was justified in that case.

3.7.3 Facilitators and incentives, barriers and disincentives of financial-based reimbursement

Most experts (86%) considered decreased financial risk for payers/providers, greater affordability and cheaper price of the PM to be among the main facilitators and incentives that may result from the implementation of FB models while one expert (14%) had another opinion due to the uncertainty that FB models could actually achieve these financial benefits (question 6, Table 3, Appendix 3). A specific example was provided for melanoma where the combination of new treatments could easily mount up to 400,000 euros per single patient and experts expressed views that little increase in benefit lead to significant increase in price which could bring affordability issues. Experts added that PM might not be cheaper as compared to non-PM but it was important to ensure that it was at least more effective than non-PM approaches, e.g. thus money spent could achieve greater value.

With regards to barriers and disincentives resulting from PB models, experts had quite different views with two experts (29%) considering limited patient access to be the main barrier, while two others (29%) thought that limited patient access along with limited utilisation of PM (due to caps) to be the main ones, and three experts (42%) had other views (question 7, Table 3, Appendix 3). Experts suggested that as PM approach was essentially a shift in paradigm from drug-centred to patient-centred, reimbursement for PM should shift from applying the traditional discounting schemes because they could potentially limit or slow access to PM for patients, thus increasing costs for society as patients could end up being treated with PM further down the line after non-PM approaches have been exhausted, and the shift in reimbursement could be based on value instead of financial agreements with potentially involving all stakeholders including patients early on in the reimbursement process.

57% of the experts considered that the implementation of FB models can mainly achieve financial gains, such as acceptable cost-effectiveness ratio as a result of decreased price and lower price of PM, while one expert (14%) though these gains would be accompanied with limited utilisation of PM and two experts (29%) had another opinion (question 8, Table 3, Appendix 3). However, experts with other opinions suggested that FB models such as confidential rebate, price volume agreement or a net discount may result in access issues but may also provide a way to ensure access to these therapies in smaller, less rich countries (experts clarified that this was usually the industry approach which is not without challenges). Another expert added that agreeing FB models on broader level such as the EU might be beneficial for lowering the price. A second expert added that sometimes providing quicker access to medicines that can potentially fulfil unmet medical needs combined with FB arrangement could be also beneficial to patients in some instances, however, this view was contradicted by an expert who pointed that this should be done on individual basis as there is large clinical uncertainty involved. In addition, it was noted that PB models may be better

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suited to achieve early access but it was pointed that in Belgium, for example, there were cases where it was considered unethical to withdraw reimbursement for treatments with early access after their effectiveness could not be established.

3.7.4 Time horizon; applicability and transferability of financial-based reimbursement

The most appropriate contract time horizon for FB models according to the experts was considered to be the mid-term that lasted maximum of 5 years (71%) (question 9, Table 3, Appendix 3). One expert added that time horizon is different between different reimbursement applications, which could be a challenge in daily HTA practice.

The experts did not agree that the main criticism of FB models is the lack of transparency (undisclosed rebates) as according to them the lack of transparency was also what allowed access to PM in smaller countries with less resources. Other experts expressed the view that the transparency should be regulated on an EU level to make it feasible to disclose rebates after a time period. A specific example was pointed for Germany where rebates were disclosed which lead to small rebates subsequently (question 10, Table 3, Appendix 3).

Experts did not agree that FB models are an intermediate step to PB models as according to them these two types of reimbursement models served different purposes. Other experts expressed the view that FB models could bridge the gap for drugs with uncertain efficacy, especially where the outcome cannot be easily measured in the real world but FB models didn't have to be a necessary step nor would actually guarantee the subsequent implementation of PB models (question 11, Table 3, Appendix 3).

The experts thought that FB models could be made applicable to LMIC and transferable across different EU countries by ensuring more collaboration between countries and increasing transparency related to the models. A suggestion was made to create registries (with the support of industry) that help tracking patients where there were limited resources, in order to support utilisation caps that would allow European-aligned list price. Another expert expressed the view that FB models can be made applicable to LMIC by a tailored approach which differs between counties and providing more options to make models fit in these countries rather than just one option for Europe (question 12, Table 3, Appendix 3).

Other experiences or examples that relate to reimbursing PM included (question 12, Table 3, Appendix 3) the Drug Access Protocol which is a collaboration between physicians association, the healthcare institutes, and the health insurance companies in the Netherlands to provide patients' access to innovative treatments within oncology as soon as possible that was working with a kind of pay for proof like system, and also paying for value and collecting data.

4 DISCUSSION AND CONCLUSION

The two workshops organised by the HEcoPerMed consortium were designed to elicit the opinions of experts in the field of PM. Opinions were sought regarding best practice for cost-effectiveness modelling of PM innovations and identifying suitable financing and reimbursement models that can stimulate their development, facilitate their uptake in healthcare systems and ultimately increase patient access. The results of the two workshops are complementary as they highlight the importance of a well-equipped economic evaluation framework for PM in applying reimbursement models that reward manufacturers for the actual value of PM innovations in healthcare. In turn, the alignment of the economic evaluation and reimbursement processes would enhance further public & private partnerships to fund R&D

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projects of PM as the involved risks and rewards would be clearer and better communicated between the partners.

These relationships were apparent in the results of the two workshops that showed that one of the prerequisites for the adoption of financing and reimbursement models that ensure risk- and benefit-sharing for PM among stakeholders is an economic evaluation framework that can capture the costs and benefits of PM adequately. More specifically, the main challenges were the lack of transparency and the absence of a suitable reimbursement tool for adopting financial-based reimbursement models and the uncertainty about the outcomes to be measured, collecting data for these outcomes from the existing healthcare structures, and the inclusion of value elements in the reimbursement agreements for the adoption of performance-based reimbursement models. Uncertainty around clinical effectiveness and safety of PM technologies at time of reimbursement were highlighted as key limitations that need to be addressed both in case of economic evaluations and financing and reimbursement models.

Our workshops have also shown that performance-based models may be more appropriate than financial-based models for PM but they can only be implemented into healthcare systems if supported adequately by economic evaluations. As such, the workshops confirmed that the HEcoPerMed guidance for economic evaluations of PM was designed appropriately, comprehensively, and is a step forward in the goal to harmonise the economic evaluation approaches in this health care area. Our results also pointed that the allocation of testing costs to subsequent treatments should be made in a way that does not punish test and treatment manufacturers, while considering how innovation could be rewarded as well the effect of applying broad gene panels in daily clinical practice. Moreover, the relationship between surrogate and final outcomes should be stated explicitly. Some specific (more technical) recommendations for health economists included the development of early economic models, as well considering patient-level modelling for PM. However, patient-level modelling might not be always feasible and model structures should be chosen so that they can help to answer the specific decision problem. Furthermore, a societal perspective could be adopted in a potential scenario analysis, if this perspective is not in the main analysis. Items in the guidance were grouped according to highlighted themes/domains which was considered helpful for the users.

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5 REFERENCES

1. Personalized Medicine Coalition. Personalized Medicine and Value Assessment Frameworks: Context, Considerations, and Next Steps. White paper 2017. Available from: https://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_and_VAFs.pdf.
2. Vegter S, Boersma C, Rozenbaum M, Wilffert B, Navis G, Postma MJ. Pharmacoeconomic Evaluations of Pharmacogenetic and Genomic Screening Programmes. PharmacoEconomics. 2008;26(7):569-87.
3. Beaulieu M, de Denus S, Lachaine J. Systematic review of pharmacoeconomic studies of pharmacogenomic tests. Pharmacogenomics. 2010;11(11):1573-90.
4. Vellekoop H, Huygens S, Versteegh M, Szilberhorn L, Zelei T, Nagy B, et al. Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine. PharmacoEconomics. 2021;39(7):771-88.
5. Payne K, Annemans L. Reflections on Market Access for Personalized Medicine: Recommendations for Europe. Value in Health. 2013 2013/09/01/;16(6, Supplement):S32-S8.
6. Touchot N, Flume M. Early Insights from Commercialization of Gene Therapies in Europe. Genes (Basel). 2017 Feb 17;8(2).

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6 APPENDIX 1 – AGENDA

Virtual Workshop 1
Date: 24.09.2020
Venue: Microsoft Teams

Time (CET)	Agenda item
Joint session	
10:00 - 10:15	Introduction and housekeeping rules
10:15-10:45	Opportunities and challenges for health economics of personalized medicine *Keynote speaker: Sarah Wordsworth* 5 minutes discussion
10:45-11:15	HEcoPerMed Consortium and ICPerMed
11:15-11:30	Break
11:30-12:30	Guidance - Recommendations for economic evaluations of personalised medicine discussion for clarification questions – 15 minutes
12:30-13:00	Case study selection rationale Overview of case study selection Rehearsal of polling software – 5 minutes
13:00-14:00	Break
3 parallel separated sessions	
14:00-14:30	Overview the personalized medicine case study Oxford: ToxNav iMTA: NTRK Syreon: MODY
14:30-16:00	Structured discussion about the feasibility of application of the guidance items in the context of the case study Oxford: ToxNav iMTA: NTRK Syreon: MODY
16:00	End of Meeting

Virtual Workshop 2
Date: 20.04.2021
Venue: Microsoft Teams

Time (CET)	Agenda item
Joint session	
10.00 – 10.10	Introduction and housekeeping rules
10.10 – 10.50	*Keynote Lecture* Personalised Reimbursement for Personalised Medicine? A Tour of Innovative Funding Pathways in Europe **Richard Charter**

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Time (CET)	Agenda item
	Vice President MedTech Market Access, Europe & Asia Pacific at AliraHealth; Co-Chair of ISPOR Special Interest Group on Medical Devices and Diagnostics
10.50 – 11.00	Break
11.00 – 11.15	ICPerMed and the PerMed family **Ejner Moltzen** Chair ICPerMed; Director Innovation Fund Denmark
11.15 – 11.30	Break
11.30 – 12.05	Financing and reimbursement of personalised medicine – findings from a review
12.05 – 13.00	Break
3 paralell separate sessions	
13.00 – 15.00	Parallel group structured discussion on Financing and Reimbursement of personalised medicine
15.00 – 15.30	Wrap-up of group discussions

7 APPENDIX 2 – PARTICIPANTS

Virtual Workshop 1

Date: 24.09.2020

Venue: Microsoft Teams

Organizer: Syreon Research Institute on behalf of HEcoPerMed consortium

Participants:	**Consortium:** Andreas Weinhäusel, Apostolos Tsiachristas, Balázs Nagy, Gábor Kovács, Heleen Vellekoop, László Szilberhorn, Manuela Kienegger, Maren Walgenbach, Matthijs Versteegh, Maureen Rutten-van Molken, Rositsa Koleva-Kolarova, Sarah Wordsworth, Simone Huygens, Susanne Giesecke, Tamas Zelei, Wolfgang Ballensiefen **External:** names anonymised

Virtual Workshop 2

Date: 20.04.2021

Venue: Microsoft Teams

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Organiser: Health Economics Research Centre (HERC), Nuffield Department of Population Health, University of Oxford on behalf of the HEcoPerMed consortium

Participants:	**Consortium:** Apostolos Tsiachristas, Balázs Nagy, Heleen Vellekoop, László Szilberhorn, Manuela Kienegger, Maren Walgenbach, Matthijs Versteegh, Maureen Rutten-van Molken, Rositsa Koleva-Kolarova, Sarah Wordsworth, Simone Huygens, Susanne Giesecke, Tamas Zelei, Wolfgang Ballensiefen **External:** names anonymised

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8 APPENDIX 3 – QUESTIONS AND ANSWERS BY GROUPS

Table 1. Group 1 questions and answers

Question	Answers	Mentimeter results
Q1: In your opinion, does the current landscape of R&D financing encourage or hamper the development of PM?	A). It enables PM development	2
	B). It hampers PM development	3
	C). Neither enable nor hamper PM development	1
	D). Other	1
Q2: In your opinion, which R&D financing models particularly facilitate the development of PM?	A). Public financing	0
	B). Private financing	0
	C). Public-private mix	8
Q3: Can you point out any examples or ideas that are appropriate to finance R&D of PM?	A). Yes, I can	8
	B). No, I can't	0
Q4: In your opinion, which scenario is more feasible?	A). Scenario A based on split development of PM, e.g. public partners perform early R&D, private partners perform the remaining stages of R&D	2
	B). Scenario B based on shared development of PM, e.g. all partners collaborate in all stages	2
	C). Both scenarios	3
	D). Neither A nor B	0
	E). Other	1
Q5: In your opinion, do you expect any other facilitators and barriers in addition to the ones already listed?	A). Yes, I do	5
	B). No, I don't	1
	C). Other	1
Q6: In your opinion, should partners benefit from data exclusivity?	A). Yes, data should be owned by the partner who developed them	0
	B). No, data should be owned by all partners	2

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	C). Other	7
Q7: In your opinion, under the proposed scenarios how can publicly funded research institutions (including academia) and SMEs become equal partners with development companies instead of their suppliers of innovation?	A). Through contributing to funding	0
	B). Through providing in kind contribution, e.g. expertise, data	0
	C). Through sharing public resources (e.g. routinely collected data, large datasets, outputs of publicly funded research)	0
	D). All of the above	6
	E). Other	2
Q8: In your opinion, under the proposed scenarios how can public authorities justify the investment of public funds in high risk R&D projects of PM?	A). By steering innovation where innovation is most needed	0
	B). By the expected benefits for patients	0
	C). By expected benefits for society	0
	D). All of the above	6
	E). Other	2
Q9: In your opinion, under the proposed scenarios how can we share the risks and benefits between stakeholders?*		
Q10: Are you aware of any arrangements for funding education related to PM?*		
Q11: How to make financing models applicable to Low and Middle Income Countries in Europe and transferable across different EU countries?*		
Q12: What is the (potential) role of venture capitalists, philanthropists, and social investment bonds (SIBs) in the financing of R&D for PM?*		

* answers for open-ended questions are only provided in the text of the report

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Table 2. Group 2 questions and answers

Question	Answers	Mentimeter results
Q1: Do you consider performance-based models as appropriate and feasible for reimbursing PM?	A). Very appropriate and feasible	7
	B). Somewhat appropriate and feasible	1
	C). Not appropriate and feasible	1
	D). Not appropriate and feasible at all	1
	E). Other	0
Q2: Can you expand on the appropriateness and feasibility of performance-based models with regards to different types of PM (e.g., tests, targeted and gene therapies)?	A). They are appropriate for all types of PM	1
	B). They are not appropriate for any type of PM	0
	C). They are appropriate for some types of PM (please say which ones)	7
	D). Other	1
Q3: What necessary prerequisites need to be in place for performance-based models to be successfully implemented and used for reimbursing PM?	A). Post-marketing arrangements	0
	B). Legislative arrangements	0
	C). Health technology assessment	1
	D). All of the above	8
	E). Other	1
Q4: What units should be used for reimbursement?	A). Individual	2
	B). Sub-group of patients/population (course of therapy being the smallest unit)	6
	C). Whole group of patients/population	0
	D). Other	1
Q5: What health services should be covered for reimbursement?	A). Only the PM	1
	B). The PM and the companion test/drug	5
	C). All related treatments/diagnostics	3
	D). Other	1
Q6: What outcomes should be used and measured in performance-based models?	A). Clinical outcomes (e.g., specific clinical indicators, PFS, OS, etc.)	2
	B). Quality of life outcomes (PROMS)	0
	C). Both clinical and quality of life outcomes	3

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	D). Overall value (to be defined)	2
	E). Other	2
Q7: How to translate outcomes (including patient reported outcomes) and clinical benefits into value?*		
Q8: How would you define, measure and reward value, especially when the benefits accrue in the long term and payments are made in the short term?*		
Q9: Whose value should be rewarded in performance-based models?	A). Only the value of the patient/s	3
	B). The value of patients and close family	1
	C). The value of current and future patients, and their families	1
	D). The value of current members of society	1
	E). The value of current and future members of society	3
	F). Other	0
Q10: When should payment be initiated in performance-based models?	A). At the time of treatment delivery with rebates if treatment fails	2
	B). When outcomes are achieved as a lump sum	0
	C). In instalments after milestones are achieved	5
	D). Other	2
Q11: What facilitators and incentives do you think may result from the implementation of performance-based models for reimbursement?	A). Shared financial risk between health providers and manufacturers	4
	B). Greater affordability (due to reimbursement based on outcomes)	0
	C). Improved access for patients	2
	D). All of the above	1
	E). Other	2
Q12: What barriers and disincentives do you think may result from the implementation of performance-based models for reimbursement?	A). Financial disincentives for manufacturers	0
	B). Shifting of payments towards the future	1
	C). All of the above	0
	D). Other	8
Q13: What do you think is an appropriate contract time horizon for performance-based models?	A). Short-term, 1 year	0
	B). Mid-term, up to 5 years	7
	C). Long-term, longer than 5 years	1
	D). Other	1

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Q14: Can you point out any other experiences or examples that relate to reimbursing PM that are not mentioned so far?	A). Yes, I can	3
	B). No, I can't	5
Q15: How to make performance-based reimbursement models applicable to Low and Middle Income Countries in Europe and transferable across different EU countries?*		

* answers for open-ended questions are only provided in the text of the report

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Group 3 questions and answers

Question	Answers	Mentimeter results
Q1: Do you consider financial-based models as appropriate and feasible for reimbursing PM?	A). Very appropriate and feasible	0
	B). Somewhat appropriate and feasible	5
	C). Not appropriate and feasible	0
	D). Not appropriate and feasible at all	0
	E). Other	2
Q2: Can you expand on the appropriateness and feasibility of financial-based models with regards to different types of PM (e.g., tests, targeted and gene therapies)?	A). They are appropriate for all types of PM	0
	B). They are not appropriate for any type of PM	1
	C). They are appropriate for some types of PM (please say which ones)	5
	D). Other	1
Q3: What necessary prerequisites need to be in place for financial-based models to be successfully implemented and used for reimbursing PM?	A). Post-marketing arrangements	0
	B). Legislative arrangements	1
	C). Health technology assessment	1
	D). All of the above	4
	E). Other	2
Q4: What units should be used for reimbursement?	A). Individual	4
	B). Sub-group of patients/population (course of therapy being the smallest unit)	3
	C). Whole group of patients/population	0
	D). Other	2
Q5: What health services should be covered for reimbursement?	A). Only the PM	1
	B). The PM and the companion test/drug	4
	C). All related treatments/diagnostics	3
	D). Other	0
Q6: What facilitators and incentives do you think may result from the implementation of financial-based models for reimbursement?	A). Decreased financial risk for payers/providers	1
	B). Greater affordability	0
	C). Cheaper price of the PM	0
	D). All of the above	5
	E). Other	1

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Q7: What barriers and disincentives do you think may result from the implementation of financial-based models for reimbursement?	A). Limited utilisation of PM (due to caps)	0
	B). Limited patient access	2
	C). All of the above	2
	D). Other	3
Q8: What do you think can be achieved by implementing financial-based models to reimburse PM?	A). Decrease the price of the PM	1
	B). Limit utilisation of PM	0
	C). Achieve acceptable cost-effectiveness ratio as a result of decreased price	3
	D). All of the above	1
	E). Other	2
Q9: What do you think is an appropriate contract time horizon for financial-based models?	A). Short-term, 1 year	0
	B). Mid-term, up to 5 years	5
	C). Long-term, longer than 5 years	0
	D). Other	2
Q10: A main criticism of financial-based models is the lack of transparency (e.g. undisclosed rebates or arbitrary volume/cost caps). Could you think of ways to overcome this?*		
Q11: Financial-based models are currently the most widely used risk-sharing reimbursement models. Many consider them as an intermediate step to performance-based models. Would you agree with this statement? (please elaborate)*		
Q12: How to make financial-based reimbursement models applicable to Low and Middle Income Countries in Europe and transferable across different EU countries?*		
Q13: Can you point out any other experiences or examples that relate to reimbursing PM that are not mentioned so far?	A). Yes, I can	1
	B). No, I can't	5

* answers for open-ended questions are only provided in the text of the report

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