Health-economic evaluation of precision medicine in cancer care - literature review and analysis of methodological considerations

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Foreword

Precision medicine holds the potential to revolutionise health care delivery, and the train has already left the platform. By stratifying patients based on individual characteristics, a more patient tailored care may lead to better patient outcomes. However, this new paradigm challenges the way healthcare interventions are evaluated in terms of costs and health outcomes.

The complexity of advanced diagnostics, tailored medicines and preventive interventions together with increasing stratification pose challenges to how HTA bodies assess the cost-effectiveness of implementing new medical technologies. So far, HTA has been able to rely on market authorisation demanding large scale prospective randomised controlled trials for generating efficacy and effectiveness data. Precision medicine changes this landscape. The use of health economic models, where pragmatic approaches to these challenges are possible, will likely be an important tool to ensure that effective therapies are available to patients. The flexibility to test alternative inputs and potential outcomes may also mitigate the risk of resources being spent on therapies with limited or no effectiveness.

This report outlines some of the current challenges of precision medicine by reviewing the literature and identifying gaps not previously raised. The aim is to extend the current knowledge of challenges in evaluating precision medicine interventions.

The report has been developed as a part of IHE's partnership in the VINNOVA-funded innovation milieu Test Bed Sweden for Clinical Trials and Implementation of Precision Health in Cancer Care[1]. We would like to extend a thank you to VINNOVA for making this report possible, as well as to all the partners in the Test Bed milieu.

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Managing Director, IHE

[1] https://www.testbedswedenphc.se/

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Summary

Precision medicine has the potential to revolutionise health care. The rapid evolution of diagnostics, treatments, and methods to deliver care based on the individual's unique characteristics promises to increase health gains. These advances also bring new challenges on how to determine whether new and innovative methods are cost-effective in relation to the current standard of health care delivery. Cost-effectiveness information of new medicines is required in many countries across Europe and globally to be included on lists of accepted therapies. The reimbursement decisions then rely in part on the information on costs in relation to health outcomes provided from a cost-effectiveness analysis but also other aspects including equity, affordability, and health care infrastructure.

With precision medicine, the unit of analysis in health economic evaluations is no longer only a single medical product but it is becoming increasingly important to consider the whole care pathway. Precision therapy requires precision diagnostics which identifies suitable individuals and tailor treatment dosing. Precision diagnostics can also be used to rule out treatment due to high risk of adverse events or to inform on presence of biomarkers known to be associated with lower or no effect.

Methods for estimating cost-effectiveness were developed to meet needs in an era when large-scale randomised controlled trials provided data comparing novel interventions to placebo and to active compounds used in standard of care. Ideally, trials enrolled enough patients to determine the added (health) benefit of the novel intervention.

Precision medicine challenges this convention as it relies on more detailed information on patient and treatment characteristics to tailor treatment to each unique individual. There are ongoing methodological developments to assess efficacy and clinical effectiveness handling these specific characteristics of precision medicine. Questions have also been raised whether traditional economic methods for evaluating the cost-effectiveness of health care interventions may need any development or adaptation. For instance, does precision medicine require clarification in health economic evaluation guidelines regarding data requirements and recommendations for design and analysis?

This report reviews topics raised in health-economic and clinical oncology literature based on a pragmatic literature review. It also adds some further considerations. The report concludes that the methods used in health economics are not dependent on the availability of rigorous phase 3 data to be able to assess cost-effectiveness. Cost-effectiveness analysis and other economic evaluation methods have several tools to deal with uncertainty about effect sizes such as sensitivity analysis and scenario analyses. In that sense, the challenges of precision medicine in terms of greater statistical uncertainty of results can be dealt with using already available tools.

However, from a decision-maker perspective, the interpretation of uncertain results on cost-effectiveness because of uncertain data on treatment effects then goes back to the origin of uncertain data on clinical effectiveness. This report endorses ongoing and promising development of new strategies for assessing treatment effects alongside trials evaluating precision medicine therapies. This includes methods making greater use of health data registers and new matching methods to identify so called synthetic controls. Such comparisons are a step forward and adds valuable information on outcomes as observed in standard of care, the preferred comparator in health-economic evaluations.

1. Background

1.1 Precision medicine

Precision medicine, precision health, stratified medicine, targeted therapies, and personalised medicine are terms sometimes used interchangeably. They all relate to the growing opportunities to individualize treatments and other health interventions to each person's characteristics beyond historically standard clinical data based on a population mean. This include, but is not limited to, advances in genomic profiling (1-3) and life style. However, differentiation of treatments between patients is not new. Doctors have long been guided by tests related to disease conditions when choosing treatment. For instance, it is more than 120 years since different blood types were first identified and now the International Society of Blood Transfusion recognises 43 different blood group systems (4). These improvements in matching to individual patients has changed prospects for patients in need of a blood transfusion throughout the 20th and 21st centuries.

Today's interest in precision medicine relates to the recent opportunities to consider patient-level variation and individualized treatment schemes together with a growing understanding of new methods to collect and analyse data. The literature and general debate use multiple related and overlapping terms to the describe the potential for increased individualization in health care. There is no agreed formal definition of precision medicine, or the related terms. Usually, descriptions cover treatments and other interventions tailored for individual variability based on genetic profile, biomarkers, and other possible traits. The overall aim of precision medicine is then to improve outcomes where the effectiveness of interventions differs depending on measurable characteristics of the individual and to reduce potential side-effects. The increased understanding of associations between individual characteristics and treatment effectiveness may also reduce that number of treated patients where test results show little or no prospect of benefit from the specific treatment. Thus, precision medicine may be seen as the opposite of a one-size-fits-all-approach where large patient groups receive the same medicine and dosage with different outcomes if the treatment efficacy depend on individual characteristics.

This report uses the term precision medicine with the general definition described above in the review of the literature on methodological challenges for economic evaluation of individualised therapies. It is also the starting point for the report's considerations for future research aiming to incorporate health economic aspects in health technology assessment (HTA) of interventions in precision medicine. In general, the same basic strategies and principles apply for an economic evaluation of interventions in precision medicine as for other interventions in health care. Nevertheless, several aspects of precision medicine imply that there are empirical challenges. This report summarizes key observations from the recent literature addressing economic evaluation of precision medicine with references to diagnostics and treatments in oncology.

1.2 Cancer care and precision medicine

Oncology is an area of medicine where stratification, based on e.g., genetic biomarkers, is prominent and often a part of routine care. For example, in lung cancer, several genetic variants have been associated with disease risk (5). Also, more and more treatments approved by the Food and Drug Administration (FDA) target single biomarkers (6). Despite having come a long way in the implementation of precision medicine in oncology, further challenges remain.

Oncology per definition can be attributed to a genetic variant, a mutation, occurring. Identifying the most effective treatment strategy for a patient diagnosed with a specific disease-causing genetic variant is a continually evolving process. Novel genetic variants of significance (or unknown significance) are identified continuously and drug discovery or drug repurposing to treat illness caused by the specific variant follow these discoveries. Thus, oncology has come far but not reached its end point.

A sometimes challenging characteristic of individualised therapies is the need for comprehensive diagnostic testing to identify the specific patient's characteristics, e.g. certain phenotypes and molecular profiles, that can determine treatment outcome. This often requires precision diagnostics that are not part of routine care at the point of introduction (7, 8) which implies that not only the cost of the therapy itself, but also the new diagnostic requirements, are subjected onto the health care provider. Novel therapies are (in most cases) under patent protection, which leads to higher initial costs of e.g., drugs while under patent compared to after patent expiration (9). The cost of anticancer drugs has also been rising in the past years due to higher costs of research and development for such treatments (10, 11). The cost of genomic profiling has been declining rapidly since the introduction of next-generation sequencing (NGS), Moreover, as the introduction of next-generation sequencing have lowered the cost of genomic profiling, more data has been generated which has increased the cost of data interpretation and clinical decision-making (12). This emphasises that economic evaluation of precision medicine compared to standard of care must consider all aspects of the treatment pathway.

This report is organised as follows: Section 2 gives an outline of health technology assessment, why it is needed and key concepts and tools. Section 3 outlines the methods and materials. Section 4 presents the review of papers discussing economic evaluation in precision medicine. Section 5 builds on the results and recommendations from the reviewed papers and the general framework for health economic evaluations. It summarises important differences between economic evaluation of precision medicine and mainstream economic evaluation of standardized treatment in homogeneous groups. The section also discusses alternative approaches to the evaluation, including the identification of relevant comparators, with specific reference to study designs other than the traditional randomized clinical trial to estimate treatment efficacy, safety, and effectiveness. Section 6 concludes the main findings in the report.

1.3 Objective

This report aims at identifying and highlighting key methodological challenges for economic evaluation of precision medicine. A pragmatic literature review will seek to identify what has been described previously. Following the review additional considerations not identified in the review will be described. This report serves as a cross-section in a rapidly evolving field, hopefully many of the challenges raised herein will be solved in the coming years.

2. Health technology assessment (HTA) and health economic evaluation – a brief background

Health technology assessment (HTA) is a multidisciplinary process where technologies and interventions intended for use in the health care sector are systematically evaluated to inform decision makers of their economic value. This requires that clinical benefit has already been established in definitive or in part.

To gain entry to the European pharmaceutical market, companies submit a marketing authorisation application for their new pharmaceutical interventions to the European Medicines Agency (EMA). After evaluation, the product may be granted marketing authorisation by the European Commission (13). The role of the EMA is to ensure that the drug has a tolerable safety profile (e.g., risk- and severity of adverse events in relation to the therapeutic benefit) and that the summary of product characteristics (SmPC) is in order so that healthcare professionals and patients have sufficient information on how to use the product (14). The corresponding body in the USA is the FDA.

Many countries in Europe have established processes for HTA where national and regional agencies have defined roles and responsibilities. Examples of such agencies are the National Institute for Health and Care Excellence (NICE) in the United Kingdom (15), the Dental and Pharmaceutical Benefits Agency (TLV) in Sweden (16) and the Norwegian Medicines Agency (NoMA) in Norway (17). This report does not cover the variations in country specific organisation, details of mandates or instructions for submitting application for marketing authorisation, pricing, and reimbursement. A common request for HTA is, however, that additional evidence on economic value and cost-effectiveness, beyond the efficacy and safety of the product, is required. This includes e.g. comparative effectiveness to the current standard of care and expected clinical benefits of implementation of the new product, and implications for the health care organisation such as care pathways including diagnostics and follow-up. An important part of an HTA is the analysis of cost-consequences from implementation and the cost-effectiveness of the product compared to current standard of care. The rest of this section provides a brief introduction and background to health economic evaluation in the context of HTA, why it is needed and how cost-effectiveness is defined and analysed.

2.1 Why is HTA needed?

The aim of an HTA is to provide decision makers with an evaluation of the new medicinal product as compared to current standard of care. From the decision maker's perspective, it is important to know that a product has a positive effect and that it is safe. The decision maker needs an analysis of consequences for patients, the health care organisation and costs to determine the value of adding the new medicinal product to recommended treatments. This assessment will then rest on inter alia the comparative effectiveness of the product and the proposed costs but also on the expected downstream consequences in terms of health benefits and longer-term health care needs and costs. A standard HTA consists of two equally important sections: the evaluation of clinical effectiveness and the evaluation of the cost-effectiveness in the specific health care context.

Health-care systems in Europe are characterised by third-party financing where patients at the point of consumption pay low or no fee for health care services. Third party financing may be

organised in the public through taxation (e.g. the Nordic countries and the United Kingdom), through mandatory social insurance (the Netherlands, Germany, France) and private insurance may exist in parallel. Third-party financing implies that resource allocation in health care cannot rely on the same mechanisms as the markets for food, clothes, and bicycles where buyers and sellers interact. Resource allocation in health care systems with third-party financing have other decision principles. There is a growing trend that decisions to include new interventions need to be accompanied by explicit evaluation in terms of value for money where added costs are compared to expected health benefits. This means that any decision on implementing a new drug, a new test, or a new type of suture must be made with consideration of cost-effectiveness. In most cases, the system already employs a mean of handling whatever the new intervention is intended for. A higher cost of the new medicinal product compared to current standard of care will require a reallocation of the budget means from other uses within the health care sector. Shifting resources to the new patient group then crowds out treatment of other patient groups. Such re-allocation can be motivated in cases where the new medicinal product generates more patient benefits compared to the old use. Health economic evaluation methods assist in such assessments.

Recently, the European Union adopted a new regulation on how HTA-assessments s be conducted in the member states. The regulation states that the member states will, on an EU level, conduct joint clinical assessments (JCA), joint scientific consultations (JCS), and horizon scanning. The JCA is intended to provide an overview of relevant patient populations and subgroups, relevant comparators, and health outcomes. The JCA will contain a scientific analysis of clinical effect. However, the new HTA-regulation also stipulates that each member state will still have the final say on whether a medical technology provides added value to their health systems and decide on pricing and reimbursement. This implies that the JCA will not lead to reduced burden on national HTA-bodies in terms of the health economic analysis and evaluation of cost-effectiveness.

2.2 Economic evaluation

One important part of an HTA is the economic evaluation. Once the clinical effectiveness of a novel intervention in the health care system has been established, it is necessary to investigate whether it is *cost-effective*, meaning that the cost of the new intervention in relation to current standard of care is *acceptable* in relation to the health benefits generated by the new intervention in relation to current standard of care.

The economic evaluation includes collecting all the relevant evidence regarding both the current standard of care and the novel intervention, which can be anything from clinical trial data on clinical effectiveness to the number of bed-days a treatment-related adverse may lead to. The key is that it should include *all relevant* data.

Once the data have been collected and organised, the purpose of the evaluation is to determine what course of action generates the most value. This depend on, among other things, the threshold value of cost-effectiveness (this can also be seen as society's willingness to pay for a new intervention) in the setting for which the evaluation is being conducted. There are many ways of conducting economic evaluations; one trusted workhorse in health economics is that of cost-effectiveness analysis using health economic decision models.

2.2.1 Cost-effectiveness analysis

In most cases, to establish whether a new intervention is expected to be cost-effective in the health care system, an analysis of the expected costs and outcomes is necessary to inform the decision process.

Cost-effectiveness analysis (CEA) as a term is used interchangeably with cost-utility analysis (CUA). The *theoretical difference* between the two is that in CEA, the health outcomes can be described as any quantifiable unit, e.g., number of heart attacks prevented, whereas in CUA, the health outcomes are described as quality adjusted life-years (QALY) (see section 2.2.2). In *practice* there is no real difference between the two and the methodology is the same. Henceforth, CEA will be used to depict both CEA and CUA, making no distinction between them

The purpose of the analysis is to calculate the incremental costs and effects of introducing a novel drug, device, or technology into the health care system compared to the most relevant alternative. In most cases, the relevant alternative to a new intervention is the current standard of care for the intended patient population. In some cases, when there is no current standard of care, the alternative would be "to do nothing".

In CEA, the total cost of the intervention and the comparator (e.g., standard of care as noted) is estimated, as well as the total health outcomes they both generate. In the analysis, all relevant costs should be considered depending on the perspective of the analysis. In some cases, only costs incurred within the health care system are considered (a payer perspective), and sometimes the analysis considers all costs that are incurred in society as a whole (a societal perspective). The societal perspective considers both costs incurred in the health care system and costs from e.g., productivity losses or indirect costs such as patient travel time or informal care are considered. A third approach is also possible, where the perspective is that of a third-party payer, most often an insurance company. The third-party payer perspective is most frequently used in e.g., the US market where private insurance is the most prevalent form of health insurance.

After estimating the total costs and total health produced (expressed as QALYs), an incremental cost-effectiveness ratio (ICER) is calculated (Equation 1). The ICER is a measure of the cost of producing one extra unit of health using the new intervention as compared to the comparator alternative.

$$Equation\ 1. \qquad \frac{Cost_{Intervention} - Cost_{Comparator}}{QALY_{Intervention} - QALY_{Comparator}} = \frac{\Delta Cost}{\Delta QALY} = ICER$$

To estimate the total costs and total QALYs, it is necessary to also estimate the impact the new intervention will have on the disease trajectory. With the uncertain nature of doing these estimates prior to introduction, as is most often the case, analysts refer to using decision analytic models.

2.2.2 Quality-adjusted life years (QALY)

In many cases, as noted, QALYs are used as the primary health outcome in a CEA. The QALY is a measure of longevity weighted by health-related quality of life (HRQoL). To elicit QALYs, HRQoL is measured on a scale between 0 (same as death) and 1 (full health). Longevity is measured objectively, e.g., in a clinical study an individual is either alive or dead. However, beyond the clinical study, extrapolation is often required. HRQoL is however a subjective measure. HRQoL used to elicit QALYs can either be measured in the population for which the intervention is intended or that has the disease/condition of interest, or in a representative

sample from the general population. The measurement of HRQoL for use in calculating QALYs (often called "utility weights" or "health utilities") can be performed either with direct or indirect methods (18).

Direct methods

In this section, three viable approaches of direct methods are discussed, however there are additional methods available. Direct methods include time-trade-off (TTO), rating scales, and standard gamble (SG). The rating scales used are, e.g., visual analogue scales where the respondent simply marks on a line measuring 0 to 100 where they feel that their HRQoL is or would be given the condition. This method does not include risk aversion. TTO offers the choice of either living with the current condition for a set period of time or in full health for a reduced period of time. The quota between the two options is then the utility weight for that condition. TTO includes preferences but not explicitly risk aversion. SG is the theoretically most appropriate method, albeit challenging to comprehend even for seasoned health economists. In this method, the respondent is given the choice of either continuing to live with the current condition or take a (theoretical) one-off treatment that could either cure the condition and provide perfect health, or cause instant death (18).

Indirect methods

The use of direct methods to elicit HRQoL or utility weights is often challenging for respondents to fully grasp. As a result, indirect methods have been developed where, e.g., questionnaires are used. The most requested indirect method is the EQ-5D questionnaire, developed by EuroQol-group (19). The EQ-5D questionnaire has two current versions with five dimensions: the EQ-5D-3L and EQ-5D-5L. The 3L has three levels and the 5L five levels. Other generic instruments are the SF6D (which is based on the SF36 form) (20) and the Health Utility Index (HUI) (21). These generic instruments are easier to comprehend than the direct methods. However, they have slightly different scales and using more than one instrument for the same health economic analysis may introduce instrument bias (18).

2.2.3 Decision analytic models

One tool in the health economic toolbox is the decision analytic model. These models are in essence mathematical sequences of probabilities of events occurring during the analysed time period. Each event in the model is assigned with e.g., a cost and/or an impact on mortality or morbidity (usually expressed as reduction in quality of life, a component in the estimation of QALYs). A model is only as good as the data you feed into it; therefore, data is collected from various sources to build a model that reflects reality to the greatest extent possible. In Table 1 examples of data categories and sources are listed. The list is far from exhaustive and may differ between populations, regions and disease areas.

Table 1. Data categories and common sources

Data	Source(s)
Cost data	Regional price lists, micro costing studies in the literature
Treatment effect	RCT, observational studies
Survival	RCT, registries
Quality of life	Literature, RCT
Prevalence of biomarkers	RCT, registries, observational studies

The versatility of data sources also introduces various degrees of uncertainty into the model estimates; this is mitigated via various sensitivity analyses where the impact on the ICER from varying one, two, or all parameters (inputs) at a time. All models are burdened by uncertainty and it is up to the decision maker to decide whether the uncertainty of an analysis is too great to e.g., base a positive recommendation for reimbursement/introduction on the model outcomes. The less uncertainty a model has, the greater the likelihood that the data input to the model is costly to acquire.

2.2.4 Willingness to pay and thresholds for cost-effectiveness.

The notion of 'cost effective' stems from the question whether the additional cost in relation to the (health) benefit expected from implementation of e.g., a novel medicine is acceptable. Typically, in health care systems where health technologies are evaluated through an HTA process based on QALYs, the cost per QALY gained must be lower than the maximum cost that society is willing to pay to gain one QALY. This is then referred to as the threshold value. This threshold can either be explicit or fluid (i.e., can be influenced by e.g., severity). An explicit threshold can be estimated in various ways or simply arbitrary. However, the actual cost that is acceptable (what is actually paid) may vary depending on the level of uncertainty of the underlying health economic evaluation. If there is a high degree of uncertainty, payers risk overpaying per QALY *actually* gained. For example: if the *expected* QALY gain is 1 and the *actual* QALY gain is 0.8, with an ICER of 100 and the willingness to pay at exactly 100, the payer will pay 120 per actual QALY gained.

For example, in Sweden, the willingness to pay varies with severity and rarity of the condition. The Swedish parliament has decided that resources should be allocated to those with the greatest needs. The TLV interpretation of this is that only severity should impact the willingness to pay, whereas the NT-council's interpretation is that both severity and rarity matters (22).

However, if an intervention is found to be cost-effective (or even cost-saving), it is not a guarantee for implementation. When deciding on implementation and/or reimbursement, additional aspects may be considered, such as the total budget impact of a particular technology.

Unless the new intervention produces more health at a lower cost or produces less health at a higher cost, as compared to the comparator, an ICER says very little about the cost-effectiveness. One way to determine whether an intervention is cost-effective is by plotting the incremental costs and QALYs on the cost-effectiveness plane (Figure 1). When the incremental costs and QALYs are either higher/more or less/fewer respectively a threshold value is necessary.

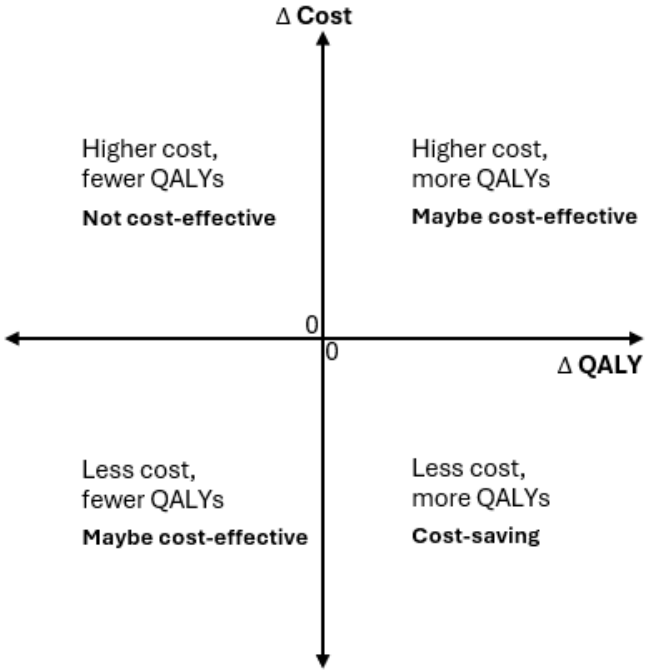

Figure 1. The cost-effectiveness plane.

2.2.5 Other methods of economic evaluation

There are more tools in the health economic toolbox than CEA to estimate the cost-effectiveness and overall financial impact of novel interventions in the health care system, e.g., cost-minimization analysis (CMA), and budget impact analysis (BIA).

2.2.5.1 Cost-minimization analysis

When it can be expected that two interventions have the same health outcomes, e.g., two medical devices with identical ability to accurately measure blood pressure by different mechanisms, CMA can be adopted instead of CEA. In a CMA, the effect component of the CEA can be excluded from the analysis and only the costs are considered, where the less costly intervention should be implemented. This method should primarily be used when one of the alternatives is already in use in routine care.

2.2.5.2 Budget impact analysis

As CEA or CMA only answer the question of whether a new intervention is cost-effective, another type of analysis can often be found coupled with a CEA or CMA, namely a BIA. This type of analysis estimates the actual impact the introduction of a novel intervention has on the health care budget. It considers both the costs associated with the novel intervention and the number of patients eligible for treatment during e.g., a budget year. The total cost for the novel intervention minus the cost of current care is then the incremental cost, which constitute the actual impact on the budget. A negative budget impact is preferred over a positive impact as this would allow resources to be allocated elsewhere in the system. Albeit in many cases, these savings are not easily identified.

3. Method and material

Two searches, one in PubMed and one via Google search engine, identified papers published since January 2018 addressing the methodological challenges of the economic evaluation of precision medicine. These searches used broad search terms: precision medicine, economic evaluation and oncology. One author (OF) screened articles for relevance based on title and abstract. Selected articles were further screened for contents regarding methodological challenges for economic evaluation of interventions in precision medicine. Analogous to qualitative studies, this pragmatic search observed a "saturation" in terms of which challenges were raised for economic evaluations of precision medicine. A total of six publications were selected based on their relevance. Most topics and challenges were recurrent through the six selected publications and both authors (OF and KSC) agreed that addition of more publications was unlikely to add new challenges to the analysis. Table 2 lists the included publications including summary data on topics raised.

Table 2. Included studies

First author (Year) (Reference)	Title	Areas in report covered
Weymann (2018) (23)	Economic Evaluations of Next-Generation Precision Oncology: A Critical Review.	Modelling
Vellekoop (2021) (24)	Guidance for the Harmonisation and Improvement of Economic Evaluations of Personalised Medicine.	Care pathway, Modelling, Perspective, Uncertainty, Data
Pataky (2022) (25)	Tools for the Economic Evaluation of Precision Medicine: A Scoping Review of Frameworks for Valuing Heterogeneity-Informed Decisions	Frameworks
Pollard (2022) (26)	Defining a Core Data Set for the Economic Evaluation of Precision Oncology	Data
Love-Koh (2018) (27)	The Future of Precision Medicine: Potential Impacts for Health Technology Assessment	Care pathway, Modelling, Uncertainty, Future
Chan (2021) (28)	The Past, Present, and Future of Economic Evaluations of Precision Medicine at the Committee for Economic Analyses of the Canadian Cancer Trials Group	Future

4. Review

In the era of precision medicine, patient groups get diminishingly smaller. This leads to clinical trials becoming more and more difficult to conduct in a fashion that satisfies HTA-agencies. This is not only the case in oncology but in any therapeutic area where precision medicine is a candidate for implementation. There are certain challenges that arise when conducting economic evaluations in the era of precision medicine. This section attempts to summarise and describe important contributions from the literature. In the introduction of each subcategory, a summary of relevant considerations is provided in highlighted textboxes. These are the authors of this report's interpretation of what has been raised. The considerations may be raised in more than one of the reviewed papers.

4.1 Frameworks

Key findings

- Stratification of patients and/or treatments and/or testing should only be considered when stratification is expected to generate more net health or net monetary benefit than a population-based approach.
- Cost-effectiveness estimates of introduction/use of novel technologies could be misleading to policy makers when not considering the uptake and utilization of these technologies.

Pataky et al (2022) (25) highlight four analytical frameworks suitable for estimating value of heterogeneity-informed decisions.

The first approach describes **the value of stratification,** which means that treatments and patients should be stratified in a manner that maximizes net health benefit (NHB) or net monetary benefit (NMB). This is achieved by limiting treatment to groups where the value of treatment is the greatest. The primary outcome measure here is then the sum of NMB/NHB in cost-effective subgroups minus the NMB/NHB in all other subgroups. This implies that when the willingness-to-pay is too low, no patients should be treated. In contrast, when its high enough, every patient should be treated rendering the value of stratification to be zero.

The second framework describes the **expected value of individualised care and** highlights the expected value (or loss thereof) of not considering patient-level heterogeneity; in other words, using a population-based approach instead of a targeted, stratified approach. Thus, considering stratification of patients and treatments, the NMB/NHB should exceed that of population-based care. This does not imply that treatment should be limited to some patients, but that individualised care is the best option if the cost of identifying individual-level factors of heterogeneity is less than the expected value of individualised care.

Third, they discuss the **value of heterogeneity** which is similar to the value of stratification with the addition of varying each parameter that influences stratification and plotting an effectiveness frontier where NMB/NHB is plotted in relation to population-based interventions. It also allows for consideration being taken to heterogeneity and uncertainty by comparing subgroup- and population-based decisions with the current level of information compared to a world with perfect information.

The discussion in the last framework is primarily intended for policy decisions. It considers the **loss with respect to efficient diffusion** where one attempts to estimate the realised value of

technologies by comparing different policy alternatives with subgroup-based utilisation scenarios. The framework considers heterogeneity in both cost-effectiveness and uptake. This can be utilized to compare different policy alternatives by e.g., providing better access to current and introduction of new technologies.

4.2 Care pathway

Key findings

- Test- and care pathways will likely be complex and difficult to identify, increasing the need for expert elicitation to define where in the pathways new technologies are most likely to be introduced.
- Stratification may lead to bias in treatment and reimbursement decision as factors correlated with, e.g., ethnicity or social status may weigh decisions to favour certain population subgroups.
- Suboptimal treatment and follow-up may arise from complexity of, e.g., diagnostic pathway or treatment regimens that require perfect adherence from patients and treating physicians.
- Patient understanding of risks and probabilities, or lack thereof, may lead them to be information averse to, e.g., genetic risk profiles and subsequently undermine optimal treatment strategies.

Precision medicine potentially pose significant changes to the way health care is delivered. Before treatment starts, patients are likely to be subjected to various stratifying testing regimens, transforming care from one-pathway-fits-all to one-pathway-fits-me. As a result, there will be an extensive number of potential care pathways for patients treated with precision medicine. Introduction of novel tests and/or treatments in this landscape of complex pathways challenges HTA agencies. For example, tests can be used at undefined places in the care pathway and at various timepoints; they can also provide information regarding more than one condition. This highlights a need for expert elicitation to define the most probable care pathway for patients treated with an evaluated intervention or the current standard of care (27).

The stratification of patients into smaller subgroups also give raise to some concerns regarding equity and equality that HTAs must be mindful of. Certain external factors such as socioeconomic status increase the risk of e.g., cardiovascular disease (29). In addition, genetic variation differs between ethnic groups. As an example, the BRCA1 and BRCA2 mutations are more prevalent in people of Ashkenazi Jewish heritage (30). People with BRCA1 and BRCA2 mutations carry absolute lifetime risks of female breast cancer at 60-70% respectively (31, 32) as well as an absolute risk of ovarian cancer of 44% and 17% (32). Therefore, it is important for HTAs and decision makers to include factors that may lead to certain groups being overlooked in treatment and reimbursement decisions. In addition to this, the fast pace of technological innovation may render HTA reviews obsolete with a higher pace than traditionally, increasing the burden on HTA agencies to keep recommendations up to date (27).

Another this to consider is that patients may be less adherent to precision medicine treatments as they come with prerequisite tests and diagnostic workups. When coupled with physician compliance to testing and/or treatment regimens, they may increase uncertainties regarding the care pathway in praxis. Other raised concerns are that patients in some cases may lack fundamental understanding of risks and probabilities and may be information averse regarding e.g., genetic risk profiles. This could contribute to suboptimal follow-up and treatment (24).

4.3 Modelling

Key findings

- All relevant treatment pathways should be identified and reasons and rationale for inclusion and exclusion should be given.
- Models should capture outcomes for both patients who have a false positive and false negative test result when analysing diagnostic tests.
- When tests have continuous outcomes, it is advisable to use cut-offs that can be varied in sensitivity analyses.
- Complexity of care pathways may increase the computational burden on economic models, rendering Markov-type model structures insufficient.
- Contradictory to the intention with precision medicine, the increased stratification of patients and treatment increase the uncertainty of outcomes of economic models.
- It is not necessary to make any diversions from national guidelines when it comes to discounting and the perspective (i.e., what costs and outcomes are considered) when evaluating precision medicine.

In a 2018 review of modelling studies in oncology where NGS had been considered, a total of 55 studies were included and 86% considered panel testing. More than half of the included studies considered a North American setting and about one quarter considered a European setting (23). Only about one fourth of studies were based on data from clinical trials, suggesting that NGS is not utilised in a great extent in trial settings (23). It should be noted that the included studies were published in 2016 or earlier and that NGS was still in its relative infancy at this time.

When developing decision analytic models in precision oncology it is advisable to identify all *relevant* test-treatment pathways. Rationale for their inclusion in the evaluation process is also recommended as there will likely be pathways that are excluded due to being e.g., seldomly adopted on an aggregate level (24). When the test is used to stratify patients, it is important to distinguish the outcomes for patients who receive false negative and false positive test results. This as the precision of tests (the sensitivity and specificity) as well as the composition of patient subgroups may change over time. In addition, trial results may be valid only in small subgroups.

If tests are modelled in sequence, the between-test dependency should be addressed and there could be reason to include a waiting period in economic models to capture the delay between symptom, test, and subsequent treatment. This should especially be considered when the waiting time is attributed with increased risk of morbidity and/or mortality. When testing for hereditary mutations, cascade testing should be included if relevant for the decision problem to capture the full impact from testing.

The complexity of care pathways will likely increase the computational burden and complexity of decision-analytic models going forward. This could render the traditional Markov-type model structures insufficient since the number of health states needed to be explicitly modelled will be enormous. The authors suggest that other methods, such as microsimulation models and discrete event simulations, may be better equipped at handling evaluations of precision medicine. When tests have continuous outcomes, cut-offs should be employed, allowing for different cut-offs for the same tests. The cut-offs should be clearly defined and varied in sensitivity analyses (27).

If the economic evaluation, and subsequently the decision analytic model, considers a test where the outcome of the test informs risk of disease and/or inherited traits, the outcome could have a positive and/or negative impact on patients and their relatives, e.g., in terms of autonomy or stress. There are some concerns that these outcomes are poorly captured by traditional measures (e.g., QALYs) (27).

Although the idea with precision medicine is to treat each individual based on their own personal characteristics, it is impossible to achieve this kind of stratification in decision analytic models. Instead, stratification will lead to cohorts that are more homogenous but with more uncertainty and models will need to consider e.g., intervals rather than absolute values of treatment effect (24).

Where structural uncertainty is present, e.g., in the test-treatment trajectory or other issues connected to the decision problem at hand, these should be reflected in the analysis if possible. Where parameterisation is possible of these uncertainties, it is advisable to include the possibility of estimating the impact via sensitivity analysis (24).

4.3.1 Perspective

The **perspective and discounting** should be aligned with the national guidelines issued by the relevant HTA body. This is to avoid precision medicine interventions to be premiered over other interventions in the health care system. For example, it might be tempting to adopt a societal perspective when evaluating advanced therapy medicinal products (ATMPs) where treatment is curative, especially in children, as the potential QALY gain and cost-savings incurred by treating an otherwise fatal or heavily debilitating condition would be significant (24).

4.3.2 Uncertainty

Key findings

- If managed entry agreements are necessary for the introduction of a novel technology, the implications in, e.g., uptake should be reflected in the model.
- Test prices are not synonymous with test costs.
- Costs of tests should be included to a various degree. The cost should be included if a new therapy requires a novel test to be introduced. If a new therapy utilises an already introduced test, some of the test cost should be attributed to the new therapy.
- Head-to-head comparisons of targeted therapies may be difficult to conduct, including by network meta-analyses.
- When utilising observational data to estimate (relative) effectiveness of targeted therapies, careful study design and understanding of the utilised data is necessary.
- The use of clinical expert opinions will likely increase. It may be necessary to consult more experts to mitigate uncertainty coupled with opinions.
- Models should allow for flexibility in assumptions regarding uptake of test-treatment pathways and strive to reflect the target population.
- Real world data may decrease the uncertainty in economic evaluations of precision medicine interventions in the long run.

In all models, various degrees of uncertainty are present. Three major topics were identified (costs, clinical effectiveness, and treatment pathway); albeit they may intersect at various points, this review tries to distinguish between them for readability.

Costs

Diagnostic and prognostic tests are important components in precision medicine. It is often easy to find a *price* for a test as there are plenty of commercialised tests (e.g., 23andMe or OncoTypeDX (33, 34)) or tests performed within the health care sector with prices listed in various pricelists. However, the price of a test is not synonymous with the *cost* of a test. These costs can vary greatly depending on the laboratory, the type of sequencing platform used, the competence of the bioinformatician analysing the data, and more. This makes it difficult to use a universal cost input for the tests (24, 27). If the test is already routinely performed in the health care system, the cost may be excluded in part. However, the adverse events related to testing should always be included if they pose a significant clinical risk (24).

When novel treatments are expected to be costly, and some form of managed entry agreement (MEA) is expected to be necessary to facilitate implementation, this should also be reflected in the model. This is because MEAs are likely to impact the possible uptake of e.g., treatment or diagnostic testing and potentially the cost-effectiveness of the intervention (24).

Clinical (relative) effectiveness

The issue of stratifying patients into smaller subgroups, thereby reducing sample sizes, render e.g., trial results to be valid only in small subgroups and head-to-head comparisons difficult. In addition, comparative effectiveness analyses (e.g., network meta-analysis) will be difficult or incomplete if no common comparator is available to link trials. Increasing the need for expert interviews to fill these gaps and increasing demand on the methodology that their judgements are elicited. Novel trial designs (e.g., basket, umbrella and adaptive trials) are expected to be more suitable for precision medicine therapies, however, they are consequently expected to require additional sources to completely capture pathways in decision models. An increased need for observational studies is noted to assess precision medicine interventions in the future (27).

Observational studies are often dependent on the population being studied and the outcomes are not always transferable to the evaluated population. This means that when conducting an economic evaluation where the clinical effectiveness of a treatment guided by a diagnostic test, the evaluation may be biased if the population in the clinical trial has a higher prevalence of the diagnostic marker than the observational data. This as the observational data was collected using a potentially less sensitive test. This highlights that careful study design is important when utilising observational data in economic evaluation of e.g., NGS driven precision oncology (23, 35).

In essence, the idea behind precision medicine is to reduce the uncertainty of, e.g., treatment effect and outcomes in patients by tailoring treatment with consideration to the individual patient's characteristics and preferences. However, this is seldom the case. Instead, patients are stratified into groups, albeit smaller groups than traditional medicine. This paradoxically increases the uncertainty of economic evaluations of precision medicine interventions. Small patient groups in clinical trials and synthetic control arms based on observational data amplifies the uncertainty regarding treatment effect. As it may be difficult to reduce this uncertainty, analysts could find themselves more heavily dependent on expert elicitations for model inputs. To mitigate the uncertainty coupled with expert opinions, it is recommended that several experts are consulted, that their input is synthesised, and that the spread used in sensitivity analyses (24).

Treatment pathway

The effectiveness of precision medicine treatments is dependent on 1) the stratification of patients and treatments and 2) the adherence to the optimal treatment pathway both by physicians and patients. Some concerns exist that the patients' and physicians' behaviours may influence the clinical effectiveness and subsequent cost-effectiveness of precision medicine interventions (24, 27). This may be in part due to health care professionals' learning curves of using precision diagnostics or omics-based treatments, or patients failing to e.g., comprehend the concept of risks and probabilities (27).

Failure to comprehend risks and probabilities may lead to patients being information averse regarding e.g., genetic risk profiles that would then lead to suboptimal follow-up and treatment. In this respect, models should allow for flexibility in the assumptions regarding uptake of ideal test-treatment pathways. Emphasis should be given to reflect the target population, as well as possible alternative pathways (24)

The complexity of the care pathway discussed in Section 4.2, and subsequent complexity of decision-analytic models coupled with smaller sample sizes, will increase the uncertainty surrounding cost-effectiveness estimates presented to decision makers, some of which can be mitigated by data collection through real-world observations to reduce uncertainty in the long term (27).

4.4 Data

Key findings

- Clinical trials of precision medicine interventions often lack a randomised control group.
- Data on biomarkers will need to be better included in clinical trials of precision medicine to facilitate evidence generation on analytic validity, clinical validity, and clinical utility. This is important both for the economic and the clinical assessment.
- When surrogate endpoints are used to estimate final effectiveness outcomes, transparency on the methods and rationale used will be necessary.
- A core dataset for economic evaluation of precision oncology has been developed (see Table 4) This can be used as a base line for data collection protocols in clinical trials.

Small sample sizes, surrogate endpoints and single-arm trial designs do not fully meet the evidentiary requirements for economic evaluation. The absence of a randomised control group receiving standard of care is a common point of concern raised, recognising the divide between the need of better and more precise information compared to the opportunity cost of delaying decision making both to patients but also society (28).

Clinical trials in the sense of randomised controlled trials (RCT) will likely be problematic going forward in the era of precision medicine. This, however, does not mean that RCTs will not be present. Instead, with patients being stratified into smaller subgroups, the complexity of trials will increase, and more emphasis will be placed on the link between test results and clinical outcomes. To mitigate the smaller subgroups, greater international collaboration is needed so that the number of eligible patients enrolling in trials increases. Biomarkers need to be better incorporated into clinical trials as evaluating potential biomarkers will require evidence on analytic validity, clinical validity, and clinical utility (28).

Emphasis should be given to using effectiveness data from studies with two *or more* treatment strategies. When surrogate endpoints are used to estimate the final effectiveness outcome, the sources used and the assumptions taken regarding the correlation between the surrogate endpoint and the actual endpoint (e.g., progression-free survival instead of overall survival) should be clearly specified. If outcomes from a single-arm study are used to derive effectiveness, external data can be used to create a synthetic control group or comparator.

When the evaluated treatment is dependent on e.g., a genetic marker, the prevalence of the biomarker can be different in the study population and the population that the synthetic control arm is based on. This would render the estimated control arm unsuitable for economic evaluation. However, if the prevalence is known in both populations, the prevalence relative prevalence can be adjusted. Special attention should also be given to the prognostic value of the biomarker. When comparing to e.g., standard of care, the method used to estimate prevalence and/or prognostic value of the marker in the trial may be "better" than the one used in routine care, which would introduce some bias and skewness to the results of the evaluation. It is imperative to specify the sources used to estimate the relationship between markers and the clinical outcomes and provide strong rationale for any assumptions made.

When extrapolating survival, it is suitable to assess the appropriateness, not only by statistical fit, but also by consulting clinical experts. Using population-based survival for e.g., patients who are "cured" from cancer could be inappropriate as there may be other factors that make their actual survival different from the general population. Hence, consideration should be given to whether there is an increased morbidity and mortality in the evaluated population in the long term (24).

In 2022, Pollard et al (26) undertook the task of defining a core data necessary for the economic evaluation of precision oncology. Albeit the list is not exhaustive for all settings and all scenarios, it is a first step towards harmonising data collection to facilitate economic evaluation of precision oncology. The authors reviewed the literature, focusing on evaluations in precision oncology and rare diseases, and coupled this with a modified-Delphi process to ensure that the data set reflected a feasible collection of data.

Seven data challenges were highlighted in two distinct areas of economic evaluations in precision oncology: *uncertainty and biological heterogeneity*, and *methodologic transparency* (Table 3)

The core dataset identified to cover the challenges mentioned in Table 3 include six different categories: demographic and socioeconomic factors, clinical characteristics, genomic elements, cancer treatment, patient outcomes and resource utilization.

Table 3. Challenges in economic evaluations in precision oncology (26)

Uncertainty and biological heterogeneity	Methodological transparency
Complex clinical pathways	Simplifying assumptions do not reflect real-word conditions and spillover effects. Risk of bias.
Spill-over effects	Next generation sequencing technologies relevant to multiple conditions may fail to apply appropriate or relevant comparator(s)
Reliance on estimation of health outcomes without strong evidence of comparative effectiveness, inconsistent accounting for health-related quality of life and personal utility estimates	Cost-effectiveness thresholds are not uniform
Downstream costs poorly characterized	

The data requirements identified are to some extent self-evident to a health economist familiar with economic evaluations e.g., patient date of birth and biological sex, or the need for preference-based outcome measure to estimate health outcomes. A summary of the relevant data is found in Table 4, see table 4 of the source paper for the full list (26).

Table 4. Summary of data to be collected as a core data set (26)

Category	Data to be collected
Demographic and socioeconomic factors	Patient identifier, date of birth, sex
Clinical characteristics	Tumour group, subgroup, and histology. Date when diagnosis, recurrence and metastasis established.
Genomic elements	Dates and types of testing done historically, and the reports associated with those tests. Date of tumour biopsy with flagging if metastatic or radiated. Patient's DNA not from tumour biopsy (e.g., blood sample) for comparison. Sequencing reports with information on mutations, whether findings are actionable or informative (e.g., mutations identified as VUS). If germline mutations identified, type of sequencing performed. Dates and costs of consultation, test sample acquisition and preparation, sequencing, bioinformatics, validation, interpretation, counselling and number of counselling visits.
Cancer treatment	Whether treatment is systemic, surgical, or radiotherapeutic. Information regarding each treatment modality, e.g., which surgery or which drug. Date of surgery or treatment start, site, intent of treatment (curative or palliative). Whether treatment was initiated pre- or post-sequencing and guided by genomic profile. If genomics-informed treatment not given when relevant, give reason why.
Patient outcomes	One preference-based outcome measure (e.g., EQ-5D or EORTC QLQ C30), date of death, clinically relevant secondary endpoints, date of disease progression, clinician assessed best response on genomics-informed and usual care, and costs of cascade testing and interventions.
Resource utilization	Types and dates of hospitalisations, physician visits, imaging, nongenomic laboratory tests and noncancer prescription drugs. Preferably pre and post NGS. Costs of drugs, tests, visits, imaging etc.

VUS: variant of unknown significance, EQ-5D: euroqol 5-dimensions, EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality-of-life Core Questionnaire, NGS: Next Generation Sequencing

The role of real-world evidence and potential future increase in dependency for reimbursement decisions highlight that improvements to the health care infrastructure may be needed for systematic and appropriate data collection. This includes both the type of data and how it is collected in practice. Real-world evidence can be used to generate a synthesised control group for instances when no RCT is available. The authors discuss which method is better (e.g., propensity score matching) and problematise around influences to turn to machine learning algorithms (28).

4.5 Future

Key findings

- Complex algorithms will likely be essential in precision medicine going forward.
- Health-apps are expected to complement data collected in clinical trials.
- Omics-based biomarkers will have an increased relevance.
- Real-world data follow-up will become increasingly important to show effectiveness in small subpopulations with structured recording of key data.

Three areas where future development would likely be significant were identified: complex algorithms, health apps, and omics-based biomarkers. In summary this implies that the authors expect precision medicine to be data driven to a greater extent than today and that this data will be collected both through different omics (e.g., genomics, proteomics etc) and via apps on smartphones or other devices (27).

It is noted in the literature that prospective economic evaluations may be required to run in parallel with clinical trials where test costs and test sensitivity/specificity are considered. Another concern for the future is the management and storage of large quantities of data. To illustrate a comprehensive overview of the patient, e.g., in terms of risk profile or eligibility for trial enrolment, the treating physician will need access to everything from electronic health records to clinical trial data and data collected from health apps or wearable devices. These data will also facilitate better long-term follow-up than e.g., prospective trial data collection (28).

5. Considerations not raised in the review

In this section additional considerations relevant to economic evaluation that were not identified in the review are discussed.

5.1 Current modelling methods are likely sufficient to handle the challenges arising from precision medicine

Precision medicine comes with challenges in that treatments and diagnostics must demonstrate efficacy, safety, and cost-effectiveness. These requirements are already put on health technologies and therefore not necessarily unique to precision medicine. Traditionally, pharmaceuticals have been evaluated both in clinical trials (Phase 1 all the way to Phase 4) with clear intervention and control (placebo in many cases) groups. The result of this is that methods employed for evidence generation are tailored to these types of data. The (economic) modelling methods can therefore be distinguished from the evidence generation methods. For example, a Markov chain that can accommodate all the various sequences of where a test comes into a care pathway can have an exponentially growing number of required states, making it suboptimal for that case (given that the decision problem requires it, see Section 5.5). Complex pathways and time dependent risks, et cetera, can be handled by employing modelling methods that are more flexible than a Markov model.

As noted in Section 4.3, the traditional Markov model may underperform for certain types of decision problems and settings, the various methods available to employ in economic evaluations will likely be able to cope well with the different characteristics of precision medicine. For example, discrete event models or micro simulation models are excellent methods with great flexibility for timing, risks, and other time dependent factors to be accounted for satisfactorily. The paradoxical reality of this is that when employing more sophisticated modelling approaches, the necessity of good data and quantity of data increases. This, in turn, implies that there is currently no real need to develop new methods for economic modelling. Instead, the challenges lie in the evidence generation in terms of efficacy and safety.

5.1.1 Time to take a step back?

In this review, several points regarding the treatment pathway complexity, sequencing of tests and treatments are raised. At the same time, concerns are highlighted about the availability of, or unavailability of, data to inform these factors to be incorporated into health economic models. The proposed solutions to handling the complexity of precision medicine in terms of health economic modelling is thus to 1) increase the model complexity in terms of how the care pathways are dynamic and 2) adopt more advanced modelling methods such as micro simulation and discrete event simulation.

The problem that arises from this is that there is scarce data on what the comparator alternative is. And as also mentioned, the place for the intervention in the care pathway. Complex microsimulation models or discrete event simulation models often have an appetite for a lot of data to produce reliable results.

Perhaps the solution to modelling in precision medicine, before the widespread introduction of big data and complex AI-algorithms, is to take a step back. To not worry about the complexity of the care pathway in the economic models but instead make simpler models that use as much of the data available as possible. And then instead be transparent about the uncertainty of

cost-effectiveness estimates generated by the models and focus rationale in HTA-decisions on the unmet needs. And then, using prospective real-world data collection and real-world evidence synthesis, develop more and more complex models as more data is accrued after introduction into real world settings.

5.2 Testing

Stratification of patients in health care delivery to identify candidates for e.g., novel targeted therapies or inclusion in screening programmes is often done using various tests (36, 37). These tests are undertaken to access and generate information. The tests can be diagnostic, treatment guiding, or predictive in nature. The purpose of testing can potentially influence the relevance of the test to the decision problem being evaluated. A diagnostic test is performed to set (or rule out) a diagnosis.

When patients are stratified based on different tests performed in sequence, providing precise therapies are more dependent on the preciseness of the test results. In essence, there is a trade-off or cut-off where tests need to be precise enough (i.e., sensitivity and specificity must be greater than x) for it, on average, to be cost-effective to deploy tests to stratify patients and deliver targeted therapies.

5.2.1 Treatment-guiding test

Treatment-guiding tests are performed to determine the most appropriate treatment for an individual based on e.g., genetic factors such as ALK rearrangements in non-small cell lung cancer (38). When treatment guiding tests are necessary to initiate targeted treatment, it is imperative to provide robust rationale as to why the costs associated with the test are included or excluded from the analysis. Also, it is likely necessary to describe the population in which initial testing occurs. For instance, has the population been stratified previously? If yes, this will likely need to be clearly stated. If the prior stratification is not part of routine care, it is advisable to consider including also this step in the analysis.

5.2.2 Predictive test

Predictive tests are performed to estimate e.g., the lifetime risk of cancer or risk of cardiovascular disease (30-32, 39, 40). Often, data collected from predictive tests (e.g., for hereditary genetic mutations) carries with it more information than the intended testing sought to retrieve. For example, if testing for BRCA1 in a person with (or without) breast cancer comes back positive for an hereditary variant, only the risk of breast cancer (and sometimes ovarian cancer) is traditionally included in economic evaluations (41).

This, despite that hereditary variants of e.g., BRCA1 also increase the risk of other diseases such as pancreatic cancer and Fanconi's anaemia (42). Typically, incidental findings are not considered in an economic analysis of a test. However, the risk profile of a hereditary variant cannot be considered incidental and, as such, the information retrieved is simply ignored. Although the clinical relevance of this is unclear, for a cost-effectiveness approach it will likely need to be considered going forward. If additional risks are attributed to the variant, a rationale will likely be necessary as to why, or why not, the complete risk profile is considered in the analysis.

Testing guidelines may reduce the effectiveness of tests (e.g., when guidelines for testing are too restrictive). Ethical considerations in the testing guidelines may also impact their

effectiveness, e.g., when the health care provider is not able to contact first degree relatives of persons with confirmed hereditary, pathogenic, variants in their genome.

Predictive testing is at its essence a screening procedure where tests are performed to identify persons with e.g., risk of disease. In principle, screening interventions require that there is an effective treatment and/or preventive intervention available for those who are identified.

In the case of pathogenic hereditary genomic variants with risk of developing e.g., cancer, it may be cost-effective to offer surveillance programmes to those who are confirmed carriers. However, the threshold regarding risk for, and the severity of, the attributed condition will likely impact the cost-effectiveness of such interventions. There are currently no clear guidelines on when being a carrier of a pathogenic risk variant would prompt resources to be allocated. Perhaps in the future, persons with a high enough risk score would be considered "unwell" despite e.g., not having developed a tumour.

5.3 Storage of test information

The value of testing is determined by the usefulness of the information given by the test. The use of the information can be either direct (guide treatment, make diagnosis, or estimate risk of disease and subsequent enrolment into screening programmes) or indirect (build biobanks, research/clinical trials, storage for future re-assessment of e.g., variants of unknown significance and compatibility with partner for conception if autosomal recessive mutations identified).

Depending on whether use of information is then direct or indirect, the necessity of storing the information varies. If the test is performed to make a diagnosis, the information is not clinically relevant to store for the tested patient after the diagnosis is made and can be discarded. However, despite the direct value of the information being realised, an indirect value of e.g., use in research is still potentially waiting to be realised. Then the question arises whether it would be both cost-effective and ethically appropriate to store the information. We will leave the ethical aspects out of this report and focus on the relevance for efficient and effective resource allocation in the health care system.

As the cost of genetic tests is dropping and the amount of information generated in relation to the cost is increasing, there is a potential break-even point where storing information for the future is more costly than simply performing a new test when the information is needed again. Storing a human genome requires a lot of data storage space. The cost of maintaining servers with adequate encryption and security measures, factoring in physical storage of servers and the electricity required, is likely substantial and will increase exponentially. Eventually additional data (especially for those who have died) will not add to the knowledge base and needs to be discarded, these processes will also have an associated cost.

It is likely not necessary for secondary use of genomic data to store entire genomes. Instead, a number of, e.g., binary questions that can be answered "yes or no", or by selecting specific segments of the information of interest that should be stored. Questions such as "is this mutation present?" or "this phenotype is present and these variations from the reference genome are suspected to be the cause" would reduce the amount of data needed to be stored compared to the entirety of the genome.

These costs could potentially be relevant to include in an economic analysis where large quantities of data will require storage and management as a result of introducing a new technology.

5.3.1 Re-assessment of variants of unknown significance

As the understanding of the human genome grows, it may be necessary or appropriate to re-assess previous genetic test results. A variant of unknown significance (VUS) is a term used in genomics to describe a genetic variation that has been detected in a person's DNA, but its effect on health or disease is not yet clear.

In genetics, a variant refers to a difference in the DNA sequence from what is typical or normal. Some variations are well understood and are known to cause specific diseases or traits. For most genetic variants, there is no known impact on health. These are referred to as VUS.

The interpretation of VUS is complex and often requires further investigation. This may involve additional laboratory testing, analysis of family history and medical records, and comparison to other known variants. In some cases, large-scale genetic studies or new research findings may provide more information about the impact of a VUS on health.

It's important to note that the presence of a VUS does not necessarily mean that a person has or will develop a disease. However, it also does not guarantee that a person is healthy. VUS are still an area of active research, and as more is learned about genetics, the understanding of VUS may change. This, in turn, may influence cost-effectiveness estimates. Should the analysis include handling of VUS? Should the model explicitly consider what the outcomes are for patients who are carriers of VUS? This will be necessary for analysts to consider when setting up their decision problem and subsequent analysis.

5.4 Data from clinical trials

In addition to the key data set described by Pollard et al (26) (See Section 4.4), the authors of this report would like to add that e.g., **in-trial follow-up** of **patient- and physician adherence** to both testing and treatment regimens will likely be necessary to identify differences in effectiveness and patient outcomes based on adherence to precision medicine treatment regiments and defined care pathways as this may impact the cost-effectiveness of precision medicine interventions. Potentially it may also act as a pseudo-control in case the trial does not have an explicit control-arm. If adherence is sub-par, analysis of efficacy in patients with perfect adherence compared to patients with limited adherence could act as an early indicator for treatment efficacy. This data will be an important addition to health economic analyses where these factors are considered in e.g., economic models.

5.5 Decision problem as an indicator for complexity

Many of the challenges discussed in this report are dependent on how the decision problem is formulated. For example, if the purpose of the economic evaluation is to assess the cost-effectiveness of a novel targeted therapy where a competitor therapy already exists and no additional test/diagnostics are necessary, the diagnostic pathway can be left out of the analysis. As patients are already identified with current standard of care , it should not influence the cost-effectiveness of the new intervention. However, the challenges with small patient numbers and uncertainty around efficacy data remain and needs to be addressed accordingly.

If the novel intervention require new diagnostics, complexity arises from both the opportunity cost of allocating staff to operating e.g., new machinery and interpreting test outcomes, and from the necessity of establishing the best procedure for identification of eligible patients, the prevalence of the relevant marker, and the required sensitivity and specificity of the test.

If the evaluation is of a new diagnostic technology in isolation, where a current test is already available (i.e., a novel test that is 'better' than the current), all the downstream effects of using the new diagnostic technology should be considered. Here arises potential issues with efficacy data available for treatments where the current, less effective, test has been used. As the sensitivity and specificity of the two tests will then determine how many patients that are incorrectly diagnosed as ineligible or eligible for subsequent treatment options. This implies that the treatment outcomes may be biased by the diagnostic test used to identify patients treated previously. Here, real-world data collection may be beneficial for both the efficacy estimate for the subsequent treatment and the diagnostic test.

5.6 Is more always better? Additional information and health related quality of life

One aspect of diagnostic testing, especially in oncology, is the impact on a person's HRQoL from additional information on their risk-profile for developing disease or likelihood of being cured from a current disease. For instance, a patient may find out that his/her tumour is due to a specific genetic variation for which there is, or is not, a targeted therapy.

Therefore, it will be of high importance to determine these effects and to have a clear understanding of when and where they should be included in an analysis. For example, when including cascade testing of patients with known germline variants, the relative of the index patient may have a negative impact on their HRQoL from being made aware of potentially being a carrier of the same variant. And subsequently the outcome of the test may influence their HRQoL again. Perhaps a spike in HRQoL is plausible when a person who has been informed of being at high risk of being a carrier of a germline variant undergoes testing and is confirmed to not be a carrier of said variant. It is also plausible that such a test result may actually boost your HRQoL (for a short period at least) beyond your HRQoL prior to obtaining the information regarding your relative. There are plenty of other plausible cases where information may influence a person's HRQoL that may be considered when conducting economic evaluation of precision medicine.

6. Conclusion

The individualisation of care in precision medicine is similar to stratification of people with cancer based on selected factors. A consequence is that a previously common disease condition, e.g., breast cancer, becomes a broader set of unique and less common conditions with similar traits but different treatment pathways. Identifying these pathways and considering them in economic evaluations will be both important and challenging.

Precision medicine pose challenges to HTA and economic evaluations in health care. These challenges are not necessarily new but the way to address them may differ from current standards. The complexity of decision problems, subsequent analyses, reimbursement and resource allocation decisions must be addressed by manufacturers of medical technologies, health care systems, and researchers alike.

Economic evaluation in the era of precision medicine will need to manage discrepancies regarding the level of information available and sometimes required to make informed decisions. Economic evaluations may thus be pragmatic in their design. As precision medicine become routine care and precision diagnostics become more prevalently used, the information available regarding e.g., patient's genomic profile will increase. This will lead to issues of unbalanced level of information regarding patient characteristics between data collected in e.g., trials investigating novel interventions and data collected as part of standard of care diminishing over time. Another potentially important aspect of the accruement of increasing volumes of data will be how to store it, who will store it, and how to ensure that unauthorised access is limited. This overview did not explicitly consider these challenges and their implications for economic evaluation of precision medicine. However, going forward the issue of data volumes and data storage and the implications this may have for the cost-effectiveness of e.g., novel diagnostic methods may be of interest to investigate further.

Traditionally statistically significant efficacy estimates from large randomised controlled trials have been the foundation of HTA and economic evaluation. In precision medicine, small patient groups may lead to less statistical precision of estimates. This can however be mitigated by utilizing health economic modelling methods where the point estimates and their attributed uncertainty can be considered through sensitivity analyses.

In summary, precision medicine entails tailoring therapies to each patient based on their specific characteristics. This stratification will lead to a lower level of evidence on clinical efficacy and clinical effectiveness, and thus impact on estimates of cost-effectiveness compared to standard of care. To improve the quality of evidence supporting these three metrics, investments in clinical research, follow-up, registries, and HTA capabilities are needed. The key is that the balance between need of robust evidence and access to novel precision therapies is not shifted towards either side. In other words, we should not overinvest in new and promising but unproven technologies; at the same time, we should not underinvest in the framework and capabilities necessary to generate evidence of long-term cost-effectiveness of these technologies.

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