Editorial

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Personalized Medicine

HEcoPerMed, personalized medicine from a health economic perspective: lessons learned and potential opportunities ahead

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> "This tension between technology pull and push on the one hand – brought about by the potential benefits of PM – and the desire to spend healthcare resources efficiently is the background to the research reported in this special issue"

First draft submitted: 1 July 2023; Accepted for publication: 5 July 2023; Published online: 22 September 2023

Keywords: cost effectiveness • cost • cancer • diabetes • health economics • health outcome • histology-independent • pharmacogenomics • quality adjusted life year • tumor-agnostic

We are pleased to introduce this special issue of *Personalized Medicine*, presenting the main findings and lessons learned from the Healthcare and Pharma-economics in Support of the International Consortium for Personalized Medicine – ICPerMed project (HEcoPerMed), to a wide and diverse audience that includes non-health economists. HEcoPerMed is a Coordination and Support Action funded by the European Commission.

Personalized medicine (PM) may bring lifesaving and life-altering benefits to patients. Examples include (1) personalized screening for the presence of risk factors or disease (e.g., increased screening frequency for patients at increased risk of hypertrophic cardiomyopathy), (2) obtaining information about disease prognosis to tailor treatment (e.g., OncotypeDX Breast Recurrence Score test), (3) identifying likely (non)responders to treatment (e.g., testing for *NTRK* gene fusions in tumor cells so that tyrosine receptor kinase [TRK] inhibitors can be provided to cancer patients who test positive), (4) identifying patients who may experience adverse drug reactions to adjust the dose or the choice of medicine (e.g., DPYD testing prior to capecitabine or 5-fluoracel chemotherapy), (5) cell therapy (e.g., chimeric antigen receptor T-cell therapy) and (6) gene therapy (e.g., Zolgensma® for spinal muscle atrophy).

However, the increased use of PM brings challenges to healthcare systems around the globe that wish to make these interventions available within cost-constrained healthcare policy goals. Furthermore, there are challenges for the analytical methods used to assess relative costs and benefits of PMs when compared with alternative personalized or nonpersonalized approaches. This tension between technology pull and push on the one hand – brought about by the potential benefits of PM – and the desire to spend healthcare resources efficiently is the background to the research reported in this special issue.

The health economic approach to PMs

Health economics is a branch of economics concerned with efficiency, effectiveness, competitiveness, value and behavior in the production and consumption of health and healthcare. One area of health economics is health technology assessment (HTA). HTA is a comprehensive evaluation of a technology (e.g., a PM intervention)

which specifically addresses the comparative effectiveness of healthcare interventions, as well as their cost, cost–effectiveness, safety, ethical, organizational, social and legal aspects. An essential component of HTA is an economic evaluation. This is a comparative analysis of two or more alternative interventions in terms of both their costs and health consequences. The most common type of economic evaluation is a 'cost–effectiveness analysis' where the results are expressed as an incremental cost–effectiveness ratio (ICER). This ratio indicates how much it costs for, in this case, the personalized intervention to generate one additional quality-adjusted life year (QALY) compared with standard of care (SoC). If the ICER is lower than the maximum acceptable ICER (the threshold value) then the new intervention is considered cost-effective. The result of an economic evaluation can also be expressed as the incremental net monetary benefit (INMB), which is calculated as the difference in QALYs between the personalized intervention and the SoC times the threshold value minus the difference in costs. If the INMB is greater than zero, the new intervention is considered cost-effective.

Does PM produce more health than other treatments, & at what costs?

Many personalized interventions produce QALY gains. In HEcoPerMed's systematic literature review, 279 PM interventions involving gene profiling or correcting pathogenic gene mutations were compared with their non-PM counterfactuals. We found a mean gain of 0.26 QALYs per patient, which reflects a net present value of 3 months in perfect health [1]. The variation was large, with 6% of PM interventions rendering more than 1 QALY and a maximum gain of 11.9 QALYs. At the same time, we found that the mean INMB was negative and the median just above zero. This illustrates that health gains for an individual patient may not translate into added value for healthcare systems and society. There are several reasons for this. Firstly, there are situations in which many people have to undergo an expensive test to identify the few patients that may benefit from the personalized treatment, which can drive up the costs of test–treatment combinations. This specifically applies to some rare genetic mutations. Secondly, as a consequence of value-based pricing, manufacturers commonly factor the lifetime downstream health gains and cost savings of PM into the price of PM. This especially applies to medicines and depends on the competition on the market. These high prices can entirely offset the value of the health gains. So, when asked whether a PM intervention offers value for money, perspective really matters!

An illustrative example of a high number-needed-to-test is HEcoPerMed's case study on tumors with *NTRK* gene fusions [2,3]. For cancer patients with locally advanced or metastatic solid tumors that carry these fusions, the EMA recently approved the first two histology-independent treatments. Histology-independent treatments are treatments that are provided based on specific genetic marker(s) of tumors, regardless of the tissue of origin of the tumor. For patients with *NTRK*-positive tumors, we estimated that the cost–effectiveness of tumor-agnostic treatment with a TRK-inhibitor was almost international (int.) €33,600 per QALY in The Netherlands. This would commonly be considered cost-effective, given the disease severity in patients with these tumors. However, when the costs and consequences of the most optimal strategy of screening all eligible patients for *NTRK*-positive tumors were taken into account, the ICER climbed to more than int.€142,600 per QALY, a figure that is much higher than the conventional threshold values. This, a more than fourfold increase in the ICER, was due to many cancer patients having to undergo immunohistochemistry and RNA testing to find the few ones that would benefit from the treatment because of the very low prevalence of *NTRK* fusions. The benefit of TRK inhibitors to the few patients with *NTRK*-positive tumors was diluted across the large number of patients tested (only 0.30% of those who were tested were treated with the TRK inhibitor). Similar results were found for the UK, where a threefold increase in ICER was observed, and in Hungary, where a twofold increase was observed.

Our observation that the cost consequences of introducing PM are often larger than anticipated does not only apply to rare genetic mutations. PM almost always requires some form of testing or data-generating infrastructure, regardless of the data involved (e.g., laboratory data, clinical data, preference data or something else). Establishing and paying for such infrastructure is an integral part of a successful strategy in adopting PM. The acceptance of the costs of testing as an integral part of PM implies that the costs and benefits associated with testing must be accounted for in any economic evaluation of PM [4]. However, the impact is certainly not always as big as in the NTRK case study.

Using PM to better stratify patients to existing treatments: benefit for all?

We have the view that there is a world to win when using genetic tests to better stratify patients to established rather than new therapies. This view was strengthened by HEcoPerMed's literature review, in which tests to identify patients likely to experience adverse drug reactions, followed by adapted treatment, tended to have a positive

net benefit [1]. Many of the risk-stratified interventions pertained to established therapies like antidepressants or clopidogrel for patients with acute coronary syndrome.

This view is further substantiated by HEcoPerMed's case study on the ToxNav® DNA test, in which breast cancer patients were tested for 18 *DPYD* gene mutations to identify those with an increased risk of severe toxicity from common fluoropyrimidine-based chemotherapies due to these mutations [5,6]. Risk-stratification followed by dose-adaptation was found to be dominant over SoC, leading to both health gains (more than 930 QALYs per 10,000 women in the UK) and net cost savings (around €387 million per 10,000 women in the UK). The ToxNav® test was also found to be cost-effective in The Netherlands where it also led to both health gains and net cost savings, and in Hungary where the incremental costs per QALY gained were very small (less than int.€1000 per QALY gained).

The results of HEcoPerMed's third case study are also in line with the large and possibly under-recognized potential of improving health and reducing costs by informed targeting of existing therapies. This case study compared different testing strategies (varying combinations of the maturity-onset diabetes of the young [MODY] risk calculator, an autoantibody test and a DNA test) to identify patients mistakenly diagnosed as Type 1 diabetes patients, while they have MODY caused by a genetic mutation in the *HNF* or *GCK* genes and respond poorly to insulin [7]. The strategy in which the MODY risk calculator was followed by an autoantibody test and then the expensive genetic test was the preferred option as it was cost saving compared with no testing in Hungary, The Netherlands and the UK. Switching patients who tested positive from the ineffective insulin treatment to either sulphonylurea or diet adaptation also avoided complications and improved quality of life.

Assessing net benefit of PM is not without challenges: guidelines

In each of the case studies presented in this issue of *Personalized Medicine*, the cost–effectiveness of the PM intervention was assessed by building a cost–effectiveness model where different types of evidence, such as baseline risks, treatment effects, costs and quality-of-life values (utilities), were combined. These models commonly extrapolate the results of clinical trials to the long term (often to individuals' lifetime). They can also expand the number of relevant comparators beyond those included in clinical trials, position the investigated intervention into the patient pathway and simulate real-world conditions. Once a core model is built, it can be adapted to different countries and populated with country-specific input data. That provides valuable insights into differences in cost–effectiveness of a particular PM intervention between countries. The *NTRK* case study nicely showed that the value of expensive PMs may be higher in high-income countries with an advanced level of healthcare (UK, The Netherlands) than in countries with a lower income level (Hungary). This is largely related to the relatively high incremental costs of these medicines compared with the costs of SoC in Hungary. As a result, the budget impact as a percentage of the total healthcare expenditure is much greater in Hungary than in the UK and The Netherlands. It is likely that in these lower-income countries' quicker wins can be made from the wider implementation of nonpersonalized interventions than from personalizing interventions.

Cost–effectiveness modelling is not specific to PM, but its execution can be complicated by several factors leading to greater uncertainty in study results. These factors 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 and unexpected test findings. For such reasons, a specific guidance with 23 recommendations for health economic modeling of PM was developed in the HEcoPerMed project [4]. Each of the case studies was modelled according to this guidance. In a separate paper in this special issue, we reflect on and discuss the application of the modeling guidelines to the three case studies [8].

Why is there a need for evidence on net benefit?

Why do we need evidence like we generated for the case studies? The answer is simple. Investigating which PM interventions provide net benefits, not only for the individual, but also for society as a whole, supports reimbursement authorities in prioritizing the allocation of resources to PM interventions that provide most value for money. In all healthcare systems in the EU and beyond, healthcare interventions compete for scarce financial, technical and human resources. Simply put, a healthcare euro can only be spent once, that is, if we spend it on treatment A, we have to forgo treatment B. One could argue, why not increase the healthcare budget? But if that is done by increasing taxes or premiums for health insurance, the problem of displacement is expanded to the wider economy and the budget available for other public goods and services such as education and the combat against

climate change is reduced. 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.

Incentivizing the use of PM: clinical guidelines, payment & reimbursement models

Providing evidence on the net benefits of PM is not sufficient to change clinical practice. We need implementation strategies that stimulate the adoption of PM interventions with proven benefit in clinical practice. This requires a behavioral change among professional care providers and patients. Such change can be enhanced through the incorporation of economic evidence in clinical guidelines and clinical decision support tools that stimulate the appropriate use of PM (i.e., value-base healthcare). But that may not be sufficient. Health economists can play a pivotal role in incentivizing the appropriate use of PM by designing payment and reimbursement models for PM. Another literature review study in the HEcoPerMed project has suggested that this can include 1) establishing dedicated codes for companion diagnostics and genetic tests that reflect the value of the test; 2) aligning the reimbursement of companion diagnostics and targeted therapies by combining these into a reimbursement package; 3) implementing performance-based payment 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 4) agreements on coverage with evidence development to generate real-world data regarding the performance of the PM to reevaluate reimbursement decisions [9].

Diverging requirements of the EMA & reimbursement agencies hinders access & uptake

What also needs to be addressed is the delay in access to PM that results from limited overlap between the requirements for EMA approval and for market access in specific Member States, which leads to longer discussions about pricing and reimbursement than necessary. 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. First, the relative efficacy 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 HEcoPerMed's *NTRK* case study, where the TRK-inhibitor was granted market access by the EMA based on single-arm data, only to find local reimbursement authorities desiring evidence on relative effectiveness, an issue that could not be informed by the trial data. Second, the prognostic value of the genetic biomarker was unknown: patients who test positive might have better, worse or equal prognosis as compared with those who test negative, thereby complicating the assessment of relative effectiveness. In the *NTRK* case study, we estimated the prognostic value of *NTRK* fusions in a very small number of patients to allow us to estimate a 'synthetic' comparator arm [10]. While this approach may constitute a short-term solution for the information needs of national decision-makers, it is a temporary solution at best.

Conclusion

In conclusion, in the HEcoPerMed project we reviewed the evidence on the net benefit of PM; advised on innovative funding, payment and reimbursement models and developed a guidance for health economic modelling of PM. We then applied the guidance to the three case studies presented in this issue of *Personalized Medicine*. HEcoPerMed's findings and the lessons learned culminated in a position paper covering 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. Part of this position paper served as the basis for this editorial; the entire position paper can be accessed through the project's website [11]. With the completion of HEcoPerMed we have only shed a light on a small part of the challenges in PM. Future research could focus on other dimensions of health economics. For example, how increasingly small indication areas – due to far reaching stratification of treatments – impact on market power, price competition among originators and the possibility for biosimilars to enter the market. Another area of interest would be synthesizing routinely collected data from different sources to inform health economic models of personalized prevention.

Financial & competing interests disclosure
The HEcoPerMed project has received funding from the EU's Horizon 2020 research and innovation program under grant agreement No. 824997. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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

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