HEcoPerMed

Position Paper: “Personalised Medicine from a Health Economic Perspective” - Lessons Learned and Potential Opportunities Ahead

Findings & Statements by the HEcoPerMed consortium

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GLOSSARY AND ABBREVIATIONS

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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1 INTRODUCTION AND AIM

The HEcoPerMed project **(Healthcare and pharma economics in support of the International Consortium for Personalised Medicine – ICPerMed)** is a cooperation and support action (CSA) funded by the European Commission (EC). It is part of the so-called ICPerMed "family" of projects and initiatives that support the research and implementation of personalised medicine in Europe and beyond.

HEcoPerMed was designed in response to the need for robust evidence on the societal value of Personalised Medicine (PM) to support faster adoption of and wider equitable access to value-based PM. An important part of the evidence required is information on the **long-term effectiveness and cost-effectiveness of distinct PM approaches**, which is the **focus of this position paper.** Industry, reimbursement agencies and healthcare payers require this evidence at various stages of the life cycle to help determine whether to continue the development of PM interventions, introduce them into routine health care, or discontinue reimbursing them. However, to accelerate adoption and broaden access, industry, clinicians and payers require more than just robust evidence. They also need innovative ways of funding research and innovation (R&I), as well as alternative payment and reimbursement models that accelerate the implementation of PM in European healthcare systems. Proposing such innovations in funding and payment was also within the scope of HEcoPerMed.

To date, the **scientific output** from HEcoPerMed includes two systematic literature reviews – one on the net benefit of PM and another on financing and reimbursement models for PM – which are good practice guidelines for modelling the cost-effectiveness of PM, and a demonstration of the application of these guidelines in three purposively selected **case studies** in which:

- an extended genetic panel for DPYD testing (TOXNAV) was used to identify poor metabolizers of fluoropyrimidine-based chemotherapy and to personalize the dose so as to avoid serious toxicity;
- a next-generation sequencing (NGS) RNA test was used to detect the presence of rare neurotrophic receptor tyrosine kinase (NTRK) fusions in tumour tissue to identify those eligible for histology-independent treatment with the NTRK-inhibitor entrectinib
- a genetic test was used to screen for the presence of maturity-onset diabetes of the young (MODY), the most common form of mono-genetic diabetes, in which insulin treatment is not beneficial

Together, these outputs provide the main basis for this position paper, which describes these findings and the lessons learned from HEcoPerMed for an **audience including industry, reimbursement authorities, payers, health economic researchers and policy-makers** at European, national, and regional level, to support their decision-making on the development and implementation of value-based PM approaches. We present these findings and lessons in the form of 12 statements in chapter 3. The position paper starts with a general explanation as to why there is a need for cost-effectiveness research of PM in chapter 2. For readers who are less familiar with health economics and cost-effectiveness research, we have included boxes explaining the main methods.

2 Executive SUMMARY

Purpose of position paper

This position paper discusses the contribution that economic evaluations can make to decisions surrounding the allocation of limited health care resources in personalised medicine (PM). In particular, the paper examines the role that health economic models can play in the context of Health Technology Assessment (HTA).

Why is the paper important?

PM combines data from many different sources and aims to increase treatment effectiveness by individualizing health care interventions, which provides a departure from a common "one-size-fits-all" approach in health care delivery. However, some PMs, such as gene therapies, are considered expensive and it is sometimes unclear what their benefits are. Given that many European countries face the challenge of limited budgets for health care, the HEcoPerMed project was designed to provide evidence on the value of PM to promote the appropriate adoption and equitable access to value-based PM. This position paper reports the information and evidence generated during the HEcoPerMed Project to support the future directions for PM across European health care systems.

Our methods

The position paper was generated by combining the outputs produced during the HEcoPerMED project such as literature reviews, model guidance documents and health economic analyses across several clinical cases studies. These outputs are summarised and shaped into lessons learned from HEcoPerMed for different audiences including industry, reimbursement authorities and policy-makers to support decisions on the development and implementation of value-based PM approaches.

Main findings

Our findings and the lessons learned culminated in 12 statements which cover areas relating to efficiency and equity in the delivery of PM, the value of a PM technology over its entire lifetime, and alternative approaches to the reimbursement of PM and their relative success. We report that the costs of introducing PM may be larger than usually identified. The appropriate use of PM can be enhanced, not only by using cost-effectiveness data in reimbursement decisions, but also by adding evidence into clinical guidelines, policy implementation strategies, and clinical decision support tools. It can further be enhanced by the wider adoption of innovative payment and reimbursement models that accelerate access in exchange for the sharing of risks.

Future directions

When performing economic evaluations of PM in the future, all changes to the care pathway should be identification and all downstream cost and benefits related to patient care pathways should be reported so as to enable policy-makers to make informed choices. To provide more timely access to new PM interventions that are shown to be cost-effective from these economic evaluations, the evaluations should be carried out as early as possible and the results shared among EU Member States. Finally, to be able to fund any cost-effective PM interventions, the evidence requirements of various European regulatory and reimbursement authorities should be better aligned going forward.

3 PERSONALISED MEDICINE – POTENTIALS AND PRECONDITIONS

3.1 Perspective matters

Personalised Medicine (PM) – is essential for improving the effectiveness of many public health and healthcare interventions as it overcomes the current limited approach of "one-size-fits-all" and the unhelpful notion of the "average" individual. There are several definitions for "personalised medicine" but, following ICPerMed, HEcoPerMed uses 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."*

PM is a **multifaceted concept** that often combines data from many different sources to individualize interventions. When focusing on the use of genetic information to inform clinical decisions, it includes the following examples: 1) testing to screen for diseases or genetic markers in asymptomatic populations to individualize their screening intervals and disease prevention strategies, 2) testing to provide information on disease prognosis to tailor treatment, 3) testing to identify treatment responders and non-responders to provide therapy to those most likely to benefit and avoid side-effects in those unlikely to respond, 4) testing to identify patients who abnormally metabolize drugs, as a result of which they experience adverse drug reactions that may be avoided by adjusting (dose) or modifying the treatment, and 5) gene therapies.

The health gains of PM for the individual patient can be substantial. For example, in cancer, the targeted therapy trastuzumab has increased the cure rate of primary HER2-positive breast cancer and has improved overall disease survival in the adjuvant and metastatic setting.

In our systematic literature review comparing 279 PM interventions involving gene profiling or correcting pathogenic gene mutations with their non-PM counterfactuals, we found a mean gain in quality adjusted life years (QALYs) per patient of 0.26 (median 0.03), with 6 % of PM interventions rendering more than 1 QALY. However, the mean incremental net monetary benefit (see box for further explanation) was negative and the median just above zero. Although there is a lot of variation between interventions, this illustrates that **health gains for an individual patient do not automatically translate into substantial added value for healthcare systems and society.** A potential reason for this, especially regarding rare genetic mutations, is that many people must have an expensive test to identify the few patients that may benefit from PM, which can drive up the costs of test-treatment combinations. In addition, the lifetime downstream health gains and cost savings of PM are commonly factored into the price of PM (especially medicines), which could entirely offset the value of the health gains. Furthermore, unequal access to PM within and between countries – for example, because of budget constraints – might contribute to increasing health inequalities. In addition, unexpected test findings may raise ethical dilemmas or trigger interventions with lifetime consequences for patients and their relatives.

PM approaches can transfer their potentials for the patients into the reality of health care systems only when Health Technology Assessments (HTA) are performed to ensure **net benefits** not only for the individual, but also for society as a whole. For that to happen, reimbursement decision-makers and payers need to make much more use of information resulting from HTA analyses in their decision-making.

3.2 Why is there a need for HTA of personalised medicine?

Healthcare **resources are scarce**. In many EU countries, there is an increasing shortage of staff, hospital bed capacity and a limited budget. During the Covid-19 pandemic, people started to truly understand the meaning of **"displacement"**. While resources were needed to save the lives of those infected, consultations, diagnostic investigations, surgeries, and therapies were postponed for those not needing emergent care. Simply put: healthcare euros can only be spent once, i.e., if we spend it on treatment A we have to forgo treatment B. If the healthcare budget is increased by increasing taxes or premiums for health insurance, the problem of displacement is expanded to the wider economy and a reduced budget may be available for other public goods such as education, climate change, and other public services. Moreover, increasing taxes or insurance premiums beyond a certain point jeopardizes the market competitiveness of countries, which in turn could lead to reduced funds available for healthcare.

In all healthcare systems in the EU and beyond, healthcare interventions compete for financial, technical, and human resources. An **economic evaluation** can help identify interventions that produce the

most health within a given budget and prioritise the allocation of resources to them. The outcome of this type of evaluation is generally expressed as an **incremental cost-effectiveness ratio (ICER)**, which reflects how many additional resources are needed for an intervention so as to generate one additional quality adjusted life year (QALY), in comparison to the next best (in terms of effectiveness) alternative intervention (often the standard of care). This ICER is a valuable estimate in its own right as an efficiency ratio. However, it can also be compared against a **threshold value (i.e., the maximum acceptable ICER)**, which can be defined based on different approaches. This comparison tells us if a new intervention is more (ICER<threshold) or less (ICER>threshold) efficient in creating health than an intervention that could be displaced if the new intervention was introduced in the healthcare system.

An economic evaluation can also play a key role in the price-setting of innovations, as it enables us to determine the maximum price at which the ICER of an intervention stays below the threshold value of the ICER, i.e., the **headroom** of the price.

However, allocation of scarce resources is guided not only by efficiency considerations. Healthcare policy-makers also care about the distribution of health and health gains across different population groups. In some countries, these equity considerations have led to an increase in the threshold value of the ICER for (end-of-life) interventions in severely ill patients or patients with rare conditions. This increases the likelihood of these interventions being reimbursed. Besides efficiency, affordability, and **equity considerations**, societal acceptance also plays a role in resource allocation decisions. Societal acceptance is often guided by common European values such as solidarity for those in greatest need and trust in social justice.

This position paper focuses primarily on the contribution of economic evaluations to the unavoidable need to make choices in healthcare. An economic evaluation can be positioned as the heart of a wider **Health Technology Assessment (HTA)**, which – as defined by the EUnetHTA (European Network for HTA) core model – is a comprehensive evaluation approach of a technology (i.e., healthcare intervention) addressing comparative effectiveness, costs, economic evaluation, safety, ethical, organisational, social, and legal aspects.

The application of economic evaluations often involves the construction of a **cost-effectiveness model** in which different sources of evidence, such as baseline-risks, treatment-effects, costs, and quality-of-life values (utilities), are combined. These models commonly extrapolate the results of clinical trials to the long-term (often to the lifetime of individuals). They can also expand the number of relevant comparators beyond that included in clinical trials, position the investigated technology into the patient pathway, and simulate real-world conditions. Cost-effectiveness modelling is not specific to PM, but its execution can be complicated by several factors leading to greater uncertainty, which include limited data due to small populations inherent in the stratification of patients in PM, lack of or methodologically weak comparative effectiveness studies, complex and country-specific test-treatment combinations, as well as unexpected test findings. In terms of terminology, cost-effectiveness models are also referred to as health-economic models, something that is confusing to people outside this scientific field, as Health Economics is a science that is much broader than HTA (see text boxes for further explanation).

Health Economics

Health economics is a branch of economics concerned with issues related to efficiency, effectiveness, value and behaviour in the production and consumption of health and healthcare. This scientific discipline emerged from the observation that the healthcare market is very different from markets for many common consumer goods and services where the law of supply and demand affects prices. There are several key differences. Firstly, the decision to consume a healthcare service is not made voluntary but is a necessity that results from the occurrence of an illness. Secondly, there is an information asymmetry between doctors (suppliers) and patients (demanders). Contrary to other markets in which consumers know what they want and can judge the quality of a product, doctors have more knowledge and patients depend on doctors to act in their best interest. However, doctors make profit from selling services, which can lead to a conflict of interest. Thirdly, doctors are not paid directly by the patient. Instead, the patient pays money to an insurer in the form of either a premium (if the insurer is a private company) or a tax (if the insurer is the government) and the insurer pays the doctor. Hence, the health insurer is the third-party agent of the principal (i.e., the patient). Health insurance may lead to moral hazard, i.e., patients and doctors order more than is necessary because the insurer will pay anyway. It may also lead to adverse selection, i.e., insurers selecting people in good health who consume fewer services. Universal coverage can prevent that. Fourthly, externalities frequently arise, most notably in the context of health impacts, for example, from an infectious disease such as COVID-19, where vaccination affects people other than the patient vaccinated. These differences explain why extensive government intervention is required, for example, to regulate who pays for insurance and how much (health insurance market), who provides which services (healthcare service provision market), or what an insurer will pay for and how much (healthcare provider market). Health economists analyse these and many other markets that exist in the healthcare sector.

Health Technology Assessment

One of the disciplines in Health Economics is Health Technology Assessment (HTA). HTA is a comprehensive evaluation approach of a technology (i.e., healthcare intervention) addressing comparative effectiveness, costs, economic evaluation, safety, as well as ethical, organisational, social and legal aspects. HTA seeks to inform health policy-makers by using the best scientific evidence available in regard to the aforementioned aspects, for example, to support decision-making on the reimbursement of a technology by healthcare insurance.

Health Economic Evaluation

An essential component of an HTA is a health economic evaluation. This is a comparative analysis of two or more alternative technologies (i.e., healthcare interventions) in terms of both their costs and health consequences. Four different types of economic evaluations are distinguished, which differ in terms of the health consequences that are analysed. In a cost-utility analysis, the health consequences are expressed in quality-adjusted life years (QALYS) and, in a cost-effectiveness analysis, in natural units such as life years or number of events. In a cost-benefit analysis, the health outcomes are translated into a monetary value, and a cost-minimization analysis focuses on comparing the costs as the health consequences of the alternative technologies are equal. The term "cost-effectiveness analysis" is also used as a synonym for economic evaluation in general.

The outcome of a cost-utility analysis is expressed as an incremental cost-effectiveness ratio (ICER) that indicates how much it costs for the new intervention to generate one additional QALY in comparison with standard of care. If the ICER is lower than the maximum acceptable ICER (the threshold value) then the new intervention is cost-effective.

The outcome of a cost-benefit analysis is expressed as the incremental net monetary benefit (INMB) or the incremental net health benefit (INHB). The INMB is calculated as the difference in QALYs between the new intervention and the standard of care times the threshold value minus the difference in costs. The INHB is calculated as the difference in QALYs minus the difference in costs divided by the threshold value. If the INMB and the INHB are greater than zero, the new intervention is cost-effective.

4 FINDINGS AND LESSONS LEARNED

4.1 The cost consequences of introducing PM are larger than usually identified

A challenge for the adoption of PM is that successful provision of PM treatments is dependent on the availability of testing infrastructure that enables stratification of patients to specific treatments or prevention strategies. Data on personal (clinical) characteristics is crucial to match the individual needs of a patient with available interventions. These data can come in many shapes and sizes, such as measuring protein expression, preferences of patients for mode of administration, or whole genome sequencing. Regardless of type, all data for PM can be generated by some form of testing infrastructure. As such, paying for and establishing testing infrastructure is an integral part of a successful strategy in adopting PM.

The acceptance of the test costs as an integral part of PM implies that the costs and benefits associated with testing must be accounted for in any economic evaluations of PM. For instance, a new genetic treatment that benefits a small group of patients may not be very costly, but it may require a wide-scale screening phase which may expose healthcare payers to larger costs than the cost of the genetic treatment itself. A comprehensive health economic model should include the additional costs and benefits of the test infrastructure when adopting PM interventions. Another often overlooked issue when dealing with test infrastructure is that testing itself takes time and may lead to treatment delays. If these delays were associated with increased morbidity or mortality, the costs and health outcomes attributable to these delays should be incorporated into the cost-effectiveness model.

An illustrative example is HEcoPerMed's case study on neurotrophic receptor tyrosine kinase (NTRK) fusion. For patients with (NTRK) positive tumours, we estimated that the cost-effectiveness of the tumour-agnostic treatment was almost €42,000 per QALY (Table 1). This would commonly be considered cost-effective, given the disease severity in patients with locally advanced or metastatic solid tumours. However, when the costs and consequences of screening all eligible patients for NTRK positive tumours were taken into account, the ICER climbed to about €130,000 per QALY (i.e., well above the conventional threshold values) (Table 2). This more than 3-fold increase in the ICER was because many cancer patients had to undergo immunohistochemistry and/or RNA testing due to the very low prevalence of NTRK fusions. The benefit of TRK inhibitors to the very few patients with NTRK positive tumours was diluted across the large number of patients who had been tested (only 0.30% of those who were tested were treated with entrectinib).

***Table 1**. Cost-effectiveness of entrectinib in NTRK+ cancer from a societal perspective (year 2020)*

Strategy	Costs (in €)	QALYs	ICER
Entrectinib for NTRK+	133,285	2.19	
SoC for NTRK+	72,151	0.730	
Incremental	61,134	1.457	41,973

***Table 2**. Cost-effectiveness of testing followed by entrectinib or SoC versus not testing and SoC for all from a societal perspective (year 2020)*

Strategy	Costs (in €)	QALYs	ICER
Testing, Entrectinib for NTRK+ patients, SoC for NTRK- patients	77,213	0.989	
No NTRK testing, SoC for all patients	76,639	0.985	
Incremental	574	0.0044	130,333

4.2 The value of a PM technology over its entire lifetime is poorly understood

There are ongoing discussions as to what extent the current cost-effectiveness models are suitable in the establishment of the long-term benefit of technologies. It is beyond doubt that there are scientific spillovers of new technologies and new scientific knowledge that is generated in an R&I process. Future innovators can build on both successful and failed prior innovations. We may think, for example, of successfully repurposed drugs. It is argued that this element of value would justify a higher price for PM interventions that are scientific breakthroughs, such as cell and gene therapies. Including scientific spillovers in cost-effectiveness analysis would involve the challenge of finding a balance between static efficiency and dynamic efficiency. The current cost-effectiveness framework is focused on static efficiency, which is the maximisation of health benefit with an optimal combination of the interventions currently available. If the evaluation framework was to be moved towards achieving dynamic efficiency, it would maximise health benefits by optimally combining interventions over a period of time (i.e., current and future interventions). Although this framework would stimulate and reward innovation with higher prices, we currently do not have any widely accepted methods which could be used to estimate the future value of innovation in present terms. Moreover, dynamic efficiency would likely reduce access to current interventions in exchange for faster access to future innovations.

The time horizon of a cost-effectiveness model reflects the observation of a cohort of patients often up until their death, while the time horizon of a technology might be longer (or shorter). To achieve a proper assessment of value, these longer time horizons may need to be considered, including, but not limited to price declines after patent expiration or the introduction of competitive interventions, technology obsolesce and replacement estimates, and the large extent of uncertainty in these estimates. Price declines after patent expiration are achieved in Europe by means of a set of interlinked regulations and incentives to stimulate the adoption of cheaper generic alternatives. However, this is mainly observed for small molecule drugs for which production is less complicated and less costly than for biologicals and personalized treatments. Patents might not be the only barrier for new treatments to come to market. There is likely to be too little competition in some of the smaller markets for PM, with high prices maintained after patent expiration unless technologies are replaced by other innovations. From the perspective of the decision-maker, it may therefore be understandable that the desired time horizon of the evaluation is that of a cohort of patients likely to benefit from the drug. Economic models providing that information may, however, be less suitable for the estimation of the total value generated by new PM technologies and whether this value is well-distributed between consumers and producers now and in the future.

4.3 There are still substantial efficiency gains to be made by investing in PM interventions that target existing care better

The term “personalised medicine” may be too general as it conceals sizeable differences in the net benefit of different PM interventions where there were both highly negative and highly positive values across different types of interventions. For example, gene therapies were found to have greater health benefits than other types of PM interventions. However, they were also associated with higher costs and significantly lower net benefit, suggesting that prices for gene therapies are higher than their benefit (as captured with current economic evaluation frameworks). Contrary to that finding, PM interventions where the testing phase focused on identifying patients likely to experience adverse drug reactions had a trend toward a positive net benefit. Many of these risk stratification interventions pertained to existing therapies. There seems to be a lot of potential in better stratifying patients to existing therapies as compared to offering new treatments. This finding points to the large and probably underused potential in improving health and reducing costs by informed targeting of existing therapies. In essence, that would increase the cost-effectiveness of current treatments by personalizing them and, therefore, the efficiency levels of the entire healthcare system.

This finding is substantiated by the ToxNav case study by an extended genetic panel (ToxNav test) that evaluated the cost-effectiveness of introducing an upfront DPYD genetic testing prior to fluoropyrimidine-based chemotherapy (e.g., capecitabine or 5-fluoracil(5-FU) for metastatic breast cancer patients. ToxNav results allowed for the identification of patients who metabolise these drugs poorly due to genetic mutations and in choosing whether to adjust the dosing or provide second-line chemotherapy. The PM intervention was compared to the current Standard of Care in the United Kingdom, which is no genetic testing followed by standard capecitabine and 5-FU dosing. The economic evaluation demonstrated that the Standard of Care strategy led to higher costs and lower QALYs as compared to the ToxNav strategy (£555,30 mln GBP vs £241,90 mln GBP; QALYs 17243.5 vs 17988.3, respectively (Table 3). Consequently, upfront DPYD testing was found to be the dominant strategy, e.g., the one that produces more health gains (QALYs) at a lower cost, which was also confirmed by extensive sensitivity analyses.

***Table 3**. Cost-effectiveness of DPYD testing prior to capecitabine or 5-fluoracil(5-FU) for metastatic breast cancer from a UK healthcare perspective (2019/2020, cohort of 10,000 simulated women)*

Strategy	Costs (in £ mln)	QALYs	ICER
Standard of Care	555.3	17243.5	
ToxNav strategy	241.9	17988.3	
Incremental	-313.4	744.8	dominant

4.4 A cost-effectiveness analysis should model entire patient pathways so as to have more alignment with and impact on clinical guidelines

Instead of isolated models comparing two or a number of alternative options at a particular phase in the patient pathway, it is more useful to assess the impact of risk stratification using a full disease model of the entire patient pathway. Although these models are usually more complex, their benefits become apparent when they are employed to evaluate multiple different healthcare interventions for the same disease. As such, it is feasible to assess testing strategies, test combinations, test-treatment combinations and treatment sequences in one cost-effectiveness model. These features enable decision-makers to judge the cost-effectiveness of not only single PM interventions but also more complex health care strategies. Information from such models is more likely to be utilized in clinical guidelines as well.

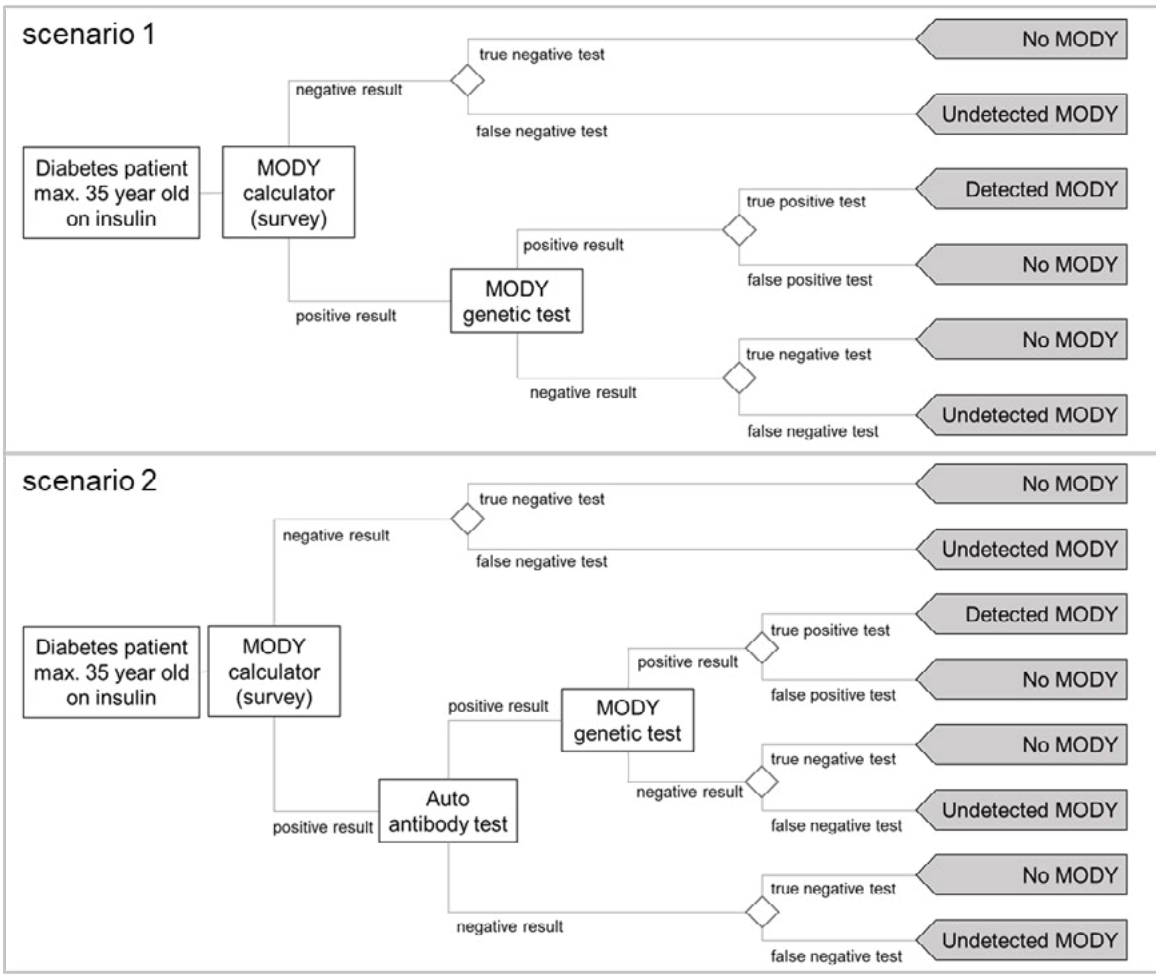
A key consideration for the decision about which diagnostic and treatment routes are to be included should be the extent to which they are relevant given the decision-making context. In HEcoPerMed, we have demonstrated this in our case study on diagnosing Maturity Onset Diabetes of the Young (MODY), which compared different patient stratification methods. The model included a decision tree for the test options and a disease progression and treatment model with sub-models for six important complications of diabetes. Diabetic patients younger than 35 years treated with insulin filled out a risk stratification questionnaire (MODY calculator). Patients with a high-risk profile according to this questionnaire could either be tested with a next-generation sequencing test immediately (scenario 1) or have an auto-antibody test to detect type I diabetes first, followed by a next-generation sequencing test for auto-antibody negative patients only (scenario 2) (Figure 1).

There was an almost 200-fold difference between the cost of the traditional lab test and the high-tech genome sequencing method. Our results showed that, irrespective of the patient stratification process, detecting MODY patients and switching them to a more adequate therapy saved not only on treatment costs but – as a result of better Haemoglobin A1c (HbA1c) control – also on long-term complication-related costs. Patients who tested positive switched from the ineffective insulin treatment to either sulphonylurea or diet adaptation. The patients' quality of life also improved due to this therapy switch and complications were avoided. Our results also showed that placing the auto-antibody test (scenario 2) in between the MODY risk calculator and the expensive genetic test could significantly reduce the cost of finding MODY patients compared to using only the combination of the questionnaire and genetic testing. Patient stratification with the inclusion of an autoantibody test became not only cost-effective but also cost-saving, which was a far more attractive policy scenario for payers. Table 4 summarizes the results of the different MODY screening strategies.

***Table 4.** Results of the MODY screening strategies*

	Costs (in €)	QALYs	Delta Cost (in €)	Delta QALY	ICER
No screening	7,516	12.1488			
MODY screening without autoantibody test	7,574	12.1536	58	0.004754	12,244
MODY screening with autoantibody test	7,503	12.1535	-12	0.004707	-2,640

Figure 1. *Decision tree of the test strategies to diagnose MODY*



4.5 It is debatable whether current economic evaluations fully appreciate the value of innovative PM approaches

It has been argued that the high prices of some types of PM, especially cell and gene therapies, are justified, as PM has benefits that are not captured in conventional cost-effectiveness analysis. As a solution, it was proposed to update the current economic evaluation framework in order to capture additional elements of value. An increasing number of countries is considering moving in this direction by requiring the adoption of a societal perspective and the inclusion of potential gains in productivity and the reduction of informal care costs. Furthermore, some countries already include equity considerations in resource allocation decisions, often by increasing the ICER threshold for end-of-life treatments, severe (life-threatening diseases), or rare diseases.

However, the debate mostly concentrates on which benefits (or elements of value) to include when measuring the value of PM. Some frequently mentioned additional elements of value which it is argued should not be included in the QALY include the value of hope, the value of a cure, real-option value, and insurance value. Individuals may indeed be willing to pay more for a treatment that – in addition to QALY gains – offers hope of being among the long-term responders, the opportunity to lead a “normal” life after being cured of a highly progressive and severely disabling disease, the option of benefiting from a future innovation, and the notion of being insured in case they require very expensive treatments. There are three main concerns associated with including these additional elements of value in economic evaluations. Firstly, there is a high risk of double counting benefits, as some of the additional elements could be (partially) captured by the QALY metric. For example, people’s hopes and dashed hopes (note that the negative impact of PM on additional elements of value is often ignored) for the future are associated with the current level of stress and anxiety that is included in the QALY. The value of being cured is already reflected in the survival gain and the quality of life during these additional

Table 5. *Stylised example of the consequence of including value of hope*

Treatment	Cost-effectiveness threshold (t)	ΔQALY	Δcost	Value of hope	Incremental net monetary benefit*
T1 (standard approach)	$50,000	2	$80,000		**$20,000**
T2	$50,000	2.5	$80,000	0	$45,000
T1 (including value of hope)	$50,000	2	$80,000	**$30,000**	**$50,000****

**Incremental net monetary benefit = (t * ΔQALY) – Δcost*

***Incremental QALYs are higher for T2. However, T1 offers "hope", while T2 does not. In this example, placing a monetary value on "hope" increases the incremental net monetary benefit of T1 from $20,000 to $50,000. This may lead to the prioritisation of T1 over T2, despite T2 offering higher QALY gains.*

years of life. Secondly, the methods for measuring additional elements of value are under development. Thirdly, there is scepticism among reimbursement authorities and academics about including additional elements of value in reimbursement decisions, as this could displace interventions that generate greater gains in length and quality of life than in the additional elements of value, as illustrated with the stylised example in Table 5.

4.6 Appropriate use of value-based PM in everyday clinical practice needs to be stimulated by incorporating cost-effectiveness considerations into clinical guidelines and decision support tools

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. The results of HTA studies can also be used more often to stimulate "appropriate use" of PM in a real-world setting. "Appropriate use" of PM refers to prioritising PM interventions with proven added value over interventions without proven added value (some of which may be even potentially harmful) in the everyday clinical treatment of individual patients, ceteris paribus. This is also referred to as the provision of value-based health care. This requires increased knowledge of existing HTA evidence and behavioural change among professional care providers and patients. Such change can be enhanced through the incorporation of economic evidence in clinical guidelines, policy implementation strategies, and clinical decision support tools that stimulate the appropriate use of PM. Currently, these guidelines and tools frequently rely on the 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 or the additional cost to the payer of deviating from the clinical guidelines. Specifically, for PM interventions that require costly testing of a large group of people to identify a few candidates for treatment, testing could be performed only after a clear distinction between relevant patients to be screened using pre-screening risk stratification strategies (similar to the MODY case study in HEcoPerMed) or only after preceding tests have ruled out other diagnoses. Another example is the clear definition of the cut-off values of a test, below which further intervention is not efficient.

4.7 The horizon of PM can be scanned and early HTA can be used to identify promising PM interventions and set future price points

Early HTA refers to HTA in the early phases of product development, usually well before a definitive evaluation of cost-effectiveness can be made and the decision for marketing authorisation by regulatory bodies. Exploring the potential value of a PM intervention at its development phase for different potential target populations can help governments, health care payers, and manufacturers to identify potential areas of future disagreement and provide them with options for action at an early stage. Due to personalization (e.g., the composite use of tests 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

the combined cost-effectiveness of test-treatment interventions are all challenging. On the other hand, when regulators and payers grant early access (e.g., Early Access Programs) to the innovative PM technologies, input from early HTA is a key determinant of decisions. There is a large degree of uncertainty around the efficacy and accuracy of PM data as often only surrogate outcomes are available and the target population and the treatment setting might change. The diagnostic accuracy of the technology is likely to vary depending on disease types and subgroups of the 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 play, which will interact with the product development context, e.g., R&I partnerships and exit strategies. Under these circumstances, the judgement on the future of a PM intervention is greatly dependent on several unforeseen factors. Elicitation of expert opinion may have a 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, early HTA can play a crucial role in the internal decisions of manufacturers, and it will also identify points for (dis)agreement between them and regulators regarding conditional market access and reimbursement at an early stage. Demonstration of uncertainties and directions on further data collection will also be a beneficial by-product of early HTA. Early HTA will help in mapping the missing information in a structured and timely manner and can play a decisive role in the future of PM.

4.8 The use of collaborative financing models for R&I of tests and treatments in PM is urgently needed

There is a need for an appropriate financing ecosystem to enable PM to achieve its full potential and to generate a positive net benefit for society. Traditionally, academia and small and medium-sized enterprises have undertaken early R&I in PM while large scale manufacturers led the commercialisation and translation of personalised diagnostics and treatments. This financing model leads to the suboptimal reward of public institutes for investing in PM discovery and early phases of R&I, as well as to a substantial financial risk exposure of PM manufacturers to the uncertainty surrounding the development and market access phases of PM. As a result, there is limited trust between all parties involved in R&I of PM that obscures optimal investment in innovation.

This approach to research, however, is evolving and large research consortia have been consolidated that could enhance R&I for PM. Involving public and private partners in the financing for R&I of PM could not only pool together substantive investment resources but also provide opportunities for upscaling R&I, as well as sharing research facilities, databases, expertise and experience. Collaborations between academia, government, the pharmaceutical industry and charities provide promising new avenues. Examples of such collaborations include:

a) the Eisai – University College London (UCL) collaborative drug discovery alliance;

b) the Bioscreening Technology Group and the Adhiron Screening Facility utilising funding from academia, government, charities, industry and the European Commission;

c) dedicated centres for oncology research and networks of Centres of Excellence in Europe that connect academic, clinical and industrial partners, small and medium-sized enterprises, as well as 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 provided opportunities for industry to access funding under the Innovative Medicines Initiative (IMI) programme. The European Commission programmes (H2020) for Research and Innovation have also been developed to support innovative small and medium-sized enterprises in the diagnostic area.

Other examples include the International Immuno-Oncology Network that is a collaboration between Brystol Myers and the Netherlands Cancer Institute, the Dana-Farber Cancer Institute, the Royal Marsden NHS Foundation Trust, the Institute of Cancer Research and the 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.

Health economics can play a pivotal role in these collaborations by providing an estimate of the financial risks involved in the R&I of PM, forecasting the potential benefits for the stakeholders involved in the agreement, and recommending a system to reward each party to the agreement for the contributed investment, undertaken risks, and share of the (future)

value of the PM intervention. Such a system can be realised by linking the reimbursement/payment of PM with the financing of its R&I. For example, innovation in PM can be rewarded by accounting for and paying for value. However, it should be noted that such a reward system should be flexible with regards to the generation of new evidence related to PM value and the emergence of competing PM technologies.

4.9 Reimbursing PM based on performance could alleviate the burden of upfront payments, and share risks and benefits between payers and providers/manufacturers

Currently, PM is reimbursed via existing reimbursement models that commonly do not involve the sharing of financial risk between payers and providers or manufacturers, and do not take into account the performance (i.e., effectiveness) of PM. For example, incorporating the cost of molecular diagnostic tests into existing DRGs and using locally and nationally negotiated tariff-based payments (e.g, in EU5 countries: Germany, France, Spain, Italy and UK) can often result in underpaying or misaligning reimbursement between tests and drugs that 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 being generated. In addition, such evidence-based schemes can be used to improve patient access, address regulatory concerns, and simplify reimbursement decisions. However, it should be noted that in some healthcare systems it is easier not to grant reimbursement for a PM intervention on the first instance than to withdraw it from the market if the expected benefits are not realised. Recently, gene therapy manufacturers have increasingly offered performance-based agreements in European markets such as outcome-based rebates for treatment failure or payments in instalments for interventions including Kymriah®, Yescarta®, Zynteglo®, Zolgensma® and Strimvelis®, as well as coverage with evidence development for Kymriah® and Yescarta®.

It is generally suggested that financial-based reimbursement models, such as rebates and volume caps, can reduce the impact on the healthcare budget and improve the 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. Reimbursement of PM could be further improved by 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 the case of treatment failure especially for highly priced gene, cell and targeted therapies, and using real-world data regarding the performance of the PM to re-evaluate reimbursement decisions.

4.10 Equity issues are large and unaddressed: The highly innovative area of personalised medicine makes it challenging to ensure access for all

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 prerequisites of clinical validity and utility for diagnostic and predictive genetic testing will place patients in low and middle-income countries in a disadvantaged position. 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 an advanced 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, capacity issues, including lack of a specialised work-force and testing/analysing infrastructure, volume restrictions, administrative barriers, lack of population specific data, competency, expertise, and financial support, limit access to expensive PM therapies. However, in lower-income countries with a lower average health status, there is more potential to benefit from high-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

struggle more with within-country variation, lower-income countries struggle with the equity issues due to their limited financial and infrastructural capacity. One example of such an issue is the reference pricing system that results in a narrow price corridor within the European community and in relatively high prices in European countries with lower purchasing power. Value-based pricing that enables price differentiation of PM between countries can offer a solution to this equity issue, but it requires solutions for other market dynamics such as parallel trade because of the free movement of goods in the EU.

There is no question that equity concerns will vary across 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 in applying PM across Europe.

4.11 Different evidence requirements of European regulatory and Member State reimbursement authorities delay access to PM

As there is limited overlap between the requirements for European medicine Agency (EMA) approval and for market access in specific Member States, discussions about pricing and reimbursement are potentially longer than necessary. EMA, responsible for assessing the quality, safety and efficacy of a drug, does not bear costs in mind and does not test relative effectiveness as they are not making decisions on reimbursement but on whether a new drug can enter the market. Therefore, evidence submitted to meet EMA requirements does not meet the requirements of several Member States in their reimbursement discussions.

The issue is pressing, as there are increasingly more decisions for market authorization of PM treatments stratified to patients with some genetic biomarkers based on single arm studies. This poses two main challenges. Firstly, the relative effectiveness of PM must 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). A typical example is the NTRK case study, where both entrectinib and larotrectinib were granted market access by EMA based on a single arm data, only to find local authorities desiring evidence on relative effectiveness, an issue that could not be informed by the trial data. Secondly, the prognostic value of the genetic biomarker is unknown: patients who test positive might have better, worse, or equal prognosis as compared to those who test negative, thereby complicating the assessment of relative effectiveness. In the NTRK case, we estimated the prognostic value of NTRK fusions in a very small number of patients to allow us to estimate a comparator arm. While this approach may constitute a short-term solution for the information needs of national decision-makers, it is a temporary solution at best.

4.12 To improve timely access to cost-effective new therapies, the economic evaluations of PM should be conducted earlier and be shared among EU Member States

While there are public efforts such as EUnetHTA to establish relative efficacy reports, such efforts are not present for economic evaluations, most likely because EU member states differ in opinion about what constitutes a fair price for a new PM intervention as a result of the national decision-making context (such as different national comparators and country-specific societal preferences). Interestingly, the resulting practice is that pharmaceutical companies develop evidence (a central or “global” cost-effectiveness model) that is subsequently submitted to several Member States after some input variables have been adapted to meet national requirements. Independent research is also performed in the academic setting, but this is usually undertaken separately and often does not form any part of the discussions about the value of PM between payers and manufacturers. It is unclear as to why there is no place for the development of a core European economic evaluation model that can be adapted to the national needs of Member States. Such an effort would allow increased transparency on input data and can be developed during EMA procedures to speed up subsequent negotiations between industry and Member States. This is particularly relevant in the context of PM, where an upfront recognition of data limitations and estimates of cost-effectiveness can help identify where current reimbursement frameworks might not be fit for purpose. Recent initiatives such as horizon scanning and purchasing partnerships between Member States indicate that collaboration is possible and should be stimulated.

Centralized assessment, however, still faces issues in connection with the transferability of assumptions, input data and outcome validation. It is essential to separate the transferability of data and methodology from the transferability of recommendations and policy decisions. Consistent methodology can increase the transparency of assessment while decreasing the need for human and financial resources. On the other hand, directly transferring HTA recommen-

dations or policy decisions across countries with potentially different health-care priorities can lead to suboptimal allocation decisions in the local markets.

EUnetHTA was a first and important development in the harmonization of methodologies across countries. They developed the “HTA Core Model” to focus on the joint production of relative effectiveness assessments, which can be used as a basis for national value assessments. As such, the HTA Core Model aims to standardize reporting of HTA, as well as to standardize the effectiveness input data where possible. The approach encourages explicit consideration of 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.

When applied to PM, a collective approach to assess the value for money of PM interventions could facilitate the development of joint efforts by member states to strengthen public-private partnerships for financing R&I of PM at EU level that provide larger rewards for investment, share risks among a larger pool of involved parties, and exploit value of synergies (e.g., due to economies of scale). In addition, such an EU-wide HTA model could form the base of unifying reimbursement of PM across the EU by adopting a reimbursement model that accounts for widely agreed elements of value, secures equity between member states, and fulfils the appetite of manufacturers for large markets. 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 the policy relevance of HTA recommendations in all EU countries.

5 CONCLUSION

In all healthcare systems, both in the EU and beyond the EU, healthcare interventions compete for the same financial, technical, and human resources. An economic evaluation can help identify interventions that produce the most health within a given budget and prioritise the allocation of resources to them.

When performing an economic evaluation of PM, a comparison should be made between the new situation, in which PM is implemented, and the current situation. To fully inform policy-makers on the new situation, all changes to the care pathway that are needed for the identification, stratification, and treatment of eligible patients need to be accounted for and all downstream cost and benefits need to be reported. Consequently, the costs of introducing PM may be larger than usually identified. That specifically applies to expensive drugs that require wide-scale expensive upfront testing for rare biomarkers. On the other hand, there seems to be a large and probably underused potential to improve health and reduce costs by informed targeting of existing therapies. In essence, that would increase the cost-effectiveness of current treatments and, therefore, the efficiency levels of the entire healthcare system. To improve timely access to cost-effective new PM interventions, economic evaluations of PM should be conducted earlier and be shared among EU Member States. Furthermore, evidence requirements of European regulatory and reimbursement authorities should be better aligned. However, there are ongoing discussions as to what extent the cost-effectiveness models are suitable to establish the long-term benefits of PM and capture all elements of the value of PM. Our current cost-effectiveness analyses focus on static efficiency. The time horizon is commonly that of the lifetime of a fixed cohort of patients, while the life cycle of a technology used in PM might be longer or shorter. Moving towards dynamic efficiency would likely stimulate and reward innovation but at the expense of access to current interventions. Likewise, including additional elements of value could displace interventions that generate greater gains in length and quality of life than in the additional elements of value. HTA researchers should contribute to raising awareness of this debate among policy-makers. Appropriate use of PM can be enhanced, using not only cost-effectiveness data in reimbursement decisions, but also through the incorporation of this evidence in clinical guidelines, policy implementation strategies, and clinical decision support tools. It can be further enhanced by the wider adoption of innovative payment and reimbursement models that accelerate access in exchange for sharing of risks.

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7 SCIENTIFIC OUTPUT OF HECOPERMED

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Cost-effectiveness model of different screening strategies for Maturity Onset Diabetes of the Young (MODY)

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

8 IMPRINT

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