HEcoPerMed

Health Economics for Personalised Medicine

Deliverable

Workshop Report, D5.2

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History of changes			
Version	Date	Changes	Author
1	10/21	Pre-workshop position paper	DLR
2	11/21	Workshop report, Draft, sent out to be commented by stakeholders	DLR
3	11/21	Workshop report, comments by stakeholders integrated	DLR
4	12/21	Final version	DLR

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SUMMARY

The Coordination and Support Action (CSA) HEcoPerMed started with a kick-off meeting in January 2019, Brussels. The consortium has a very high share of scientific tasks and achievements. Thus, the project consists of six partners from five European countries. It represents four academic institutions such as universities and university-based scientific institutes, research and technology organisations (AIT), a funding organisation (DLR) and an SME (Syreon).

The duration was originally planned for three years, but has been extended for 6 months due to the ongoing pandemic situation. Within work package 5 "Communication and Dissemination", two scientific and strategic workshops and a final conference were originally planned. The 1st workshop was planned in September 2020 and the 2nd workshop in March 2021. Due to the ongoing Covid-19 pandemic, the 1st workshop was postponed two times and replaced by two online workshops dedicated to the scientific work packages.

The 2nd workshop had also been postponed twice and finally took place in a hybrid format in October 2021, Budapest. In this event the recent project results and findings were presented and discussed along with a 1st version of a so called HEcoPerMed "Position Paper". As preparation the developed "Position Paper" was sent out together with 13 guiding questions to all invited experts in advance of the workshop. At the event the "position paper" was presented in the plenum incl. a live stream and discussed in detail in three working groups on the basis of the guiding questions. One working of the groups was on-site and the two others were organised and moderated online. The results of these session were presented and finally discussed on the 2nd day of the workshop.

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1 BACKGROUND OF THE EVENT

On behalf of HEcoPerMed consortium ("Healthcare- and pharma-economics in support of the International Consortium for Personalised Medicine – ICPerMed"), the partners DLR and Syreon Research Institute organized an Advisory Board meeting and a two-day hybrid workshop with international experts and representatives from a wide range of stakeholders, experts and researchers. These included, for example health economic and personalised medicine researchers, policy and funder, e.g. the European Commission, ICPerMed and regional funders, healthcare payers as well as test technology developers/manufacturers and national competence authorities. The event and the report are a task within work package (WP5) of the EC funded consortium. The event has also been announced as by invitation only on the HEcoPerMed and ICPerMed webpage: News – HEcoPerMed

2 AIM OF THE EVENT

The aim of the workshop was to present and discuss the project achievements to date as well as the "Position Paper", which was send to all invited experts before the workshop. At the workshop, the internally and additionally developed "Position Paper" was presented and discussed in plenum as well as more deeply in three parallel working groups using a set of guiding questions. Originally the workshop should have been face-to-face in September 2020 and then in April 2021. After postponing the workshop twice because of the still ongoing COVID-19 pandemic and the different travel restrictions, the workshop was converted to a hybrid event.

3 ORGANISATION AND PREPARATION OF THE EVENT

For the workshop, the consortium identified and invited around 150 experts from all relevant areas and sectors across Europe and beyond. Excluding the consortium partners, 50 experts had confirmed their participation and finally 7 experts participated on-site and minimum 43 experts participated online.

From the identified experts of the two previous virtual research-related workshops (September 2020 for WP2 and April 2021 for WP3) all invitees were informed directly at the respective workshop about the Budapest Workshop and were invited.

Only the participants received informational material one week prior to the workshop, that included the final workshop agenda, the 1st draft of the "Position Paper", 13 related guiding questions, information about the consortium and organisational information about the hotel/venue and the travel reimbursement (see also under 10. Appendix of this document).

On the first day of the workshop, after two plenary sessions, the internally developed position paper was presented and discussed in three parallel working groups based on guiding questions. On the second day the results of the working groups were presented. In addition, four future scenarios of personalised medicine were presented and discussed.

4 WORKSHOP INTRODUCTION AND “POSITION PAPER” DRAFT DEVELOPEMENT

The HEcoPerMed Workshop on “Personalised medicine specific health economic and payment modelling” was hosted by the Syreon Research Institute, Hungary and organised by DLR on behalf of the HEcoPerMed consortium with financial support from the European Commission. The basis of the workshop were the achievements of the partners in the WP 1, 2, 3, 4 and 5 as well as the additionally developed “Position Paper”. The concept of this document has been developed by DLR and has been adapted and written by all HEcoPerMed partners. Finally, the document was intensively edited by Sarah Wordsworth prior to forwarding the draft to all participants one week before the event.

The workshop was structured around several plenary sessions which were streamed and parallel working-group sessions, two online and one on-site for discussion of the Position paper and the included statements / recommendations. For further information, please see agenda in the appendix. To support and activate the discussion DLR and the partners developed a set of guiding questions. All sessions had moderators and note-takers from the consortium. The major finding and a summary of the discussions in the parallel sessions were presented on the second day to the plenum with another chance for discussion. A general introduction was given to the participants to support the discussion and to explain the objective, target groups and procedure.

5 PLENARY SESSION: WELCOME

On Tuesday 5 October, the host of the event, Balazs Nagy from Syreon, Hungary, introduced the HEcoPerMed consortium online and on-site to the auditorium and gave a brief overview of how the CSA came into being. The HEcoPerMed CSA was launched in 2019 and is a CSA with a very high proportion of scientific tasks and deliverables. Thus, the project consortium consists of six partners from five European countries. It represents four academic institutions such as universities and university-based scientific institutes, research and technology organisations (AIT), a funding organisation (DLR) and a SME (Syreon).

As the responsible head of Unit for HEcoPerMed at the European Commission, Carmen La Plaza Santos presented the interest and related activities to achieve higher impact and support for innovations in the health area. She also summarised the past and future initiatives to achieve these goals, incl. the upcoming European Partnerships, ICPerMed, and the related coordination and support actions like HEcoPerMed. After the welcome by the European Commission, Ejner Moltzen (ICPerMed chair) introduced the International Consortium for Personalised Medicine (ICPerMed) including its aims, achievements, partners and future plans. Relating to HEcoPerMed he emphasised the aspects which lessons ICPerMed and other stakeholders can learn according to PM approaches. Last but not least, the participants were welcomed by Manuela Kienegger from AIT the coordination of the CSA HEcoPerMed.

6 THE HECOPERMED ROAD SO FAR – SPOTLIGHTS ON PROJECT ACTIVITIES & RESULTS

Maureen Rutten-van Mölken, HEcoPerMed partner from the Erasmus University Rotterdam, presented the project achievements, lessons learned and results on behalf of the consortium. These include, among others, a systematic review, an article on “Guidance for the

Harmonisation and Improvement of Economic Evaluations of Personalised Medicine", three personalised medicine related health economic case studies and a submitted manuscript about "Reimbursement and Payment of Personalised Medicine".

Afterwards, the host, Balazs Nagy from Syreon, explained the aim and concept of this workshop which is the discussion and further development of the "Position Paper: Personalised Medicine - How Health Technology Assessment ensures Value-based Implementation". Subsequently the three Parallel Work Groups (two online and one on-site started their presentation and discussion about the draft "Position Paper" and a group-specific selection of recommendations/statements of this document.

On the second day the HEcoPerMed presentations were completed by an introduction to development and outcome of four future scenarios of PM by Manuela Kienegger (AIT) and a general introduction to the "Position Paper" the aim, target groups, the possible impact and next steps by Wolfgang Ballensiefen (DLR).

7 PARALLEL WORK GROUPS

The participants of the workshop were divided into three working groups in advance. One group took place on-site, the other two online. The online working groups were chaired by Sarah Wordsworth from University of Oxford, Great Britain and by Simone Huygens from Erasmus University Rotterdam, The Netherlands. The onsite working group were chaired by Tamás Zelei from Syreon, Hungary.

Each working group started with an introduction of the position paper and the 13 guiding questions with which the Position Paper should be discussed.

Guiding questions:

1. Are the recommendations in the HEcoPerMed "Position Paper" complete and precise?
2. From your own experiences, do you have any aspects or best-practice which we should consider for the "Position Paper"?
3. What is the aim and significance of health technology assessment (HTA) and health economics especially for personalised medicine (PM)?
4. Do we need adapted HTA and health economic (HE) evaluation models when it comes to PM?
5. What kind of further HTA/HE-related research is needed to assess PM?
6. Are for example patient's needs, ethical and societal aspects sufficiently considered in recent HTA and HE assessments?
7. How independent and objective is HTA/HE-modelling of PM at the present?
8. Should HTA/HE aspects be considered in an early development phase of PM?
9. Are there significant variations in HTA/HE evaluation of PM in European countries?

10. Which PM-related perspectives and development beyond HTA/HE should be considered and be part of the ““Position Paper”, e.g. regulatory, commercial or legal aspects?
11. What lessons can be learned from the HTA/HE evaluation of rare diseases?
12. In what way PM-related prevention strategy could be assessed by existing HE models?
13. Do you have any suggestions for the communication and dissemination of the “Position Paper”?

8 SUMMARY OF THE DISCUSSION AND SUGGESTIONS OF WORKING GROUPS

This section summarizes the main subjects of the discussion and comments related to the 1st draft of HEcoPerMed “Position Paper” within the three parallel working groups on October 5th and the summaries given by the moderators of these sessions on October 6th 2021.

Overall, all participants welcomed and supported the idea of a strategic document on this topic and felt that it could be very useful. According to most participants, the recommendations are quite complete, but could be more precise on some aspects and issues, e.g. the incentives for doctors to adopt personalised medicine in practice should be further elaborated.

A general introduction chapter, figure or box should be added at the beginning of the document with several general definitions and explanations, such as: What is health economics? What are the topics and achievements of relevant research and modelling? What are the differences between health economics research and modelling compared to Health Technology Assessment (HTA)?

Patient participation can provide valuable input in research and development, in regulatory decisions for HTA and in the post-marketing phase. However, due to personalisation the exact identification of these decision-making bases for PM can become more complicated than for traditional technologies and approaches. Patient and caregiver perspectives should be relevant in PM, as usually limited evidence is available and additional factors that are less considered in traditional decision-making frameworks may play a significant role. Furthermore, joint assessments of comparative effectiveness combined with localised assessments of patient pathways, comparators, budget impact and cost-effectiveness seem to be a viable pragmatic solution in areas of PM for all European countries. It may be helpful to develop and adopt appropriate PRO measures that reflect patient burden.

Higher income countries in the EU often struggle with country-specific variation (e.g. socio-economically disadvantaged population, or population in rural areas). However lower income countries regularly face equity issues drawn from their financial and infrastructural limitations (e.g. narrow price corridor due to reference pricing).

There is also a need to further develop and explain what is unique to personalised medicine (PM) in the context of health economic research and modelling. Also, measures should be considered that help to identify and remove barriers to the introduction of innovations related to PM. For further discussion, several experts were willing to provide literature references. It was pointed out that the document should not contain contradictory statements or any recommendations.

It was noted, that consistent methodology could increase the transparency of PM evaluation, while it could in parallel reduce the need of human and financial resources. The highly innovative area of personalised care makes it challenging to ensure access for all. Moreover, substantial variation may be observed in the utilization of PM technologies across different patient groups, regions, treatment modalities and disease types. In general value-based pricing and whether it should be considered in negotiations between manufacturers and payers about sharing the value has been discussed. Additionally, the effect of these negotiations on the society need also be considered sufficiently. Furthermore, decisions on sharing value between manufacturers and payers may depend on the timing of negotiations and the HTA step (before or after approval).

It was also pointed out that public-private agreements could support research and development and an example from Andalusia was given, where the university of Granada, Pfizer and a regional office work together in research on the genetic basis of diseases and the influence of genetic inheritance in the body's response to certain drugs. Here a crucial question is whether the identified benefits are actually distributed fairly?

In addition, one of the participants suggested that we can also learn from public-private agreements in developing countries, for example like the ones for the fight against tuberculosis.

In wealthier countries in comparison to lower income countries, more research funds are allocated to the development of relatively expensive genomic technologies. This leads to a lack of diversity in the genetic data collected which consequently leads to limited generalizability of evidence. Thus, it is essential to separate the transferability of data and methodology, from transferring recommendations and policy decisions.

The interpretation of a "threshold" is quite challenging, i.e. whether in terms of the supply side (k-threshold) or demand side (v-threshold) and the extent to which risk aversion and uncertainty can and have to be represented in a threshold.

9 OUTLOOK AND NEXT STEPS

The comments and suggestions of the workshop participants will be considered to develop the next version of the "Position paper". Further input and information might also be provided via mail. However, no further general consultation of participants or additional experts and stakeholders is currently foreseen. The final document will be launched and published along with a final HEcoPerMed conference in April 2022, most likely in Brussels.

This report and the final Position Paper will be published on the HEcoPerMed webpage and disseminated through various channels, e.g. via ICPerMed. Furthermore, it is likely to be a major input for the upcoming ICPerMed documents and activities, including the next workshop also dedicated to health economic aspects of PM, which is planned for June 2022. Other presentation and communication opportunities will be identified and considered, e.g. at the annual ISPOR conferences or for the planned European Partnerships in the health cluster.

10 APPENDIX: EVENT AGENDA AND "POSITION PAPER" 1ST DRAFT

Agenda

Monday, October 4th 2021

HEcoPerMed **Consortium Pre-meeting**

Venue: Continental Hotel Budapest, Dohány utca 42-44

17.00 - 19.00h HEcoPerMed consortium and Advisory Board on-site and via Microsoft teams: Click here to join the meeting, Find a local number, Phone Conference ID: 477 213 011#

Advisory Board – *Welcome by coordination*

Presentation of **HEcoPerMed achievements** and next steps

Feedback and Discussion on the "**Position Paper**"

Workshop preparation

19.30h **Dinner** for all participants who are already present and want to join

Tuesday, October 5th 2021

HEcoPerMed Workshop
"Personalised medicine-specific health economic and payment modelling"

Venue: Continental Hotel Budapest, Dohány utca 42-44

11:30 – 12.00h Workshop registration

12.00– 13.00h *Light Lunch*

13.00h Welcome (Plenum Hybrid, on-site and online)
Click here to join the meeting, Find a local number, Phone conference ID: 321 959 237#

Balázs Nagy, Syreon, Hungary (host and moderation)
Carmen Laplaza Santos, European Commission (Health Innovations)
Ejner Moltzen, Innovation Fund Denmark, ICPerMed chair
Manuela Kienegger, Austrian Institute of Technology, *Coordination*

13.50h The HEcoPerMed road so far – Spotlights on Project Activities & Results
Maureen Rutten-van Mölken, Erasmus University Rotterdam, The Netherlands
Sarah Wordsworth, University of Oxford, United Kingdom

Systematic Reviews

"Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine"

Case Studies of three different Personalised Medicine approaches

Reimbursement and Payment of Personalised Medicine

Aim of the workshop

15.00h Coffee / Break

15.30h – 17.30h Parallel Work Groups

incl. a flexible 15 min. break

*Discussion of and along the "*Personalised Medicine - How Health Technology Assessment ensures Value-based Implementation*" (HEcoPerMed, draft) as well as the results and findings of HEcoPerMed, the guiding questions and other related projects, consortia or initiatives.*

On-site Group/s (Budapest)

Group A (attending participants and moderated)

"Position Paper"– Guiding questions, pools and the *drafted* set of HEcoPerMed statements

(*Moderation*: Tamás Zelei, Syreon, Hungary)

Group B (*if required*, attending participants and moderated)

"Position Paper"– Guiding questions, pools and the *drafted* set of HEcoPerMed statements

(Moderation: Rositsa Koleva-Kolarova, University of Oxford, United Kingdom)

On-line Groups (via Microsoft Teams)

Group 1 (online participants and moderated)

"Position Paper"– Guiding questions, pools and the drafted set of HEcoPerMed statements (*Moderation*: Sarah Wordsworth, University of Oxford, United Kingdom)

Click here to join the meeting, Find a local number, Phone Conference ID: 923 796 39#

Group 2 (online participants and moderated)

"Position Paper" – Guiding questions, pools and the drafted set of HEcoPerMed statements

(*Moderation*: Simone Huygens, Institute for Medical Technology Assessment, The Netherlands)

Click here to join the meeting, Find a local number, Phone Conference ID: 268 325 683#

19.30h Networking Dinner on the boat in Budapest

Wednesday, October 6th 2021

Venue: Continental Hotel Budapest, Dohány utca 42-44

9.00h Welcome (Plenum Hybrid, on-site and online via Microsoft Teams)
Balázs Nagy, Syreon, Hungary
Click here to join the meeting, Find a local number, Phone Conference ID: 270 346 591#

9.10h *"HEcoPerMed Future Scenarios for Personalised Medicine"*
Manuela Kienegger, Austrian Institute of Technology

9.30h *The HEcoPerMed "Position Paper"*
Wolfgang Ballensiefen, DLR, Germany

HEcoPerMed "Position Paper"
Aim of the document and statements
Next steps and outlook

10.00h Summary and Discussions of the Work Group outcome
Maureen Rutten-van Mölken, Erasmus University Rotterdam, The Netherlands

Conclusion of the break-out Sessions

General Feedback of each Session (~15min.)

Comments and Feedback for the HEcoPerMed Statements

12.30h Closing Remarks and Outlook
Sarah Wordsworth, University of Oxford, United Kingdom

13.00h Lunch Buffet and End of Event

Personalised Medicine - How Health Technology Assessment ensures Value-based Implementation

HEcoPerMed

"Position Paper"

Interim Analysis, Achievements & Statements by the HEcoPerMed consortium in support of ICPerMed

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1 FOREWORD

The HEcoPerMed project (**HE**althcare- and pharma-E**co**nomics) is a consortium-based project. The project is funded by the European Commission (EC) and supports the International Consortium for Personalised Medicine (ICPerMed). Decision makers require information on the impact of personalised medicine (PM) at various stages of the life cycle to help determine whether to continue the development of PMs, introduce them into routine health care, or to withdraw certain PM approaches. HEcoPerMed was designed in response for the need for evidence on the added value of PM approaches and the demand for faster adoption and wider access to value-based PM. Part of the evidence based required is health economic information on the long-term benefits and costs of PM, which is an important focus of the HEcoPerMed Project.

2 PERSONALISED MEDICINE – PROMISE AND REALITY

The term "personalised medicine" is defined in various ways. However, both ICPerMed and HEcoPerMed use the definition provided in the European Council Conclusion on personalised medicine for patients (2015/C 421/03). This definition states "[…] *that it is widely understood that personalised medicine refers to 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*."

Personalised medicine (PM) is a multiform concept, when focusing on the use of genetic and other information in medical decision making, it includes testing to screen for diseases or genetic markers in asymptomatic populations. Testing is also used to provide information on disease prognosis, to identify treatment responders and non-responders and to identify patients who may experience adverse drug reactions. There are some high-profile examples of the use of PM in routine care. For example, in cancer, the targeted therapy trastuzumab has increased the cure rate of HER2-positive breast cancer and has improved overall disease survival.

The potential health gains of PM for the individual patient could be substantial, but the overall added value to health care systems and society can still be limited. One potential reason for this, is that especially for rare genetic mutations, many people have to be tested to identify the few patients that may benefit from PM, which can drive up PM costs. Also, downstream health gains and cost savings of PM are commonly factored into the price of PM, which could offset the short-term value of any health gains. Furthermore, because of budget constraints, some patients might not have equal access to PM even if there is likely to be potential patient health gain. PM approaches can only transfer their promises for the patients into the reality for health care systems, when the Heath Technology Assessments (**HTA**) and the heath economic (**HE**) evaluations are performed to ensure benefit not only for the individual, but also for the society as a whole.

The implementation of PM approaches can affect citizens and patients throughout Europe and beyond. Therefore, a multi-disciplinary concerted effort is needed from national and regional governments and European institutions whose responsibility it is to determine the use of PM (or not) in their respective health care systems.

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HEcoPerMed uses health economic research methods to establish and perform value-based assessments using appropriate health economic models. The aim of this "HEcoPerMed Position Paper" is to describe how **HTA** and **HE** can contribute to decision making at various stages of the personalised medicine approaches. Furthermore, it offers different target groups, such as policy makers and others working in personalised medicine, health economics-based statements to support the development and implementation of value-based PM approaches.

To date, the outputs from this project include PM-related guideline development, systematic reviews and three case studies. These outputs provide a basis for this position paper and specifically include:

1) A paper on the "*Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine*" suggesting 23 recommendations which provide a comprehensive list to modellers of PM and to evaluators and reviewers of PM models.
2) A review on "*Financing and reimbursement models for personalised medicine: a review to identify current models and future options* ", which identified and analysed innovative funding models to support research and development of PM approaches and innovative payment models to support quicker adoption and wider access to PM.
3) A paper focusing on the current evidence base on the added value of PM.

3 HEALTH ECONOMICS AND HEALTH TECHNOLOGY ASSESSMENT – NEED, LIMITATIONS & BENEFIT

- Health economics as a discipline has existed for over 50 years with a primary focus on the analysis of efficiency, values, and behaviours, related to the use of health and healthcare. It goes beyond economics by absorbing knowledge and ideas from other disciplines, including biostatistics, cognitive psychology, decision theory, demography, epidemiology, ethics, political science, public administration, and others. HTA is a subset of health economics. It draws mostly on the methods of economic evaluation in healthcare, but interacts with clinical medicine, epidemiology, biostatistics, health outcome measurement and data synthesis.

QUESTIONS OF HTA TO SUPPORT DECISION MAKING

Decision makers can use HTA to help them to:

- identify potential patient populations,
- know the public health priority of the treated disease,
- get reliable information about the safety and efficacy profile of the intervention,
- consider equity aspects,
- assess the potential health gain for patients,
- ensure the optimal allocation of resources – efficiency/cost-effectiveness
- make sure there is sufficient resource available – budget impact
- ensure access to the patients.

- HTA steers difficult considerations in multidisciplinary and multi-professional contexts and provides ways for decision-makers to organize their thinking about the choices they have to make. The HTA process often puts emphasis on the:

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- Synthesis of research findings on effectiveness of health interventions,
- Evaluation of cost and cost effectiveness
- Appraisal of social and ethical implications of the diffusion and use of health technologies and organisational implications and
- Identification of best practices in health care, thereby enhancing safety, improving quality and saving costs.
- However, as much of the process is necessarily deliberative, the content of HTA strongly depends on the decision makers involved, who may come from many areas: public servants, private or public insurance agencies, employer organisations, innovators of health technologies, manufacturers or even trade unions.
- Grasping fully the technical aspects of HTA is not necessary for all stakeholders. They should, however, understand enough about the method of analysis, and the processes of actually conducting an assessment to be able to critically judge economic evaluation results. Jurisdictions, similar to stakeholders, can also differ in how they use HTA results. Some health care systems, place priority on clinical evidence from trials, sometimes supported with information on the potential budgetary implications from technology adoption. In contrast, an increasing number of systems inform decisions by directly synthesizing clinical evidence with costs and health outcomes data to assess whether additional benefits of a new technology are accompanied with affordable costs. An early task in any HTA is therefore to make a list of relevant stakeholders and decide when and how their representatives might be involved and what kind of methods could be used throughout this process.
- Despite common principles, and the learning lessons from other jurisdictions, the process of HTA, and more particularly its economic evaluation component, requires a national approach. The differences between countries implies that the results of an economic evaluation conducted in one setting might not be directly applicable to another. As a result, country-specific evaluations are needed that reflect the needs of the decision-makers in a particular country. Differences in the culture, organisation of health care and other sectors of the economy may shape the patterns of care between settings and hence change the way in which costs and benefits are accrued. Nevertheless, international efforts to develop and apply standards may help in the harmonization of HTA initiatives within Europe and across the globe.

4 AIM OF THIS POSITION PAPER

This paper aims to explore the barriers to the appropriate and timely adoption and wider implementation of PM interventions for society (Chapter 5). The paper also provides insights into how health economics and HTA can be used to help mitigate these barriers (Chapter 6).

Health economics can help to identify appropriate funding arrangements to support research and the development for new tests and treatments (section 6.1). HTAs can be used to evaluate the cost-effectiveness of tests, treatments, and test-treatment combinations, both while they are still in the development stage (section 6.2) and once an (approved) product is available (section 6.3). Once new products are ready for use, HTA can also be used to establish a fair price for new innovations (section

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6.5), aid in the design of reimbursement and payment arrangements (section 6.6) and provide insight into how new innovations might be best implemented in clinical practice (section 6.7).

Additional sections discuss the transferability of HTAs across countries (section 6.4), how patient perspectives can add to traditional evaluation frameworks (section 6.8), and which equity considerations may be relevant in the development and implementation of PM (section 6.9).

In Section 7 we suggest a set of 25 statements to support discussions for PM focus and efforts. These statements are arranged into three areas one with mainly an International & European, one with a national & regional and a third with the HTA & HE perspective.

5 BARRIERS TO ADOPTION AND IMPLEMENTATION OF PERSONALISED MEDICINE

- The barriers to the adoption of PM at national level are well documented [Horgan et al., 2014]. Most of the barriers are related to suboptimal financial incentives for stakeholders, a lack of economic evidence and clear guidelines for country adaptation. There are also issues with pricing and contracting, and limited and segmented budgets for research and implementation. An overview of such barriers and recommendations to overcome them is provided in Table 1.
- In HecoPerMed we have extensively focused on the barriers related to the financing of R&D and reimbursement of PM. This is because the financing of R&D for PM has a direct impact on the level of investment in innovation and upscaling of basic research. Barriers to financing research in PM can relate to the existing discordance between research priorities on several levels, international, national and regional. In addition, legal issues, intellectual property rights and privacy/ethics issues such as the lack of harmonisation of legal and ethical guidelines concerning data and sample sharing, as well as licensing concerns which require dedicated policies to help overcome them can discourage international endeavours and initiatives to finance PM R&D. The lack of established or strong links between potential commercial and academic partners can also pose a barrier to investment in PM R&D.
- Decisions on reimbursement have a direct impact on the implementation and adoption of PM in clinical practice. Solving reimbursement issues for PM with proven clinical and cost-effectiveness can help to optimise their use in health systems.

Key barriers to reimbursing PM relate to affordability, the use of existing reimbursement schemes and codes for novel PM, including gene and cell therapies, molecular and genetic/genomic tests, and the variation and misalignment of the reimbursement of test-treatment combinations, to name a few. In the case of expensive gene and cell therapies that are delivered as one-off treatments, upfront payments bear huge financial risk for payers due to the lack of evidence for the benefits of these therapies and the sustainability of health outcomes in the long run. In addition, existing reimbursement schemes often pose a barrier to positive reimbursement decisions. An example of that is the code stacking fees used to reimburse molecular and genetic/genomic tests. In cases where many codes are used to bill a single test due to the lack of a dedicated billing code for the test, payers may refuse to reimburse the costs to providers.

Furthermore, existing HTA processes are often not suited to evaluate the long-term benefits of novel of one-off treatments, nor the combined benefits of test-treatment combinations which can be a

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barrier to achieving a positive reimbursement decision in some countries. Performance-based reimbursement has been suggested to overcome the shortcomings of existing reimbursement schemes, however, it should be noted that these schemes could be challenging to implement in current healthcare systems due to additional data requirements, high administration costs to collect, store, and analyse data, and perverse incentives in case patients switch between payers.

Many barriers are related to funding of R&D, assessing value, pricing, and payment-incentives and health economics and HTA can help to overcome them.

Table 1. Overview of main barriers to adoption and implementation of PM, by stakeholder groups

Stakeholder group	Barrier
Citizens and patients	• Lack of awareness of the possibilities of PM • Reluctance to donate data because of privacy concerns • Lack of awareness of the economic value of data • Limited access to PM
Academia	• Great competition for research funding to develop PM • Limited access to meaningful data • Legal and practical difficulties in linking data from different sources • Little knowledge on technology transfer and contracting
Commercial test developers	• No appealing revenue models • Lack of appropriate incentives
Biotech pharma SME's	• Difficult to obtain funding and high costs of capital • Lack of resources to scale-up to commercial volumes
Big pharma	• Difficult to obtain funding and high costs of capital • Higher costs of R&D than for non-PM • Long duration between approval and reimbursement decisions • Higher failure rate • Development of companion diagnostic tests lags behind the drug development
Physicians	• Person-centred care requires a new way of thinking • Little attention for prevention and early treatment

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	• Lack of genetic knowledge • Lack of inclusion in clinical guidelines • Lack of embedding in current treatment pathways, especially when current pathways are disrupted • Some tests can only be ordered from centres of expertise and not from common labs • Lack of interoperable ICT structure to share data
Pharmacists	• Little direct contact with patients • Insufficient counselling skills
Hospitals	• Lack of laboratory capacity • Lack of reimbursement of tests, especially when used for prevention in non-symptomatic patients • Absence of reimbursement code leading to code stacking • Budget silos within one hospital
Regulatory authorities	• Increasingly immature evidence with increasing uncertainty on efficacy and safety
Reimbursement authorities	• Difference in opinion on most appropriate endpoints • Difference in opinion on type of evidence that is considered sufficiently convincing • Difference in opinion on feasibility of generating the required level of evidence
Payers	• High prices that factor in the potentially large health gains and large savings of PM • Lack of consensus on what is a fair price • High impact on drug budget • High budget impact of testing when prevalence of disease is low • Great uncertainty on long-term impact of PM • Payment model with inappropriate incentives
National/regional governments	• No sense of urgency to transition to PM • Lack of a clear vision on PM • Lack of central policy and guidance on PM • Lack of appropriate legal framework

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Across stakeholder groups	• Little convergence between different disciplines • No shared vision of change-strategy

Sources: De Graaf et al., Waardebepaling, implementatie en bekostiging van voorspellende testen in Nederland. November 19, 2019; Implementatiebarrières voor PHC in Nederland. PHC Alliance, 2021

Many barriers are somehow related to funding of R&D, assessing value, pricing, and payment-incentives and health economics and HTA can help to overcome them.

6 THE ROLE OF HEALTH ECONOMICS AND HTA TO HELP OVERCOME SOME BARRIERS IN PERSONALISED MEDICINE

6.1 Funding of research and development

Health economics can contribute to helping overcome the existing barriers in financing research and development (R&D). We have identified several public-private collaborations engaged in funding R&D for PM that could inspire further collaborations. These include collaborations between academia, government, pharmaceutical industry, and charities. For example a) the Public private partnerships between National Cancer Institute funded by National Institutes of Health (NIH) American Recovery and Reinvestment Act (ARRA) funds and venture capital–backed companies through the Small Business Innovative Research (SBIR) programme in the USA, b) the dedicated collaboration between the American Heart Association, academic medical centres, patient advocacy groups, and private partnerships (Health eHeart Alliance) for cardiovascular research in USA, c) AstraZeneca's Open Innovation Initiative, GSK's Centre for Therapeutic Target Validation (CTTV) and the Eisai University College London (UCL) collaborative drug discovery alliance; d).dedicated centres for oncology research and networks of Centres of Excellence in Europe that connect academic, clinical and industrial partner, small and medium enterprises, governmental and non-profit organisations.

There are also collaborations between governments and the pharmaceutical industry which include pharmacogenetics research in Europe, which access core funding from governments, small industrial contracts and funds from charitable foundations. In addition, the EU Sixth Framework and FP7 Programme provides opportunities for industry to access funding under the Innovative Medicines Initiative (IMI) programme. The European Commission programmes (H2020) for Research and Innovation are also developed to support innovative small and medium-sized enterprises in the diagnostic area.

Furthermore, the "Grant-and-Access" programme in the United States, for example, funds drug development for rare diseases, based on risk-sharing agreement, e.g. using federal grant to subsidise drug development in return for cap on the price. Other examples include the International Immuno-Oncology Network that is a collaboration between Brystol Myers and the Netherlands Cancer Institute, Dana-Farber Cancer Institute, The Royal Marsden NHS Foundation Trust, the Institute of Cancer Research, and Johns Hopkins Kimmel Cancer Centre; Pfizer, Eli Lilly, AstraZeneca, and the National Institutes of Health's National Clinical and Translational Sciences programme that funds preclinical and clinical feasibility studies for new uses of shelved compounds.

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Health economics could have a pivotal role in these collaborations by providing an estimate of the financial risks involved in the R&D of PM, forecasting the potential benefits for the stakeholders involved in the agreement, and recommending a reward system for the investment through reimbursement of PM.

6.2 Early-HTA of Test-Treatment Combination

Early HTA occurs during the product development phase, usually before the marketing authorisation is granted by regulatory bodies. Estimation of the value of newly developed PM technologies at early stage can determine the personalized technology's future. Exploring unmet medical needs, burden of disease, value proposition, pricing strategies, willingness and ability to pay on payor end and returns on investment can either hamper, delay or speed up the development process. Due to personalization (e.g. the composite use of test followed by an intervention) the accurate identification of these decision principles may become more complicated for PM than for traditional technologies. Stratification of patient/user pathways, evidence generation, data collection, and expectations on combined (e.g. test-treatment) cost-effectiveness are all challenging. On the other hand, when regulators and payers grant early access (e.g. Early Access Programs) to the innovative PM technologies inputs of eHTA is a key determinant of decisions.

In the early phase of product development, the estimation of the value is vital for developers, investors, HTA bodies, payers and patients. There is large uncertainty around the efficacy and accuracy of PM data, often only surrogate outcomes are available, the target population and the treatment setting might be open to changes. The diagnostic accuracy of the technology is likely to vary depending on disease types and subgroups of patient population in which the technology is applied and may change over time. Multiple personalized treatment scenarios with regards to settings, population and data may come into the spotlight which will interact with the product development context, e.g. R&D partnerships and exit strategies. In these circumstances the judgment on the future of the PM technology is very vulnerable to several unforeseen factors. Elicitation of expert opinion may have key role, especially in setting up the direction of future development and determining the evidence that should further be generated to decrease the uncertainty of existing clinical data. Thus, the experience of analysts, decision makers, experts and the right mixture of knowledge, assumptions, ideas and risk assessment can be successful.

All in all, eHTA can play crucial role in the internal decisions of technology developers, and it will also clarify the perspectives of early conditional market access and reimbursement. Demonstration of uncertainties and directions on further data collection will also be a beneficial side-product of early HTA. The tools of eHTA will help mapping the missing information in a structured and timely manner and can play a decisive role in the future of the PM technology.

6.3 Full HTA of Test-Treatment Combination

A challenge for the adoption of PM is that successful prescription of PM treatments is dependent on the availability of a testing infrastructure enabling stratification of patients to specific treatments. Indeed, to allow personalized treatment, data on personal characteristics have to be collected enabling a match between patient and treatment. These data can come in many shapes and sizes such as measuring protein expression, preferences of patients for mode of administration, or whole genome

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sequencing. However, one common trait is that all types of data require some form of testing infrastructure. As such, paying for and implementing a test infrastructure is an integral part of a successful strategy to adopting PM.

However, accepting that the test infrastructure is integral to the success of PM means accepting that the associated costs and benefits of testing are to be accounted for in economic evaluations of PM: a new treatment may not be very costly in and of itself, but when it warrants a wide scale investment (to, for example, screen a large group of patients to identify a small subgroup that may benefit from treatments), it exposes payers to larger health care expenditures than those only related to treatments. A full economic evaluation based on modelling can identify the additional costs the test infrastructure brings when adopting PM. However, conducting those types of studies comes with several modelling challenges. In the Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine, developed in HEcoPerMed, recommendations are given on how to estimate the benefit of PM treatments to best inform decision-makers on the total costs and benefits of adopting PM.

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Suggestions to help support the estimation of costs and effects of test-treatment combinations

With regards to the scope of the economic evaluation, all (downstream) costs and health outcomes of all relevant test-treatment pathways for both individuals who test (false-)positive and individuals who test (false-)negative should be included. Also, if relatives of index patients become eligible for genetic testing when the index patients test positive for a specific genetic marker, the costs and health outcomes of testing relatives should also be included in the economic evaluation of the index patients. Another often overlooked issue when dealing with test infrastructure, is that testing itself takes time. If there is a notable risk of increased morbidity or mortality as a result of waiting periods, incorporate in the model the costs and health outcomes due to the waiting periods.

Appropriately including the costs and benefits is not without specific challenges, nor is it without controversy. It may, for example, seem unfair to "first movers" to allocate 100% of the additional testing costs to the treatment under evaluation. The first pharmaceutical or medical device companies that require a specific test to identify the right patients for their products 'incur' all costs in the economic evaluations, while the same test may later be used for other medical products. However, it is an accurate reflection of the decision problem at hand: the new treatment cannot be implemented in clinical practice without also implementing said test and so the cost-effectiveness of their combination should be assessed. When the stratification for the new treatment can be done with a test that is already part of current practice, none or only a proportion of the testing costs may be allocated to the new treatment.

A specific challenge is the estimation of benefit of PM when a new treatment is stratified to patients based on a new genetic biomarker. The issue is pressing, as there is an increase in the market authorization of PM treatments stratified to patients with some genetic biomarker based on single arm studies. This poses two challenges. The relative effectiveness of PM has to be estimated using external data (as it was not collected in the trial). Without a comparator group, it is not possible to identify to what extent a new PM treatment is better than alternatives that are already on the market. However, the estimation of such a comparator is difficult when one has to rely on historical data in which the new genetic test was not included (as it is new). As a result, the prognostic value of the genetic biomarker is unknown: patients who test positive might have better, worse or equal prognosis to those who test negative complicating the assessment of relative effectiveness. In the guidance we therefore suggest to find ways to estimate the prognostic value of the genetic marker as well as differences in its prevalence across the different data sources used for decision analytic modelling.

PM requires personalisation, which in turn requires some form of test. Appropriately accounting for this test-treatment combination is vital for the assessment of the benefit of PM.

6.4 Transferability of HTA and joint Assessment in PM

Health technology Assessment (HTA) is a tool that when applied appropriately, can support unbiased, evidence-based decision-making in PM. However, transferability is an important aspect when conducting HTA in different EU countries at various development levels. It is essential to separate the transferability of data and methodology, from transferring recommendations and policy decisions.

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Consistent methodology can increase transparency of assessment while decreasing the need for human and financial resources. On the other hand, directly transferring HTA recommendations or policy decisions across countries with potentially different health-care priorities can lead to suboptimal allocation decisions.

The European Network for Health Technology Assessment (EUnetHTA) was built to harmonize HTA methodologies across the European Union. EUnetHTA developed the HTA Core Model to focus on joint production of relative effectiveness assessment, which can be used as a basis for national value assessments. The HTA Core Model approach encourages explicit considerations on the transferability of relative effectiveness assessment across countries and recommends national HTA assessment based on similar methodologies, which ultimately reduces duplication of efforts while adhering to key scientific principles. The use of EUnetHTA methods and joint clinical assessments linked to localized assessments of patient pathways, budget impact and cost-effectiveness seems to be a feasible pragmatic solution for all European countries in the field of PM.

Avoiding duplication of work would be even more beneficial for lower income countries that generally have a worse health status and less public resources for health care; therefore, they have an even greater need to make well thought-out, evidence-based policy decisions. Joint HTA work organised in a permanent system would strongly support scientific accuracy and policy relevance of HTA recommendations in all EU countries.

6.5 Fair pricing

What constitutes fair pricing of medicines is difficult to define and depends on the stakeholders' perspective. Recent efforts and initiatives by the WHO have outlined that pricing of medicines should ideally: a) be fair to both manufacturers and payers, b) not hamper innovation, be affordable to health systems and payers, c) maintain sustainable production, and d) offer sustainable access to patients to quality health products. In essence, a fair price is the price that covers the manufacturing costs and ensures a reasonable profit that reflects the value of the product to the consumer while maintaining affordability for payers. However, defining a "reasonable profit that reflects value" is challenging as shareholders are driven by profit maximisation rather than corporate responsibility. With regards to PM, fair pricing is even more challenging due to the smaller number of patients that will benefit from personalised therapies and the heterogeneity of health outcomes among patients while R&D costs for PM may still be high. The development of gene and cell therapies, for example, is a costly endeavour and usually these are very highly priced and generally considered not cost-effective. Several gene and cell therapies (e.g., ChondroCelect, MACI, Provenge, Glybera) were subsequently withdrawn from the pharmaceutical market due to affordability issues related to the high prices of these therapies and the uncertainty in their long-term benefits.

Value-based pricing and indication-based pricing have been suggested as means to differentiate the pricing between different groups of patients or different indications. This would enable payers to reimburse PM according to its outcomes and cost-effectiveness and manufacturers to get a return on the R&D investment plus a "reasonable" profit. Value-based and indication-based pricing can be difficult to achieve, though, as data about the performance of the PM in different groups may be lacking. In addition, generating, collecting and analysing such data adds costs and is time-consuming. Value-based and indication-based pricing might not be attractive to manufacturers as they tend to launch medicines at a list price that just about meets the cost-effectiveness threshold established in different countries or is not considered cost-effective. In case further reductions in price are required

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by the regulatory bodies in the respective countries these are usually negotiated and achieved through confidential discounts and rebates. Transparency with regards to R&D costs, as well as shedding light on the actual prices that different payers pay for new medicines (usually achieved by confidential negotiations between the manufacturer and different payers) are argued to help achieve fairer prices. Payers and the public (i.e. tax payers) need to gain confidence in the pricing of PM in order to accept it as fair. In addition, transparency could ensure that public funds are spent to pay for effective PM with a reasonable profit margin, and the public is not paying twice, e.g. in case there was substantial investment of public funds in R&D.

6.6 Reimbursement and payment

Currently, PM is reimbursed via existing reimbursement models that do not involve sharing of financial risk between payers and providers or manufacturers, and do not consider the performance (i.e. effectiveness) of the PM. For example, applying existing DRG codes in the USA to reimburse costly CAR T therapies, or fee-based payment models to reimburse genetic tests and companion diagnostics, can often result in underpaying or refusing payment to providers altogether which could limit the adoption and use of these PM in clinical practice.

Reimbursing PM via performance-based agreements could alleviate the burden of upfront payments, and share financial and uncertainty risk between payers and providers. Early pre-approval dialogue between payers and providers/manufacturers to agree on health outcomes that will be assessed and for which data need to be collected could help facilitate the application of performance-based agreements in practice. Coverage with evidence development is often a preliminary step to value-based pricing and reimbursement and could be used to facilitate the reimbursement and adoption of PM while the necessary clinical and cost-effectiveness evidence is generated. In addition, such evidence schemes can be used to improve patient access, address regulatory concerns, and simplify reimbursement decisions, however, it should be noted that in some health systems it is easier not to grant reimbursement on the first instance than to withdraw it when the PM has not proved its benefits.

Financial-based models such as rebates and volume caps could be used to reduce the impact on the healthcare budget, and improve affordability and cost-effectiveness of new treatments. Financial-based models could also be used as an intermediate step while generating the real-world evidence of the effectiveness and benefit of PM that will help re-evaluate reimbursement decisions. Health economics could support reimbursement by providing the framework to evaluate benefits and costs of PM, especially the long-term effectiveness of one-off treatments, and the combined effectiveness of test-drug combinations.

Reimbursement of PM could potentially be improved by:

- **Establishing a clear HTA framework for assessment of benefits and costs of test-drug combinations and one-off therapies.**
- **Establishing dedicated codes for companion diagnostics and genetic tests that reflect the value of the test.**
- **Aligning the reimbursement of companion diagnostics and targeted therapies by combining these into a reimbursement package.**
- **Implementing performance-based models that will decrease the financial risk for payers in case of treatment failure especially for highly priced gene, cell and targeted therapies.**

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- **Using real world data of the performance of the PM to re-evaluate reimbursement decisions.**

6.7 Appropriate use in real-world practice

Historically, cost-effectiveness evidence has primarily been used to inform 'yes or no' reimbursement decisions, while its potential to improve efficiency in everyday clinical practice is underutilized. After introduction into the market, results of HTA studies can be used to stimulate 'appropriate use' of PM in the real-world setting. 'Appropriate use' of PM refers to delivering PM interventions with proven added value and refraining from applying interventions without proven added value in the everyday clinical treatment of individual patients, given the context at hand. This is also referred to as the provision of value-based health care. This requires increased knowledge of existing HTA evidence and behavioural change of professional care providers. Such change can be enhanced through the incorporation of cost-effectiveness considerations in clinical guidelines and decision support tools that stimulate the implementation of these guidelines. Currently, these guidelines and tools mainly rely on evidence of effectiveness without considering efficiency arguments. However, treatment guidelines could additionally be based on evidence about the amount of health gains per euro invested. Specifically, for PM interventions that require costly testing of a large group of people to identify a few candidates for treatment, one could think of a clear distinction between a patient in whom testing is relevant and a patient in whom it is not (or only after preceding tests have ruled out other diagnoses) based on cost-effectiveness considerations. Another example is the clear definition of cut-off values of a test, below which further intervention is not efficient.

Appropriate use in daily practice often starts with the treatment options and infrastructure that local professionals in local hospitals have at their disposal. In countries where such decisions are not made at a national level, individual professionals can use HTA results in local negotiations with health insurers on future investment in and reimbursement of PM interventions.

HTA studies can investigate whether there is an association between the scale at which an intervention is implemented on the one hand and the costs and the quality of care on the other hand. This is particularly relevant in PM, as these interventions often target relatively small subgroups. When scale matters, HTA results can be used to inform decisions on centralising testing or treatment infrastructure in order to improve outcomes and reduce underutilization of capacity. Examples in which centralisation of PM services has improved efficiency include genetic testing, counselling and treatment for rare heredity congenital disorders.

6.8 Patient Perspectives

Patient perspectives can be very relevant in PM as there is usually limited evidence available and additional factors which are not considered in the traditional decision framework can have a substantial role. Early patient involvement can increase the added value of the interventions, the following outline summarize the potential roles and benefits of patient involvement in different phases of product life cycle:

<u>Patient roles in R&D</u>

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Patients can support different stages of the development process, but their input is especially valuable in case of the following steps:

- Understanding the disease and reveal real unmet medical need
- Development of clinical trial concept
- Selection of meaningful patient related outcome measures and clinical trial endpoints
- Ensure that interventions address real needs of patients (measured with adequate PROs and patient experience instruments)
- Facilitate study recruitment

Patient roles in regulatory decisions

Formalized regulatory processes leave limited opportunities for patients to provide input but patients can have a role in the validation of presented patient experience data, as well as they can provide valuable insight to the authorities to consider patient perspectives during the critical appraisal of submissions.

- Consideration of patient preferences by regulatory bodies may increase patient centricity of decisions.

Patient roles in HTA

- In the HTA process patient preferences can be considered as supportive evidence to complement traditional clinical and economic evidence.
- Various levels of involvement can be defined from data collection, through collaboration to full formal integration of patient voices into the HTA process.
- Patients can provide support at various steps:
    - support and validation of economic model concepts to incorporate key aspects that matter the most to patients
    - investigate attributes related to benefits, risks, administration, travel burden and out-of-pocket costs
    - investigate the acceptability of issues such as adverse events and uncertainties,
    - investigate the importance of different outcome measures
    - examine preferences of subgroups (e.g., age groups), especially for therapies with uncertain long-term consequences
    - help to perform the HTA from a wide societal perspective (patient and caregiver burden)
    - help to identify and assess additional value elements of the PM intervention

Patient role in post-marketing

- Assessment of real-world effectiveness can be strongly supported by active patient participation
- Outcome based contracts relying more on patient preferences can shift the emphasis on value domains important for patients

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- Individual preferences can have a substantial role in real life therapeutic decisions. Investigation of these can improve personalization in case of new technologies

Patients can support decisions throughout the entire life cycle of PM products/interventions. Increased recognition of their perspectives and active involvement into decision making can increase patient centricity of PM technologies.

6.9 Equity Considerations

Equity has an important role in PM. The highly innovative area of personalised care makes it challenging to ensure access for all. Substantial variation may be observed in the utilization of PM technologies across different patient groups, regions, treatment modalities and disease types. Even in high-income countries, unequal access to PM becomes an issue for marginalized sectors and under-served populations such as the socio-economically disadvantaged population, or people in rural areas (1, 2). Highly innovative PM technologies necessitate patients' flawless entry to healthcare facilities, with respect to location or affordability. There is a prerequisite to be linked to services with trusted providers that are usually large academic medical research centers routinely investigating genetic information. For example, adequate personalized care for chronic patients requires multiple clinical encounters, good access to medication, and continuous update of treatment plans (2). This necessitates advanced health care infrastructure, know-how and a flexible system, available in the most developed countries.

There is also a tendency in the international domain that research funds are allocated to the development of relatively expensive genomic technologies in wealthier countries. This results in the lack of diversity in the collected genetic data which consequently leads to limited generalizability of evidence across ethnic groups, especially in less economically developed regions. There is a real threat that inequity in access to genetic research, genetic discrimination, and lack of adherence to internationally accepted requisites of clinical validity and utility for diagnostic and predictive genetic testing will place patients in low- and middle-income countries in a deprived position (3). Similarly, to overcome the problems of limited generalizability, population diversity in genetic databases and evaluating genetic scores in conjunction with other disease factors will be needed to ensure a more equitable impact of precision medicine.

One can anticipate that the value of PM may be higher in the most developed countries with a high level of health care compared to lower-income countries where quicker wins from the wider implementation of non-personalised technologies are still possible. In these jurisdictions' administrative barriers (e.g. limited reimbursement, volume restrictions, etc.), lack of population specific data, competency, expertise, and financial support limit access to expensive PM therapies (4, 5). However, in lower income countries with lower average health status there is more potential to benefit from higher value care, which would meet the vertical equity criteria of providing more access to those with more needs. While higher income countries in the EU will struggle more with within country variation, lower income countries will face with the equity issues drawn from their financial and infrastructural limits. One example of such an issue is the reference pricing system that results in narrow price corridor within the Community and in relatively high prices in EU countries with lower purchasing power parity. Value based pricing that enables countries to pay different price for each PM

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technology can handle such an equity issue. Although it may bring other market dynamics to the fore such as parallel trade and free movement of goods.

There is no question that equity concerns will vary across the European jurisdictions. The above examples show that the toolset of HTA and health economics needs to be applied in a stepwise, cautious manner with respect to country specific circumstances, and that the consequent implementation of HTA methodologies will be a key prerequisite towards more equitable systems applying PM across Europe.

7 HECOPERMED CONCLUSIONS AND STATEMENTS

There is a need for further evidence about the clinical and personal utility as well as economic value of PM and its benefits compared to standard practice. Once clinical and personal utility as well as economic sustainability are proven in a precisely defined indication, a strategy for the communication and dissemination of the possibilities, challenges and potential benefits of PM should be developed. Economic evaluations can and have to determine the added value of personalised medicine approaches for patients, health systems and society. That value should go beyond gains in survival, quality of life and cost savings, which are currently the heart of HTA. We have produced a set of statements to support discussions for PM focus and efforts. These statements are arranged into three areas one with mainly an International & European, one with a national & regional and a third with the HTA & HE perspective.

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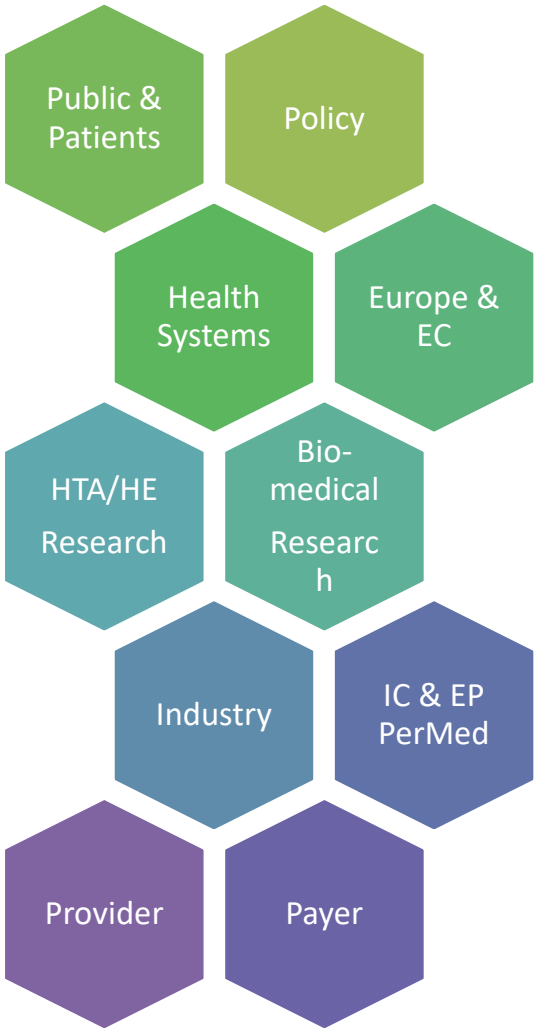

Fig. 2 Central target and stakeholder groups for this document, its analysis, conclusions and statements (see below).

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7.1 Statements with a European and International Perspective

There is a need for further evidence on the clinical and personal utility and of PM as evidence on the economic value of PM relative to non-PM standard practice. It is crucial to provide such evidence, so that for example health and research ministries and other decision makers can make PM a priority research area. Once clinical and personal utility and economic viability are established, a strategy for the communication and dissemination of the possibilities, challenges and potential benefits of PM should be developed. Economic evaluations can help to determine the added value of personalised medicine approaches for patients, health systems and society. Scientists and especially as health economic and outcomes researchers should investigate the value of PM and provide evidence.

(1) Statement 1.1

Health economic and outcomes researchers should focus first on the reference case for HTA which is often the use of quality adjusted life years.

The nature of PM requires additional attention to be paid to details of health economic decision models. However, the evaluation of their benefit should not be judged differently from other health care interventions that compete for the same health care budget.

(2) Statement 1.2

HTA & HE models should be generated and existing models should be adapted considering PM-specific aspects and contexts.

As the requirements for (European medicine Agency (EMA) approval are different from the requirements for market access in specific Member States, with limited alignment between the two, discussions about pricing and reimbursement are potentially longer than necessary. Much of this delay is arguably mainly caused by differences in opinion about what constitutes a fair price for a new PM treatment.

(3) Statement 1.3

The regulatory frame work needs to be considered and if necessary aligned and adapted to support HTA & HE evaluations of PM.

HTA & HE assessments are often conducted by or on behalf of pharmaceutical companies when they prepare dossiers for reimbursement submissions following EMA approval. Independent research is also performed in the academic setting, but this is often not part of discussions on value between payers and manufacturers.

(4) Statement 1.4

The communication and alignment of commercial and academic players should be fostered to ensure sufficient HTA & HE assessments.

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It could be advantageous to improve the consideration of needs and benefits of the therapies/drugs for citizens and patients and where feasible and reasonable to also consider the Ethical, Legal and Social Implications (ELSI).

(5) **Statement 1.5**

The need and benefit of the citizens and patients as well as ELSI aspects should be sufficiently considered in HTA & HE assessments.

At the European level the adaption of a suitable pricing and reimbursement framework represents a significant challenge. For example, there are very large differences between Member States in terms of wealth and the availability and share of healthcare resources. However, equitable access for all citizen's and patients should ideally be developed at the national level. Current methods of calculating prices are far from transparent and often not linked to a given technology's added value and performance. For reimbursement, the main challenge is budget constraints and single technology analyses. Mostly prices are calculated on the basis of existing comparator and standards of care costs. This limits the possibility of paying per performance or per outcome reached on an individual patient. Thus, there might be innovative methods of pricing and budget prioritisation possible overcoming this situation.

(6) **Statement 1.6**

A European pricing and reimbursement framework should be established to ensure equitable access for all patients - regardless of economic or geographic status – considering sustainable for health systems.

Public-private agreements help to ensure sustainable investment in R&D of PM. Each partner can build on and contribute to the agreement with their relevant expertise and assets at one or more phased on the PM development. European authorities can facilitate the process by harmonising research priorities on European, national and regional levels within the EU and providing support with relevant funding calls. In addition, harmonising legislation and regulation related to PM, intellectual property rights and privacy/ethical guidelines across the EU can further facilitate investment in R&D.

(7) **Statement 1.7**

Public-private agreements have to be developed or adapted as they ensure sustainable investment in R&D for PM.

There might be a mid- and long-term benefit, if European, national and regional funders would design suitable funding models to enable cross-sector working in PM-research, incl. HTA/HE and regulatory aspects and requirements.

(8) **Statement 1.8**

Suitable funding models should be designed to enable cross-sector working in PM research, incl. HTA & HE aspects and requirements.

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7.2 Recommendations with National and Regional Perspectives

In principle, value-based pricing (VBP) could be an appropriate approach, as health economic related models need to be explicit about the added value and provide evidence to underpin the value. However, this does not mean that all value created by PM will automatically be factored into the price of the drug as we currently witness that for expensive cell and gene therapies. Some, like the gene therapies for SMA and Duchenne disease, not only leads to very large Quality-Adjusted Life Years (QALY) gains, but also to large downstream savings in life-long costs. Industry sometimes uses to increase the price of drugs up to the point that the incremental cost-effectiveness ratio (ICER) remains just below the threshold value. This should be acknowledged, but correspondingly it should also be considered that the HTA framework and value-based pricing offer the perfect means to negotiate about sharing the value between manufacturer and society/payer, because they provide the evidence needed for these negotiations.

(**9**) **Statement 2.1**

HTA frameworks and value-based pricing should be considered for negotiation about sharing the value between manufacturer and society & payer.

It is likely that the boundaries of value-based pricing (VBP) are reached for the very expensive cell and gene or other innovative therapies such as orphan drugs, therefore a form of rate of return pricing should be considered and developed.

(**10**) **Statement 2.2**

For expensive innovative therapies a rate of return pricing should be considered and developed.

When PM is defined in such a way that it also includes person-centred care in frail elderly, palliative care, care for complex multimorbid patients etc., then value should be broadened to include wellbeing and experience provided as health gains may no longer be achievable.

(**11**) **Statement 2.3**

The definition of value should be broadened to include wellbeing and experience with the care, because where health gains may no longer be achievable.

Value-based pricing (VBP) by definition leads to price differences between countries, because the savings in downstream costs depend on the price-level in a specific country. However, it might be reasonable to assume that countries have different prices for the same drug. Thus, industry information might not be fully transparent about the actually pricing policy after discounts and financial- or performance based managed entry agreements (MEAs). Otherwise, that would restrict access to expensive drugs in low- and middle-income countries, as reference pricing and parallel trade in the EU are an important principle of the free movement of goods in Europe.

(**12**) **Statement 2.4**

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The European, if not international, impact of pricing should be considered for HTA & HE modelling.

There has been a certain added value and benefit when an early dialogue and cooperation between researchers and payers, patients, regulators and industry could be established in the process of a PM approach development.

(**13**) **Statement 2.5**

Where feasible, early dialogue and cooperation between researchers and payers, patients, regulators and industry should be established in the development of a PM approach.

It might be worthwhile to establish and adopt a shared risk-and-benefit mechanism that also has a 'full cost of the patient' view. Mechanisms exist that can be valuable in the case of new evidence generation while ensuring access to innovation. These mechanisms have been called conditional coverage agreements (CCA) and include a range of practices including "coverage with evidence" or "risk sharing agreements". A thorough assessment should be run to test the applicability of these approaches for PM.

(**14**) **Statement 2.6**

An optimised and overall healthcare financing strategy should be designed in light of PM and other innovative approaches.

It would be advantageous both mid and long-term if biomedical and clinical PM researchers are willing and able to explain HTA/HE models, there impact, needs and development.

(**15**) **Statement 2.7**

Biomedical and clinical PM researchers should be supported to acquire general or specific HTA & HE knowledge to enable them to critical judge HTA inputs and results.

7.3 Health Economic Evaluation of PM Approaches in General

The existing additional leaves of the value flower have to be recognised and analysed. To achieve this, they have to be well identified and further investigated by multidisciplinary research efforts. However, even if some individuals are willing to trade-off some of their health in exchange for these additional value-elements, this does not have to lead to the society paying for them. Hence, not include them in the base-case of an HTA, unless this would be in line with country-specific HTA-guidelines that apply to all interventions.

(16) Statement 3.1

The set of value elements should be updated and incorporated into the country-specific HTA-guidelines.

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Societal decision making based on economic evaluations helps societies to be transparent about which prices they do and do not accept for treatments increasing the health of their population.

(**17**) **Statement 3.2**

Adaptive and transparent economic evaluations are needed for societal decision making.

The development and modelling of PM approaches can be time consuming. However, the lack of the established procedures and rules may result in other forms of waste, such as higher prices or inconsistent decision making.

The assessment of the value of PM through economic evaluations will increasingly require information on the prognostic value of biomarkers. Without good quality European and national databases on both outcomes (survival) and biomarkers, it will not be possible to adequately assess value.

(**18**) **Statement 3.5**

High quality European and national databases on both outcomes (survival) and biomarkers are needed.

The testing sequence that precedes the initiation of a treatment can be very costly. Countries that do not conduct tests standard (e.g. genomic) have to be aware that introducing PM can raise additional health care expenditures as large numbers of people need to be tested to find a rarer smaller sample of patients that can benefit from a treatment.

(**19**) **Statement 3.6**

Countries need to be aware that introducing PM approaches can increase expenditures as large numbers of people & patients need to be tested to define stratified patient groups that can benefit by the PM treatment.

MEA's are a means to offer timely access to expensive drugs with high uncertainty on the budget impact and/or effectiveness. However, the industry might not be able to be fully transparent on the conditions of the MEA. Nevertheless, there are different levels of transparency. Industry can be transparent about the existence of a MEA, and about the evidence on effectiveness, risk/benefit etc. that is generated during the term of a MEA but cannot be transparent on the link between performance and actual payment.

(**20**) **Statement 3.7**

Approaches to offer timely access to expensive drugs (MEA) should be communicated as transparently as possible for further improvement of HTA & HE modelling.

Industry anticipates the possibility that they have to enter into a MEA and propose a high initial drug-price, knowing they will be reduced as part of the MEA. When PM is defined in such a way that it includes the many different forms of eHealth and mHealth such as home telemonitoring, then a large amount of data might be collect without clear vision on how exactly to use these data to personalise

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treatment. It should be considered in developing and validating prediction rules that guide per personalised treatment, e.g. at what hospitalization-risk should an algorithm using data from telemonitored heart failure patients raise an alarm and lead to clinical action?

(**21**) **Statement 3.8**

Innovative approaches like eHealth and mHealth should be considered in developing and validating prediction tools that guide per personalised treatment.

During the COVID crisis and the related vaccine development people were willing to contribute to scientific research as they were convinced of the urgency. The same sense of urgency can be assumed by the large number of people worldwide that suffer from a rare and other disease for which there is no treatment available yet. Thus, more people might be encouraged to donate their health or life style data for the greater good of scientific innovation. Also, many might be willing to do so, provided that data-protection and privacy legislation prevents misuse of their data.

(**22**) **Statement 3.9**

Fostering the awareness and willingness of the public and patients to support PM and HTA & HE research efforts with their health or life style data to ensure innovation in the future is crucial.

It is likely that whole genome sequencing (WGS) of all cancer patients and ones with other severe or rare diseases in which genetic mutations may be an important cause or driver, even if we currently do not have interventions to treat them. By collecting the data, we generate evidence on the natural history of people with a specific mutation; data which can later we used in the control-arm of a study on a new intervention. In one of the HEcoPerMed case studies (entrectinib treatment) the survival curves of the control group for the prognostic value of the NTRK mutation were adjusted, even if that was based on just a small number of patients. Therefore, if WGS becomes standard it is likely that costs will decrease further rapidly.

(**23**) **Statement 3.10**

Whole genome sequencing (WGS) <u>should</u> become a standard diagnostic in some rare diseases and some cancers so the related costs could decrease further.

In parallel to the PM therapy and treatment approaches also PM-related prevention strategies are developed. Also, for these HTA & HE models for the evaluation and assessment should be considered, developed and adapted.

(**24**) **Statement 3.11**

HTA & HE models for the evaluation PM-related prevention strategy should be considered, developed and adapted.

New models for pricing and reimbursement require discussion. Where patients provide their personal health data and member states invest in infrastructure, the pricing of products and services that bring innovation to market has to be adapted. Reimbursement has to ensure fair

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rewards for the research investment and risks taken by the producer, but also affordability for the entire health system as well as equity for each patient. Decision-makers need sound economic and medical evidence to support their decision-making process. Funding organisations should collaborate with healthcare providers to identify a disease or group of diseases as a paradigm for PM and fund research on relevant health economics related to PM.

(**25**) **Statement 3.13**

Health economics research of PM to support decision-makers should be encouraged and supported.

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9 GLOSSARY AND ABBREVIATION

COVID	Coronavirus SARS-CoV-2
ELSI	Ethical, Legal and Social Implications
EC	European Commission
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
EP PerMed	European Partnership for Personalised Medicine
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
GDPR	General Data Protection Regulation
HE	Health Economic/Economy
HTA	Health Technology Assessment
HEcoPerMed	"HEalthcare- and pharma-Economics in support of ICPerMed
ICER	Incremental cost-effectiveness ratio
ICPerMed	Interanion Consortium for Personalised Medicine
ICT	Information and communication technology
NCA	National Competent Authorities (Regulatory Authorities)
NTRK	Neurotrophic Tyrosine-Receptor Kinase
MEA	Management Entry Agreements
MS	Member States
QALY/QALYs	Quality-Adjusted Life Years
Patients W.A.I.T.	Patients Waiting to Access Innovative Therapies. The INDICATOR provides a benchmark of the rate of availability and waiting times in European countries.
PerMed/PM	Personalised Medicine
R&D	Research and Development
VBP	Value-based pricing
WGS	Whole Genome Sequencing
…	

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