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Concepts of ‘personalization’ in personalized medicine: implications for economic evaluation

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Abstract

Context—This paper assesses if, and how, existing methods for economic evaluation are applicable to the evaluation of PM and if not, where extension to methods may be required.

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Author contributions: WR and KP conceived the framework underpinning this paper. WR lead writing the manuscript with large contributions by KP; US initiated and coordinated the ONCOTYROL workshops; PS, BJ, UR conducted literature searches and documented the workshops; OA updated the literature searches; all authors and in particular AM and RL provided substantial intellectual input; all authors were involved in writing and read and approved the final version of the manuscript. All authors act as guarantors individually.

Method—Structured workshop with a pre-defined group of experts (n=47), run using a modified nominal group technique. Workshop findings were recorded using extensive note taking and summarised using thematic data analysis. The workshop was complemented by structured literature searches.

Results—The key finding emerging from the workshop, using an economic perspective, was that two distinct, but linked, interpretations of the concept of PM exist (personalization by ‘physiology’ or ‘preferences’). These interpretations involve specific challenges for the design and conduct of economic evaluations. Existing evaluative (extra-welfarist) frameworks were generally considered appropriate for evaluating PM. When ‘personalization’ is viewed as using physiological biomarkers, challenges include: representing complex care pathways; representing spill-over effects; meeting data requirements such as evidence on heterogeneity; choosing appropriate time horizons for the value of further research in uncertainty analysis. When viewed as tailoring medicine to patient preferences, further work is needed regarding: revealed preferences, e.g. treatment (non)adherence; stated preferences, e.g. risk interpretation and attitude; consideration of heterogeneity in preferences; and the appropriate framework (welfarism vs. extra-welfarism) to incorporate non-health benefits.

Conclusion—Ideally, economic evaluations should take account of both interpretations of PM and consider physiology and preferences. It is important for decision makers to be cognizant of the issues involved with the economic evaluation of PM to appropriately interpret the evidence and target future research funding.

Introduction

The concept of ‘personalized medicine’ (PM) is generally used to describe interventions which seek “to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics” in addition to clinical patient characteristics [1]. PM raises a number of challenges for clinicians and healthcare systems including: the escalating number of available tests; the rapid development of testing technologies; the falling unit cost per mutation tested; the potential of diagnostic and screening technologies to determine subsequent individual care pathways. Combined, these challenges support the requirement for economic evidence to be produced to feed into PM reimbursement and coverage decisions.

The promise of PM is that only patients likely to receive benefit, or not be harmed, will be treated, and hence avoid the unnecessary dis-benefits and costs of ineffective healthcare interventions and associated adverse effects. A number of commentators have observed that the promise of PM is yet to be realized partly due to the lack of a sufficiently robust clinical and economic evidence base to support the widespread use in clinical practice [for example, see: 2, 3-7]. Published systematic reviews have suggested there are limitations in the quantity and quality of economic evaluations of examples of PM, such as pharmacogenetic and pharmacogenomic applications [8-11]. Annemans et al (2013) identified ten specific methodological challenges for model-based cost-effectiveness analysis of PM interventions which relate to difficulties involved with their potential use at different stages of a care process, the need to model dynamic care pathways (i.e., treatment algorithms rather than

fixed regimens) and the increasingly small patient subgroups [5]. Further challenges arise if the economic evaluation of PM is understood as an evaluation of the benefits, harms and cost-effectiveness at the individual patient level [12, 13], where individual preferences may be used to derive a measure of *individualized* expected treatment effect in cost-effectiveness analysis. It is unclear whether current evaluative frameworks (underpinned by the extra-welfarist viewpoint) are directly applicable to inform the design and conduct of economic evaluations of PM [5, 14].

The aim of this paper is to describe two distinct, but linked, interpretations of the concept of PM (personalization by ‘physiology’ or ‘preferences’) that emerged from an expert workshop. The paper first presents the general findings from the workshop and then goes on to discuss the specific challenges associated with implementing these concepts in the design and conduct of economic evaluations for reimbursement and coverage decisions at the population level. Specifically, the paper assesses if, and how, existing methods for economic evaluation are applicable to the evaluation of PM and if not, where extension to existing methods may be required.

Methods

A series of structured workshops on the methods and use of health technology assessment (HTA) in PM was held with invited key experts (n=47). The 47 participating experts (see online Appendix 1) attended at least one of the workshops of whom 32 (68%) were from Europe: Austria (n=15); UK (n=5); The Netherlands (n=4); Germany and Switzerland (n=2 each); Denmark, Norway, Finland (n=1). In addition, there were representations from: USA (n=10); Canada (n=3); Australia (n=2). Experts were identified by publications retrieved by a targeted literature search as well as from recommendations from the Society for Medical Decision Making (SMDM) and Health Technology Assessment international (HTAi). The three structured workshops were each run in 2012 (Innsbruck, Oslo and Bilbao) and followed a modified nominal group technique [15]. Findings from the workshop were recorded using extensive note taking and summarised using thematic data analysis.

Published HTA key principles and guidelines were identified *via* a targeted internet search of the homepages of HTA organizations in Europe, Australia and North America and of HTA networks (EUnetHTA, INAHTA). Electronic searches of the databases Medline, Embase and The Cochrane Library and hand searching of journal articles written by known authors in the field were run between February 2011 and March 2012 (led by PS). This search was subsequently updated in February 2014 (by OA) for use by the economic evaluation sub-group.

Results

The key emerging finding from workshop discussions was that the basic principles and methods of economic evaluation are appropriate for PM, in general, and PM in oncology, specifically. There was a preference for model-based cost-effectiveness analyses to facilitate the evidence-based synthesis of multiple data sources and long-term patient-relevant outcomes in a structured decision-analytic framework.

A second key emerging finding was that, taking an economic perspective, two distinct, but linked, interpretations of the concept of PM exist (hereafter termed ‘concepts’) which involve specific challenges for the design and conduct of economic evaluations: (1) using physiological biomarkers and/or (2) using individuals’ preferences for ‘personalizing’ medicine. The remaining sections of this paper discuss the implications of the two distinct concepts of personalization for the design and conduct of methods of economic evaluation.

Figure 1 provides a structured overview of methodological issues and shows how, for the physiology-based interpretation of PM, the issues can be classified in terms of implications for model structure, data, and analysis of uncertainty and heterogeneity. For the preference-based interpretation of PM, the issues relate to revealed preferences, stated preferences, and the general role of preferences in the evaluative framework.

Physiology-based personalization

According to a recent systematic review and appraisal of published definitions of “personalized medicine”, the term corresponds with detecting differences in the physiological characteristics of patients to target medical interventions [1]. A number of specific technical and data driven challenges were identified that need to be addressed to create valid and sufficiently robust cost-effectiveness (cost-utility) analysis of PM, which are described in the following sections.

Structuring the decision problem—The first set of challenges centre around the need to clearly specify the decision problem for an economic evaluation of PM.

Representing complex care pathways: Technological advancements in genetic sequencing and identification of biomarkers, with associated improvements in information technology, have made it feasible to test multiple biomarkers to inform treatment choices, or use algorithms with combinations of parameters (for example: baseline risk and mammographic density) to target screening interval strategies. Furthermore, next generation sequencing (NGS) and whole genome or exome sequencing in theory allow identifying mutations in multiple genes for multiple conditions in parallel. As a consequence, the number of pathways to include into a model-based economic evaluation may grow exponentially with the number of biomarkers used for stratification. Also, patients may be offered genetic-based diagnostics earlier in the diagnostic pathway than currently possible, which may increase the demand for services. Furthermore, large numbers of tests, and mutations tested for, comes with a risk of generating incidental findings that may induce harm by overdiagnosis and substantial downstream costs [16].

The predominant approach used in the decision-analytic economic evaluation of single test-intervention combinations and single genetic-based diagnostic tests is to represent the impact of the new technology on a population of patients using for example, a Markov state transition cohort model [17-19]. Taking into account the need to analyse highly complex pathways, patient histories, and treatment options as well as the need to analyse the impact of PM on service capacity means that it may be desirable to replace cohort based models by individual-level models such as state-transition microsimulation or discrete event simulation [20, 21]. However, further methodological work on whether, and how, to efficiently conduct

individual-level models is needed because the inclusion of all possible permutations of clinical pathways into a microsimulation model can lead to highly demanding data input requirements and extremely high computational resources.

Accounting for spill-over effects: Personalization can mean that the target population of an economic evaluation may expand beyond the individuals being tested, and treated, as genetic information is shared between family members. In the specific case of a defined family mutation, this information can be obtained precisely with laboratory tests. Valuing health effects should consider that the relevance of a gene mutation is likely to differ between the index patient and relatives. For example, if colorectal cancer patients are tested to identify if they are suffering from hereditary cancer (Lynch Syndrome), the index patient may gain potentially limited benefit as they can only receive information about disease prognosis. In contrast, relatives may gain substantial benefits from avoided cancers due to increased surveillance [22]. A further complicating factor when considering spill over effects is the limited evidence base on the extent to which information on genetic-related conditions is passed on to other family members and on the uptake of subsequent testing in family members.

Data requirements for populating decision-analytic models—Three key issues were considered to be of particular relevance when representing personalization of medicine in a decision-analytic model: the need to be able to represent heterogeneity of the prognosis and treatment effect [23]; the need to understand the accuracy, capability and uncertainties associated with the diagnostic test; and, finally but perhaps most challenging on a practical level, the need to deal with gaps in the available evidence base.

Identifying evidence of heterogeneity in baseline risk and/or treatment effect: Clear evidence of heterogeneity in either baseline risk and/or treatment effect within a patient population is a basic requirement for using a technology to personalize medicine. This ‘personalization’ can be interpreted as finding evidence of identifiable sub-groups of a study population to subsequently identify and target subgroup-specific treatment strategies. It should also be acknowledged that study designs, data collection and analysis that recognize the need to capture heterogeneity and impact on patient sub-groups come with their own challenge of increased costs due to the additional complexity [24]. It is important that subgroups are clinically plausible and implementable. It is also desirable for the evidence base identifying between-patient heterogeneity to come from pre-specified analyses. Statistical methods used to identify and investigate subgroup effects for HTA purposes have been reviewed recently [25], and a methodological framework to determine the optimal number (and specification) of subgroups in cost-effectiveness analysis for decision making is beginning to emerge [24].

Impact of test thresholds on cost-effectiveness: Frequently, results from tests using biomarkers or genetic characteristics are often not binary but continuous. Even dichotomous tests become continuous when multiple test results are combined in diagnostic scores. Such continuous parameters or scores are then often dichotomized for clinical implementation and determination of further actions by setting a cut-off value to categorize patients into test-

positive and test-negative individuals. Typically, clinical considerations, and methods like receiver operating characteristic (ROC) curves, along with weighted consequences are used to evaluate the benefit-harm balance and calibrate diagnostic tests or diagnostic scores. However, changing the cut-off value of a test or score will have an impact on the benefit-harm balance and cost-effectiveness, as it affects the size of the intervention group and the conditional probabilities of prognosis. A more considered approach may be to plot the costs and effects of changing test thresholds in the cost-effectiveness space and to assess the link between changing test thresholds and the cost-effectiveness of different treatments [26].

Dealing with gaps in the evidence base: When personalizing medicine, healthcare is being tailored to specific subgroups of patients with decreasing sample sizes, which implies that it is more likely that the evidence supporting the health effects, and use of healthcare resources, for these sub-population groups is also limited. When conducting a decision-analytic cost-effectiveness analysis of PM, the decision analyst has the two options (1) to construct the model and limit the care pathways being represented by taking account of the data available or (2) to construct the model to represent the complexity of the decision problem but compensate for the lack of data using expert elicitation.

The use of expert elicitation is expanding but there are still significant limitations in the methods to generate point estimates and appropriately represent the distribution of the data elicited [27]. Personalization of medicine will result in the need for more data and different types of data to accurately reflect the impact of a diagnostic on a patient care pathway. Ideally, these data should continue to be sourced from RCTs supported by well-designed prospective observational cohorts analyzed with appropriate methods and adjustments for confounding [28]. However, it is unlikely that all data required will be readily obtained from these 'ideal' data sources and the robust application of expert elicitation methods may be needed. There is, however, an associated need to put in place approaches to systematically revisit cost-effectiveness analysis of PM at later stages of the technological life cycle.

Analysis of uncertainty—Decision makers will not only want to know the relative cost-effectiveness of a PM strategy but also want to understand the current level of uncertainty in the available evidence base and whether it is worth conducting further research to reduce this uncertainty. Large scale RCTs and observational studies are costly and may put some patients at risk, so that the investment of scarce resources into further research needs to be balanced against its potential benefits.

Quantifying the value of further research: Value of information (VOI) methods provide a framework to quantify the need for further research [29, 30]. Of particular relevance in the context of personalization of medicine is that the population VOI of a specific decision depends, in part, on how many patients (the relevant study population) are affected by the technology adoption decision. This might be a fundamental problem for increased personalization and hence, smaller relevant patient populations. There is likely to be high parameter uncertainty in many aspects of the decision problem, which suggests a need for more evidence. However, the population VOI may be relatively low because of the impact of the small relevant patient population; hence, indicating no need for further research [31]. This infers a need to collect robust evidence about the relative cost-effectiveness of PM but

at a low cost. Identifying and analysing data sources, such as sickness fund or NHS routine data, may provide a means to generate such evidence that warrants further exploration by decision analysts.

Appropriate time horizons: Another key piece of information to estimate population VOI is data on the pace and character of technological progress. VOI estimates incorporate an assumed time horizon for the decision, which reflects the life cycle of the new intervention before it is replaced by advances in technology. The appropriate length of technology life cycles for value of information analysis is an unanswered empirical question [32]. The emerging trend in PM is that the number of biomarkers available for targeting care and options is likely to continue to increase dramatically. This infers a relatively short product life cycle and time horizon for any technology adoption decision. Therefore, the VOI associated with one specific biomarker is likely to be relatively low because of the short time frame of the decision. On the other hand, in most instances the existing biomarker remains relevant to decision making and is not substituted but complemented by additional biomarkers to more accurately stratify the patient population which implies a longer time horizon. This adds more complexity to conducting an accurate VOI as the effective time horizon of a single 'biomarker' is not readily quantifiable.

Preference-based personalization

PM involves better information about a patient's likelihood to respond to a treatment or to develop adverse effects. In addition to objective health benefit, such data adds to the information available to patients which could be used to better incorporate subjective preferences into treatment choices. Most cost-effectiveness (and cost-utility) analyses assess the mean incremental effects and costs associated with the available treatment options [33]. If PM is interpreted as better accounting for patient preferences (at a population level), this has a fundamental impact on the role and methods of economic evaluation as preferences can also be used to define what constitutes expected 'benefits' or 'harms' and thus determine the quantified expected effect from a treatment [see e.g. 34].

Revealed preferences: uptake, adherence, and impact on (non)adherence—

Patient, and clinician, preferences can affect the decision to adhere, and continue to adhere, to a prescribed healthcare intervention. Understanding the reasons for non-adherence has been identified to be an important step to improve treatment effectiveness, minimize adverse drug events, and thus maximize patient health [35]. In the context of PM, two different aspects of analyzing (non)adherence are relevant. First, the uptake of the test, as well as adherence to the treatment recommended on its basis, is typically uncertain. Evidence on the uptake parameters is of high importance to estimate the health gains and costs associated with the use of a biomarker [31]. Second, it has been claimed that PM, by providing patients with additional information that the prescribed treatment is more likely to provide benefit with fewer adverse events, increases adherence (compared with a non-personalized option which would also be available) [36]. There is a lack of empirical evidence supporting these claims which could be remedied, for example, by designing randomized trials or by using health insurance claims data to compare patient decisions about test and treatment uptake between those receiving personalized and non-personalized care. Alternatively, RCT data

could be corrected for non-adherence using causal methods such as the parametric g-formula, marginal structural models or g-estimation [37].

Stated preferences—The role of preferences reaches beyond the use of PM and its impact on health gain and costs. The next sections describe some potential broader impacts.

Risk attitude: Strategies for PM can provide clinicians and patients with additional information on the relative risk of an adverse event occurring from a particular treatment. However, health care professionals, health care regulators and patients may be prepared to accept different levels of risk reduction and have different relative preferences for the trade-off between anticipated benefits, and the risk of adverse reactions from the same technology. Therefore, robust and reproducible methods of eliciting preferences for risk-benefit trade-offs need to be used to ensure the health valuations incorporated in the economic assessment are valid and sufficiently robust to provide a solid evidence for coverage decisions on PM. Stated preference methods, such as discrete choice experiments (DCEs), are now commonly used to measure preferences for healthcare treatments in terms of their constituent attributes [38, 39]. They may also offer a solution to the quantification of risk-benefit trade-offs [for example see: 40] if they are cognizant of the challenge of including risk in a DCE [41]. This information in itself can provide useful standalone evidence for decision makers. However, the challenge remains on how to incorporate such identified stated preferences for the relative value of risk reduction and benefits and use them within a formal economic evaluation framework.

Risk perception: The usefulness of providing patients with information about risk, or of incorporating risk attitude, and making it more explicit in the economic evaluation is further complicated by cognitive errors which are well documented in dealing with probabilities. Patients may make trade-offs between health benefits from paternalistic care and individual benefits from preferences-based PM. For example, tests with indeterminate results may affect the behavior of patients in a different way than tests with a clear detection of a mutation. Patients under suspicion of having Lynch Syndrome, which have received a clearly positive result, are more likely to participate in additional screening over the next 12 months, than patients who received an indeterminate result and who are likely to misinterpret their test result as to be truly negative. Therefore, to avoid health damage due to a misunderstanding of test results, the test has to be complemented by appropriate risk communication methods [42]. More generally, further work is necessary to incorporate results from behavioral economics into research on the appropriate economic evaluation of PM [43].

Incorporating heterogeneity in preferences: Patient preferences regarding risks, but also regarding health states are likely to differ. For example, patients with low-risk prostate cancer can either undergo active surveillance or prophylactic surgery. It has been shown that the health state valuations of certain adverse effects, such as sexual dysfunction, can affect the decision about which is the optimal intervention in terms of relative cost-effectiveness [34]. A related issue might emerge if genetic screening extends to several diseases. If patients differ with regard to which diseases they want to include in a 'screen', such

heterogeneous preferences would likely affect the prevention strategy that is best for the individual. Individual patients' and societal mean valuations of health benefits may thus differ for the different strategies. Tailored evidence would be needed to adequately inform such heterogeneous preference and patients. This links issues in personalization according to both physiology and preferences.

Only recently have decision analysts tried to incorporate preference heterogeneity into cost effectiveness analysis [13]. Generally, methods of analysis used in DCEs allow detailed quantification of the presence of heterogeneity in preferences, at the sub-group (latent class) [44] or individual level [45]. Basu and Meltzer actually extended the concept of incorporating preference heterogeneity further to individualise the analysis and estimate individual treatment effects [12]. Another approach to account for preference heterogeneity is the concept of the expected value of individualized care (EVIC). EVIC is analogous to the concept of the expected value of perfect information. It is based on decision-analytic cost-effectiveness modelling and involves assigning a monetary value to a decision under perfect knowledge about individual health state valuations compared with a decision made on the basis of mean values [13].

Evaluative framework—The evaluation of new technologies by statutory health insurance and tax-funded health care systems is typically based on notions of medical need rather than preference satisfaction. These are fundamentally different categories; while desires expressed by preferences are subjective and unlimited, needs such as the need for physical health is easier to quantify and limited; while desires can remain unsatisfied, unmet needs are associated with some kind of serious harm such as impediments to successful social participation [46, p. 109, 47]. Therefore, the discussion of the role of preferences in healthcare decision making is directly related to the question about the appropriate framework for economic evaluation. The two predominant normative frameworks discussed in the literature are welfarism and extra-welfarism [48].

Welfarist viewpoint: Welfarism rests on a long tradition of economic theory. From a welfarist viewpoint, scarce resources should be allocated in a way to ensure that individual preferences are satisfied to the highest possible extent. In the absence of functioning markets and disregarding further distributional aspects, aggregated net willingness to pay (WTP) provides a measure of the desirability of a healthcare intervention which can be compared with its net costs. This is because, by means of WTP, individuals can directly compare their benefit from a healthcare intervention with other alternative goods which they can purchase [48].

Generally, if there is a trend towards PM in a preference-based understanding, this may strengthen the role of welfarism as the framework for economic evaluation. Specifically, PM is typically associated with the use of genetic markers which provide benefits to patients which are not captured by standard measures of health status such as the EQ-5D. This includes the direct benefit of knowing about one's future health prospects which may have no clinical consequences [49, 50]. Therefore, some authors have argued that welfarism is the most appropriate normative framework for evaluating PM. This is because welfarist

evaluation frameworks can account for such benefit by using willingness to pay within a cost-benefit analysis [51, see also: 52].

To date, no full cost-benefit analyses for PMs can be found in the literature, which may be the result of methodological [53] but also theoretical challenges that need to be addressed. The prevailing current view of most health economists therefore, appears to follow the extra-welfarist evaluative framework [14].

Extra-welfarist viewpoint: Typically, in decisions about whether a new intervention should be covered by social health insurance, it is assessed whether it provides health benefit so that it is suitable to alleviate need for healthcare. Increasingly, also the costs associated with the health gain are taken into consideration [54, 55]. This corresponds with an evaluative framework which extends beyond individual preference satisfaction as the only relevant benefit and, therefore, has been labelled “extra-welfarist” [48]. In its predominant form, it is implemented by assuming the benefit of interest, by decision makers allocating healthcare resources, should be the maximization of health benefit, corresponding with meeting health needs to the greatest possible extent [56]. Also other objective functions are under discussion [57]. Extra-welfarism does not preclude the use of methods for preference elicitation. However, they are seen as inputs to further specify a socially defined goal of health care rather than a representation of aggregated individual choice [48]. Therefore, the use of preferences and preference elicitation methods in PM needs further reflection.

To include non-health benefit into an extra-welfarist evaluation, the societal objective function could be complemented by measures representing the value of informed decision making (“empowerment”) [58]. A range of questionnaire-based instruments for measuring empowerment exist [58]. As far as such self-determination goes beyond desires and has a measurable impact, for example, on the individuals' successful social participation, their use is consistent with a needs-based view of resource allocation. Autonomy as well as health is frequently subsumed among basic needs [47]. However, to date none of the instruments are suitable for use in economic evaluations, for example due to the lack of established weights for each ‘empowerment state’ [59]. Furthermore, more evidence is needed to show that ‘information’ from personalizing medicine does indeed lead to patients being empowered to achieve self-determination [60]. Finally, if such additional benefit dimensions are to become part of an economic evaluation, it is also necessary to understand if, and how trade-offs between health gains and other goals of PM, such as empowerment, should be made.

Discussion

Existing evaluative (extra-welfarist) frameworks and principles and methods of economic evaluation appear appropriate for PM. However, there are specific challenges for the design and conduct of economic evaluations that centre on how the ‘P’ in ‘personalized medicine’ is understood: (1) using physiological biomarkers combined with the clinical patient characteristics and/or (2) using patient preferences to personalize medicine.

The current use of PM is oriented towards a clinical and physiological view rather than the preference-based interpretation of PM [1]. This prevailing view may be due to the fact that

the debates in the literature are strongly influenced by researchers representing the science of genetics and genomics. It can be argued that this interpretation is more appropriately described by the term “stratified medicine” [1].

In addition to pure clinical/physiological characteristics, however, patient preferences play an important role in evidence-based medicine, too, and their integration into clinical guidelines has been called for [61, 62]. The issues presented in this paper demonstrate that the preference-based interpretation of PM merits attention in the design and conduct of economic evaluations [12]. The two interpretations of PM, and the impact on methods of economic evaluation, are likely to interact. For example, novel biomarkers provide increasingly complex information (e.g., in the case of genomic profiles) and both for physicians and patients it is difficult to appropriately handle information about risks. Accordingly, both concepts and their implications have to be well understood together in order to realize the promises of PM for better, less harmful and more cost-effective patient-oriented health care.

Limitations

We did not aim to generate a formal consensus view but rather presented some emerging key issues that we consider are necessary to inform the debate on if, and how, to improve current methods of economic evaluation in the context of PM. We report emerging views based on (subjective) qualitative data collected from a selection of experts, definitions of terms from the literature and our interpretation of the published literature. Nevertheless, the qualitative research methods applied were considered appropriate given our work addressed such a large topic.

Our work did not aim to meet all the requirements for a systematic literature review but rather presented a structured and focused overview of the relevant literature. This approach was considered necessary because the topics addressed here would need a number of different systematic searches; for example, physiology-based stratification can be discussed under the topic of “personalization”, but also “heterogeneity”, “subgroups”, or “diagnostic markers”.

Implications for further research

The two concepts of PM have important consequences for (i) the design and conduct of economic evaluations, but also, (ii) in terms of directing a potential research agenda to generate a robust evidence base for PM to be introduced into clinical practice. Understanding the “P” in terms of physiology, this research agenda is likely to include collating more evidence from robust prospective observational studies and its proper analysis but also the need to pay close attention to heterogeneity in treatment effect when designing RCTs of PMs. Given the potentially low value of information associated with the evidence gaps in PM, new and less costly ways of collecting evidence may be needed to validate model-based cost-effectiveness estimates.

Understanding the “P” in terms of preferences implies that research programs should aim to understand revealed preferences for PM and the potential impact of preference heterogeneity for treatment effects and to understand risk attitude and quantify the relative value attached

to risks and benefits. Also, further theoretical work will be necessary to clarify which benefits should be quantified and whether valuing the impact on health gain alone is sufficient to ensure that economic evaluation helps to exploit the full potential of further personalizing medicine to society.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points for decision makers

- Personalized medicine (PM) is generally defined as the use of physiological biomarkers to stratify healthcare.
- This paper introduces two potential interpretations of personalization of medicine: in addition to using standard clinical patient characteristics, (1) using physiological biomarkers to stratify healthcare interventions to patient subpopulations and/or (2) using individuals' preferences for personalizing medicine.
- Existing evaluative (extra-welfarist) frameworks and methods are generally appropriate for the economic evaluation of PM. There are, however, specific methodological and practical challenges that depend on how the concept of 'personalization' is interpreted.
- Decision makers should be cognizant of the broad potential implications of personalized medicine including the role of preferences; they may use the framework presented here to identify points to consider for promoting cost-effective PM and areas where to appropriately target research funding.

Figure 1. Structured overview of methodological issues in the economic evaluation of personalized medicine