HEcoPerMed

Health Economics for Personalised Medicine

Deliverable

1.1

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Authors:	Heleen Vellekoop, Simone Huygens, Matthijs Versteegh, Maureen Rutten-van Mölken
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SUMMARY

Personalised medicine (PM) refers to treatments that take into account differences between individual patients rather than group means, making use of technological innovations that enable detailed profiling. Health economic modelling refers to an analytic endeavour that identifies costs and benefits of treatments, which is relevant to guide decision-making. As increasingly many PM interventions are coming onto the market, several challenges for the health economic modelling of PM interventions have been identified. The aim of Work Package 1 (WP1) of the HEcoPerMed project is to provide a comprehensive overview of these challenges, as well as suggestions on how to address them in health economic models. In this deliverable we describe the result of the work in WP1, as well as the methods deployed. The main result is guidance targeted toward modellers of health economic models and those evaluating health economic models ('end-users'). An overview of the main contents of this report follows below.

Defining personalised medicine in HEcoPerMed (Ch. 3)

'Personalised medicine' may be somewhat of a confusing term as arguably all healthcare is personalised to some extent, and indeed several definitions of the term are in use. Within this document, PM is defined as *a medical model that bases therapeutic choice on the result of gene profiling or big data analytics or aims to correct pathogenic gene mutations*. Three main PM categories are identified: (i) interventions guided by gene profiling, (ii) genetic modification therapies, and (iii) interventions guided by big data analytics.

Methods (Ch. 4)

A mixed methods approach was used to gather input for the guidance. Firstly, a scoping review was performed (section 4.2). After this, a systematic literature review of economic evaluations of personalised medicine was conducted. 3,572 studies were title/abstract screened, out of which data was extracted for 196 (section 4.3). Eighteen semi-structured interviews were held with modelling experts and end-users (section 4.4) of health economic models.

The scoping review consisted of a targeted literature search, in which existing literature describing challenges in the modelling of PM was identified. A list of modelling challenges was extracted from the identified studies and, after discussions between the authors and with the HEcoPerMed consortium partners, categorised into main topics. The overview of main topics was subsequently used to inform the interview templates. It was also used during the data extraction phase of the systematic literature review. The modelling methods used in the identified studies were compared against the overview of main topics; whenever the methods addressed any of the topics, they were recorded.

The results of the scoping review, the systematic literature review, and the expert interviews provided input into discussions between the authors. Deliberations were continued until consensus between the authors was reached regarding the structure and content of the guidance. Subsequently, the guidance was discussed with the other partners in the HEcoPerMed consortium and iteratively adapted.

Results (Ch. 5)

The papers identified in the scoping review are reported and a brief description of their contents is provided (section 5.1). Additionally, the main topics extracted from the papers are listed, including a brief explanation for each topic. The modelling methods identified in the systematic literature review are described for each main topic (section 5.2). Responses by the interview candidates were also categorised according to the main topics and are presented in summarised and paraphrased form (sections 5.3 and 5.4). Section 5.5 contains the guidance for health economic modellers and end-users, consisting of an in-depth topic-by-topic description and a set of 28 accompanying recommendations. Examples of good modelling practices are also included.

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Shown below are an overview of the topics, including a short description (table 3 in the document), and an overview of the accompanying recommendations (table 9 in the document).

Table A. Topics relevant in modelling PM interventions identified in the scoping review.

Topics	Short description
Modelling test-treatment combinations	The combination of a test and subsequent treatment is key in personalised medicine. The economic evaluation of these test-treatment combinations raises several possible complexities, including: - Multiple possible positions of the test in the clinical pathway, as it may be applied at different time points and/or in varying combinations with other tests - (Downstream) consequences of introducing a new test into clinical practice, including for those with a negative test result - Test performance (sensitivity, specificity, positive predictive value, negative predictive value) may be dependent on the patient population and/or correlated with the outcomes of previous tests - Large variation in cost of testing - During waiting times for test results or start of treatment patients may be at risk of disease progression or mortality.
Effectiveness data from non-randomised (controlled) studies	The more stratification takes place due to PM, the smaller patient subgroups become. This complicates evidence generation in the traditional RCT manner. Therefore, alternative trial designs are being developed, such as umbrella, basket and adaptive designs. There might be an increased need for the use of observational data (e.g. (historical) cohort studies and registry data).
Extrapolating outcomes for interventions aiming to cure	At the time of health economic evaluation, the effectiveness data is often too immature to have observed cures as a result of interventions that are aiming to cure. This results in uncertainty about the extrapolation of long-term outcomes of these interventions, including the duration of treatment effect.
Discounting	In PM, there may be large upfront costs, while the benefits stretch far into the future. Some argued that this may ask for a deviation from standard discount rates.

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Values beyond the current patient	It could be argued that a societal perspective is more appropriate to use in the context of PM, especially in cases of potentially life-saving treatments (such as gene therapies) that can cause a lifelong reduction in productivity loss and use of informal care services. A genetic test may identify a condition that is the result of a germline mutation, which means that relatives might also be at risk and should receive testing through a cascade screening programme.
Values beyond the QALY	Some have argued that the QALY insufficiently captures the full value interventions may have. The ISPOR Value Assessment Framework Special Task Force identified a range of 'additional' values beyond the QALY (6), some of which might be especially relevant in PM.
Equity	Biomarkers used for stratification might correlate with equity-relevant variables, such as ethnicity and socioeconomic status. Also, patients in remote areas or lower socioeconomic groups may have less access to advanced testing methods.
Uncertainty analysis	Modelling of PM interventions may come with a great amount of uncertainty, for several reasons mentioned in the previous topics in this table. Therefore, uncertainty analysis is even more important when modelling a PM intervention.
Managed entry agreements	PM interventions may come with a hefty price tag, as well as significant uncertainty about their clinical effectiveness. In response to this, healthcare payers may opt to use managed entry agreements (MEAs) to share the risks with the manufacturers. The parameters of these MEA may be included in the health economic model.
Modelling imperfect implementation	A health economic model can assume perfect implementation (i.e. the intended use of the intervention) or include an estimate of suboptimal implementation. In the latter, patients' uptake of testing and treatment adherence and clinicians' adherence to protocols and guidelines may be considered in health economic evaluations.

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Table B. Checklist of recommendations for good health economic modelling practice in PM.

Topic	Subtopic		Recommendation
Modelling test-treatment combinations	Positioning	1	Consider if the modelled position of the test in the clinical pathway is in line with clinical practice.
	Consequences of testing	2	If a test is not part of routine care, ensure that the (downstream) costs and benefits of testing for both individuals who test positive and individuals who test negative are included in the model.
	Test performance	3	Ensure that the data on the test performance are the latest available and obtained in a population that is in line with the modelled population.
		4	When multiple tests inform treatment decisions, the interdependence between tests should be considered.
		5	Clearly define the cut-off values that are used to define the different outcomes (e.g. positive/negative, high/medium/low risk) of a test.
	Practice variation	6	If there is a risk of disease progression or mortality during waiting periods, these waiting periods should be explicitly incorporated into the model.
	Waiting times	7	Consider all costs associated with tests, including costs of testing in patients with negative test-results and downstream costs resulting from the test.
Effectiveness data from non-randomised (controlled) studies	Incomplete or absent RCT data	8	Where possible, use effectiveness data from trials with two active comparator arms or data from (network) meta-analysis, rather than observational data collected under conditional reimbursement programmes. If such data is not available, perform value of information analysis and/or sensitivity analysis that can be used to inform the design of any future trials.
	Historical cohorts	9	When effectiveness is estimated using historical cohorts, account for the trend in efficacy of the comparator over time, in order to correctly attribute differences in efficacy to the treatment.

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	Unknown mutation status in comparator group	10	When using a historical cohort to estimate the effectiveness of a treatment for a patient population with a specific gene mutation, obtain data on the distribution of the gene mutation of interest in the historical cohort, as well as data on the prognostic value of the gene mutation.
Extrapolating outcomes for interventions aiming to cure	Cures in health economic modelling	11	When modelling the outcomes for interventions aiming to cure, the cure assumption and the choice of survival model used for extrapolation beyond the observed trial period should not only be informed by statistical fit of the model to the observed data, but also by expert opinion.
	Excess mortality	12	When modelling the survival curves for interventions aiming to cure, apply excess mortality among long-term survivors, rather than assuming these patients are fully cured by applying age- and gender-specific general population mortality.
Expert opinion		13	When expert opinion is used to estimate quantitative model parameters, use a formal method to synthesise the opinions of the experts into a probability distribution.
Discounting		14	PM interventions should be subject to the same discount rates as other interventions within the same jurisdiction.
		15	For interventions with large upfront costs and benefits that stretch into the future, the impact of differential and/or hyperbolic discounting should be investigated in sensitivity analyses.
		16	When using differential discounting for models that include future cohorts, the discount year should be mentioned for every modelled cohort.
Values beyond the current patient	Perspective	17	An economic evaluation of PM should be conducted from the same perspective as other interventions within the same jurisdiction.
	Caregiver burden	18	For jurisdictions that employ a societal perspective, caregiver burden can be included on the cost-side of the economic evaluation.
		19	Incremental cost-effectiveness ratios with and without caregiver burden should be presented separately.
	Caregiver burden	20	For both a societal and a healthcare perspective, the costs and benefits of conducting tests in others than the index patient should be included.

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Values beyond the QALY		21	Do not include additional elements of value in the base-case analysis. When additional elements of value are included in scenario analyses, ensure possible elements of harm have been equally considered and are included in the analysis if relevant.
Equity		22	Consider whether aspects of the intervention under consideration or of the assumptions made in the health economic model are likely to have equity consequences.
Uncertainty analysis		23	When using patient-level simulation models, ensure that stochastic uncertainty as a source of difference between intervention and control group is eliminated.
		24	Acknowledge the presence of structural uncertainty and plot the ICERs of scenarios that have an important impact on the results in the cost-effectiveness plane.
Modelling imperfect implementation	Patients' uptake of testing	25	Patients' uptake of testing should be included in economic evaluations for decision-makers that allow evaluations assuming suboptimal implementation.
	Patients' treatment adherence	26	Patient adherence should be included in economic evaluations for decision-makers that allow evaluations assuming suboptimal implementation. Whether patient adherence requires a separate input parameter depends on the effectiveness evidence.
	Clinicians' adherence to protocol and guidelines	27	Clinician adherence should be included in economic evaluations for decision-makers that allow evaluations assuming sub-optimal implementation. Whether clinician adherence requires a separate input parameter depends on the effectiveness evidence.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ADA-SCID	Adenosine deaminase deficiency–severe combined immunodeficiency
AGREEDT	AliGnment in the Reporting of Economic Evaluations of Diagnostic Tests and biomarkers
BRCA	Breast cancer
CAR	Chimeric antigen receptors
CAR-T	Chimeric antigen receptor T cell
CHD	Coronary heart disease
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CRPC	Colorectal cancer and polyposis
CT	Computed tomography
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPCAM	Epithelial cell adhesion molecule
ERG	Evidence review group
EUnetHTA	European Network for Health Technology Assessment
FDA	US Food and Drug Administration
FISH	Fluorescence in situ hybridisation
GPAP	Gefitinib Patient Assistance Program
HEcoPerMed	Health Economics for Personalised Medicine
HER2	Human epidermal growth factor receptor 2
HSCT	Haematopoietic stem cell transplant
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
INMB	Incremental net monetary benefit
ISPOR	The Professional Society for Health Economics and Outcomes Research
KM	Kaplan Meier
LY	Life years
MEA	Managed entry agreement
MS	Multiple sclerosis
MUD	Matched unrelated donor
NGS	Next-generation sequencing

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Abbreviation	Meaning
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophin receptor tyrosine kinase
OS	Overall survival
PM	Personalised medicine
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PSA	Probability sensitivity analysis
QALY	Quality adjusted life year
RCT	Randomized controlled trial
SCT	Stem cell transplant
SHELF	SHeffield ELicitation Framework
STA	Single technology assessment
UK	United Kingdom
US-ICER	Institute for Clinical and Economic Review in the United States
VoI	Value of information

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1 HOW THIS DELIVERABLE LINKS TO OTHER DELIVERABLES

Deliverable 1.1 of the HEcoPerMed project provides guidance on the health economic modelling of personalised medicine (PM). The guidance consists of:

- a (check)list with recommendations for the health economic modelling of PM;
- a discussion of the recommendations in the checklist, including examples from published cost-effectiveness models of PM.

The guidance was based on the following sources:

- a scoping review of the methodological literature on modelling in PM;
- a systematic review of the published and grey literature reporting model-based economic evaluations of PM;
- semi-structured interviews with experts of health economic modelling of PM;
- semi-structured interviews with end-users about their information needs for decision-making on pricing and reimbursement of PM
- discussion of draft versions of the guidance within the HEcoPerMed consortium.

The protocol for the systematic literature review was included in Deliverable 1.2 of HEcoPerMed.

Deliverable 1.1 feeds directly into Deliverable 2.2. In Work Package 2, which will culminate in Deliverable 2.2, the guidance will be applied by three partners in the HEcoPerMed consortium (Syreon Research Institute, University of Oxford, Erasmus University Rotterdam), who will each build a model for a PM intervention. In addition, Deliverable 1.1. will be discussed with modelling experts and end-users during Workshop 1. Based on both activities, the guidance will be iteratively adjusted when necessary.

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2 INTRODUCTION

Personalised medicine (PM) aims to focus on individual differences between patients rather than group means, making use of technological innovations that enable increasingly detailed profiling of individual patients. Amidst increasing pressure on healthcare budgets, PM may provide opportunities to allocate healthcare budgets more efficiently by offering expensive therapies (i.e. preventive, diagnostic, curative or monitoring interventions) only to patients that have a high likelihood to benefit from it.

Indeed, a commonly cited promise of PM is that unnecessary, ineffective or harmful treatments will be prevented by better targeting treatments, leading to cost savings and less adverse events.(1) While this promise is intuitively appealing, more evidence of PM reducing costs or improving cost-effectiveness is needed. Commercially marketed medical products, such as medicines, are often priced at the margin, following companies' analysis of 'what the market can bear'. This results in prices that are de-linked from the size of the benefits for patients, reducing the cost-effectiveness and societal affordability of the innovations. Therefore, there is a need for economic models that evaluate the cost-effectiveness of PM interventions.

However, the economic evaluation of PM interventions is not always straightforward, as several issues create challenges for the health economic modelling of PM. For example, a higher degree of stratification of patients leads to increasingly small subgroups of patients, which complicates evidence generation on effectiveness and leads to increased uncertainty due to limited data availability. The long-term effects of potentially curative PM interventions (e.g. gene therapies) have not been observed yet, resulting in uncertainty around the duration of the treatment effect of these therapies. There may be additional values of PM interventions beyond the quality adjusted life year (QALY) that are worth considering, such as the 'value of knowing'.

This report provides an overview of these and many other challenges that may occur in the economic modelling of PM. Several of the challenges that will be discussed have been raised in other contexts as well – e.g. the modelling of rare diseases, preventive interventions, treatments for infectious diseases, and diagnostic tests. Hence, a change in health economic modelling methods specifically for PM may not be warranted. Nonetheless, the myriad of challenges that converge in the evaluation of PM, call for a comprehensive overview and discussion of the challenges.

In this deliverable, we report on the results from Work Package 1, which aimed to develop guidance on health economic modelling of PM, by means of a scoping review, a systematic literature review and interviews with modellers and end-users.

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3 DEFINING PERSONALISED MEDICINE IN HECOPERMED

While there are numerous definitions of personalised medicine (PM), the European Council Conclusion on PM for patients (2015/C 421/03) defined PM as *"a medical model using characterisation of individuals' phenotypes and genotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention"*. We took this definition as the starting point of the HEcoPerMed project. However, the definition is broad, and one may argue that virtually all medical interventions could be labelled PM. Aside from the difficulties involved in defining a literature search strategy that would match this definition, such a search would likely identify thousands of economic evaluations published over the last decades. In order to ensure our work would be focused and meaningful, we opted to narrow down the definition of PM – as outlined below.

Similar to the European Council Conclusion, which speaks of "characterisation of individuals' phenotypes and genotypes" and "tailoring the right therapeutic strategy", we assume PM is described by a *stratification* phase and a *therapeutic strategy* phase. In the stratification phase, information is gathered in order to characterise individuals and stratify them correspondingly. In the therapeutic strategy phase, patients are treated according to this stratification (note that treatment is not necessarily curative; it may be preventive, palliative or 'do nothing'). Throughout the rest of this document, we will indicate the combination of stratification and therapeutic choice as *test-treatment combination*.

While medical decision-making tends to be primarily based on symptoms and biological information (i.e. measurable indicators of the body, including e.g. physiological and molecular biomarkers and patient characteristics such as age and sex), numerous other factors are generally considered – including patient preferences and capabilities. In our interpretation of PM, we focus on medical interventions based on biological information, in line with a previous systematic review investigating the use of the 'personalised medicine' concept in the academic literature.(2) To further narrow the scope of our analysis, while adhering to the concept of 'personalisation', we concentrate on interventions based on the biological information that enables distinguishing one individual from the next: information on the genotype. This includes interventions that use gene data during the stratification phase, as well as interventions aiming to modify genes during the therapeutic choice phase. As we acknowledge that highly personalised treatments may be achieved by combining several types of information (beyond genotype data) in a sophisticated manner, we also include interventions that are informed by big data analytics.

The definition of PM used throughout this document is: *Personalised medicine is a medical model that bases therapeutic choice on the result of gene profiling or big data analytics or aims to correct pathogenic gene mutations.*

Within this definition, we identified three main categories of PM interventions.

1. Interventions guided by profiling of gene mutations
    a. Profiling germline mutations

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b. Profiling somatic mutations

2. Genetic modification therapies

3. Interventions guided by big data analytics

Interventions guided by profiling of gene mutations

While ‘genetic testing’ and ‘genomic testing’ are used interchangeably by some, others use ‘genetic testing’ to denote the profiling of hereditary gene mutations, and ‘genomic testing’ to describe the profiling of mutations that have occurred in tumours. To avoid misunderstandings, we instead use the descriptions ‘germline’ and ‘somatic’. Germline mutations are hereditary and present in virtually every cell in the body because they were present in the parents’ reproductive, whereas somatic mutations occur later in life and are present only in certain cells. The latter can generally not be passed on to offspring.

Note that the profiling of gene mutations does not always require sequencing of the genes themselves. Profiling of gene mutations may be done by investigating messenger RNA (sometimes called ‘gene expression profiling’ or ‘transcriptomics’) or specific proteins (‘proteomics’).

Genetic modification therapies

The category ‘Genetic modification therapies’ captures interventions aiming to correct pathogenic gene mutations using genetic engineering methods. Currently, the most common form involves the delivery of healthy copies of a specific gene to relevant cells using a (viral) vector. In the future, therapies in which part of a patient’s DNA is removed or altered (i.e. gene editing) may become available.

Interventions guided by big data analytics

While ‘big data’ is somewhat of an elusive concept, it is generally associated with: very large amounts of data; the combination of different types of data; and highly advanced methods for data processing, such as machine learning.

Figure 1 provides a draft version of our PM framework, which illustrates our interpretation of PM graphically. With this framework, we aim to acknowledge that most healthcare is personalised to some extent (and could be called ‘personalised medicine’, depending on the perspective one takes), while also indicating the subset of healthcare that we decided to focus on. The ‘Information gathering’ box shows that there are different types of parameters that may be used to stratify patients, and that these parameters have a varying differentiation power (i.e. ability to distinguish individual patients from each other). As mentioned above, in principle only biological parameters with the highest differentiation power (i.e. genotype data) are included in our definition of PM. Other types of parameters and biological parameters with less differentiation power are only included if:

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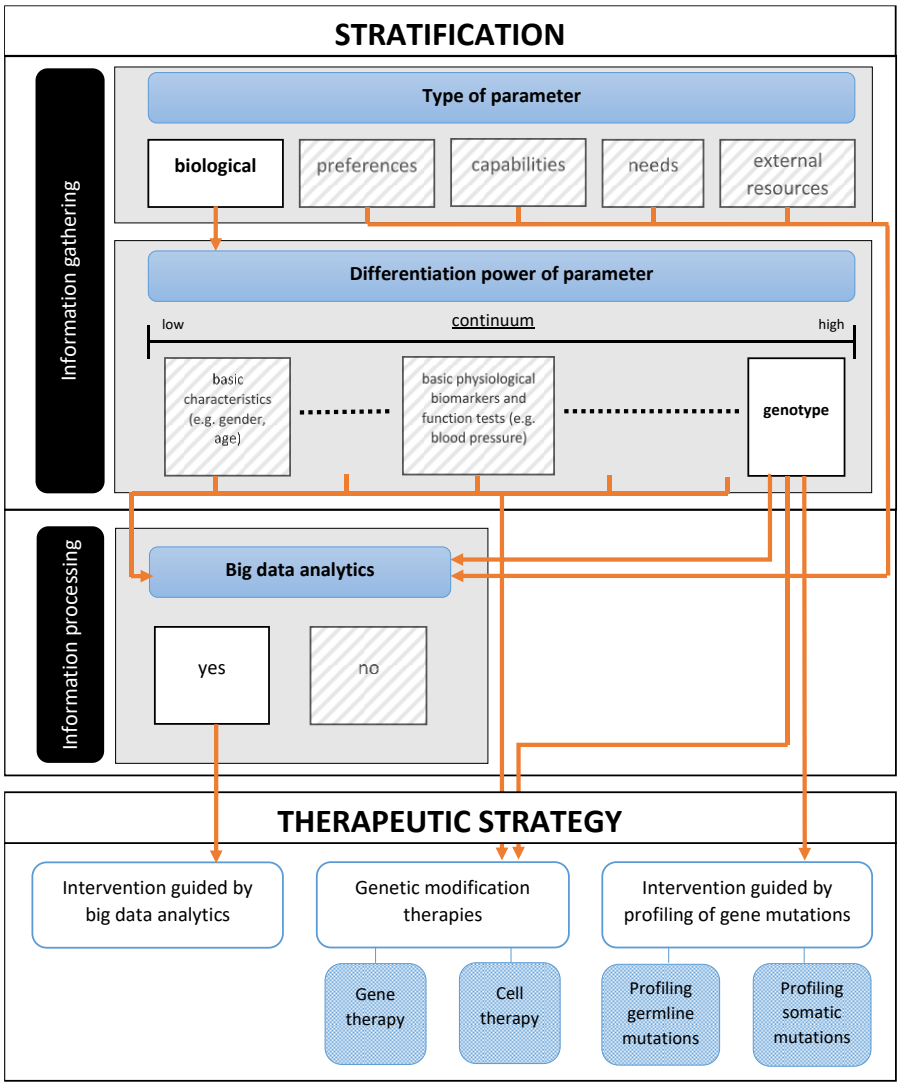
(i) They are combined using big data analytics

(ii) They are used to inform a treatment that affects the genotype

The 'Therapeutic strategy' box outlines the three main categories we identified within PM. 'Interventions guided by the profiling of gene mutations' are, by definition, informed by genotype profiling during the 'Information gathering' stage, hence the straight arrow from *genotype* to *Intervention guided by profiling of gene mutations*. The decision to provide a gene therapy to patients might be based on genotype profiling or on other biomarkers (or a combination of both), hence why two arrows lead into *Gene therapy*: one from *genotype*, one from the remaining biological parameters. Three arrows lead into *Big data analytics* as big data analytics may be informed by genotype and/or other biological parameters and/or non-biological parameters. This framework may be iteratively adapted during later stages of the HEcoPerMed project.

Figure 1. Draft PM framework



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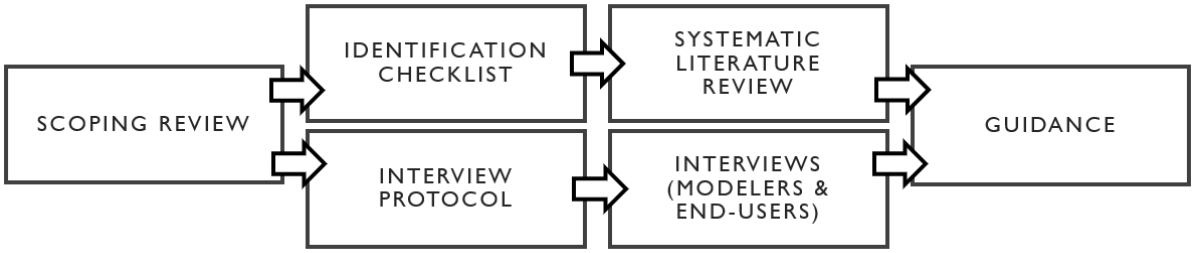
4 METHODS

4.1 Overview of methods to develop the guidance

When designing the guidance, we decided upfront that it would not include generic items that are common to every health economic evaluation, as these are extensively covered by existing checklists and frameworks. Instead the guidance focuses on those items that warrant specific attention in PM and provides an add-on to general guidelines regarding issues that are especially important when evaluating PM interventions. Hence, we did not cover issues like the specification of the decision problem, the specification of the time horizon, the currency and year of the unit costs etc.in the guidance. The target population of the guidance are researchers undertaking health economic evaluations for PM interventions, but also those reviewing the results of such economic evaluations (e.g. to make or advice on reimbursement decisions). An overview of the methods we used to develop the guidance is provided in Figure 2.

Figure 2. Overview of methods to develop the guidance



At the start of the project, we performed a scoping review of the methodological literature on modelling in PM to identify the challenges of health economic modelling of PM (section 4.2). Based on this scoping review, we developed an 'identification checklist', summarising the main challenges identified. We applied the 'identification checklist' to the PM evaluations that we found through a comprehensive systematic review of recent model-based economic evaluations published in scientific journals or submitted to Health Technology Assessment (HTA) bodies (section 4.3). We used the checklist to identify studies that used modelling methods to address the identified PM challenges.

Parallel to the systematic literature review, we held semi-structured interviews with health economic modellers and end-users of health economic models (i.e. those who use findings from HTA studies in decision-making) regarding the challenges summarised in the 'identification checklist' (sections 4.4 and 4.5).

Based on the information gathered in the scoping review, promising modelling methods identified in the systematic review, and information gathered through interviews with relevant experts and end-users, we developed guidance for good health economic modelling practice in PM. We summarised the guidance in a (check)list with recommendations for health economic modelling of PM.

We shared the draft version of the guidance with the partners in the HEcoPerMed consortium who provided general feedback during a telephone conference and written feedback on specific issues. We

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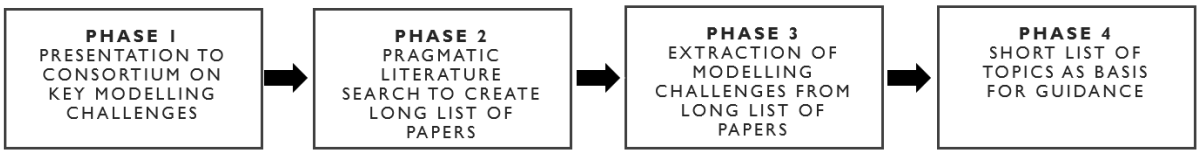
refined the guidance based on this feedback. Furthermore, we will further refine the guidance based on experience with the guidance in developing models for the three case studies in Work Package 2 and based on feedback from modelling experts and end-users gathered during Workshop 1.

4.2 Scoping review

For the scoping review, we used a mixed methods approach involving expertise of the consortium and a pragmatic literature search. The approach consisted of four phases as summarised in Figure 3.

Figure 3. Four phases in the scoping review



Phase 1 - In January 2019, we presented key challenges for the economic evaluation of PM as identified in several papers to the consortium.(1, 3-8)

Phase 2 - We conducted a pragmatic literature search to identify studies that either provide an overview of health economic modelling issues in PM or explore specific methodological challenges informed by suggestions for relevant papers by consortium members, snowballing through the reference list of the studies from phase 1 and targeted searches in Google Scholar.

Phase 1 and 2 resulted in an initial list of methodological papers.

Phase 3 - We extracted challenges for the economic evaluation of PM from this list of papers.

Phase 4 - Researchers HV, SH, MV and MR grouped the list of topics into a final topic set that informed both the data extraction of the systematic literature review (i.e. the 'identification checklist') and the topic list for the semi-structured interviews.

4.3 Systematic literature review

The systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (9) and registered in the International Prospective Register of Systematic Reviews (PROSPERO). The protocol for the systematic literature review was included in Deliverable 1.2. In the following, an updated summary of these methods is provided.

4.3.1 Search strategy

On 13th March 2019 the Embase, Medline Ovid, Web of Science and Google Scholar databases were searched using search terms describing model-based economic evaluations and PM. On 16th May 2019, an additional search was performed in the Centre for Reviews and Dissemination (CRD) Database, EconLit and the websites of the National Institute for Health and Care Excellence (NICE) and the Institute for Clinical and Economic Review in the United States (US-ICER). Search terms are provided in Appendix 1. De-duplication was performed using the method described by Bramer et al.(10)

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The search was limited to studies published in English in or after 2009. A 10-year time frame (2009-2019) was chosen because the fields of health economic modelling and PM both advance swiftly and studies may become outdated relatively quickly.

4.3.2 Study selection

The in- and exclusion criteria are illustrated in Figure 4. Studies were included if they reported model-based economic evaluations considering costs and health outcomes of PM interventions (according to our definition described in Chapter 3).
Studies were excluded if:

- the intervention was not assessed using a cost-effectiveness model;
- the intervention under consideration did not meet our definition of PM;
- the intervention did not exist yet (i.e. hypothetical or yet to be developed interventions);
- final outcomes (expressed as life years (LYs) or quality-adjusted life years (QALYs)) were not included in the model;
- the model did not extrapolate outcomes beyond the observed period or time horizon of the underlying clinical study.

Two independent reviewers (HV, SH, MV and/or MR) assessed whether the first 30% of studies (using alphabetical order) met the inclusion criteria based on title/abstract screening. After this, the results of the two reviewers were compared and discussed. If the difference in inclusion decisions was more than 5% of the assessed publications, another 10% of the articles was independently screened by both reviewers. Subsequently, a similar divergence assessment happened. If the discrepancy was more than 5% of the selected studies again, another 10% was screened in duplicate. If there was still more than 5% discrepancy after 50% of the total amount of studies was assessed, the entire title/abstract screening was done by two reviewers. A similar process was used for the full-text screening, though here the initial batch was 10%, to ensure comparison and discussion of the results between the two reviewers early in the process. In the case of disagreement, consensus was reached with the help of a third reviewer.

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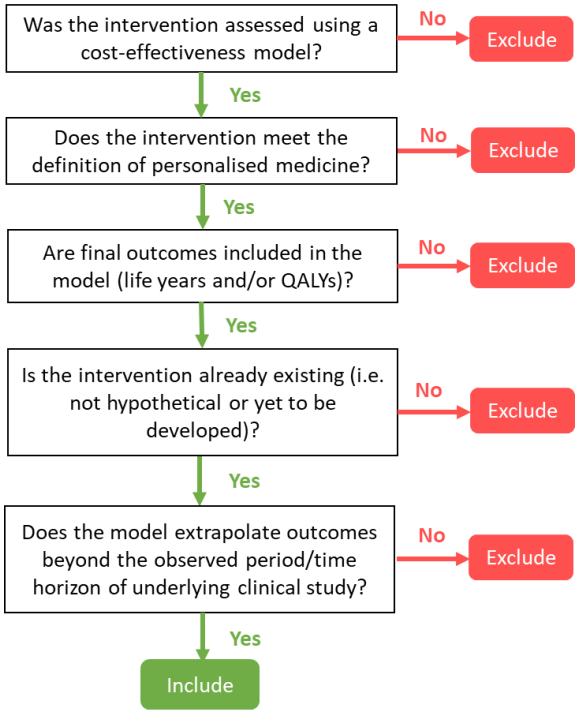
Figure 4. In- and exclusion criteria flowchart



4.3.3 Data extraction

After full-text screening, included studies were subdivided in the PM categories outlined in Chapter 3. Using the identification checklist reported in Chapter 5.1, studies that considered specific challenges in modelling PM were identified. The methods used to handle these challenges were summarised and examples of good practice were included in the guidance.

4.4 Interviews with modelling experts and end-users

Potential interview candidates were identified from our own network, the network of other consortium members, and authors of the papers identified in the scoping review. The potential interview candidates were invited for the interviews by email. The first interviews were held at the Annual European Conference of The Professional Society for Health Economics and Outcomes Research (ISPOR) in November 2019 in Copenhagen. The other interviews were held during telephone conferences with at least two of the Work Package 1 members.

Every interview started with a general introduction of the project, the goal of the interview, and our definition of PM. Then, the interview candidate was asked to share his or her experience with and the challenges they encountered in health economic modelling of PM. Subsequently, the topics identified in the scoping review were discussed in more detail. Every question was introduced with a short description of the topic using a PowerPoint presentation that was shared with the interview candidates several days before the interview was planned. There were two versions of the interview protocol: one

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for modelling experts (Appendix 2) and one for end-users (Appendix 3). The interviews with modelling experts focused on the specific modelling challenges in health economic modelling of PM, while the interviews with end-users focused on their information needs for decision making about pricing and reimbursement of PM. At least one of the Work Package 1 members attending the interview made notes and the interview was recorded with permission of the interviewee candidate. Two researchers (MV, MR) extracted the most important responses from the interview notes. These responses were categorised by topic and summarised in paraphrased responses. The paraphrased responses were sent to the interviewees for their approval.

4.5 Development of the guidance

The guidance was informed by:

(i) findings from the literature on methodological challenges identified in the scoping review,

(ii) examples of good practices from the systematic literature review,

(iii) the responses from the interviewees,

(iv) authors' opinion.

Findings (i)-(iii) (described in more detail in sections 4.1-4) provided input into discussions between the authors (HV, SH, MV, MR). Deliberations were continued until consensus between the authors was reached regarding the structure and content of the guidance. Subsequently, the guidance was discussed with the other partners in the HEcoPerMed consortium and iteratively adapted. The guidance (provided in section 4.5) contains an in-depth description of the challenges that occur when modelling PM interventions, as well as recommendations on how to address these challenges.

To ensure that all recommendations are widely supported by modelling experts and end-users of health economic models, the guidance will be discussed at Workshop 1, at which we expect approximately 100 modelling experts and end-users to participate.

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5 RESULTS

5.1 Scoping review

5.1.1 Phase 1

The methodological issues extracted from our starting-list of papers and discussed at our first consortium meeting were summarised under 8 headings: 1) scoping (e.g., impact of increased stratification on model complexity, data needs and timing of assessment), 2) model structure (e.g., need of individual-level simulation, conditionality of tests, impact of different cut-of values for continuous test outcomes), 3) time horizon (e.g., extrapolation in case of a 'cure', including benefits for future generations), 4) evidence synthesis (smaller trials, innovative trial designs, more observational data, greater reliance on expert opinion), 5) broadening the definition of value (e.g., including the value of informed decision making, ruling-out, knowing and not-knowing, cure, incidental findings, spill-overs), 6) costs (e.g., large upfront costs prior to potential cure, high-priced drugs, varying test costs), 7) uncertainty (e.g., smaller of greater uncertainty due to PM, greater need for value of information analysis) and 8) equity (e.g., strata associated with socio-economic status, ethnicity, reimbursement consequences of greater uncertainty for small strata).

5.1.2 Phase 2

The papers identified in phase 2 (including the ones used in phase 1) are listed in Table 1.

Table 1. Results of phase 2 of the scoping exercise in alphabetical order on first author.

No.	Reference
1	Annemans, L., Redekop, K., & Payne, K. (2013). Current methodological issues in the economic assessment of personalized medicine. Value in Health, 16(6), S20-S26.
2	Buchanan, J., Wordsworth, S., & Schuh, A. (2013). Issues surrounding the health economic evaluation of genomic technologies. *Pharmacogenomics*, *14*(15), 1833-1847.
3	Bullement, A., Hatswell, A., Parkinson, B., & Bharmal, M. (2019). Health technology assessment of curative interventions-an old problem with new issues. Value & Outcomes Spotlight, 5(3), 16-18.
4	Cope, S., Ayers, D., Zhang, J., Batt, K., & Jansen, J. P. (2019). Integrating expert opinion with clinical trial data to extrapolate long-term survival: a case study of CAR-T therapy for children and young adults with relapsed or refractory acute lymphoblastic leukemia. BMC medical research methodology, 19(1), 182.
5	Degeling, K., Koffijberg, H., & IJzerman, M. J. (2017). A systematic review and checklist presenting the main challenges for health economic modelling in personalized medicine:

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	towards implementing patient-level models. Expert review of pharmacoeconomics & outcomes research, 17(1), 17-25.
6	Drummond, M. F., Neumann, P. J., Sullivan, S. D., Fricke, F. U., Tunis, S., Dabbous, O., & Toumi, M. (2019). Analytic considerations in applying a general economic evaluation reference case to gene therapy. Value in Health, 22(6), 661-668.
7	EUnetHTA (2015). Personalised medicine and co-dependent technologies, with a special focus on issues of study design.
8	Jönsson, B., Hampson, G., Michaels, J., Towse, A., von der Schulenburg, J. M. G., & Wong, O. (2019). Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. The European Journal of Health Economics, 20(3), 427-438.
9	Lakdawalla DN, Doshi JA, Garrison Jr LP, et al. Defining elements of value in health care—a health economics approach: an ISPOR Special Task Force report [3]. Value in health. 2018; 21: 131-39.
10	Love-Koh, J., Peel, A., Rejon-Parrilla, J. C., Ennis, K., Lovett, R., Manca, A., ... & Taylor, M. (2018). The future of precision medicine: potential impacts for health technology assessment. Pharmacoeconomics, 36(12), 1439-1451.
11	Marsden, G., & Towse, A. (2017). Exploring the Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products: Is the NICE Approach Fit for Purpose. Office of Health Economics, London.
12	Othus, M., Bansal, A., Koepl, L., Wagner, S., & Ramsey, S. (2017). Accounting for cured patients in cost-effectiveness analysis. Value in Health, 20(4), 705-709.
13	Ouwens, M. J., Mukhopadhyay, P., Zhang, Y., Huang, M., Latimer, N., & Briggs, A. (2019). Estimating lifetime benefits associated with immuno-oncology therapies: challenges and approaches for overall survival extrapolations. PharmacoEconomics, 37(9), 1129-1138.
14	Pearson, S. (2019, January). Early Experience with Health Technology Assessment of Gene Therapies in the United States: Pricing and Paying for Cures. In Seminar Briefings (No. 002112). Office of Health Economics.
15	Peters, J. L., Anderson, R., & Hyde, C. (2013). Development of an economic evaluation of diagnostic strategies: the case of monogenic diabetes. BMJ open, 3(5), e002905.
16	Rogowski WH, Grosse SD, Schmidtke J, et al. Criteria for fairly allocating scarce health-care resources to genetic tests: which matter most? European Journal of Human Genetics. 2014; 22: 25-31.

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17	Rogowski, W., Payne, K., Schnell-Inderst, P., Manca, A., Rochau, U., Jahn, B., ... & Siebert, U. (2015). Concepts of 'personalization' in personalized medicine: implications for economic evaluation. Pharmacoeconomics, 33(1), 49-59.
18	Shinkins, B., Yang, Y., Abel, L., & Fanshawe, T. R. (2017). Evidence synthesis to inform model-based cost-effectiveness evaluations of diagnostic tests: a methodological review of health technology assessments. BMC medical research methodology, 17(1), 56.
19	Terkola, R., Antoñanzas, F., & Postma, M. (2017). Economic evaluation of personalized medicine: a call for real-world data.
20	Towse A, Garrison Jr LP. Economic incentives for evidence generation: promoting an efficient path to personalized medicine. Value in health. 2013; 16: S39-S43.
21	Yang, Y., Abel, L., Buchanan, J., Fanshawe, T., & Shinkins, B. (2019). Use of Decision Modelling in Economic Evaluations of Diagnostic Tests: An Appraisal and Review of Health Technology Assessments in the UK. PharmacoEconomics-open, 1-11.

5.1.3 Phase 3

The topics extracted from the 21 papers on the economic evaluation of PM are listed in Table 2.

Table 2. Extracted topics from studies included in the scoping review.

Paper (reference in Table 1)	**Extracted topics**
1	Annemans et al. review methodological issues in the economic evaluation of PM. They list as most important topics the scope of the assessment (in the light of heterogeneous testing practices), the accuracy of diagnostic tests, the combination of several tests, greater uncertainty, data gaps, the need for early HTA and values not captured by the QALY.
2	Buchanan reported 4 categories of issues specific to economic evaluations in genomic tests: analytical approach (perspective, time horizon, choice of comparator), costs and resource use (costs of testing and communicating results, lack of national pricing tariffs for genomic tests, repeated tests), measuring outcomes (capturing relevant outcomes, personal-utility, cost-benefit analysis, individual vs population outcomes), measuring effectiveness (unknown behavioral response to tests, low quality evidence, complex data) and other (heterogeneity in standards between labs, investing in comparative studies).

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3	Bullement described issues with curative interventions: uncertainty in long-term clinical effectiveness and solutions to these issues such as managed access programs, the applicability of traditional modelling methods with a specific focus on survival extrapolation, and the high cost of treatment which can be mitigated through risk-sharing agreements.
4	Cope et al report how expert opinion could be elicited and integrated with survival data.
5	Degeling et al. report on challenges in modelling PM. Following a review they developed a checklist of 10 challenges: Modelling patient-level process, modelling patient preferences, modelling physicians preferences, taking diagnostic performance of test into account, modelling combinations of tests, modelling companion diagnostics, study-specific outcome measures, data gaps, greater uncertainty due to complex analyses and absence of guidelines.
6	Drummond et al. conclude that gene therapy does not require a new 'reference case', but do argue that gene therapies have some specific properties that require further considerations. These are summarised in a checklist which points the attention to clinical effectiveness, elements of value (severity, caregivers, insurance value, scientific spillover, lack of alternatives, substantial improvements in life expectancy) and 'other', which includes discounting and uncertainty.
7	The European Network for Health Technology Assessment (EUnetHTA) discussion paper concludes that the current HTA methods are appropriate for the evaluation of PM but warns for the risk of biased conclusions in HTA reports that, for PM, are increasingly based on lower level evidence than randomised controlled trial (RCT) evidence.
8	Jönssen et al. report the results of an expert panel which reviewed current principles and practices of HTA in relation to advanced therapy medicinal products. The topics prioritised by the panel were uncertainty (as a result of the nature of the underlying lower quality evidence), discounting (due to the timing of costs and benefits), health outcomes and value (not captured by the QALY).
9	Lakdawalla et al. define twelve potential elements of value that may be considered in economic evaluations. Four elements that are conventionally included in economic evaluations: QALYs, net costs, productivity, and adherence-improving factors. Eight additional elements of value: reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spill overs.
10	Love-Koh et al. conducted a pragmatic literature review and interviewed experts. They identify several challenges for HTA agencies when evaluating precision medicine. They

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	summarise under four headings: scoping (increased volume of technologies and complex decision-problems), modelling (reliance on observational data, more subgroups/low sample size, increased pathway complexity, reliance on expert opinion), decision-making (increased structural / decision uncertainty, behavioral uncertainty, unequal uptake of technologies, equity issues) and review (frequency of guidance updates).
11	Marsden and Towse, in their appraisal of the NICE assessments for cell therapies and regenerative medicines, argue that the current methodological toolkit could be applied to cell and regenerative assessments, but also state that it not necessarily should be applied. They argue that exploring the impact of managed entry agreements ('innovative financing mechanisms') could be more relevant than addressing parameter uncertainty and argue for exploring different discount rates.
12	Othus et al. investigate the impact of using a cure assumption on the cost-effectiveness of ipilimumab.
13	Ouwens et al. investigate different extrapolation methods for survival models and validate the predicted data with updated survival data from longer follow-up than that on which the survival was estimated.
14	Pearson describes the issues that the US-ICER institute encounters when valuing gene therapy and lists the following: uncertainty about clinical effectiveness, additional elements of value (values beyond the QALY), integrating social values into value-based pricing and producing policy-relevant values for cures.
15	Peters et al. investigate testing in monogenic diabetes and discuss, among other things, issues around uptake of testing and adherence to referral advice.
16	Rogowski et al. (2014) provide an overview of ethical and economic concepts for prioritising scarce health-care resources toward genetic tests.
17	Rogowski et al. (2015) held an expert workshop to identify potential issues with the current HTA methodological toolkit when applied to PM. The group identified that 'personalised' in PM could refer both to preferences or physiological biomarkers predicting response. Challenges for HTA, in relation to biomarkers predicting response, are: the complexity of care pathways, the inclusion of spill-over effects in others, accounting for heterogeneity of baseline risk, the impact of test thresholds on cost-effectiveness, limited evidence, the choice of time horizons and dealing with uncertainty. With regards to preference the listed challenges are: uptake of the test and the intervention, the relation between adherence and personalisation, adherence, potential biases in stated preferences, heterogeneity in preferences and the relevant perspective for including non-health benefits.

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18	Shinkins et al. reviewed 20 United Kingdom (UK) HTA reports to see in which ways accuracy was included in the economic evaluations. The modelling was evaluated with respect to the data informing test accuracy, how the test accuracy informed the model, if the model was used to identify optimal cut-of values for the test, if dependency between tests was accounted for and how different test setting (in the primary care setting) were accounted for.
19	Terkola et al. summarise challenges identified by other authors in the evaluation of PM and list: dealing with real world data on test accuracy, a lack of registry data across jurisdictions to obtain insights in costs and effects, costs of the test, limitations of the QALY concept, complexities in treatment pathways resulting in increased uncertainty.
20	Towse et al. argue that promoting an efficient path to PM is going to require appropriate incentives for evidence generation including: 1) a greater willingness on the part of payers to accept prices that reflect value; 2) consideration of some form of intellectual property protection (e.g. data exclusivity) for diagnostics to incentivise generation of evidence of clinical utility; 3) realistic expectations around the standards for evidence; and 4) public investment in evidence collection to complement the efforts of payers and manufacturers.
21	Yang et al. reviewed 55 UK HTA reports that used decision analytic modelling to estimate the cost-effectiveness of diagnostic tests. They report a list of elements in which this modelling could be improved, specific to tests, which were: a clear justification for including or excluding comparators, a systematic evaluation of the quality of the efficacy data, accounting for interdependence and sequences in tests.

5.1.4 Phase 4

An overview of topics and a short description created in Phase 4 is provided in Table 3. The topics are discussed in more detail in the following chapters.

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Table 3. Topics relevant in modelling PM interventions identified in the scoping review.

Topics	Short description
Modelling test-treatment combinations	The combination of a test and subsequent treatment is key in personalised medicine. The economic evaluation of these test-treatment combinations raises several possible complexities, including: - Multiple possible positions of the test in the clinical pathway, as it may be applied at different time points and/or in varying combinations with other tests - (Downstream) consequences of introducing a new test into clinical practice, including for those with a negative test result - Test performance (sensitivity, specificity, positive predictive value, negative predictive value) may be dependent on the patient population and/or correlated with the outcomes of previous tests - Large variation in cost of testing - During waiting times for test results or start of treatment patients may be at risk of disease progression or mortality.
Effectiveness data from non-randomised (controlled) studies	The more stratification takes place due to PM, the smaller patient subgroups become. This complicates evidence generation in the traditional RCT manner. Therefore, alternative trial designs are being developed, such as umbrella, basket and adaptive designs. There might be an increased need for the use of observational data (e.g. (historical) cohort studies and registry data).
Extrapolating outcomes for interventions aiming to cure	At the time of health economic evaluation, the effectiveness data is often too immature to have observed cures as a result of interventions that are aiming to cure. This results in uncertainty about the extrapolation of long-term outcomes of these interventions, including the duration of treatment effect.
Discounting	In PM, there may be large upfront costs, while the benefits stretch far into the future. Some argued that this may ask for a deviation from standard discount rates.
Values beyond the current patient	It could be argued that a societal perspective is more appropriate to use in the context of PM, especially in cases of potentially life-saving treatments (such as gene therapies) that can cause a lifelong reduction in productivity loss and use of informal care services.

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	A genetic test may identify a condition that is the result of a germline mutation, which means that relatives might also be at risk and should receive testing through a cascade screening programme.
Values beyond the QALY	Some have argued that the QALY insufficiently captures the full value interventions may have. The ISPOR Value Assessment Framework Special Task Force identified a range of 'additional' values beyond the QALY (6), some of which might be especially relevant in PM.
Equity	Biomarkers used for stratification might correlate with equity-relevant variables, such as ethnicity and socioeconomic status. Also, patients in remote areas or lower socioeconomic groups may have less access to advanced testing methods.
Uncertainty analysis	Modelling of PM interventions may come with a great amount of uncertainty, for several reasons mentioned in the previous topics in this table. Therefore, uncertainty analysis is even more important when modelling a PM intervention.
Managed entry agreements	PM interventions may come with a hefty price tag, as well as significant uncertainty about their clinical effectiveness. In response to this, healthcare payers may opt to use managed entry agreements (MEAs) to share the risks with the manufacturers. The parameters of these MEA may be included in the health economic model.
Modelling imperfect implementation	A health economic model can assume perfect implementation (i.e. the intended use of the intervention) or include an estimate of suboptimal implementation. In the latter, patients' uptake of testing and treatment adherence and clinicians' adherence to protocols and guidelines may be considered in health economic evaluations.

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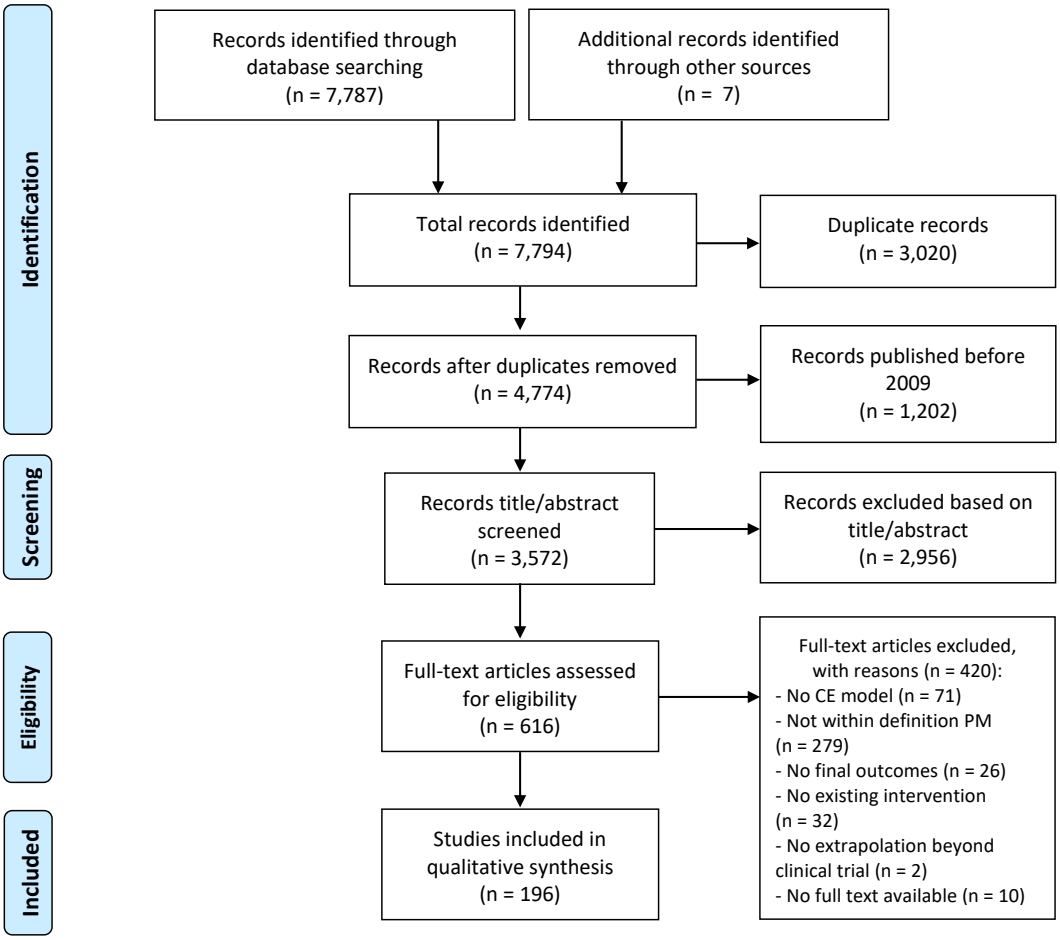
5.2 Systematic review

5.2.1 Study selection

The systematic literature search identified 7,651 publications, of which 196 were included after full-text screening. Twelve studies evaluated gene therapies, 103 studies evaluated germline mutation profiling-guided interventions, 80 studies evaluated somatic mutation profiling-guided interventions, and 1 study evaluated both germline and somatic mutation profiling-guided interventions. No studies evaluating big data analytics to aid clinical decision-making were identified. The study selection is summarised in a PRISMA flowchart in Figure 5 and the references of included studies are provided in Appendix 4.

Figure 5. PRISMA flowchart of study selection



5.2.2 Identification of studies addressing the PM challenges

Based on the identified challenges (Table 3), an 'identification checklist' was developed to identify studies that addressed one or more of these challenges in an economic evaluation of a PM intervention. The identification checklists and the results of this identification process are provided in Table 4. Table 4 shows the numbers of papers that addressed each modelling challenge. The references of the identified studies are provided in Appendix 5.

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Table 4. Results of application of identification checklist to included studies in the systematic literature review.

Identification checklist	Gene therapies (n=12)	Omics profiling-guided interventions		
		Germline mutations (n=103)	Somatic mutations (n=80)	Germline and somatic mutations (n=1)
Conditionality of test sequences and/or test outcomes	0	13	5	0
Turnaround time from test or treatment decision until initiation of patient management strategy	2	3	4	0
Methods to compensate for bias in studies with small target population	1	1	1	0
Methods to compensate for bias in observational studies	3	0	1	0
Methods to compensate for bias in using a historical cohort for comparator data	0	0	0	0
Methods to compensate for potential bias in the extrapolation of outcomes of interventions aiming to cure	9	0	2	0
Methods to combine expert opinions into a point estimate plus distribution	0	0	0	0
Deviation from standard discount rates for reasons particularly relevant to PM interventions	3	0	0	0
Values beyond the current patient	0	26	1	0
Values beyond the QALY	0	10	2	0
Equity issues	0	0	0	0
Uncertainty analysis	0	8	0	0
Managed entry agreement included in cost-effectiveness analysis	6	0	2	0
Patients' uptake of testing	0	19	3	0
Patients' treatment adherence	0	34	4	0
Clinicians' adherence to protocols/guidelines	0	6	4	0

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In the following, the methods reported in the included studies to handle the challenges in health economic modelling of PM interventions will be discussed by topic.

Conditionality of test sequences and/or test outcomes

Test performance (specificity, sensitivity, positive predictive value, negative predictive value) is likely to vary according to the patient population in which the test is applied. For example, in Wordsworth et al.(11) the sensitivity and specificity of clinical tests for familial hypertrophic cardiomyopathy varied across age groups. Although Dong et al.(12) assume the sensitivity and specificity of a pharmacogenomic test for two epilepsy drugs are constant, they assume varying prevalence of the relevant risk alleles across ethnic groups, which causes the positive and negative predictive value of the test to be different in different ethnic groups.

Several studies incorporated dependencies between tests using conditional probabilities, such as in Garrison Jr et al.(13), where the probability of results on fluorescence in situ hybridisation (FISH) and immunohistochemistry (IHC)-tests for human epidermal growth factor receptor 2 (HER2)-expression depend on the result received on the previous test. A number of studies assume that when tests are repeated in patients with a positive result, the sensitivity and specificity of the test change over time. In a study considering a genomic classifier as an addition to bronchoscopy for diagnosing lung cancer, Feller-Kopman et al.(14) assume that repeated computed tomography (CT) follow-up imaging has an increasing specificity (i.e. decreased false-positive rate) over time. Specificity increases from 92% at the time of the index bronchoscopy to 99% at 9 months, which is when the third sequential CT scan is performed.

Turnaround time from test or treatment decision until initiation of patient management strategy

In the systematic literature review, we identified several examples of studies that modelled the time period until start of treatment. In a NICE single technology assessment (STA)(15) and Whittington et al.(16), the time between treatment decision and the actual chimeric antigen receptor T cell (CAR-T) infusion was considered in a decision tree preceding the partition survival model that was used to model long-term outcomes. In this decision tree, patients could receive the infusion, discontinue before infusion because of adverse events or manufacturing failure, or die before receiving the infusion. In a study by Doble et al.(17), the short-cycle length applied in the Markov model enabled Doble et al. to include the waiting time for the results and the outcomes after treatment within one type of model. During this waiting time patients faced a probability to die before receiving any treatment. Huxley et al.(18) applied a disutility during waiting time.

Patients' uptake of testing

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We mostly found examples of the inclusion of 'uptake of testing' in studies evaluating screening interventions for germline mutations. Uptake rates were generally included as a probability/percentage of people accepting to be tested. Uptake rates were sometimes varied depending on the (perception of) average risk within a specific subgroup. For example, Dinh et al.(19) assess a screening intervention for Lynch syndrome and assume that 70% of children of mutation-carriers will get tested for Lynch syndrome, while only 60% of siblings and parents of mutation-carriers gets tested. Rogowski (20) compares a population-based screening programme for hereditary haemochromatosis to a cascade screening programme and assumes uptake of genetic testing to be higher in the latter scenario. For the population-based programme, Rogowski (2008) considers, firstly, the percentage of individuals that requests further information after being targeted by information and adverts and, secondly, the percentage of interested individuals that finally decides to get tested. Chen et al.(21) and McKay et al.(22) take a comparable two-step approach, taking into account both the percentage of people showing up after being invited for genetic counselling and the percentage of people subsequently accepting to be tested. For their calculation of probability of uptake, Wordsworth et al.(11) gather data on acceptance rates from a local genetics clinic, as well as expert opinion on the annual probability of patients who initially declined testing to later change their mind and get tested. We found one study, Asphaug & Melberg (23) – considering the cost-effectiveness of multigene testing for hereditary breast and ovarian cancer – that assigned a probability distribution to the 'uptake of testing' parameter.

Patients' treatment adherence

Some of the studies incorporating treatment adherence assume an ideal scenario of 100% adherence in the base case but consider the effect of decreased adherence on cost-effectiveness outcomes in sensitivity or scenario analyses. Among the studies that assume imperfect adherence in the base case were mostly evaluations of screening interventions, where people identified to be at high risk were offered increased clinical surveillance, preventive surgery, or preventive drug treatment. Severin et al.(24), for example, assume only 82% of patients that have been tested positive for Lynch syndrome through a cascade screening programme adhere to the recommended frequent colonoscopy and preventive aspirin use. Eccleston et al.(25) incorporate imperfect uptake of risk-reducing surgery (both mastectomy and bilateral salpingo-oophorectomy) among epithelial ovarian cancer patients that are breast cancer (BRCA)-positive and their relatives, with differing uptake rates between BRCA1-positive and BRCA2-positive patients. Ramírez De Arellano et al.(26) incorporate declining adherence to preventive drug treatment among patients genetically predisposed to coronary heart disease (CHD) by assuming an increasing risk of a CHD event over time.

While most studies apply a correction to their clinical data to account for adherence, Reed et al.(27) assume that the health outcomes of imperfect adherence (to genetically targeted chemoprevention for prostate cancer) were already reflected in the effectiveness outcomes of the trial and only adjust down drug costs based on the number of treatment days missed.

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We found no studies that took as their base case a scenario in which mutation-carriers who know their genetic status have higher treatment adherence than patients who do not know their genetic status or who tested negative for the mutation. Nonetheless, there were a number of studies conducting scenario analysis to assess the effect of different assumptions about changed adherence among mutation-positive patients on cost-effectiveness outcomes. For example, Parthan et al.(28) assess the effect of increasing adherence to targeted statin therapy by 8% among known mutation-carriers. In their base case, Green et al.(29) assume 20% adherence to chemoprevention for women at risk of breast cancer. In a scenario analysis, they maintain 20% adherence in the comparator arm (risk prediction based on clinical characteristics), while increasing adherence in the intervention arm (risk prediction based on genetic information) in increments of 10 percentage points.

Clinicians' adherence to protocols/guidelines

A few of the studies considered clinicians' adherence to guidelines with regards to initiation of testing. Dinh et al.(19), for example, take 'current practice patterns' as the comparator for a primary screening programme for Lynch syndrome and assume that currently only 17% of patients with a malignancy are seen by a physician who considers the option of testing for Lynch syndrome (if clinical criteria are met). However, most of the studies that incorporate clinicians' adherence focus on the treatment recommendations resulting from testing. This element is mostly incorporated as the percentage/probability of patients receiving the test-based treatment. For example, Yang et al.(30) assume that 90% of patients classified as high risk on both Adjuvant! Online and Oncotype DX indeed receive chemotherapy, while 90% of low-risk patients indeed abstain from chemotherapy. Rejón-Parrilla et al.(31), evaluating a pharmacogenomic test in schizophrenia that classifies patients as poor, intermediate, or ultra-rapid metabolisers, perform a scenario analysis in which they increase the percentages of incorrectly genotyped patients (there are six 'misclassification' categories, due to the fact that there are three metabolism profiles). As 'misclassified' patients receive treatment that is not optimal for their genotype, Rejón-Parrilla et al. argue the scenario could reflect the results of clinicians not abiding by the test results. They note, however, that the scenario could also reflect human error in obtaining and analysing the DNA samples, as well as the fact that metabolism might not be determined only by genotype but by lifestyle factors too.

Assumptions with regards to imperfect adherence are mostly based on observational data. Graves et al.(32) base their 'adherence to test result' parameter on the observation that only 50% of physicians switched to a different medicine in cases where the patient was identified as a poor or intermediate metaboliser of clopidogrel. Chandler et al.(33) vary the probability of Oncotype DX testing based on observed use of the test in current clinical practice, stratified by age and tumour stage. Compagni et al.(34), on the other hand, base their probabilities for different treatment choices after a positive test result on an online survey completed by 250 physicians.

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Methods to compensate for potential bias in the extrapolation of outcomes of interventions aiming to cure

Most of the interventions aiming to cure that were identified in the systematic literature review were CAR-T treatments. CAR-T therapy is a novel cellular therapy that uses genetic engineering to alter a patient's own T-cells with synthetic receptors known as chimeric antigen receptors (CAR) that recognises and eliminates specific cancer cells.(35, 36) Different approaches to model the curative element of these treatments were used in these studies. Whittington et al. fitted a parametric curve function to the proportion of the survival curve that was downward sloping.(16) A knot was introduced at the point at which the fitted curve intersected the flat portion (i.e. slope = 0) of the observed survival curve. After this knot, patients were assumed to be long-term survivors and mortality was based on age- and sex-adjusted all-cause mortality observed in the general population adjusted for excess disease-related mortality. A similar approach was applied in the US-ICER report of CAR-T treatment and proposed by the evidence review group (ERG) in the NICE STAs of CAR-T treatments (ID1115, ID1166, ID1167).(15, 36-38) In contrast to the ERG base cases, mixture cure models were applied in the pharmaceutical company's base cases in the NICE STAs of CAR-T treatments.(15, 37, 38) Lin et al. evaluated three scenarios with varying long-term outcomes where the most optimistic scenario was based on an adjustment of the observed 1-year relapse free survival of 50% to a 5-year relapse free survival without stem cell transplantation of 40%) and the most pessimistic scenario assumed no treatment effect after 5-years (i.e. 0% 5-year relapse free survival).(39) Similar scenario analyses with varying assumptions regarding the extrapolation of the observed treatment effect (in terms of period without visual function decline) were performed in the economic evaluations of gene therapies for inherited retinal disease (40, 41) and spinal muscular atrophy (in terms of proportion of patients losing milestones after end of trial follow-up).(42)

Discounting

A reduced discount rate for costs and benefits was only identified in studies evaluating gene therapies. The choice for applying a lower discount rate in these examples was based on the NICE Methods Guide that states that a discount rate of 1.5% for costs and benefits may be considered in cases when the treatment restores individuals who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years).(43) The reduced discount rate was applied for both costs and benefits in the evaluation of Strimvelis in both the pharmaceutical company's and ERG's base case.(44, 45) However, the ERG was concerned that many patients with adenosine deaminase deficiency would not return to general population life expectancy and morbidity after successful transplant.(44) In addition, the 1.5% discount rate for costs and benefits was included as a scenario analysis in the economic evaluations of CAR-T treatment for patients (<25 years) with relapsed or refractory B-cell acute lymphoblastic.(15, 16) In contrast, the lower discount rate was not considered in the other NICE STAs of CAR-T treatments identified in our systematic literature review.

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Methods to compensate for bias in observational studies

In the absence of RCT data, Whittington et al. chose a comparator with available evidence from the most similar patient population informed by stakeholders and clinical experts.(16) In a NICE STA of CAR-T treatment (ID1115) patients with certain patient characteristics were excluded from the comparator cohort to make this cohort more comparable to the trial population.(37) However, in this subgroup of patients the stem cell transplant (SCT) rate was higher than expected. Therefore, separate parametric survival curves were fitted to Kaplan-Meier data for overall survival of patients who received SCT and those who did not. These Kaplan-Meier curves were then weighted based on the expected SCT rate. In another NICE STA of CAR-T treatment (ID1167), there were only single-arm clinical trials available to inform the efficacy of the intervention and comparators.(15) Matching-adjusted indirect comparison was conducted to increase the similarity of the populations in the intervention and comparator groups. However, the results were similar to the unmatched results and therefore the unadjusted data was used in the analysis.

Methods to compensate for bias in studies with small target population

In South et al. data of 18 patients with severe combined immunodeficiency caused by adenosine deaminase deficiency who received the gene therapy 'Strimvelis' in four similar open-label, single-arm trials were pooled and treated as if they were enrolled in a single study.(45)

Methods to compensate for bias in using a historical cohort for comparator data

None of the included studies used specific methods to compensate for bias when using historical cohorts.

Values beyond the QALY

The most commonly included value beyond the traditional health-related quality of life included in the conventional QALY was the 'value of knowing', or the (dis)utility experienced after finding out a test result. All studies incorporating 'value of knowing' considered cancer interventions. In most studies that we found, the 'value of knowing' is incorporated by adding a disutility resulting from a positive (or uncertain) test result. For example, Eccleston et al.(25) incorporate in their sensitivity analysis a disutility for receiving a positive result on a BRCA-test that lasts for one year. A few studies also add a positive utility effect after receiving a negative test result. Chandler et al.(33), for example, assume patients with a low-risk score on the Oncotype DX test experience a 0.05 utility increase for 2 years after finding out the result, while patients with a high-risk score experience a disutility of 0.05. Holland et al.(46) assume a 0.01 utility increase for 1 year after a negative BRCA-test result and a utility decrease of 0.17 after a positive test result (from a 0.92 starting utility to a utility of 0.75 after a positive test) that lasts for 5 years.

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We found significant variation in the assumptions with regards to utility effects of finding out test results. For example, Li et al.(47) evaluate a BRCA-based genetic test assessing breast cancer risk, like Holland et al.(46), yet they only assume a 0.05 disutility lasting for 1 year after a positive test result. We found no studies that assigned an additional utility to people just for knowing that they are likely to be respond to the available treatment.

We found a study that incorporated the disutility experienced after preventive mastectomy or oophorectomy (Muller et al.(48)), while we also found a study that incorporated the disutility of declining preventive total abdominal hysterectomy/oophorectomy (Wang et al.(49)). The rationale in the former is that patients experience psychological distress as a result of worsened body image, while the rationale in the latter is that patients experience psychological distress resulting from continued anxiety over possible cancer development. Wang et al. base the disutility value on a patient preference elicitation exercise they conducted, which they also use to incorporate a disutility of declining genetic testing in their model. The explanation for this disutility is that people may decline genetic testing for concerns over family and the emotional impact of finding out the results, yet experience disutility as a result of remaining uncertainty.

Values beyond the current patient

Virtually all studies we found that included 'values beyond the current patient' considered cascade screening for germline DNA mutations. In such interventions, a patient with symptoms (called 'index patient' or 'proband') is screened for a genetic cause and if a relevant mutation is indeed identified, relatives are also tested for this mutation. There was some variation in which relatives were incorporated into the model. Asphaug et al.(23) extend testing for breast- and ovarian cancer risk only to sisters and daughters of index patients, citing concerns over model complexity and mutational burden if they were to expand the analysis. Dinh et al.(19) and Severin et al.(24), among others, consider only first-degree relatives in cascade screening for Lynch syndrome. Hoskins et al.(50) include second-degree relatives only if relevant first-degree relatives have tested BRCA-positive, and assume different probabilities of having a mutation in the two groups. Gallego et al.(51) assume that first-, second- and third-degree relatives are all approached at the same time in the base case and assess the effect of approaching only first-degree relatives in a scenario analysis. Several studies incorporate 'relatives' without specifying what degree they are.

Methods to combine expert opinions into a point estimate plus distribution

None of the included studies used specific methods to combine expert opinions into a point estimate plus distribution.

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Equity issues

None of the included studies considered equity issues.

Uncertainty analysis in PM interventions

Most studies performed standard uncertainty analysis to address the uncertainty around PM-specific input parameters or structural assumptions, such as deterministic sensitivity analyses, probabilistic sensitivity analysis, and scenario analyses.

Managed entry agreement included in cost-effectiveness analysis

In all studies evaluating CAR-T treatments the managed entry agreement (MEA) that was arranged between manufacturers and payers was included in the economic evaluation. The MEAs were either patient access schemes with a (confidential) discount (15, 37-39) or outcome-based payments where the payer covers the treatment costs only if the patient achieves a certain health outcome (i.e. response at a certain time point).(16, 36, 39) The other studies evaluating gene therapies did not include a MEA in their analysis, however, the reports from US-ICER all included a threshold analysis to determine the rebate percentage necessary to reach the cost-per-QALY threshold.(36, 40, 42, 52) In the cost-effectiveness analysis of ibrutinib treatment guided by profiling of a somatic DNA mutation for chronic lymphocytic leukemia, *Buchanan et al.* considered the patient access scheme.(53) However, because the discount was confidential, an assumption about the costs of treatment needed to be made. The annual cost of treatment was therefore assumed to be £30,000 to match the upper limit of the NICE cost-effectiveness threshold and this value was varied in sensitivity analyses. In a scenario analysis, *Zhu et al.* evaluated the impact of the Gefitinib Patient Assistance Program (GPAP) in China which requires non-small cell lung cancer (NSCLC) patients to pay for six months of gefitinib after which the drug is reimbursed by the manufacturer until the end of their treatment.(54)

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5.3 Interviews with modelling experts

Fourteen interviews with modelling experts, lasting between 1 and 1.5 hours, were conducted between October 2019 and February 2020. A summary of responses by interviewees is provided in Table 5.

Table 5. Summary of interview responses of modelling experts.

Interviewee	Paraphrased response
Effectiveness data from non-randomised (controlled) studies	
IC1	Matching (such as propensity score matching) is complicated in increasingly small sample sizes since predictors are not easily identified due to a lack of statistical power
IC2	Small sample sizes increase the need for international collaboration on data sharing, such as registries, but the local governance of these registries often does not allow the pooling of international data
IC3	Many different methods are used to estimate the missing control arms of studies, but often only the preferred method is reported, which may give insufficient attention to the structural uncertainty in the selection of indirect comparison method.
IC4	While RCT's may be complicated, they are not impossible to conduct, rather they are difficult to conduct. PM, in no way, precludes conducting RCT's and following this narrative does not do justice to the true possibilities out there for conducting complicated trials. The costs of not doing these trials may be large. The main issues in PM is small sample sizes and uncontrolled data and the classic issues that arise from that, such as the unknown natural course of the disease, which is often unknown for specific new genetic mutations that are identified as drivers of tumour growth. An issue with basket trials is that they assume that the heterogeneity between tumour types and location is ancillary to heterogeneity in genetic make-up of the tumour, and that is an untested assumption. Simply put, we test a very particular element of the condition (its genetic make-up) and assume, possibly incorrectly, that this is the key and sole driver of response and progression.
IC5	Often historical cohorts are used to estimate a comparator. What is frequently forgotten is that over time medical care has improved and, hence, that the difference in efficacy is not all attributable to the intervention, while this is often the main assumption of the indirect comparison. Matching strategies are very useful to estimate comparator arms, but often the choice of covariates in the matching model has a sizable impact on the outcome, a source of structural uncertainty that is often not parameterised. One would hope to find a directed acyclic graph to be drawn up to a-priori define relevant

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Interviewee	Paraphrased response
	covariates for the matching model and solid arguments when other than the pre-defined strategies are used.
IC6	Conducting network-meta analysis will be increasingly complicated in the future due to single arm trials and uniquely defined sub-populations.
IC7	When observational data is used to estimate a control arm, missing data and errors abound. This type of data is often more subjective in nature due to the uncontrolled setting of its collection, which requires intensive collaboration with those who collected the data in the first place. Nonetheless, this 'real-world data' provides a better reflection of clinical practice such as the true population in which a drug will be provided and multiple treatment lines. However, we have gone far past the "generalisability" argument for real-world data. Observational data, regardless of whether it is a real-world registry or single-arm trial, can provide information that is unlikely obtained through randomised trials; it may provide the synthetic/real-world/historical control arms to single-arm studies of personalised medicine interventions. That is where we see most interest of clinicians.
IC8	An issue with the use of historical cohorts is that data becomes outdated rather fast due to improvements in other treatments than the one studies and improvements in the general health of the population. Also, historical cohorts have not always measured the intermediate end-points that were central to the trial or have measured them differently.
IC9	Observational data used to assess relative efficacy is worse than RCT data, and perhaps cost-effectiveness models that rely in this type of data should only be approved in research.
IC10	While observational studies better reflect clinical practice than an RCT, it is increasingly difficult to find patients with the specific mutation that is studied in an RCT.
IC11	Historical data can be used to estimate control arms but often a genomic test is new as well resulting in historical control data to be unadjusted for a specific mutation.
IC9	Limited data often results in using surrogate end-points and we need evidence on the link between surrogate end-points and long-term outcomes to be presented when these relationships are assumed in the model
IC13	Perhaps we should not perform HTA altogether when evidence of effectiveness is lacking.

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Interviewee	Paraphrased response
Interventions aiming to cure; methods to compensate for potential bias in the extrapolation of outcomes	
IC1	A cure is clearly defined: eradication of disease with no long-lasting consequences. This definition should not be confused with model results in which individuals are considered to be cured following model assumptions rather than true observations. Often it is assumed that surviving up to a certain point in time in the future can be considered a 'cure', but that is often incorrect and may not align with the underlying interaction between the treatment and the condition. While these cure models may be sensible when we understand the mechanics of the disease and can identify that disease is no longer present and that the risk of relapse is absent, then a cure model may be appropriate, but more often than not this is not known and then assuming a cure seems to be heroic. Perhaps, in interactions with key opinion leaders, we should not ask them if a person is cured, but the probability of living up to a certain point in the future.
IC3	The cure hypothesis should often be testable in historical cohorts in those that responded well to previous treatments. But perhaps the cure hypothesis is more about managed entry agreements than modelling: the assumption can be incorporated in the model, but the managed entry agreement may capture the risk of this assumption being incorrect.
IC5	Often the follow-up in trials is too short to identify someone as being cured. We must rely on the assessments of clinical experts to evaluate the cure hypothesis, or a well described mechanism of the disease that renders the cure hypothesis following treatment likely.
IC6	It is a challenge to demonstrate a 'cure' with trial data. Relying on experts is required in extrapolating treatment effects but other than what is usually done, asking experts to select their preferred extrapolation curve, a more formal process should be used in order to infer the confidence intervals, such as the SHeffield ELicitation Framework (SHELF) method. If experts select their preferred curve information is lost on the uncertainty in their choices and any parameter uncertainty explored later on can no longer be informed by the uncertainty of the experts. An important piece of information is external evidence: if we have a historical cohort, we can compare predictions of the model with this cohort.
IC7	How a cure is defined depends on the condition and the expected remaining survival. In CAR-T treatment, there is still insufficient data to assess if the condition is cured.

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Interviewee	Paraphrased response
	Simply choosing a cure model is not a sufficient approach: the model outcomes need to be tested against different parametric models and time horizons.
IC8	Simply put, there is no way to know if you are under- or overestimating long-term outcomes, which is why extensive sensitivity analyses should be conducted including those with an assumption of a waning effectiveness. If waning effectiveness is included, the model should at least consider that clinicians may explore new treatments. Nonetheless, managed entry agreements could be used to mediate the risk of incorrectly assessing the long-term benefit. Regarding cure, it should not be forgotten that patients may experience uncertainty about their disease status at each follow-up.
IC12	There are different scenarios that need to be explored; simply looking at the observed period only, projecting the findings over the lifetime and the definition of a waning period. While expert opinion plays an important role in defining the final model, we have to acknowledge that in situations of uncertainty, 10 guesses might not be much better than one guess. Perhaps the issue of uncertainty is not an issue of health economic modelling. Alternatively, other approaches to getting good value for money could be used such as competitive tendering and pay for performance agreements. The outcomes of these arrangements could even be included in the model as well as the administrative costs of the arrangement itself.
IC11	We should not evaluate PM differently: the issue of extrapolation of results is not unique to this category of treatments. Expert opinion could be elicited to infer opinions on likely scenarios, but it has to be acknowledged that sometimes we simply do not know.
IC9	The term ‘cure’ implies restoring full health and life expectancy to population levels. The cure assumption should always be tested against different time horizons and the most plausible time horizons need to be informed by both decision-makers preference and expert expectations.
IC13	When long-term effects and safety is unknown, a lifetime time horizon should not be used. Shorter time horizons may be acceptable because a two-year trial may not adequately inform a 30-year forecast.
Deviation from standard discount rates	
IC1	No need to change discount rates, to be consistent across evaluations
IC3	Differential discounting should not be used in an opportunity costs framework

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Interviewee	Paraphrased response
IC6	In PM, costs are often up-front and benefits accrue over time. If managed entry agreements are in place, these should be modelled because costs may fall in different time periods resulting in different incremental cost-effectiveness ratios (ICERs), regardless of differential or uniform discounting
IC7	There is no reason to treat PM treatments differently from others with regard to discounting
IC8	A sensitivity analysis should be conducted to understand the effect of different discounting assumptions
IC12	While there may be arguments for lower discount rates in general, the question is if PM should be evaluated against other discount rates than other therapies. The discount rate used in the economic evaluation should not reward manufactures of PM treatments over others. There are arguments for lower discount rates.(55)
IC11	All interventions should be subjected to the same discounting rules. Otherwise, where do we stop making exceptions? Preferably, the discount rate is based on empirical evidence within the relevant jurisdiction.
IC14	There is no reason to deviate from current discounting practice.
IC13	The same discounting recommendations need to be applied to all interventions.
Uncertainty analysis	
IC9	Uncertainty can be methodological uncertainty, structural uncertainty or parameter uncertainty.
IC1	Uncertainty is not unique to PM. The main difference is that some drivers of uncertainty, such as the duration of treatment effect or the relative effectiveness of treatments are jointly present. Perhaps sometimes it would be easier to present the set of assumptions that have to be made for a therapy to be cost-effective to experts and have them inform you on the likelihood of those assumptions proving to be true simultaneously. A probability sensitivity analysis (PSA) that reflects very large uncertainty may seem to be uninformative and will not tell you what to do, but it at least reflects that uncertainty is very large.
IC3	PM results in more uncertainties as treatment test-combinations inflate the number of strategies as well as multiply these strategies with different types of tests that can be used.

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Interviewee	Paraphrased response
IC4	Eliciting expert opinion is a useful way to dealing with uncertainty but first of all, their input needs to be parametrised for use in the probabilistic uncertainty analysis and second, we have to acknowledge that we are asking clinicians for input that they may be rather uninformed about as well.
IC5	Expert elicitation is often used to inform choices that are inherently uncertain. But one expert is not the other. Some standard metrics need to be reported, such as why an individual is an expert and in what, transparent questionnaires used to elicit their opinions or minutes of the meeting. Choices should be traceable to anonymised individuals rather than reporting averages to understand heterogeneity in expert opinion.
IC6	It is always important to include as much uncertainty in the analysis as possible, so value of information methods can be used to prioritise future research, but PM is not fundamentally or conceptually different from other interventions. The evidence may be limited, but the same approaches to identifying uncertainty can be applied. Parameterising structural uncertainty by using different sources all at once can be a relevant approach to dealing with structural uncertainty that may be more informative than scenario analyses (see for example Cope et al. (56)).
IC7	While parameter uncertainty in PM may be similar to other interventions, structural uncertainties abound. But often the impact of important modelling decisions is not evaluated in uncertainty analysis. For example, estimating progression free survival separate from overall survival ignores underlying competing risks. Also often overlooked is behaviour in clinical practice. Even if a biomarker has 100% sensitivity and 100% specificity, patients and clinicians may not actually use that information in their decision making. Hence, the willingness of patients and clinicians to de-escalate treatment based on a biomarker-based risk of progression, for example, should be considered in health economic analysis, since it is not the test result itself that results in different clinical outcomes, but any treatment changes that are made based on test result.
IC8	The timing of effects and costs may warrant sensitivity analysis on discount rates
IC10	The cost of genetic testing is often uncertain and may be rather heterogeneous between labs
IC11	Small sample sizes are a sizeable issue.
IC14	Models that are submitted for reimbursement decisions should adopt standard methods, such as a lifetime time horizon, regardless of uncertainty. But an often-

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Interviewee	Paraphrased response
	overlooked issue is that PM requires the combination of different data sources, and that each of these data sources has its own types of bias.
IC9	There is uncertainty as to where in the treatment pathway a test is positioned and this should be included, for example by parametrising the structural uncertainty around the test position informed by experts.
IC13	The uncertainty around clinical pathways are especially relevant to PM, but this can be handled with methods as we have now. The model structure should reflect an optimal implementation of the test. Modelling the real world (e.g. diminished effectiveness) may confound the ability to detect cost-effectiveness when practice improves.
Values beyond QALYs	
IC1	It is not correct to assume that currently values beyond the QALY do not receive any weight in decision-making. They might not be a formal part of the cost-effectiveness model, but they receive attention and value in deliberations during decision-making.
IC2	Additional elements of value might be captured by the QALY and we do not really know where additional value overlaps with current value
IC3	Some of the elements that are deemed to be values beyond the QALY are probably already captured in the QALY. If there is value that is obviously not captured in, for example, quality of life measurement, a committee will see that and value it. There is also disproportional attention to elements of value as opposed to elements of disutility. For example, knowing you live with an incurable disease may result in a lot of disutility.
IC4	Values beyond the QALY may be useful, but we need to acknowledge that this value is probably also present in interventions foregone, so the opportunity costs need to be adjusted for additional elements of value. We also need to acknowledge that when we incorporate additional elements of value in a cost-effectiveness analysis, that we are effectively willing to trade-off health against something like, for example, the value of hope.
IC5	Cost-effectiveness analysis was always intended to be just a part of health technology assessment. Sometimes HTA and cost-effectiveness analysis overlap almost completely because the cost-effectiveness model captures all relevant elements of value. In other instances, other elements of value need to be weighed in the decision-making process. There is quite a bit of talk about the value of hope, but one has to wonder: should, at equal cost-effectiveness between two treatments, a society be willing to invest societal resources in a treatment that results in slightly more hope than

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Interviewee	Paraphrased response
	another one? I do not think that generating hope apart from true realised outcomes should be rewarded.
IC6	The 'value flower' that is often discussed has petals that are overlapping -partly due to differences in definitions between researchers- which may cause double counting. With regards to the value of hope: the 'right tail' of the distribution that is considered to be the source of hope is often without any underlying data at the point of the decision, it is based on extrapolations. I am not convinced that should be rewarded by adjusting willingness-to-pay thresholds. Also, the value of hope can be negative for risk-averse individuals. The value of risk-reduction and insurance value can be important in PM. First of all, the whole point is to make sure that the benefits of treatment are stratified to a smaller population in whom greater effectiveness is achieved. At a given value of risk-averseness, this may have a value. Second, it can be worthwhile to model the insurance value for a patient population when there is a treatment available which provides protection against financial and physical risk. Finally, it is often forgotten that estimating the value for society is separate from a reimbursement decision which may involve a normative position on extent to which the realised value needs to be reflected in the price.
IC7	The purpose of the QALY metric is to compare across conditions. To allow this, it should not be subjected to a range of elements of value that may differ across analyses. Also, there is more transparency on these elements of value when they are not 'hidden' in the QALY.
IC8	Involving additional elements of value may overcomplicate cost-effectiveness analysis and its communication.
IC10	The value of hope and the reduction of uncertainty can be relevant items that we intend to measure, and we explore ways of adjusting the lambda to reflect additional elements of value.
IC12	Insurance value is not unique to private insurance systems as also collective insurance bodies may not include everything in their basic benefit package. With regards to the value of hope, we need to acknowledge that also many people are disappointed that they are not in the 'right tail' of the distribution, and dashed hope may be worse than not having hope at all. There may be utility in anticipation, for example being protected from human papillomavirus infection in the future, which may be more than simply the avoidance of QALYs lost when the disease would occur.
IC11	First and foremost: costs and QALYs are the main elements of the analysis and additional elements of value may, by and large, may already be captured by the QALY

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Interviewee	Paraphrased response
	or should not even be considered in the first place. The goal is to maximise population health which is distinct from maximising hope and anticipation. There may be elements of differentiating value against which QALYs can be traded-off, such as severity and equity. The question then becomes if indeed there is a societal preference for trading health or even social welfare against some of the other values that are being discussed.
IC14	Values beyond the QALY should be included in models, but then it should also be taken into account in the valuation of the opportunity costs.
IC13	Incorporating additional elements of value which can be called personal utility or patient preference can be done but should not be incorporated in the ICER to avoid a lack of transparency. Rather, it should be presented separately from the ICER to allow evaluation. Also, additional values can belong to clinicians, patients and decision-makers and should be reported separately.
Values beyond the current patient	
IC1	Values beyond the current patient should be taken into account as interventions may yield effects beyond the patient such as in reducing burden of caregivers. In communicable diseases one also models the effect of treating a patient has on others.
IC5	Costs and QALYs that occur in others than the patient under treatment can be included but should be reported separately for them to be identifiable as separate elements in the evaluation.
IC6	If a patient is cured, parents will have a long period without concern over the health of their child and that is a relevant treatment effect. That does not mean, however, that societies need to be willing to pay extra for achieving that value as there is a difference between assessing value and addressing the reimbursement question. Also, the opportunity costs may also have additional elements of benefit beyond the patient that is currently not included in its estimation.
IC11	If we are going to take into account the benefit of treatments in caregivers and family members, we need to address these values in the estimation of opportunity costs as well.
IC14	These can be taken into account but only if it is expected to change the decision. Otherwise it would be a waste of time and resources.
IC9	Values beyond the patient can be included but should be reported separately

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Interviewee	Paraphrased response
IC13	Values beyond the index patient are important and computationally not difficult to implement but data are often lacking. If cascade testing in family members can avoid adverse outcomes it should be modelled. In some instances, time horizons beyond the current patient's illness can be used.
Perspective	
IC1	The question on perspective is not specifically introduced or answered by new personalised treatments. In fixed health care budgets, the result of the analysis will be the same unless the budget becomes affected by savings in other non-health budgets.
IC5	In some instances, the additional value created beyond health can be so large that they have to be taken into account in the evaluation.
IC7	The issue of perspective is not specific to or related with PM
IC8	For very debilitating diseases which prevent patients from going to school the improved socioeconomic status/productivity gain needs to be taken into account
IC14	Whether or not a societal perspective should be adopted is not specific to PM.
IC13	The societal perspective should always be at least a scenario analysis if possible.
Equity	
IC1	PM, by definition, are a function of one's characteristics and as a consequence one may have a property that societies do not wish to discriminate on that perfectly aligns with probability of treatment effect. Hence, PM can increase equity concerns.
IC3	Authorities that take equity considerations serious should systematically consider equity concerns and if they do so, PM should not pose a threat to increased inequity. The whole point of PM is that individuals respond differently to treatment, so that has to be accepted from the outset.
IC5	Equity issues do not receive equal attention from the different international reimbursement authorities
IC6	The data that underlies economic evaluations may be affected by equity concerns. For example, estimating algorithms to predict treatment efficacy depends on the sufficient representation of equity-relevant groups in the training data
IC7	PM may result in increased inequality, as not everyone will get the same treatment, but its effect on equity considerations differs for each case. Accessibility to genetic tests is relevant and may differ between socio-economic groups.

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Interviewee	Paraphrased response
IC8	Personalised treatments often require quite some knowledge of genetic testing which is often not available in physicians in more geographically remote areas.
IC10	There is a concern that in private insurance settings the results of genetic tests can be used by health insurance companies in manners that was not intended when the test was conducted.
IC9	Higher susceptibility to disease following tests can result in lower admission rates or higher premiums to health insurance.
IC13	Cost-effectiveness analysis can look at subgroups in ethnic populations known to possess higher rates of pathogenic variations to allow the evaluation of equity effects. Inequity can also occur between rural and urban populations when PM technologies are concentrated in urban areas.
Conditionality of test sequences and/or test outcomes	
IC1	The model time should start when the patient undergoes the test. The population that undergoes the treatment is probably smaller than the population that underwent the test, but only looking at the group that tested positive, rather than the suspected group, results in a different scope of analysis. In principle, the costs of the test are borne by the suspected group and will need to be attributed to the treated group. Test itself might also have effects on quality of life that need to be incorporated.
IC7	If multiple tests are deployed, the timing of the test and the number tests that are conducted can be parametrised. Ideally the correlation between tests is taken into account, but this requires patient-level data, which might not always be available.
IC11	Tests can be conducted in different order and that may have treatment consequences. In breast cancer, for example, IHC and FISH can be conducted in parallel or consecutively and this may impact treatment choices. It is not clear cut how this needs to be dealt with, but it seems important to make sure that testing pathways are studies more thoroughly in clinical trials.
IC14	Conditionality of test sequences can be important but also complex to model, so first it has to be identified if it is likely to have a sizeable impact on the ICER. What can be important is to look at the added value of testing larger gene panels. That is often promoted but not necessarily a better allocation of resources if single gene panels capture the relevant actionable insights.

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Interviewee	Paraphrased response
IC9	When tests are performed sequentially, and at different time-points, the disease status and the probability of disease changes over time and this needs to be taken into account when possible, but often there is insufficient data.
IC13	Multiple tests are often conducted at once or in series and as a consequence identifying a comparator can be complicated
Time period until start of treatment	
IC6	The model should start when the test procedure starts. An example is CAR-T therapy: often survival functions are applied in the model from receiving treatment onwards, while in reality the time from harvesting T-cells until infusion should also be modelled. Patients may die in the interval from harvesting to infusion and this is an integral part of the analysis.
IC7	The turn-around time of the test should be included. In CAR-T therapy patients have to await the customisation of their treatment and may receive chemotherapy in the meantime, but sometimes they may not survive up to the point in time where they can receive the treatment.
IC12	It is important that the test used in evidence generation and evaluation is the same as the test used in real practice, which may be affected by lab-differences. The costs of the test need to be assessed against their true costs, which often depends on whether a lab conducts the test or the test is commercially marketed. In general, I would not include the costs of downstream tests that follow genomic testing because these tests are conducted for different reasons.
IC11	The time period between testing and receiving treatment may vary and may largely affect results, which is a prominent issue in conditions with high mortality. Using sufficiently small cycle lengths allows taking this issue into account.
IC9	In the evaluation of gene therapies, there has often been a whole diagnostic process in identifying a certain mutation which is often omitted from cost-effectiveness analysis. The question is if the patients are at risk during the waiting period, if that is the case it should be included in cost-effectiveness analyses, and otherwise, it should not be included on the effect side but only on the cost side.
IC13	Including waiting time is very important especially when there is a narrow window for the intervention, such as with pre-school children with neurodevelopmental or other conditions. A diagnosis that comes too late is the same as missed diagnosis.
Patients' uptake of testing & treatment adherence	

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Interviewee	Paraphrased response
IC6	The hypothesis is that who are tested adhere to treatment better because there is less uncertainty about the probability of success. However, this effect is already accounted for in the assessment of effectiveness. Generally speaking, it is difficult to account for adherence separately, as it is unknown to what extent adherence is already accounted for in the assessment of effectiveness.
IC7	For whole genome sequencing it is important to, up front, decide if patients are willing to be exposed to incidental findings wish not to be informed about those findings. We have done research into different services models to implement delivering additional findings in routine practice. From another study by the Melbourne Genomic Health Alliance and from literature, it is known that the moment at which additional findings are offered (e.g. during the first genetic counselling session in which the provision of primary findings is also discussed, or at a later point) impacts the uptake.
IC13	Willingness to be tested, the anxiety of knowing and not knowing, is a part of personal utility.
Clinicians' adherence to protocols and guidelines	
IC7	There is a use for preference studies into the association between the accuracy of a study and the likelihood that a clinician will use the results in treatment decisions in clinical practice.
IC11	Like patients, clinicians may not adhere to the outcome of a test, due to patient or clinician preference.
IC14	The real-world use of tests is often suboptimal. Tests are often only prescribed when common first or second line treatments do not have sufficient effectiveness. Similarly, clinicians do not adhere to the test the way we expect them to and that should be included in the model.
Miscellaneous	
IC3	Meta analyses become increasingly complicated due to PM: treatments can no longer be easily pooled.
IC2	Personalised pathways mean that cohort type models may be less appropriate than microsimulations which may be better in taking into account patient characteristics that drive treatment choices.
IC4	Capacity constraints are a serious concern in PM: tests are not as available as we may think they are.

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Interviewee	Paraphrased response
IC4	We evaluate test-treatment combinations and it is not possible to separate the elements of value that arise from the test from those that follow from treatment.
IC4	Issues in PM can be categorised in methodological issues, such as the appropriate evaluative framework, technical issues, such as programming challenges resulting from complex sequences, practical issues, such as data availability or knowing the unit costs of the test and organisational issues, such as how to pay for test treatment combinations. While there may be practical and organisational concerns, these should not be confused with methodological ones or used to push alternative evaluative frameworks for PM compared to other interventions.
IC5	Decision-uncertainty is often on the size of the QALYs gains, not the costs of the tests.
IC5	It is not easy to deal with negative test results, for which the treatment pathway is often diffuse which can mean that a range of comparators needs to be used.
IC7	It is a misunderstanding that discrete event simulation models require a lot of data. They are more flexible models than Markov-type models and is a more natural representation of reality.
IC10	Conducting a genomic test can have large psychological consequences for patients that underwent them and often creates demand for more downstream tests.
IC12	The evaluation of PM is not necessarily different from the assessment of rare diseases or targeted therapies which also suffer from limited data and small patient population. The main issue of PM is that all the limitations occur simultaneously.
IC12	When the European Medicines Agency (EMA) approves treatments based on limited evidence as is currently the case, we can count on having less RCT data in the future to base our evaluations on.
IC12	Perhaps commissioning trials is a better way forward than working with observational data gathered from conditional reimbursement.(57)
IC11	The ability to test someone does not mean that all geographic areas have the capacity, budget or knowledge to act on the result of the test.
IC14	The variation of treatments and treatment lines in oncology should be better captured in models
IC9	It is up to the decision-maker to decide if the cost of the test should be included in the cost-effectiveness analysis.

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Interviewee	Paraphrased response
IC9	The question on the distribution of reward between the test and the treatment is different from the question a cost-effectiveness analysis seeks to address.
IC13	The low prevalence of a mutation in a population is a specific challenge of PM as it hinders getting good epidemiological data.
IC13	In the case of hereditary conditions and cascade testing, clinicians have a duty of care that transcends the index patient.

5.4 Interviews with end-users

Four interviews with end-users of health economic models (i.e. decision-makers) were held between January and February 2020. The interviews lasted between 1 and 1.5 hours and are summarised below.

Interviewee	Paraphrased response
Effectiveness data from non-randomised (controlled) studies	
IC15	It is no longer realistic to assume that the reimbursement decision can follow directly after the market approval decision, due to the tendency in both the US Food and Drug Administration (FDA) and EMA to allow conditional market approval on lower quality evidence, evidence that cannot inform reimbursement decisions. The issue is not personalised medicine itself, but the fact that evidence with more uncertainty (e.g. due to small RCTs or single arm studies) is often accepted for certain health technologies.
IC16	Regulatory bodies only assess the risk-benefit relationship, while in HTA you have to take into account the existing treatments and cost-effectiveness. Regulatory and HTA agencies have different mandates.
IC17	The solution to poor quality data is not in more sophisticated modelling methods, there simply should be higher demands on manufacturers. Given the difference in demands from regulators and reimbursement agencies, manufacturers should be more aware that market approval is only first step and that further studies/data might be needed for reimbursement.
IC18	Decision-makers simply have to accept observational data to inform decisions when no other data is around.
Interventions aiming to cure; methods to compensate for potential bias in the extrapolation of outcomes	

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Interviewee	Paraphrased response
IC15	The time horizon needs to be relevant to the decision problem, hence when interventions have a long-term effect, the time horizon should be lifetime.
IC17	There is no reason to truncate the time horizon, as there is sufficient reason to assume that effects may be long lasting. This may be uncertain, but not a reason to change the time horizon.
IC18	When the cure assumption is uncertain, rules of thumb, such as a maximum time horizon of the median follow-up times two can be used. The definition of a cure is often not very clear.
Deviation from standard discount rates	
IC15	Discounting effects different from costs means implicitly assuming the that cost-effectiveness threshold would go up in the future.
IC17	Differential discount rates can be good to address the uncertainty in effects, for example through using a higher discount rate on health effects.
Uncertainty analysis	
IC15	Uncertainty is something that decision makers can deal with. A situation where there is low uncertainty about the added value of a medicine is still to be preferred, as decision makers would then not be uncertain about what they should be paying. However, high decision uncertainty can be managed to a certain extent through negotiating a lower price/discount.
IC16	It is not possible to solve uncertainty about long-term effectiveness associated with gene therapies by collecting more data, because it simply has not been observed yet. A product that has less uncertainty should be valued more than the same product with more uncertainty. Uncertainty is not be taken into account by decision makers enough currently. Uncertainty should be reflected in the price or willingness to pay threshold.
IC17	Uncertainty can be dealt with in probabilistic uncertainty analysis. When the uncertainty has been identified, it can be dealt with through for example lower prices or using different discount rates for health effects (which will also mean that a lower price is needed).
IC18	We should embrace uncertainty and be open about it. Personalised medicine does not require more uncertainty analyses than are already conducted, but we should be very transparent about the amount of uncertainty underlying a model.

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Interviewee	Paraphrased response
Values beyond QALYs	
IC15	There may be values beyond the QALY, but this does not mean that a reimbursement authority should be willing to pay for those values; optimising values beyond the QALY might not be an authority's objective.
IC16	It is plausible that the QALY does not capture all relevant values. Regardless of which value, it is more transparent to deal with additional values outside the QALY, such as through threshold weighing. Scientific spill over is not a value that ought to be included.
IC17	Some of the values beyond the QALY are already taken into account in the deliberation procedure following the health economic assessment. Several European jurisdictions already take 'severity' into account. The value of hope or scientific spill-over should not be included. Regardless of which values, it is preferable to not include these values in the QALY but adjust the willingness to pay threshold where relevant.
IC18	A decision-maker would be happy to consider additional values beyond the QALY if there is a sufficient evidence base. This could include values beyond the current patient.
Managed entry agreements	
IC15	The single-point-in-time reimbursement decision following market approval has had its time and may need to be replaced by a dynamic decision system, possibly using managed entry agreements.
IC16	Paying per QALY afterwards would take care of uncertainty, but it hands over the whole surplus to the manufacturer completely. Other way of treating uncertainty is collecting evidence over time and adjusting payment over time. But it is still difficult to prevent that the whole consumer surplus is handed over to the manufacturer.
IC17	Observational registries are expensive and those who have experience with running them are not necessarily positive about it. One may favour managed entry agreements in general, but there may be legal restrictions in a country limiting its enforcement. A higher risk premium is often a better alternative.
IC18	To make better use of the potential of managed entry agreements, those who deal with them should have a good understanding of the health economic model and the drivers of costs and uncertainties in it.
Perspective	

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Interviewee	Paraphrased response
IC17	A general issue with the societal perspective is that it, to some extent, discriminates against people who can't or don't work. There are many tricky ethical questions associated with these types of evaluation.
IC18	The societal perspective can be adopted if the societal gains included have sufficient evidence base.
Equity	
IC16	The problem is not that some subgroups might not get a treatment based on it not being effective, but there is an equity issue if a health economic model identifies that a treatment is not cost-effective in a certain sub-group and that it therefore would not be reimbursed in that subgroup.
IC17	Equity issues are not specific to personalised medicine
IC18	When personalised medicines are specialised and cost-intensive, there is no equal access between regions which may increase inequalities.
Modelling tests	
IC15	If the testing is routine practice its costs do not need to be included in the economic evaluation as it is not part of the decision-problem.
IC16	If the test is related to the treatment, then the costs of the test should be included. But the test can also be part of standard care for other reasons, then it should not be included.
IC17	The utility impact of not being among those who can benefit from new treatment is not something that should be included
Imperfect implementation	
IC15	Models should reflect reality: if drug-holidays are a thing, the model should reflect that.
IC16	Models can be used to identify subgroups where the treatment is most (cost-) effective.
IC17	The initial requirement should be that a model reflects perfect implementation, but it could be validated if that turns out to be true in the long run.
IC18	A decision-maker needs to be informed about both the optimal and the real world scenario.

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5.5 Guidance for good health economic modelling practice in PM

The following section contains the guidance for good health economic modelling practices in PM. The guidance is structured according to the main topics we identified and illustrated with examples identified in the systematic literature review. In section 4.5.13, the guidance is summarised in a checklist with recommendations. The guidance aims to be a comprehensive overview of the issues one might come across when modelling PM. We do not expect all issues to be relevant for each cost-effectiveness analysis and leave it to modellers to decide which issues are relevant to their model. Similarly, we acknowledge that the recommendations given may not always be executable but encourage modellers to address the raised issues as much as possible. The issues discussed are not exclusive to PM and may be relevant in the modelling of other interventions as well.

5.5.1 Modelling test-treatment combinations

As explained in section 3.1, the stratification/testing phase is key in personalised medicine. A comprehensive overview of aspects that are relevant for the modelling of tests and biomarkers has been given in the AliGnment in the Reporting of Economic Evaluations of Diagnostic Tests and biomarkers. (AGREEDT) checklist.(58) A number of aspects warrant particular discussion in the context of PM.

Positioning

Tests used for stratification in PM – such as gene tests – may be applied at different time points and/or in varying combinations with other tests. As a result, the number of possible pathways and comparators in a single health economic model may explode, increasing computational burden. Often it will not be necessary to model all possible pathways as some are more likely to occur than others. When choosing a subset of possible pathways to be modelled, it is important to check whether this subset is in line with prevailing opinion in clinical practice. One should always be conscious of the options that are left out of the health economic model and consider whether their inclusion would alter decision-making.

Recommendation 1: Consider if the modelled position of the test in the clinical pathway is in line with clinical practice.

Consequences of testing

When a new treatment comes onto the market that requires the introduction of a new test, it is likely that not everyone who receives the test will receive the new treatment as well. For example, while many breast cancer patients may receive HER2 testing, only those that test positive are offered HER2 targeted therapy. A model considering the introduction of a new treatment should also consider the consequences of introducing a new test. Firstly, it is important to include the costs of the test itself into the intervention costs. This should be done for the entire population that is tested and not only those that test positive. Furthermore, even though patients with a negative test result may not be eligible for the treatment under consideration, a negative test result may bring about further testing and treatment,

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affecting health outcomes and costs. If the test is not part of routine care, relevant downstream effects ought to be incorporated in the model.

Recommendation 2: If a test is not part of routine care, ensure that the (downstream) costs and benefits of testing for both individuals who test positive and individuals who test negative are included in the model.

Test performance

The performance of a test (sensitivity, specificity, positive predictive value, negative predictive value) is likely to change over time and vary according to the patient population in which the test is applied. It is therefore important to ensure that the performance parameters used to populate the health economic model were obtained from a recent study, using a population that matches well with the modelled population.

Recommendation 3: Ensure that the data on the test performance are the latest available and obtained in a population that is in line with the modelled population.

If several tests are included in the evaluation, they can be modelled as if they were performed in parallel or in sequence. Ideally the correlation between the results of the different tests is considered. However, this may be complex, especially when limited patient-level data are available. Therefore, efforts to model the interdependence between tests may focus on those situations in which this element is likely to affect the incremental cost-effectiveness ratio.

Recommendation 4: When multiple tests inform treatment decisions, the interdependence between tests should be considered.

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Example of good health economic modelling practice from the systematic literature review
Considering interdependence between test results, by Garrison et al. (2013)

Patients with HER2-positive breast cancer have a worse prognosis than HER2-negative patients but can be treated with monoclonal antibodies specifically targeting HER2, such as trastuzumab – the treatment considered in this study. HER2 status can be determined using either IHC, which measures HER2 overexpression, or FISH, which measures HER2 gene amplification. A FISH test is assumed to either be positive or negative, while an IHC test is scored as follows: 0 and +1, negative; +2, equivocal; +3, positive. The study compares an 'expanded reflex' testing approach to a standard testing approach.

In the standard approach, HER2 status is assessed using either IHC or FISH. With expanded reflex testing, patients testing negative on either test subsequently receive the alternative test for confirmation. It is assumed that 20% of patients receives FISH first, while 80% receives IHC first. In the expanded reflex testing scenario, the interdependence between the two tests is incorporated in the model using conditional probabilities based on data on the concordance between the test outcomes on the two tests (see below). In modelling the standard approach, only the outcome probabilities for either test in isolation are used ('initial FISH/IHC result'). Expanded reflex testing is estimated to render a QALY gain of 0.037 per patient treated compared to the standard approach, which is driven by a lower rate of (untreated) false negatives. Costs increase by $1455, giving an ICER of $39,721 per QALY gained.

(Conditional) probabilities

Initial FISH result	
Positive	0.21
Negative	0.79
Initial IHC result	
0	0.36
1+	0.36
2+	0.12
3+	0.16
FISH-positive after IHC	
IHC0	0.016
IHC1+	0.049
IHC2+	0.298
IHC3+	0.924
IHC result after FISH-negative	
IHC0 or IHC1+	0.66
IHC2+	0.31
IHC3+	0.03

A test result is often a continuous outcome, such as the level of PD-L1 expression in cancer cells. If the PD-L1 level is 'high', a person may benefit from immunotherapy. Varying the cut-off value that is used to determine when PD-L1 expression is 'high', may change the cost-effectiveness of immunotherapy. It is therefore important to clearly define the positivity criterion and investigate which changes in the cut-off level are likely to impact the ICER.

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Recommendation 5: Clearly define the cut-off values that are used to define the different outcomes (e.g. positive/negative, high/medium/low risk) of a test.

Practice variation

For some PM interventions, a commercial companion-diagnostic test to identify likely responders to therapy has been developed. This test may be purchased from the manufacturer of the medicine or is provided 'for free' together with the drug. Alternatively, hospital laboratories may perform the relevant test themselves, using their own resources. As there may be a large difference between the purchasing price of a commercial companion-diagnostic and the cost of in-house testing by hospital laboratories, as well as signification variation in the cost of testing across laboratories, it is important to confirm that the costs used in the model reflect costs in practice and, where relevant, account for practice variation. Test performance may also vary across laboratories.

Recommendation 6: Confirm that the costs of the test are representative for the actual costs of testing in the setting of interest and consider possible variation in costs and performance of testing across laboratories.

Waiting times

Patients who present with symptoms are generally faced with waiting times, as they do not receive treatment instantaneously. These include the waiting periods between a patient presenting with symptoms and ordering a test, between ordering a test and actually performing a test, between performing a test and getting the test-result (i.e. the turnaround time of the test), and between the test result and start of treatment. Whenever a waiting period has an impact on outcomes, it is important to explicitly include these time periods into the model. This is particularly important for conditions with a high short-term morbidity and/or mortality.

Recommendation 7: If there is a risk of disease progression or mortality during waiting periods, relevant waiting periods should be explicitly incorporated into the model.

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Example of good health economic modelling practice from the systematic literature review
Considering turnaround times, by Whittington et al. (2018)

After the decision to initiate patients on CAR-T treatment (in this case: tisagenlecleucel), patients undergo leukapheresis in the hospital so that their T-cells can be harvested, which will be used to prepare the tisagenlecleucel infusion. Not all patients who undergo leukapheresis ultimately receive the tisagenlecleucel infusion, due to adverse events during leukapheresis, manufacturing failure during the preparation of the infusion, or because they die before receiving the infusion. The time period from initiation of leukapheresis until the tisagenlecleucel infusion is explicitly included by using a decision tree. The first node in this decision tree is followed by three branches: 1) continue with the tisagenlecleucel infusion after undergoing leukapheresis, 2) discontinue before infusion because of adverse events or manufacturing failure, or 3) die before receiving the infusion. Patients who discontinued before infusion because of adverse events were assumed to be unable to tolerate other active therapies and therefore received palliative care only, while patients who discontinued because of manufacturing failure were assumed to receive clofarabine. After the decision tree, patients moved to a partitioned survival model. In a scenario analysis where the model did not incorporate waiting time by starting at infusion instead of at leukapheresis, the incremental costs increased from $329,498 to $454,892 and incremental QALYs increased from 7.2 years to 9.1 years. The increase in costs and QALYs is caused by the exclusion of patients who did not receive the tisagenlecleucel infusion and therefore had a lower treatment cost and shorter quality-adjusted life expectancy. These changes slightly increased the incremental cost-effectiveness ratio, from $46,000 per QALY gained for the model that incorporated waiting times between leukapheresis and infusion, to $50,000 per QALY gained for the model starting at infusion.

5.5.2 Effectiveness data from non-randomised (controlled) studies

Incomplete or absent RCT data

The increased stratification in PM increases the number of subgroups, creating practical challenges in obtaining RCT data on efficacy for each subgroup. Additionally, there are forms of PM for which randomisation is considered unethical or infeasible. There appears to be increasing acceptance of non-RCT evidence among regulators such as the EMA and the FDA. For example, for larotrectinib (a tumour-agnostic pharmaceutical used to treat solid metastatic tumours with neurotrophin receptor tyrosine kinase (NTRK) fusions), the EMA and the FDA considered evidence of a high response rate in combination with a long duration of response from a phase-two single-arm basket trial sufficient to grant (conditional) market approval. However, market approval based on non-RCT evidence poses challenges for HTA agencies. The more incomplete the evidence network, the harder it is to apply methods to synthesise evidence (e.g. network meta-analysis) and the greater the uncertainty around cost-effectiveness results. Yet HTA agencies need to base reimbursement recommendations on solid evidence of comparative (cost-)effectiveness.(59)

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In this backdrop, some reimbursement authorities make use of a dynamic assessment of the evidence instead of a static one-time assessment. As part of 'conditional reimbursement' or 'coverage with evidence development' programmes, data deficiencies and uncertainties are accepted for a limited time period, during which new evidence is gathered. When new evidence becomes available, the reimbursement decision is reconsidered. The UK and the Netherlands, for example, set up registries as part of conditional reimbursement programmes, seeking to alleviate the uncertainty at the time of the reimbursement decision. The observational (or real world) data that was collected in these registries was supposed to inform questions on relative effectiveness that were not yet answered upon initial approval. However, in the Netherlands the experience with this programme was not univocally positive, as the biases present in the observational data rendered answering research questions on relative effectiveness virtually impossible.(60, 61) Similar concerns have been raised about the Cancer Drug Fund.(57)

Where possible, health economic models should use effectiveness data obtained from studies with at least two active comparator arms or (network) meta-analysis. Nonetheless, if such data is unavailable, modellers may perform value of information (VoI) analysis and/or sensitivity analysis in order to inform the design of future RCTs.(62, 63) Note that, while patient equipoise may be hard to meet for early trials comparing a new active treatment to placebo, RCTs with two active comparators may both be ethical and feasible to conduct after market approval.

Recommendation 8: Where possible, use effectiveness data from trials with two active comparator arms or data from (network) meta-analysis, rather than observational data collected under conditional reimbursement programmes. If such data is not available, perform value of information analysis and/or sensitivity analysis that can be used to inform the design of any future trials.

Observational data on effectiveness

While effectiveness data from studies with two active comparator arms is preferred, modellers may sometimes have to work with data from single-arm studies. Moreover, the time horizon of a comparative effectiveness study may be too short to inform longer-term effectiveness. In these instances, observational data (e.g. from administrative databases or patient registries) may be used to provide a control arm to the single-arm study or to estimate longer-term effects. When real-world evidence is used to estimate effectiveness, appropriate statistical methods should be applied to increase the comparability of the control group to the group included in the single-arm study and reduce bias.(64, 65) Such methods include propensity score matching, inversed probability weighting(66, 67), instrumental variable analyses(68), regression discontinuity designs(69), difference-in-difference analyses(70, 71), and interrupted time series analyses.(72, 73) However, these methods commonly require large numbers of observations, which might not always be available for PM interventions. As the choice of covariates in propensity score matching models can have a sizable impact on the outcome, it is important to specify the matching model upfront and provide solid arguments when covariates other than the pre-defined ones are used.

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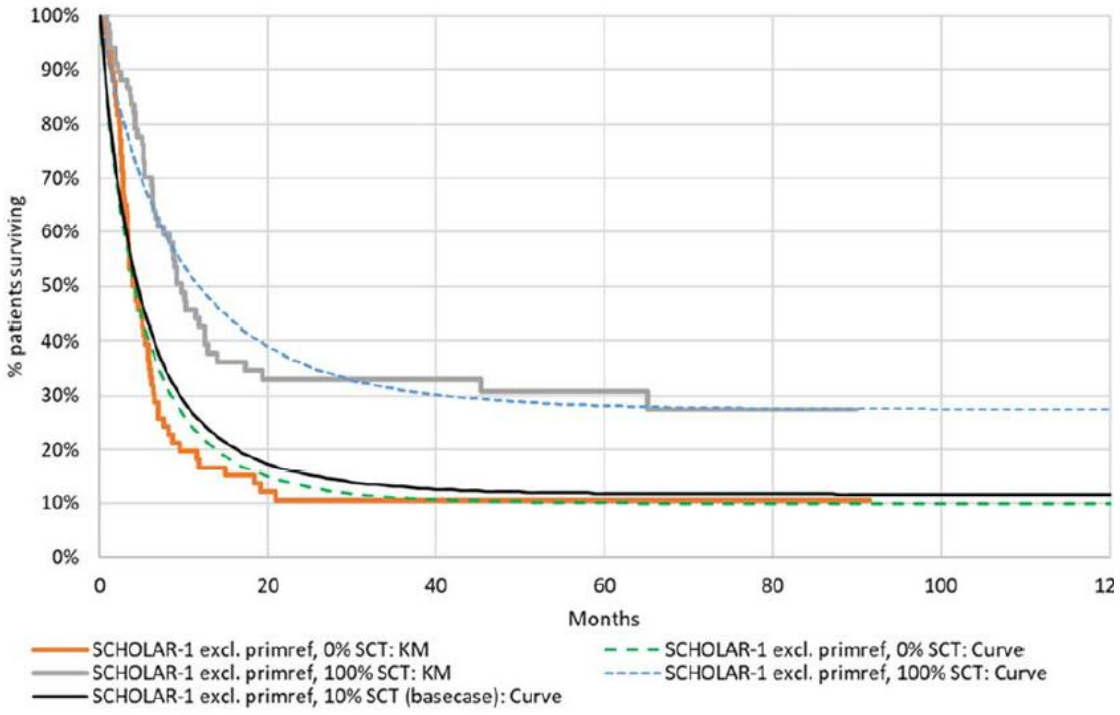
Example of good health economic modelling practice from the systematic literature review

Adjusting comparator data from an observational study to increase comparability between the intervention and comparator patient populations, in the NICE STA of CAR-T treatment axicabtagene ciloleucel (2018)

In the NICE STA of CAR-T treatment axicabtagene ciloleucel in patients with refractory diffuse large B-cell lymphoma, input data on the effectiveness of the intervention was based on the ZUMA-1 trial. As ZUMA-1 is a single-arm trial, the effectiveness of the comparator was based on another source: SCHOLAR-1 data. SCHOLAR-1 consists of data from observational cohorts and follow-up of two large RCTs including patients with refractory diffuse large B-cell lymphoma. To ensure comparability between the SCHOLAR-1 and ZUMA-1 populations, primary refractory patients and patients with Eastern Cooperative Oncology Group (ECOG) performance status between 2 and 4 or with unknown ECOG status were excluded from the SCHOLAR-1 data. Nevertheless, the proportion of patients receiving SCT in the adjusted SCHOLAR-1 data was considered unrealistically high (50.4%) by clinical experts who expected that only 10% of relevant patients would receive SCT in clinical practice. To account for this, the SCT proportion in the SCHOLAR-1 population was adjusted in the overall survival (OS) estimates. First, the OS for the SCHOLAR-1 population that underwent SCT (n=67) was obtained and survival parametric curves were fitted to the Kaplan Meier curves for this population. Then, the same was done but with patients who did not receive SCT (n=66). From these two OS curves, a weighted average OS was obtained to represent OS for a population in which 10% of patients received SCT (see the Figure 8 below).

Figure 8. Overall survival of BSC (based on adjusted SCHOLAR-1 data) with 10% SCT
(Source: NICE STA Axicabtagene ciloleucel)



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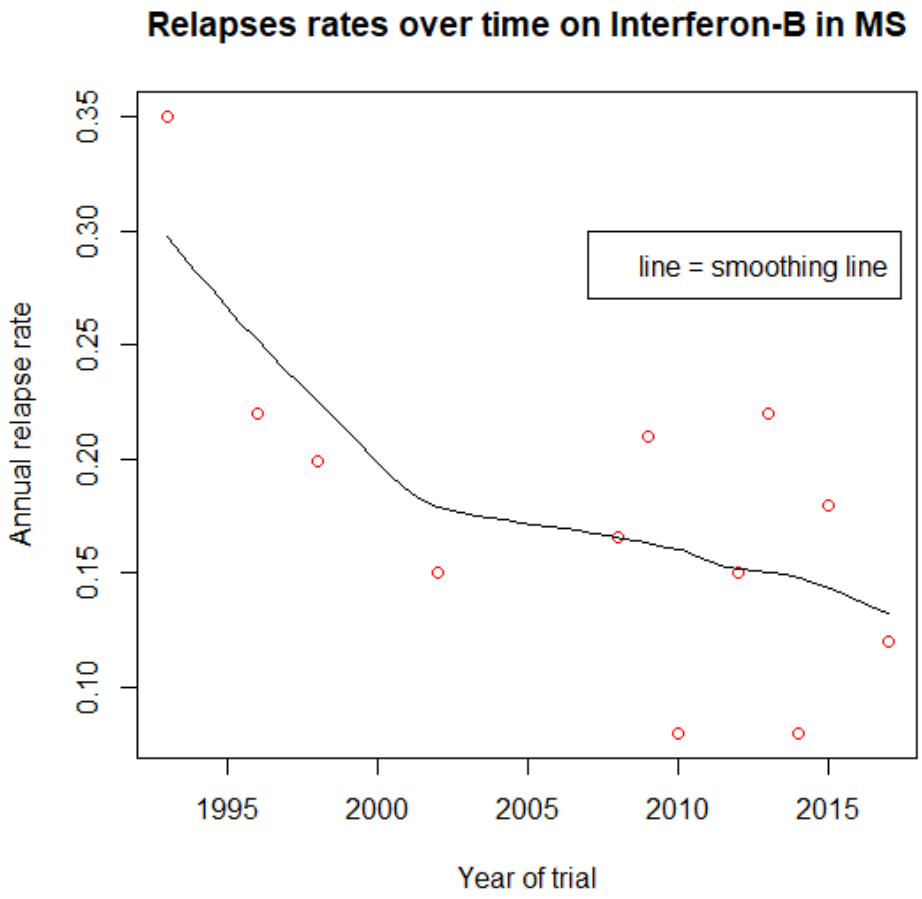
Historical cohorts

When the comparator group is based on a historical data, one must be conscious of changes over time that improve health outcomes. These changes may relate to the treatment itself, which may have improved due to, for instance, optimisation of dosing or improved add-on treatments, or to external factors, such as a reduced prevalence of a risk factor like smoking.

Figure 6 depicts the annual relapse rate in remitting multiple sclerosis (MS) patients on Interferron-β treatment between 1993 and 2017 in 19 clinical trials. It is based on data extracted from a recent network-meta analysis.(74) The figure shows that there is a declining trend in relapses in patients receiving the same treatment. The declining trend in relapse rate over time may incorrectly be attributed to a newly introduced intervention, if a time trend covariate is not included in the estimation of effectiveness. As there may also be changes in costing methodology over time, it is important to confirm that the costing approach used in the historical cohort is sufficiently similar to the one used in the intervention arm.

Figure 6. Relapse rates over time in MS patients treated with Interferon-B.



Annual relapse rate = events / person-years. Interferon-B consists of pooled data for Interferon-B-1a and 1b, in different dosages and modes of administration. Average presented for years with multiple trials. Source: author's calculations

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Recommendation 9: When effectiveness is estimated using historical cohorts, account for the trend in efficacy of the comparator over time, in order to correctly attribute differences in efficacy to the treatment.

Unknown mutation status in comparator group

For new treatments targeted to specific a gene mutation in cancer cells, using historical data to estimate the efficacy of the comparator treatment causes an additional problem. Often, past patients were not tested for the gene mutation under consideration. This means that the prognostic value of the mutations for the natural course of disease cannot be obtained through the historical cohort. It also means the distribution of the mutation in the historical cohort is unknown. Consequently, it is difficult to evaluate if the observational data used to estimate incremental effectiveness is appropriate, as the assumption that the disease progression in the comparator group (containing people with and without mutations) is similar to that in the intervention group (containing only people with the relevant mutation) cannot be validated. Estimating effectiveness in such a situation is virtually impossible.

Recommendation 10: When using a historical cohort to estimate the effectiveness of a treatment for a patient population with a specific gene mutation, obtain data on the distribution of the gene mutation of interest in the historical cohort, as well as data on the prognostic value of the gene mutation.

5.5.3 Extrapolating outcomes for interventions aiming to cure

Treatments that are more tailored to patient and disease characteristics may have a higher probability of success and possibly a higher probability of offering a cure. Several therapies aiming to cure have come on the market over recent years (e.g. immune checkpoint inhibitors). Often the duration of the effect has only been observed for a limited period of time and the extent to which the effect is sustained is generally uncertain, posing challenges for health economic modellers. It may be debated whether a treatment with an uncertain sustained effect can be considered a cure in the strict sense of ‘eradication of the initial disease and its consequences’. It may also be debated whether the treated element of the disease is its sole driver.

Cures in health economic modelling

In health economic modelling, a ‘cure’ is often defined as the point in time after which patients are no longer at risk of excess mortality and morbidity. From this point onward, patients are usually assigned the same age and gender-specific parameter values as the general population.

In oncology, cure fraction models are sometimes used to represent patient populations where a subset of the population is ‘cured’ and experiences long-term survival, while other patients do not experience such a cure. In a study by Bullement et al.(75), cure fraction models were shown to better predict survival than models that do not reflect the heterogeneity in mortality in the investigated population. Bullement et al. note: “We have shown that cure-based models may represent a useful tool for projecting survival when long-term survival is expected in a proportion of patients. However, the presence of a ‘cure

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fraction' is not evidence of a 'true' cure".(75) The US-ICER has added models that account for a cure fraction to their reference case for 'high-impact single and short-term therapies'(76), and state in their technical brief that "In cases where there is a plausible hypothesis for a potential cure and where available data show evidence of a plateau in survival, these models are likely to better fit available survival data."(77)

However, a better statistical fit on short-term data, especially for intermediate endpoints such as progression-free survival, does not prove patients have been cured. The assumption that part of the treated patients is cured (the 'cure hypothesis') requires validation by clinical experts. Moreover, statistical models that fit well to the short-term trial data, do not necessarily provide the most plausible extrapolation beyond the trial period.(78) Whether and for which proportion of the patients a treatment constitutes a cure is often only verifiable in hindsight. Hence, the cure hypothesis must be strong before it is to be used in the base case. This especially applies to economic evaluations in which the required life-time horizon involves the extrapolation of survival benefits far beyond the observed period. Furthermore, when new data become available, the extrapolations beyond the trial period should be validated be comparing the model projections with the updated data from trials.(78)

Recommendation 11: When modelling the outcomes for interventions aiming to cure, the cure assumption and the choice of survival model used for extrapolation beyond the observed trial period should not only be informed by statistical fit of the model to the observed data, but also by expert opinion.

Cure fraction modelling, in its current form, is relevant mostly for conditions with high mortality. However, some of the therapies aiming to cure on the market mainly affect morbidity. For example, the first gene therapy approved by the FDA and EMA, voretegine neparvovec (Luxturna) for the treatment of patients with retinal pigment epithelium65-mediated inherited retinal disease, aims to halt (or at least slow down) the progression of visual impairment. The duration of the treatment effect of voretegine neparvovec beyond what has been observed in trials is uncertain. While a true 'cure' would require the treatment effect to last a lifetime, this may not be realistic to assume. Like in cure fraction modelling, assumptions regarding the treatment duration ought to be thoroughly checked with clinical experts.

Excess mortality

Even when an individual no longer has a certain disease, their risk of, for example, new malignancies is higher than the risk for the general population. For example, Janssen-Heijnen et al. demonstrated that while little excess mortality after 3 to 15 years was observed in patients who were cured of melanoma and stage I breast cancer, but that patients who had suffered from other tumour types and who survived up to 10 or 20 years after diagnosis still had poorer survival than the general population.(79) The authors hypothesised that this could be due to late recurrences, secondary tumours or comorbidities associated with cancer risk factors.(79) Hence, the cure assumption may not be equally valid in different types of cancers as, depending on the histology, individuals may remain at risk for excess mortality. Therefore, applying general population mortality rates may not be appropriate for all 'cured' patients.(80) Rather than assuming a cure by applying mortality rates from the general population to long-term survivors,

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more accurate mortality rates may be based on additional data sources such as cancer registries, through which figures on conditional survival can be obtained.(81)

Recommendation 12: When modelling the survival curves for interventions aiming to cure, apply excess mortality among long-term survivors, rather than assuming these patients are fully cured by applying age- and gender-specific general population mortality.

Example of good health economic modelling practice from the systematic literature review
Extrapolating outcomes of a potential curative intervention in the ICER report of CAR-T treatment (2018)

Two CAR-T treatments for B-cell malignancies, tiasagenleuclecel (Kymriah) and axicabtagene ciloleucel (Yescarta) were evaluated in two patient populations (children with B-cell acute lymphoblastic leukaemia and adults with B-cell lymphoma) in the CAR-T report published by ICER. The effectiveness of the CAR-T treatments was based on data from clinical trials. However, the short follow-up data currently available from these trials (15.4 months for ZUMA-1, 3.7 months forw JULIET), requires extrapolation of overall survival after CAR-T treatment. The primary goal of CAR-T treatment is curing cancer. The health economic model in the ICER report was based on this curative intent. In the base-case analysis, the cure assumption was modelled by introducing a knot in the survival curve once the survival curve flattened (i.e. slope equalled zero). It was assumed that patients who survived beyond the point of the knot, which was at five years after treatment, were effectively cured and would experience a mortality risk equal to the general population, adjusted for excess mortality observed among long-term survivors of B-cell malignancies. For the paediatric acute lymphoblastic leukaemia cohort, excess mortality was modelled by applying a standardised mortality ratio of 9.1 to all-cause risk of death for long-term survivors, based on estimates from a published study. Evidence did not suggest a standardised mortality ratio greater than 1 for the adult B-cell lymphoma cohort, though the assumed mortality ratio was varied in sensitivity analysis. In a scenario analysis, the knot at five years after treatment was removed to reflect standard parametric modelling practice (i.e. without modelling a cure assumption). This can be interpreted as the lower bound for survival. Due to smaller incremental QALY gains as compared to the base-case, the ICER increased from $45,871 to $77,511 per QALY gained for tisagenlecleucel as compared to clofarabine and from $136,078 to $259,378 per QALY gained for axicabtagene ciloleucel as compared to chemotherapy.

5.5.4 Expert opinion

Given that data gaps and high uncertainty are a key issue in PM, there might be an increasing need to rely on expert opinion. When expert opinion is used to provide input for quantitative parameters in the model, formal methods to synthesise the opinions of multiple experts into a probability distribution should be used. An example is the SHELF, in which individual experts are asked to make their own quantitative judgements, after which a group consensus distribution is estimated using linear opinion pooling with equal weights.(82) Such an approach could for example be applied to the cure models where experts could be asked to assign probabilities of surviving up to certain unobserved time-points.

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Recommendation 13: When expert opinion is used to estimate quantitative model parameters, use a formal method to synthesise the opinions of the experts into a probability distribution.

5.5.5 Discounting

In health economic modelling, discounting is used to calculate the present consumption value of future costs and benefits. The rationale to do so lies in the opportunity costs of capital (i.e., the returns forgone by not investing in the most profitable alternative), time preference (people value future costs and benefits less than current costs and benefits, with their valuation diminishing as the future becomes more distant), and diminishing marginal utility (people derive less utility from future consumption than current consumption because they are expected to have a higher consumption level in the future as a result of economic growth). Through healthcare, financial resources can be transformed into health, implying exchangeability between wealth and health. Discounting is therefore applied not only to interventions' costs but also to their health outcomes.(83)

In most countries, uniform discounting of costs and benefits is recommended for reasons of consistency(84) and to avoid the postponement paradox, which shows that if benefits are discounted at a lower rate than costs, the cost-effectiveness ratio continuous to improve when the launch of the intervention is delayed.(85) The Netherlands, Belgium and Poland, on the other hand, advocate differential discounting in cost-utility analysis, where health benefits are discounted at a lower rate than cost, to account for the expected increase in the future value of health benefits (if income grows, so does the willingness to pay for health). Is has been shown that consistency can also be achieved under differential discounting.(86)

In PM, there may be large upfront costs, while the benefits stretch far into the future. Gene therapies, for example, are often given as a one-off (highly expensive) treatment, while benefits may be long-lasting. Similarly, the introduction of large-scale genetic screening programmes is likely to be very costly in the short-term but has the potential to prevent many future disease cases. This has prompted some to argue that the discount rate for benefits should be lowered in economic evaluations of PM, in order to place a higher value on future benefits.(55) Others have proposed hyperbolic discounting, in which the discount rate is gradually reduced over time.(83)

However, allowing for discount rates to be different for PM interventions would implicitly favour PM interventions over other interventions, which may not be in line with policy objectives and public opinion. To ensure comparability of ICERs across interventions, all interventions should be subject to the standard discount rates recommended in national HTA guidelines.

Recommendation 14: PM interventions should be subject to the same discount rates as other interventions within the same jurisdiction.

The discount rate applied can have a substantial impact on the results of economic evaluations. It is therefore recommended to perform sensitivity analyses with differential and/or hyperbolic discount rates. Note that it has been demonstrated that adding future cohorts to a model with differential discounting,

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which compromises a comparison of interventions with different numbers and starting years of future cohorts, will lead to lower ICERs.(87) This issue may be relevant to screening programmes, for instance.

Recommendation 15: For interventions with large upfront costs and benefits that stretch into the future, the impact of differential and/or hyperbolic discounting should be investigated in sensitivity analyses.

Recommendation 16: When using differential discounting for models that include future cohorts, the discount year should be mentioned for every modelled cohort.

One additional point worth mentioning relates to market entry agreements. When a market entry agreement is in place that moves a proportion of the large upfront costs into the future, the intertemporal effects should be accounted for by assigning the costs to the years in which they actually occur.

Example of good health economic modelling practice from the systematic literature review
Deviation from discount rates for a gene therapy, by South et al. (2018)

Strimvelis is a gene therapy for adenosine deaminase deficiency–severe combined immunodeficiency (ADA-SCID). Strimvelis was compared with haematopoietic stem cell transplant (HSCT) from a matched unrelated donor (MUD) and HSCT from a haploidentical donor in a NICE Highly Specialised Technology Evaluation. The manufacturer argued that a discount rate of 1.5% should be applied to costs and health outcomes, on the basis that "Strimvelis restores patients to full or near full health over a long time period who would have otherwise died or had a very severely impaired life". The ERG was concerned that many patients with ADA-SCID would not return to general population life expectancy and morbidity after a successful procedure (either HSCT or Strimvelis) and therefore questioned whether NICE's criteria for using a 1.5% discount rate was fulfilled. The committee therefore considered both a 1.5% and 3.5% discount rate. The ICER for Strimvelis compared to HSCT from a MUD was £74,430/QALY with a 1.5% discount rate and increased to £120,506 per QALY gained with a 3.5% discount rate. Strimvelis was dominant compared to HSCT from a haploidentical donor when applying a 1.5% discount rate and the ICER was £12,106 per QALY gained with a 3.5% discount rate.

5.5.6 Values beyond the current patient

Perspective

It has been argued that PM interventions may come with significant additional values beyond increased health for the treated patient, which ought to be taken into account by conducting economic evaluations from a societal perspective instead of a healthcare payer perspective. For example, a gene therapy that leads to a complete resolution of a disease in children may also lead to a lifelong increase in productivity, a reduction in the use of informal care and services from the social care and welfare sector, as well as a lifelong improvement in the quality of life of caring relatives.

However, the presence of such additional benefits is not exclusive to PM interventions, as societal benefits are relevant to many other interventions (e.g. neonatal care). If broader societal benefits are included for PM interventions, they should also be included for all other interventions. Otherwise, the beneficiaries of PM interventions are implicitly prioritised, at the expense of other patients.

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Recommendation 17: An economic evaluation of PM should be conducted from the same perspective as other interventions within the same jurisdiction.

In countries where a healthcare or payer's perspective is prescribed by national HTA guidelines, the effect of taking a societal perspective on cost-effectiveness outcomes may be investigated in scenario analysis. Note, however, that the cost-effectiveness threshold, whether based on opportunity cost or willingness-to-pay, will be different for interventions assessed from a societal perspective than for interventions assessed from a healthcare or payer perspective. If the regular threshold is based on a payer perspective, the ICERs of interventions assessed from a societal perspective cannot be assessed against this threshold.

Recommendation 18: PM interventions that have substantial wider societal benefits should also be evaluated from a societal perspective in a scenario analysis, if the base-case is conducted from a healthcare or payer's perspective.

Caregiver burden

It has been argued that when a societal perspective is used, the costs and effects for relatives of the treated patient who provide informal care should always be considered.(88) Caregivers may be substantially affected by the patient's treatment. For example, the treatment may increase the independence of the patient to such an extent that their caregivers are relieved of burdensome – but possibly also rewarding – caring duties.(89) In contrast, new treatments that reduce the financial burden to the healthcare system by reducing length of stay in hospitals might impose a financial and well-being burden on caregivers who fill the care gap following hospital discharge.

While caregivers are likely to experience utility changes as a result of the patient receiving treatment, there are several concerns regarding the inclusion of caregiver burden utility in economic evaluations. A key issue is that the utility of the patient is likely to be correlated with the utility of the caregiver; attempting to assess them separately may result in double counting. Furthermore, the inclusion of potential benefits of caregivers on the utility side would require the inclusion of their costs as well, which would likely also lead to double counting. A solution, with less risk of double-counting, is to include caregiver burden only on the cost-side of economic evaluations through the monetary valuation of caregiver time(90) (as proposed in already in 1998 (91)). As caregiver burden is not often measured in clinical studies, methods have been developed to estimate the hours of care provided from patients' EQ-5D data.(92)

Recommendation 19: For jurisdictions that employ a societal perspective, caregiver burden should be included on the cost-side of the economic evaluation.

Relatives at risk

A genetic test may identify a condition that is the result of a germline mutation, which means that relatives might also be at risk. When a pathogenic germline mutation is found in a patient (also referred to as 'index patient' or 'proband'), genetic counselling and testing is generally also offered to relatives

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of the patient, through so-called 'cascade testing'. Focussing the economic evaluation of a genetic test (that is not yet part of routine care) only on index patients is insufficient, as it offers an incomplete reflection of the consequences of the introduction of this test. The costs and benefits of testing relatives should be included as well.

Recommendation 20: When evaluating the introduction of a genetic test, the costs and benefits of conducting tests in relatives of index patients should be included in the model.

Example of good health economic modelling practice from the systematic literature review
Incorporating relatives of the index patient, by Gallego et al. (2015)
Patients with colorectal cancer or polyps may be referred to be tested for hereditary colorectal cancer and polyposis (CRCP) syndromes based on their family and/or personal disease history. In this study, standard care for such patients was assumed to include a diagnostic protocol that starts with immunohistochemistry of tumour tissue. If abnormal staining of the mismatch repair genes MLH1, MSH2, MSH6 or PMS2 occurs, the respective gene is sequenced in order to confirm the presence of pathogenic mutations. (In the case of MLH1 staining, the MLH1 gene is only sequenced once somatic variants in the BRAF genes have been ruled out.) Standard care was compared against an approach in which all patients referred to genetics services receive next-generation sequencing (NGS) panel testing. Four different options for the NGS panel were evaluated. The panel that was estimated to be most cost-effective includes Lynch syndrome genes (i.e. the four mismatch repair genes mentioned above, and Epithelial cell adhesion molecule (EPCAM)), as well as other genes associated with both autosomal dominant and autosomal recessive syndromes with high penetrance of colorectal cancer.
It was assumed that first-, second- and third-degree relatives of the index patient receive targeted testing for the specific pathogenic mutation found in the index patient. In cases where the mutation is associated with an autosomal recessive syndrome, it was assumed that less relatives are approached for testing than in cases with autosomal dominant mutations (6 vs. 12). The percentage of relatives in which a pathogenic mutation is identified was also assumed to be less (25% vs 45%). The health outcomes for the relatives were based on the relevant mutation and calculated using the penetrance of colorectal cancer and the median age of onset within the gene group. The ICER for the NGS panel was estimated to be $36,508 per QALY gained. In a scenario analysis, the option of testing only first-degree relatives of the index patients was assessed, rendering an increased ICER of $59,661 per QALY gained.

5.5.7 Values beyond the QALY

Some have argued that the quality-adjusted life year insufficiently captures the full value interventions may have. The ISPOR Value Assessment Framework Special Task Force identified a range of 'additional' values(6), depicted in dark blue in the value flower below. The word 'additional' is placed in inverted commas as it may be argued that at least some of these value elements are already captured

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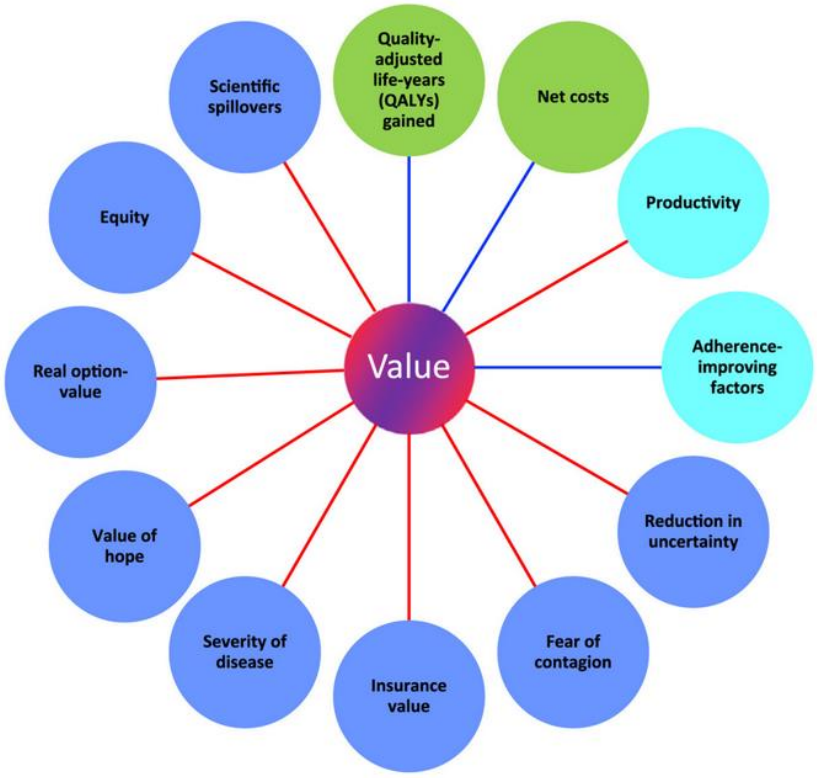
by preference-based quality of life assessments, and/or are considered by HTA agencies in deliberations undertaken in addition to cost-effectiveness analysis.

Figure 7. 'Additional' elements of value according to an ISPOR Task Force



The two green petals are included in all economic evaluations. The petals in light blue reflect elements that are commonly included in economic evaluations. Explanations of the eight remaining petals are listed in Table 6.(6)

Table 6. Additional value elements beyond the QALY

Value element	**Explanation**
Reduction in uncertainty	Improved prediction of treatment effectiveness can prevent unnecessary adverse events and trial-and-error periods. This increased certainty might improve uptake of testing and treatment adherence among patients. There might also be a psychological effect for patients in knowing a test result (e.g. feeling reassured or feeling anxious)
Fear of contagion	When a treatment for an infectious disease is available, members of the general public may experience reduced fear that the disease will spread compared to a scenario in which no treatment is available. This may have value beyond the health benefits for the patients that receive treatment.
Insurance value	Similarly, when a treatment for a disease is available, there may be value to the general public in knowing that if they are to fall ill, they will have access to treatment and will be protected from potentially high financial consequences of illness.

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Severity of disease	When two interventions offer the same absolute health gain per patient in terms of QALYs, the intervention that targets patients with a worse baseline health may be deemed of higher value.
Value of hope	When a treatment's effectiveness is highly variable, patients might value this treatment more than a treatment that has less variation around the mean. This value is explained by the hope patients hold that they are among the few lucky ones with a very good response.
Real option value	When life is extended, patients are provided the option to benefit from any future advances in medicine. Valuing this 'real option' implies that when the QALY gain is equal between two interventions, the treatment that extends life most is preferred.
Scientific spill-overs	A new discovery (e.g. a drug with a new mechanism of action) may be beneficial for the future innovations that can be built upon this discovery. Beyond the immediate value the new discovery offers in treating current patients, there might be value in its 'scientific novelty'.
Equity	When two interventions offer the same health gain, the intervention that distributes the QALYs more 'fairly' may be deemed of higher value. What is deemed fair may depend on the setting. 'Severity of disease' can be seen as an equity variable and could be argued to fall under this category.

Rather than discussing these elements of value one by one, we discuss three overarching issues that warrant specific attention when dealing with values beyond the QALY:

1. Our willingness to pay for and/or willingness to trade-off length and/or quality of life for these additional elements of value;
2. Elements of value in potentially displaced interventions;
3. The disproportional attention to elements of 'positive value' compared to elements of 'negative value' or harm.

We illustrate these issues by focussing on the 'value of hope'.

Willingness to pay and trade-off length and quality of life

For elements of value to be incorporated in economic evaluations, preference elicitation studies are required to i) identify clearly demarked elements of value, ii) demonstrate willingness to pay for these elements, and iii) demonstrate the willingness to trade-off length and quality of life against additional elements of value. For example, Lakdawalla et al. investigated the response of oncology patients to a "hopeful gamble" relative to "a safe bet".(93) They find that 71% of melanoma patients included in the study prefer a 20% chance of at least 4.5 year survival over a certain two-year survival, even though the two scenarios offer the same average survival probability. They also find that individual preferences depend on attitude toward risk and subjective life expectancy, and hypothesise that having very poor health prospects increases risky behaviour.

While Lakdawalla et al. herewith provide support for the existence of a value of hope for individual patients, it should be noted that the measured value is based on ex-ante (i.e. expected) utility in patients,

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with little attention to ex-post (i.e. realised) disappointment when not being part of the long-term survivor group. While the ex-ante position is dominant in the valuation of health, arguments have been made to incorporate ex-post valuations as well to prevent erroneous forecasting of benefit and better include experience over expectation.(94, 95) Furthermore, following a truly ex-ante perspective of valuing hope might require asking members of the general public to value it, rather than patients.

Opportunity costs

In a health system with fixed budgets, the cost-effectiveness threshold may be based on opportunity cost. Including additional elements of value in the evaluation of new therapies would require these additional elements of value to also be included in the valuation of the displaced health technologies, and the cost-effectiveness threshold to be adjusted accordingly. This may be a daunting if not impossible task. In systems with either flexible budgets or cost-effectiveness thresholds based on willingness to pay, estimating the additional elements of value in displaced healthcare may not be necessary. Nonetheless, in both systems with flexible and fixed budgets, including additional elements of value may not meet the objectives of the healthcare system. That is, while certain elements may be valuable for individuals, they may not be of value to the population/society at large. We exemplify this with two stylised examples considering the value of severity and the value of hope.

Severity is an additional element of value mentioned in the 'value flower'.(6) Several countries that consider severity of disease in their decision-making process may have a higher willingness to pay for interventions that target the severely ill. For example, in the Netherlands the cost-effectiveness threshold has been set at €20,000, €50,000, or €80,000 per QALY gained for low, medium, or high burden of disease, respectively, based on proportional shortfall.(96) This implies that decisionmakers are willing to accept a lower health gain in exchange for improving the health of the severely ill. Table 7 represents the incremental net monetary benefit (INMB) of two hypothetical treatments (T1 and T2) with high and medium severity. Based on the INMB, T1 will be favoured over T2, despite generating less health.

Table 7. Incremental net monetary benefit of two hypothetical treatments with high and medium severity.

Treatment	WTP	dQALY	dCosts	Severity	INMB
T1	€ 80.000,00	2	€ 140.000,00	High	€ 20.000,00
T2	€ 50.000,00	2,5	€ 140.000,00	Medium	-€ 15.000,00

WTP = willingness to pay for 1 QALY gained, d = delta, INMB = incremental net monetary benefit

A similar table can be created for the value of hope. In Table 8, T1 offers a value of hope, which is assumed to be valued at €45,000, roughly similar to the average individual willingness to pay reported in Lakdawalla et al.(93) Again, T1 would be favoured over T2 while generating less health, but in this case the reason is that the patients in T1 are provided hope. However, it may not be desirable to forego health in exchange for a short period of time with increased utility due to an anticipated benefit. Especially given that for the majority of patients this period will be followed by a period of potentially reduced utility when treatment response is poor (see next section). We argue that assessing if an

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element has value from the perspective of a patient is distinct from addressing the question if society should pay for generating that value.

Table 8. Incremental net monetary benefit of two hypothetical treatments with and without hope.

Treatment	WTP	dQALY	dCosts	VoH	INMB
T1	€ 50.000,00	2	€ 140.000,00	€ 45.000,00	€ 5.000,00
T2	€ 50.000,00	2,5	€ 140.000,00	0	€ -15.000,00

WTP = willingness to pay for 1 QALY gained, d = delta, VoH = value of hope, INMB = incremental net monetary benefit

Asymmetrical attention to values and harms

We observe a focus on additional positive elements of value, while a potentially equally long list of elements of harms does not receive as much attention. Examples of the latter would be the disutility from incidental findings for which there is no treatment and the 'dashed hope' when one finds out they are not among the high responders. Regarding the value of hope specifically, the loss in utility when hope is not actualised might even be larger than the utility gain from hope, given that people tend to weigh 'losses' more heavily than 'gains'. This suggests that the 'value flower' may not be an exhaustive and comprehensive overview of additional value elements. To ensure consistency and comparability across economic evaluations, modellers should not include additional value elements in the base case until more research has been done. When including additional value elements in scenario analyses, avoid an undue focus on positive elements of value by giving potential elements of harm equal consideration.

Recommendation 21: Do not include additional elements of value in the base-case analysis. When additional elements of value are included in scenario analyses, ensure possible elements of harm have been equally considered and are included in the analysis if relevant.

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Example of good health economic modelling practice from the systematic literature review
Investigating an additional element of value in a scenario analysis, by Eccleston et al. (2017)
Epithelial ovarian cancer may be caused by germline mutations in either the BRCA1 or BRCA2 gene, collectively called "BRCA gene". This study assessed germline BRCA testing among women with epithelial ovarian cancer, and among their first- and second-degree relatives if a relevant mutation is found. Relatives who test positive have a high lifetime risk for ovarian and breast cancer. As a preventive measure, they are offered increased cancer surveillance and/or risk-reducing surgery (i.e. bilateral salpingo-oophorectomy and/or mastectomy). Germline BRCA testing among women with epithelial ovarian cancer and their relatives was estimated to have an ICER of £4,339 per QALY gained, compared to no testing. In a scenario analysis, a disutility was assumed in order to reflect the psychological impact for relatives who are currently healthy but have found out through testing that they have a BRCA mutation. Based on available data, this disutility was assumed to be temporary and last for 1 year only. Incorporating the disutility increased the ICER to £6,026 per QALY gained.

5.5.8 Equity

An important distinction when discussing equity is that between equality and equity. The concept of equality is intimately linked to 'sameness' and assumes that everyone is treated the same. The concept of equity, on the other hand, relates to 'fairness'. From an equity perspective, people may have to be treated differently, for differences between (groups of) people that are deemed 'unfair' to be avoided or overcome. Equity assumes that everyone should be able to have access to the full range of opportunities and benefits.

Given that PM aims to increase differentiation among patient groups and tailor treatments to peoples' individual characteristics, PM is likely to increase inequality. While this is not problematic, the increased use of PM might also have undesirable effects on equity, for several reasons.

Firstly, inequity might increase when biomarkers and other parameters used for stratification are associated with equity-relevant characteristics such as ethnicity and socio-economic status.(3) For example, treatments for an ethnic minority with a rare biomarker may be found to be less cost-effective or have greater uncertainty around treatment effectiveness, which could lead to access to the treatment being denied to the ethnic minority.

Secondly, the focus on stratification in PM likely requires an increased use of testing, bringing a number of related equity concerns to the fore. Uptake of testing may be lower among groups with lower socioeconomic status, which may be due to financial constraints (there could be co-payments for receiving the test, as well as costs associated with travelling to a health facility and taking time off work) and/or lower awareness of the benefits of testing. Furthermore, tests may require advanced facilities (e.g. sequencing labs), which may not be available everywhere. Patients in remote and/or poor areas

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might therefore not have physical access to the test. Physicians in these areas might also be less knowledgeable about the latest developments and consequently offer a lower standard of care than physicians in urban and/or wealthy areas.

Lastly, the increasingly detailed information gathered about individuals may raise equity concerns in relation to purchasing insurance or a mortgage. Companies could misuse information on, for example higher disease risk, to increase the premiums for their products or deny individuals access to their services altogether.

While equity issues are usually considered in deliberations outside of the health economic model, modellers should be aware of potential equity consequences of the interventions under consideration, as well as of modelling assumptions made, and report on them where appropriate.

Recommendation 22: Consider whether aspects of the intervention under consideration or of the assumptions made in the health economic model are likely to have equity consequences.

5.5.9 Uncertainty analysis

Three main categories of uncertainty are generally distinguished in health economic modelling: parameter uncertainty, stochastic uncertainty and structural uncertainty. Below we outline some considerations to bear in mind when dealing with uncertainty in the modelling of PM.(97, 98)

In some PM interventions, parameter uncertainty (the uncertainty regarding the 'true' value for estimated parameters) may be lower than in non-PM interventions, while in others parameter uncertainty may be higher. The rationale in the former is that when therapies are targeted to patients who are likely to respond, the variation in and uncertainty about relative effectiveness will reduce. On the other hand, parameter uncertainty may increase because of smaller sample sizes, more single-arm studies, greater reliance on observational data and expert opinion, and a greater diversity of trial designs (e.g. basket trials, umbrella trials, adaptive trial designs, n=1 trials).

When modelling a high number of possible clinical pathways, patient-level simulation models, such as discrete event models, may be more appropriate than state-transition cohort models because of their ability to simulate a greater variety of different clinical pathways and easily include patient history into the simulation, without being restricted to a limited set of health states and cycles.(99) When using patient-level simulations, it is important to address stochastic uncertainty.(100) Stochastic uncertainty refers to the random (or unexplained) variability in model outcomes between patients facing the same prior probabilities. That is, model outcomes may be different upon re-running the model, even if the same patients are selected, simply because different values for the input parameters may be drawn. This may introduce bias into the comparison between intervention and control group. Commonly only stochastic uncertainty in time-to-event data is considered, as individual patient data may not be available for other model parameters (e.g. cost and effect). Stochastic uncertainty in times-to-event can be removed by using a set of random seeds for times-to-event that is fixed per patient, so that the same values are used for the same patient in both the intervention and control arm of the model.

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Recommendation 23: When using patient-level simulation models, ensure that stochastic uncertainty as a source of difference between intervention and control group is eliminated.

Structural uncertainty reflects the question whether the functional form of a model, determined by the various decisions and assumptions that are made when designing the model, accurately reflects reality.(100) Such decisions and assumption may relate to, for example, the position of a test in the treatment pathway, the cut-off values used to define different outcomes on a test, the clinical states to be included in the model, the methods used to synthesise effectiveness data from different sources, and the statistical model used to extrapolate survival beyond the trial period. What is presented as the base case is often not more than just one of the possible scenarios (though one that was deemed likely by the modellers and/or clinical experts). It is important to be as transparent as possible about the choices made and investigate which decisions and assumptions have a substantial impact on the cost-effectiveness results. One way to visualise the structural uncertainty would be to plot different scenarios in a cost-effectiveness plane, similar to plotting model iterations. When experts are subsequently asked to assess the likelihood of the scenarios, one may calculate a weighted average of the ICERs.

Recommendation 24: Acknowledge the presence of structural uncertainty and plot the ICERs of scenarios that have an important impact on the results in the cost-effectiveness plane.

Some forms of structural uncertainty, such as the uncertainty from differences in opinion among experts and each expert's own uncertainty may be parameterised in order to be included into the PSA.(56, 101-103) The inclusion of many forms of structural uncertainty into the PSA could explode the scatterplot of possible outcomes in the cost-effectiveness plane, rendering the scatterplot less informative, yet more truthful. When using such a scatterplot as the base-case, the base-case would reflect the uncertainty around the estimated incremental cost-effectiveness ratio informed by both parameter and structural uncertainty. What currently would be considered a base-case scenario, may then be a ‘preferred’ scenario. Value of information analysis may be useful to prioritise future areas of research in cases with a high degree of uncertainty and the possibility of large health losses when the wrong decision is made.

5.5.10 Managed entry agreements

PM interventions that have come onto the market over recent years have not uncommonly carried a hefty price tag, as well as significant uncertainty about their clinical effectiveness (e.g. some of the gene therapies and targeted oncology drugs). In response to this, healthcare payers may opt to use managed entry agreements (MEAs) to share the risks with the manufacturers. MEAs are contractual arrangements between a manufacturer and a payer that are used to improve access to expensive medicines that would otherwise not be deemed tcost-effective. There are many taxonomies of MEAs, and they generally distinguish between financial agreements, performance-based agreements, research agreements, and combinations thereof.(104) So far, MEAs have been predominantly financial, most frequently including discounts, price capping, expenditure capping, utilisation capping and price-volume arrangements. However, given the increase in PMs for which the claims of sustainable benefits are not backed-up by

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scientific evidence at the time of launch, an increase in performance-based MEAs is expected. Examples of such MEAs include money-back guarantees or conditional treatment continuations.

Since the introduction of a MEA is likely to affect the cost-effectiveness of a treatment, its consequences could be incorporated in the health economic model, in order to better inform decisionmakers. Health economic models may even be used to optimise the parameters of a MEA, such as the discount given, the period of time a medicine is given for free, the maximum expenditure cap, the time-point at which effectiveness of the medicine for individual patients is assessed. The optimisation criterion could be a combination of incremental net monetary benefit, which is most relevant from a payer's perspective, and discounted cash flow, which is most relevant from a manufacturer's perspective. The incorporation of MEA parameters into the health economic model is currently infrequently done, possibly because the conditions of a MEA tend to confidential, but it may be informative for payers and manufacturers alike.

Example of good health economic modelling practice from the systematic literature review
Including a managed entry agreement in the health economic model, by Lin et al. (2018)

The health economic model of CAR-T treatment in patients with relapsed or refractory pediatric B-cell acute lymphoblastic leukemia reflects includes the outcome-based payment scheme of the manufacturer in which the payer was responsible for tisagenlecleucel's cost only if the patient achieves initial remission, otherwise the manufacturer would cover the treatment costs (i.e. no cure, no pay). Different definitions of remission were explored in scenario analyses: any remission, remission at 6 months, and remission at 12 months. As the proportion of patients with remission decreases when the remission duration threshold for payer responsibility was longer, the ICERs (using the most optimistic relapse-free survival assumptions) also decreased: $74,000/QALY for payer responsibility for any remission, $47,000/QALY for payer responsibility if in remission at 6 months, and $28,000/QALY for payer responsibility if in remission at 12 months).

5.5.11 Modelling imperfect implementation

A health economic model may assume perfect implementation (i.e. 100% uptake and use of a test-treatment combination as intended) or include an estimate of suboptimal implementation. The approach taken often depends on the wishes of the decisionmaker. While some decisionmakers wish to base resource allocation on information about interventions' cost-effectiveness under ideal circumstances, others prefer for economic evaluations to reflect the likely reality of the interventions' implementation. Note that an analysis of the differences between realistic and ideal implementation could be used to identify areas in which efforts to improve implementation may be very valuable.

In PM, three key aspects are important in the context of imperfect implementation: patients' uptake of testing, patients' adherence to treatment and clinicians' adherence to protocols and guidelines.

Patients' uptake of testing

Patients' uptake of testing may be suboptimal for various reasons. A key reason in PM is that testing for the presence of risk factors and/or (hereditary) conditions means exposing oneself to potentially

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distressing information. While the purpose of such tests is to monitor risk factors more closely or commence timely treatment, some people may be anxious about the result and unwilling to take the test. Individuals' willingness to be tested may depend on their risk perception. For example, a first-degree relative of a BRCA-positive breast cancer patient may be more willing to receive BRCA-testing than a member of the general population. In the context of whole genome sequencing, a person's willingness to be tested may also be influenced by their attitude toward being informed about incidental findings and the extent to which they have control over whether incidental findings are reported to them.

Recommendation 25: Patients' uptake of testing should be included in economic evaluations for decision-makers that allow evaluations assuming suboptimal implementation.

Patients' treatment adherence

A hypothesis in PM is that those who are likely to be identified as potential responders to treatment will be more adherent to therapy and indeed there is some evidence to support this.(105, 106) Nonetheless, a meta-analysis of all controlled studies assessing the communication of gene-based disease risk to individuals, finds no significant effect on medication use.(107) Therefore, when modelling a genetic test, carefully consider available evidence before assuming that the implementation of the test will result in better treatment adherence.

The extent to which the relationship between adherence and outcomes should be modelled using a separate input parameter depends on the data that underly the assessment of effectiveness. If the effect estimate was taken from clinical studies that reflect the level(s) of adherence assumed in the economic evaluation, it is not necessary to model adherence separately. If, however, the effect estimate is not based on the desired adherence levels, adherence can be included separately. In the latter case, evidence should be provided to underpin any assumptions about the relationship between adherence and outcomes.(108) Note that reduced adherence does not automatically mean that intervention costs are lower. For example, people might have picked up their medicines at the pharmacist but subsequently not have taken them. In this case, health benefits may be reduced because of lower adherence, while costs are the same.

Recommendation 26: Patient adherence should be included in economic evaluations for decision-makers that allow evaluations assuming suboptimal implementation. Whether patient adherence requires a separate input parameter depends on the effectiveness evidence.

Clinicians' adherence to protocols and guidelines

Non-adherence is not limited to patients. Clinicians, too, may not use test-results in the intended way. This issue is especially relevant in PM, as genetic and genomic testing is relatively new, and clinicians' experience and understanding may be limited. As a result, patients with clinical indicators of genetic risk may not be referred to genetic services and test results may be misinterpreted or disregarded altogether. As with adherence, if the trial from which effectiveness data is drawn allowed clinician non-adherence, its effect is most likely reflected in the effectiveness estimate. If this is not the case, clinician adherence should be accounted for.

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Recommendation 27: Clinician adherence should be included in economic evaluations for decision-makers that allow evaluations assuming sub-optimal implementation. Whether clinician adherence requires a separate input parameter depends on the effectiveness evidence.

Patients' uptake of testing, patients' treatment adherence and clinicians' adherence may vary across different groups, as outlined in section 4.5.8 on equity. When incorporating these imperfect implementation variables, it may therefore be valuable to consider whether they differ between, for example, socioeconomic, geographic, ethnic, sex, or age groups.

Example of good health economic modelling practice from the systematic literature review

Incorporating the uptake of testing and treatment adherence, by Asphaug et al. (2019)

In Norway, BRCA-testing is routinely offered to patients with early-onset breast cancer, as well as to relatives of mutation-positive patients. If relatives are found to carry a pathogenic mutation, they are offered bilateral mastectomy with reconstructive surgery (to reduce breast cancer risk, for relatives > 25 years) and bilateral salpingo-oophorectomy (to reduce ovarian cancer risk, for relatives > 35 years). This study assessed the cost-effectiveness of an alternative gene panel, which includes 5 additional genes associated with increased risk for breast and ovarian cancer. Both imperfect uptake of testing and imperfect uptake of risk-reducing surgery were incorporated in the model. Uptake of testing and risk-reducing surgery among relatives of index patients were assumed to increase with age. Uptake of the risk-reducing surgeries was assumed to be higher among index patients than their relatives. The values for the uptake parameters were obtained from observational data. Beta distributions were assigned to all uptake parameters.

Description	Mean	CI	Distribution (Parameters)		
Uptake of genetic testing for female relatives of high-risk mutation carriers by age					
18–29	0.30	(0.15, 0.47)	Beta	a = 9	b = 21
30–49	0.82	(0.68, 0.93)	Beta	a = 28	b = 6
≥ 50	0.80	(0.60, 0.94)	Beta	a = 16	b = 4
Uptake of prophylactic bilateral mastectomy, positive carriers					
Index patients	0.39	(0.34, 0.45)	Beta	a = 137	b = 209
Relatives by age					
25–34	0.12	(0.08, 0.16)	Beta	a = 46	b = 333
35–60	0.11	(0.10, 0.14)	Beta	a = 108	b = 803
Uptake of prophylactic bilateral salpingo-oophorectomy, positive carriers					
Index patients	0.36	(0.34, 0.40)	Beta	a = 321	b = 554
Relatives by age					
25–34	0.10	(0.07, 0.14)	Beta	a = 39	b = 340
35–39	0.28	(0.23, 0.33)	Beta	a = 76	b = 199
40–60	0.35	(0.31, 0.38)	Beta	a = 221	b = 416

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5.5.12 Summary of recommendations - checklist

Below is a list of recommendations, which may be used by the modeller of PM interventions to check whether all aspects that are particularly relevant in PM have been adequately considered and/or addressed. The list of recommendations aims to be a comprehensive overview of the issues one might come across when modelling PM and should be seen as an add-on to existing general checklists (e.g. (109-111)). We do not expect all issues to be relevant for each cost-effectiveness analysis and leave it to modellers to decide which issues are relevant to their model. Similarly, we acknowledge that the recommendations given may not always be executable but encourage modellers to address the raised issues as much as possible. The issues discussed are not exclusive to PM and may be relevant in the modelling of other interventions as well.

Table 9. Checklist of recommendations for good health economic modelling practice in PM.

Topic	Subtopic		Recommendation
Modelling test-treatment combinations	Positioning	1	Consider if the modelled position of the test in the clinical pathway is in line with clinical practice.
	Consequences of testing	2	If a test is not part of routine care, ensure that the (downstream) costs and benefits of testing for both individuals who test positive and individuals who test negative are included in the model.
	Test performance	3	Ensure that the data on the test performance are the latest available and obtained in a population that is in line with the modelled population.
		4	When multiple tests inform treatment decisions, the interdependence between tests should be considered.
		5	Clearly define the cut-off values that are used to define the different outcomes (e.g. positive/negative, high/medium/low risk) of a test.
	Practice variation	6	If there is a risk of disease progression or mortality during waiting periods, these waiting periods should be explicitly incorporated into the model.

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	Waiting times	7	Consider all costs associated with tests, including costs of testing in patients with negative test-results and downstream costs resulting from the test.
Effectiveness data from non-randomised (controlled) studies	Incomplete or absent RCT data	8	Where possible, use effectiveness data from trials with two active comparator arms or data from (network) meta-analysis, rather than observational data collected under conditional reimbursement programmes. If such data is not available, perform value of information analysis and/or sensitivity analysis that can be used to inform the design of any future trials.
	Historical cohorts	9	When effectiveness is estimated using historical cohorts, account for the trend in efficacy of the comparator over time, in order to correctly attribute differences in efficacy to the treatment.
	Unknown mutation status in comparator group	10	When using a historical cohort to estimate the effectiveness of a treatment for a patient population with a specific gene mutation, obtain data on the distribution of the gene mutation of interest in the historical cohort, as well as data on the prognostic value of the gene mutation.
Extrapolating outcomes for interventions aiming to cure	Cures in health economic modelling	11	When modelling the outcomes for interventions aiming to cure, the cure assumption and the choice of survival model used for extrapolation beyond the observed trial period should not only be informed by statistical fit of the model to the observed data, but also by expert opinion.
	Excess mortality	12	When modelling the survival curves for interventions aiming to cure, apply excess mortality among long-term survivors, rather than assuming these patients are fully cured by applying age- and gender-specific general population mortality.
Expert opinion		13	When expert opinion is used to estimate quantitative model parameters, use a formal method to synthesise the opinions of the experts into a probability distribution.
Discounting		14	PM interventions should be subject to the same discount rates as other interventions within the same jurisdiction.
		15	For interventions with large upfront costs and benefits that stretch into the future, the impact of differential and/or hyperbolic discounting should be investigated in sensitivity analyses.
		16	When using differential discounting for models that include future cohorts, the discount year should be mentioned for every modelled cohort.
Values beyond the current patient	Perspective	17	An economic evaluation of PM should be conducted from the same perspective as other interventions within the same jurisdiction.

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	Caregiver burden	18	For jurisdictions that employ a societal perspective, caregiver burden can be included on the cost-side of the economic evaluation.
		19	Incremental cost-effectiveness ratios with and without caregiver burden should be presented separately.
	Caregiver burden	20	For both a societal and a healthcare perspective, the costs and benefits of conducting tests in others than the index patient should be included.
Values beyond the QALY		21	Do not include additional elements of value in the base-case analysis. When additional elements of value are included in scenario analyses, ensure possible elements of harm have been equally considered and are included in the analysis if relevant.
Equity		22	Consider whether aspects of the intervention under consideration or of the assumptions made in the health economic model are likely to have equity consequences.
Uncertainty analysis		23	When using patient-level simulation models, ensure that stochastic uncertainty as a source of difference between intervention and control group is eliminated.
		24	Acknowledge the presence of structural uncertainty and plot the ICERs of scenarios that have an important impact on the results in the cost-effectiveness plane.
		25	When structural uncertainties are parameterised, include them into the PSA of the base-case.
Modelling imperfect implementation	Patients' uptake of testing	26	Patients' uptake of testing should be included in economic evaluations for decision-makers that allow evaluations assuming suboptimal implementation.
	Patients' treatment adherence	27	Patient adherence should be included in economic evaluations for decision-makers that allow evaluations assuming suboptimal implementation. Whether patient adherence requires a separate input parameter depends on the effectiveness evidence.
	Clinicians' adherence to protocol and guidelines	28	Clinician adherence should be included in economic evaluations for decision-makers that allow evaluations assuming sub-optimal implementation. Whether clinician adherence requires a separate input parameter depends on the effectiveness evidence.

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6 REFERENCES

1. Rogowski W, Payne K, Schnell-Inderst P, et al. Concepts of 'personalization'in personalized medicine: implications for economic evaluation. Pharmacoeconomics. 2015; 33: 49-59.
2. Schleidgen S, Klingler C, Bertram T, et al. What is personalized medicine: sharpening a vague term based on a systematic literature review. BMC medical ethics. 2013; 14: 55.
3. Love-Koh J, Peel A, Rejon-Parrilla JC, et al. The future of precision medicine: potential impacts for health technology assessment. Pharmacoeconomics. 2018; 36: 1439-51.
4. Yang Y, Abel L, Buchanan J, et al. Use of Decision Modelling in Economic Evaluations of Diagnostic Tests: An Appraisal and Review of Health Technology Assessments in the UK. PharmacoEconomics-open. 2019: 1-11.
5. Rogowski WH, Grosse SD, Schmidtke J, et al. Criteria for fairly allocating scarce health-care resources to genetic tests: which matter most? European Journal of Human Genetics. 2014; 22: 25-31.
6. Lakdawalla DN, Doshi JA, Garrison Jr LP, et al. Defining elements of value in health care—a health economics approach: an ISPOR Special Task Force report [3]. Value in health. 2018; 21: 131-39.
7. Annemans L, Redekop K, Payne K. Current methodological issues in the economic assessment of personalized medicine. Value in Health. 2013; 16: S20-S26.
8. Towse A, Garrison Jr LP. Economic incentives for evidence generation: promoting an efficient path to personalized medicine. Value in health. 2013; 16: S39-S43.
9. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement (Chinese edition). Journal of Chinese Integrative Medicine. 2009; 7: 889-96.
10. Bramer WM, Giustini D, de Jonge GB, et al. De-duplication of database search results for systematic reviews in EndNote. Journal of the Medical Library Association: JMLA. 2016; 104: 240.
11. Wordsworth S, Leal J, Blair E, et al. DNA testing for hypertrophic cardiomyopathy: A cost-effectiveness model. Eur Heart J. 2010; 31: 926-35.
12. Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B 1502 genotyping in adult patients with newly diagnosed epilepsy in singapore. Neurology. 2012; 79: 1259-67.
13. Garrison Jr LP, Lalla D, Brammer M, et al. Assessing the potential cost-effectiveness of retesting IHC0, IHC1+, or FISH-negative early stage breast cancer patients for HER2 status. Cancer. 2013; 119: 3113-22.
14. Feller-Kopman D, Liu S, Geisler BP, et al. Cost-Effectiveness of a Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer. J Thorac Oncol. 2017; 12: 1223-32.
15. National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. 2018.
16. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients with Relapsed or Refractory Leukemia. JAMA Pediatr. 2018; 172: 1161-68.
17. Doble B, John T, Thomas D, et al. Cost-effectiveness of precision medicine in the fourth-line treatment of metastatic lung adenocarcinoma: An early decision analytic model of multiplex targeted …. Elsevier, 2017.
18. Huxley N, Jones-Hughes T, Coelho H, et al. A systematic review and economic evaluation of intraoperative tests [RD-100i one-step nucleic acid amplification (OSNA) system and Metasin test] for detecting sentinel lymph node metastases in breast cancer. Health Technol Assess. 2015; 19: I-215.
19. Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2011; 4: 9-22.

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20. Rogowski WH. The cost-effectiveness of screening for hereditary hemochromatosis in Germany: A remodeling study. Med Decis Mak. 2009; 29: 224-38.
21. Chen YE, Kao SS, Chung RH. Cost-effectiveness analysis of different genetic testing strategies for Lynch syndrome in Taiwan. PLoS ONE. 2016; 11.
22. McKay AJ, Hogan H, Humphries SE, et al. Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis. Atherosclerosis. 2018; 275: 434-43.
23. Asphaug L, Melberg HO. The Cost-Effectiveness of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer in Norway. MDM Policy Pract. 2019; 4: 2381468318821103.
24. Severin F, Stollenwerk B, Holinski-Feder E, et al. Economic evaluation of genetic screening for Lynch syndrome in Germany. Gen Med. 2015; 17: 765-73.
25. Eccleston A, Bentley A, Dyer M, et al. A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer. Value Health. 2017; 20: 567-76.
26. Ramírez De Arellano A, Coca A, De La Figuera M, et al. Economic evaluation of Cardio inCode®, a clinical-genetic function for coronary heart disease risk assessment. Appl Health Econ Health Policy. 2013; 11: 531-42.
27. Reed SD, Scales Jr CD, Stewart SB, et al. Effects of family history and genetic polymorphism on the cost-effectiveness of chemoprevention with finasteride for prostate cancer. J Urol. 2011; 185: 841-47.
28. Parthan A, Leahy KJ, O'Sullivan AK, et al. Cost effectiveness of targeted high-dose atorvastatin therapy following genotype testing in patients with acute coronary syndrome. Pharmacoeconomics. 2013; 31: 519-31.
29. Green LE, Dinh TA, Hinds DA, et al. Economic evaluation of using a genetic test to direct breast cancer chemoprevention in white women with a previous breast biopsy. Appl Health Econ Health Policy. 2014; 12: 203-17.
30. Yang M, Rajan S, Issa AM. Cost effectiveness of gene expression profiling for early stage breast cancer: A decision-analytic model. Cancer. 2012; 118: 5163-70.
31. Rejon-Parrilla JC, Nuijten M, Redekop WK, et al. Economic evaluation of the use of a pharmacogenetic diagnostic test in schizophrenia. Health Policy Technol. 2014.
32. Graves JA, Garbett S, Zhou Z, et al. The value of pharmacogenomic information. National Bureau of Economic Research, 2017.
33. Chandler Y, Schechter CB, Jayasekera J, et al. Cost effectiveness of gene expression profile testing in community practice. J Clin Oncol. 2018; 36: 554-62.
34. Compagni A, Melegaro A, Tarricone R. Genetic Screening for the Predisposition to Venous Thromboembolism: A Cost-Utility Analysis of Clinical Practice in the Italian Health Care System. Value Health. 2013; 16: 909-21.
35. Zhao Z, Chen Y, Francisco NM, et al. The application of CAR-T cell therapy in hematological malignancies: advantages and challenges. Acta Pharmaceutica Sinica B. 2018; 8: 539-51.
36. Tice JA, Walsh JME, Otunoye I, et al. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. In: (ICER) IfCaER, ed., 2018.
37. National Institute For Health And Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]. 2018.
38. National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]. 2018.
39. Lin JK, Lerman BJ, Barnes JI, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. J Clin Oncol. 2018; 36: 3192-202.
40. Banken R, Rind D, Cramer G, et al. Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value. 2018.
41. Zimmermann M, Lubinga SJ, Banken R, et al. Cost Utility of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease. Value Health. 2019; 22: 161-67.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

42. Ellis AG, Mickle K, Herron-Smith S, et al. Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value. In: (ICER) IfCaER, ed., 2019.
43. National Institute For Health And Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013.
44. National Institute For Health And Care Excellence (NICE). Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency [ID926]. 2017.
45. South E, Cox E, Meader N, et al. Strimvelis for Treating Severe Combined Immunodeficiency Caused by Adenosine Deaminase Deficiency: An Evidence Review Group Perspective of a NICE Highly Specialised Technology Evaluation Review. PharmacoEcon Open. 2019; 3: 151-61.
46. Holland ML, Huston A, Noyes K. Cost-Effectiveness of Testing for Breast Cancer Susceptibility Genes. Value Health. 2009; 12: 207-16.
47. Li Y, Arellano AR, Bare LA, et al. A Multigene Test Could Cost-Effectively Help Extend Life Expectancy for Women at Risk of Hereditary Breast Cancer. Value Health. 2017; 20: 547-55.
48. Muller D, Danner M, Schmutzler R, et al. Economic modeling of risk-adapted screen-and-treat strategies in women at high risk for breast or ovarian cancer. The European Journal of Health Economics. 2019; 20: 739-50.
49. Wang VW, Koh PK, Chow WL, et al. Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary nonpolyposis colorectal cancer in Singapore. Fam Cancer. 2012; 11: 279-89.
50. Hoskins P, Eccleston A, Hurry M, et al. Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer. A Canadian model. Gynecol Oncol. 2019.
51. Gallego CJ, Shirts BH, Bennette CS, et al. Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: A cost-effectiveness analysis. J Clin Oncol. 2015; 33: 2084-91.
52. Lasser KE, Mickle K, Emond S, et al. Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. In: Institute for Clinical and Economic Review (ICER), ed., 2018.
53. Buchanan J, Wordsworth S, Clifford R, et al. Using Genomic Information to Guide Ibrutinib Treatment Decisions in Chronic Lymphocytic Leukaemia: A Cost-Effectiveness Analysis. Pharmacoeconomics. 2017; 35: 845-58.
54. Zhu J, Li T, Wang X, et al. Gene-guided Gefitinib switch maintenance therapy for patients with advanced EGFR mutation-positive Non-small cell lung cancer: An economic analysis. BMC Cancer. 2013; 13.
55. Jönsson B, Hampson G, Michaels J, et al. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. The European Journal of Health Economics. 2019; 20: 427-38.
56. Cope S, Ayers D, Shih T, et al. Expert elicitation of long-term survival for pediatric acute lymphoblastic leukemia patients receiving CTL019 in Eliana phase II study. Blood. 2017; 130: 3377-77.
57. Grieve R, Abrams K, Claxton K, et al. Cancer Drugs Fund requires further reform. British Medical Journal Publishing Group, 2016.
58. Kip MM, IJzerman MJ, Henriksson M, et al. Toward alignment in the reporting of economic evaluations of diagnostic tests and biomarkers: the AGREEDT checklist. Medical decision making. 2018; 38: 778-88.
59. de Groot S, Rijnsburger AJ, Versteegh MM, et al. Which factors may determine the necessary and feasible type of effectiveness evidence? A mixed methods approach to develop an instrument to help coverage decision-makers. BMJ open. 2015; 5.
60. de Groot S, van der Linden N, Franken MG, et al. Balancing the optimal and the feasible: a practical guide for setting up patient registries for the collection of real-world data for health care decision making based on Dutch experiences. Value in Health. 2017; 20: 627-36.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

61. Van De Wetering E, van Exel J, Brouwer WB. The challenge of conditional reimbursement: stopping reimbursement can be more difficult than not starting in the first place! Value in Health. 2017; 20: 118-25.
62. Wilson EC. A practical guide to value of information analysis. Pharmacoeconomics. 2015; 33: 105-21.
63. Ramos IC, Maureen P, Al MJ. Determining the impact of modeling additional sources of uncertainty in value-of-information analysis. Value in Health. 2015; 18: 100-09.
64. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. . BMJ. 2008; 337: a1655.
65. White H, Sabarwal S. Quasi-Experimental Design and Methods: Methodological Briefs-Impact Evaluation No. 8. 2014.
66. Stuart EA. Matching methods for causal inference: A review and a look forward. Statistical science: a review journal of the Institute of Mathematical Statistics. 2010; 25: 1.
67. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Statistics in medicine. 2015; 34: 3661-79.
68. Angrist JD, Imbens GW, Rubin DB. Identification of causal effects using instrumental variables. Journal of the American statistical Association. 1996; 91: 444-55.
69. Imbens GW, Lemieux T. Regression discontinuity designs: A guide to practice. Journal of econometrics. 2008; 142: 615-35.
70. Ryan AM, Burgess Jr JF, Dimick JB. Why we should not be indifferent to specification choices for difference-in-differences. Health services research. 2015; 50: 1211-35.
71. O'Neill S, Kreif N, Grieve Rea. Estimating causal effects: considering three alternatives to difference-in-differences estimation. . Health Serv Outcomes Res Method 2016; 16: 1-21.
72. Jandoc R, Burden AM, Mamdani M, et al. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. Journal of clinical epidemiology. 2015; 68: 950-56.
73. Linden A, Adams JL. Combining the regression discontinuity design and propensity score-based weighting to improve causal inference in program evaluation. Journal of evaluation in clinical practice. 2012; 18: 317-25.
74. Zimmermann M, Brouwer E, Tice JA, et al. Disease-Modifying Therapies for Relapsing–Remitting and Primary Progressive Multiple Sclerosis: A Cost-Utility Analysis. CNS drugs. 2018; 32: 1145-57.
75. Bullement A, Latimer NR, Gorrod HB. Survival extrapolation in cancer immunotherapy: a validation-based case study. Value in Health. 2019; 22: 276-83.
76. Institute for Clinical and Economic Review (ICER). Adapted Value Assessment Methods for High-Impact "Single and Short-Term Therapies" (SSTs). 2019.
77. Institute for Clinical and Economic Review (ICER). Value Assessment Methods and Pricing Recommendations for Potential Cures: A Technical Brief. 2019.
78. Ouwens MJ, Mukhopadhyay P, Zhang Y, et al. Estimating lifetime benefits associated with immuno-oncology therapies: challenges and approaches for overall survival extrapolations. PharmacoEconomics. 2019; 37: 1129-38.
79. Janssen-Heijnen M, Houterman S, Lemmens V, et al. Prognosis for long-term survivors of cancer. Annals of Oncology. 2007; 18: 1408-13.
80. Janssen-Heijnen ML, Gondos A, Bray F, et al. Clinical relevance of conditional survival of cancer patients in Europe: age-specific analyses of 13 cancers. Journal of clinical oncology. 2010; 28: 2520-28.
81. Guyot P, Ades AE, Beasley M, et al. Extrapolation of survival curves from cancer trials using external information. Medical Decision Making. 2017; 37: 353-66.
82. Dias LC, Morton A, Quigley J. Elicitation. Springer International Publishing. 2018; 1: 3.
83. Attema AE, Brouwer WB, Claxton K. Discounting in economic evaluations. Pharmacoeconomics. 2018; 36: 745-58.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

84. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. New England journal of medicine. 1977; 296: 716-21.
85. Keeler EB, Cretin S. Discounting of life-saving and other nonmonetary effects. Management science. 1983; 29: 300-06.
86. Brouwer WB, Niessen LW, Postma MJ, et al. Need for differential discounting of costs and health effects in cost effectiveness analyses. Bmj. 2005; 331: 446-48.
87. O'Mahony JF, Newall AT, van Rosmalen J. Dealing with time in health economic evaluation: methodological issues and recommendations for practice. Pharmacoeconomics. 2015; 33: 1255-68.
88. Davidson T, Levin L-Å. Is the societal approach wide enough to include relatives? Applied health economics and health policy. 2010; 8: 25-35.
89. Hoefman RJ. The Impact of Caregiving. Erasmus University Rotterdam, 2015.
90. Versteegh M, Knies S, Brouwer W. From good to better: new Dutch guidelines for economic evaluations in healthcare. Springer, 2016.
91. Brouwer WB, Koopmanschap MA, Rutten FF. Patient and informal caregiver time in cost-effectiveness analysis: a response to the recommendations of the Washington Panel. International journal of technology assessment in health care. 1998; 14: 505-13.
92. Gheorghe M, Hoefman RJ, Versteegh MM, et al. Estimating informal caregiving time from patient EQ-5D data: the Informal CARE Effect (iCARE) Tool. PharmacoEconomics. 2019; 37: 93-103.
93. Lakdawalla DN, Romley JA, Sanchez Y, et al. How cancer patients value hope and the implications for cost-effectiveness assessments of high-cost cancer therapies. Health Affairs. 2012; 31: 676-82.
94. Brazier J, Rowen D, Karimi M, et al. Experience-based utility and own health state valuation for a health state classification system: why and how to do it. The European Journal of Health Economics. 2018; 19: 881-91.
95. Versteegh M, Brouwer W. Patient and general public preferences for health states: a call to reconsider current guidelines. Social Science & Medicine. 2016; 165: 66-74.
96. Versteegh MM, Ramos IC, Buyukkaramikli NC, et al. Severity-Adjusted Probability of Being Cost Effective. PharmacoEconomics. 2019; 37: 1155-63.
97. Degeling K, IJzerman MJ, Koopman M, et al. Accounting for parameter uncertainty in the definition of parametric distributions used to describe individual patient variation in health economic models. BMC medical research methodology. 2017; 17: 170.
98. Ramos IC, Hoogendoorn M, Rutten-van Mölken MP. How to address uncertainty in health economic discrete event simulation models: an illustration for chronic obstructive pulmonary disease. (submitted). 2020.
99. Degeling K, Koffijberg H, IJzerman MJ. A systematic review and checklist presenting the main challenges for health economic modeling in personalized medicine: towards implementing patient-level models. Expert review of pharmacoeconomics & outcomes research. 2017; 17: 17-25.
100. Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. Value in Health. 2012; 15: 835-42.
101. Bojke L, Claxton K, Sculpher M, et al. Characterizing structural uncertainty in decision analytic models: a review and application of methods. Value in Health. 2009; 12: 739-49.
102. Jackson CH, Thompson SG, Sharples LD. Accounting for uncertainty in health economic decision models by using model averaging. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2009; 172: 383-404.
103. Jackson CH, Bojke L, Thompson SG, et al. A framework for addressing structural uncertainty in decision models. Medical Decision Making. 2011; 31: 662-74.
104. Antonanzas F, Juárez-Castelló C, Lorente R, et al. The Use of Risk-Sharing Contracts in Healthcare: Theoretical and Empirical Assessments. PharmacoEconomics. 2019: 1-15.
105. Grant RW, Hivert M, Pandiscio JC, et al. The clinical application of genetic testing in type 2 diabetes: a patient and physician survey. Diabetologia. 2009; 52: 2299-305.

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106. Charland SL, Agatep BC, Epstein RS, et al. Patient knowledge of pharmacogenetic information improves adherence to statin therapy: results of the additional KIF6 risk offers better adherence to statins (AKROBATS) trial. Journal of the American College of Cardiology. 2012; 59: E1848.
107. Hollands GJ, French DP, Griffin SJ, et al. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. bmj. 2016; 352: i1102.
108. Boland MR, van Boven JF, Kruis AL, et al. Investigating the association between medication adherence and health-related quality of life in COPD: Methodological challenges when using a proxy measure of adherence. Respiratory medicine. 2016; 110: 34-45.
109. Evers S, Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International journal of technology assessment in health care. 2005; 21: 240-45.
110. Philips Z, Bojke L, Sculpher M, et al. Good practice guidelines for decision-analytic modelling in health technology assessment. Pharmacoeconomics. 2006; 24: 355-71.
111. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value in Health. 2013; 16: 231-50.

APPENDICES

A.1 – Search terms

Embase.com

('biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'program cost effectiveness'/de OR ((technology NEAR/3 assessment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*):ab,ti)

AND ('economic model'/de OR 'simulation'/de OR (model/de AND (economics/exp OR 'economic aspect'/exp)) OR 'decision tree'/de OR (((model OR modeling OR modelling OR simulation* OR microsimulation*) NEAR/6 (econom* OR pharmacoeconom* OR cost OR costs)) OR (decision NEAR/3 (analy* OR tree OR trees)) OR discrete-event* OR 'state transition' OR markov OR ((individual* OR patient-level*) NEAR/3 (sampl* OR simulation*)) OR (dynamic NEAR/3 transmission*) OR probabilistic* OR partition*-survival*):ab,ti)

AND ('personalized medicine'/de OR 'risk stratification'/de OR 'pharmacogenetics'/de OR 'genetic variation'/de OR 'genetic procedures'/exp OR 'genotype'/de OR 'biological marker'/de OR 'mobile application'/de OR 'personal digital assistant'/de OR 'mobile phone'/de OR 'gene therapy'/exp OR 'molecularly targeted therapy'/exp OR 'immunotherapy'/exp OR 'pharmacogenomics'/exp OR 'pharmacokinetics'/exp OR 'activity tracker'/de OR 'artificial intelligence'/de OR 'machine learning'/de OR (('algorithm'/de OR 'genetic algorithm'/de OR 'learning algorithm'/de OR 'classification algorithm'/de) AND (risk/exp OR therapy/exp)) OR 'omics'/exp OR 'pharmacogenetic testing'/de OR 'self monitoring'/de OR (((personalized OR personalised OR individualised OR individualized OR precision OR stratif* OR targeted* OR algorithm*) NEAR/6 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration OR decision*)) OR ((genetic* OR gene OR genom* OR molecular*) NEAR/3 (variation* OR technique* OR procedure* OR test OR testing OR therap* OR sequenc* OR profil*)) OR genotype* OR (biologic* NEAR/3 marker*) OR biomarker* OR telemonitor* OR (mobile NEAR/3 (applicat* OR app OR apps)) OR wearable* OR (personal* NEAR/3 digital* NEAR/3 assistant*) OR (handheld NEAR/3 computer*) OR ((mobile OR cell*) NEXT/1 phone*) OR smartphone* OR immunotherap* OR immunetherap* OR immun*-therap* OR pharmacogenomic* OR pharmacogenetic* OR

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pharmacokinetic* OR (pharmac* NEAR/3 (genomic* OR genetic* OR kinetic*)) OR (digital NEAR/3 (health OR medicine)) OR mHealth* OR eHealth* OR m-Health* OR e-Health* OR tracker* OR (data NEAR/3 analytic*) OR (artificial* NEAR/3 intelligen*) OR (machine* NEAR/3 learning) OR ((remote OR self) NEAR/3 monitor*) OR pharmacometabolom* OR metabolom* OR proteomic* OR pharmacoproteomic* OR lipidomic* OR pharmacolipidomic* OR omics OR (model* NEAR/3 (guide* OR base*) NEAR/3 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration)) OR (risk NEAR/3 score*)):ab,ti)

NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim) AND [English]/lim

Medline Ovid

(Technology Assessment, Biomedical/ OR Cost-Benefit Analysis/ OR Quality-Adjusted Life Years/ OR ((technology ADJ3 assessment*) OR (economic* ADJ3 (evaluat* OR value)) OR ((cost OR costs) ADJ3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* ADJ3 adjust* ADJ3 (life-year* OR lifeyear*)) OR qaly*).ab,ti.)

AND (Models, Economic/ OR Decision Trees/ OR (((model OR modeling OR modelling OR simulation* OR microsimulation*) ADJ6 (econom* OR pharmacoeconom* OR cost OR costs)) OR (decision ADJ3 (analy* OR tree OR trees)) OR discrete-event* OR state transition OR markov OR ((individual* OR patient-level*) ADJ3 (sampl* OR simulation*)) OR (dynamic ADJ3 transmission*) OR probabilistic* OR partition*-survival*).ab,ti.)

AND (Precision Medicine/ OR exp Pharmacogenetics/ OR Genetic Variation/ OR Genotype/ OR Biomarkers/ OR Mobile Applications/ OR Computers, Handheld/ OR Cell Phone/ OR Genetic Therapy/ OR Molecular Targeted Therapy/ OR exp Immunotherapy/ OR exp Pharmacokinetics/ OR Fitness Trackers/ OR Artificial Intelligence/ OR Machine Learning/ OR ((Algorithms/) AND (Risk/ OR Therapeutics/)) OR omics/ OR Pharmacogenomic Testing/ OR (((personalized OR personalised OR individualised OR individualized OR precision OR stratif* OR targeted* OR algorithm*) ADJ6 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration OR decision*)) OR ((genetic* OR gene OR genom* OR molecular*) ADJ3 (variation* OR technique* OR procedure* OR test OR testing OR therap* OR sequenc* OR profil*)) OR genotype* OR (biologic* ADJ3 marker*) OR biomarker* OR telemonitor* OR (mobile ADJ3 (applicat* OR app OR apps)) OR wearable* OR (personal* ADJ3 digital* ADJ3 assistant*) OR (handheld ADJ3 computer*) OR ((mobile OR cell*) ADJ phone*) OR smartphone* OR immunotherap* OR immunetherap* OR immun*-therap* OR pharmacogenomic* OR pharmacogenetic* OR pharmacokinetic* OR (pharmac* ADJ3 (genomic* OR genetic* OR kinetic*)) OR (digital ADJ3 (health OR medicine)) OR mHealth* OR eHealth* OR m-Health* OR e-Health* OR tracker* OR (data ADJ3 analytic*) OR (artificial* ADJ3 intelligen*) OR (machine* ADJ3 learning) OR ((remote OR self) ADJ3 monitor*) OR pharmacometabolom* OR metabolom* OR proteomic* OR pharmacoproteomic* OR lipidomic* OR pharmacolipidomic* OR omics OR (model* ADJ3 (guide* OR base*) ADJ3 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration)) OR (risk ADJ3 score*)).ab,ti.)

NOT (exp animals/ NOT humans/) AND english.la.

Web of Science

TS=((((technology NEAR/2 assessment*) OR (economic* NEAR/2 (evaluat* OR value)) OR ((cost OR costs) NEAR/2 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/2 adjust* NEAR/2 (life-year* OR lifeyear*)) OR qaly*))

AND ((((model OR modeling OR modelling OR simulation* OR microsimulation*) NEAR/5 (econom* OR pharmacoeconom* OR cost OR costs)) OR (decision NEAR/2 (analy* OR tree OR trees)) OR discrete-event* OR "state transition" OR markov OR ((individual* OR patient-level*) NEAR/2 (sampl* OR simulation*)) OR (dynamic NEAR/2 transmission*) OR probabilistic* OR partition*-survival*))

AND ((((personalized OR personalised OR individualised OR individualized OR precision OR stratif* OR targeted* OR algorithm*) NEAR/5 (medicine* OR therap* OR treat* OR risk OR regimen* OR

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dosing* OR duration OR decision*)) OR ((genetic* OR gene OR genom* OR molecular*) NEAR/2 (variation* OR technique* OR procedure* OR test OR testing OR therap* OR sequenc* OR profil*)) OR genotype* OR (biologic* NEAR/2 marker*) OR biomarker* OR telemonitor* OR (mobile NEAR/2 (applicat* OR app OR apps)) OR wearable* OR (personal* NEAR/2 digital* NEAR/2 assistant*) OR (handheld NEAR/2 computer*) OR ((mobile OR cell*) NEAR/1 phone*) OR smartphone* OR immunotherap* OR immunetherap* OR immun*-therap* OR pharmacogenomic* OR pharmacogenetic* OR pharmacokinetic* OR (pharmac* NEAR/2 (genomic* OR genetic* OR kinetic*)) OR (digital NEAR/2 (health OR medicine)) OR mHealth* OR eHealth* OR m-Health* OR e-Health* OR tracker* OR (data NEAR/2 analytic*) OR (artificial* NEAR/2 intelligen*) OR (machine* NEAR/2 learning) OR ((remote OR self) NEAR/2 monitor*) OR pharmacometabolom* OR metabolom* OR proteomic* OR pharmacoproteomic* OR lipidomic* OR pharmacolipidomic* OR omics OR (model* NEAR/2 (guide* OR base*) NEAR/2 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration)) OR (risk NEAR/2 score*))) AND (medicine OR health* OR patient* OR hospital* OR therap* OR genetic* OR pharmac* OR virus* OR genotype* OR disease* OR diagnos* OR cancer*) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man)))

AND DT=(article) AND LA=(english)

Google Scholar

"technology assessment"|"economic evaluation"|"cost|costs benefit|effectiveness" model|simulation|microsimulation economic|pharmacoeconomic|markov "personalized|personalised|individualised|individualized|precision medicine"

CRD

(((personalized OR personalised OR individualised OR individualized OR precision OR stratif* OR targeted* OR algorithm*) NEAR6 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration OR decision*)) OR ((genetic* OR gene OR genom* OR molecular*) NEAR3 (variation* OR technique* OR procedure* OR test OR testing OR therap* OR sequenc* OR profil*)) OR genotype* OR (biologic* NEAR3 marker*) OR biomarker* OR telemonitor* OR (mobile NEAR3 (applicat* OR app OR apps)) OR wearable* OR (personal* NEAR3 digital* NEAR3 assistant*) OR (handheld NEAR3 computer*) OR ((mobile OR cell*) NEAR1 phone*) OR smartphone* OR immunotherap* OR immunetherap* OR immun*-therap* OR pharmacogenomic* OR pharmacogenetic* OR pharmacokinetic* OR (pharmac* NEAR3 (genomic* OR genetic* OR kinetic*)) OR (digital NEAR3 (health OR medicine)) OR mHealth* OR eHealth* OR m-Health* OR e-Health* OR tracker* OR (data NEAR3 analytic*) OR (artificial* NEAR3 intelligen*) OR (machine* NEAR3 learning) OR ((remote OR self) NEAR3 monitor*) OR pharmacometabolom* OR metabolom* OR proteomic* OR pharmacoproteomic* OR lipidomic* OR pharmacolipidomic* OR omics OR (model* NEAR3 (guide* OR base*) NEAR3 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration)) OR (risk NEAR3 score*)):ab,ti

OR MeSH DESCRIPTOR Precision Medicine IN NHSEED,HTA

OR MeSH DESCRIPTOR Pharmacogenetics IN NHSEED,HTA

OR MeSH DESCRIPTOR Pharmacogenetics IN NHSEED,HTA

OR MeSH DESCRIPTOR Genetic Variation IN NHSEED, HTA

OR MeSH DESCRIPTOR Genotype IN NHSEED,HTA

OR MeSH DESCRIPTOR Biomarkers IN NHSEED,HTA

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OR MeSH DESCRIPTOR Mobile Applications IN NHSEED,HTA

OR MeSH DESCRIPTOR Computers, Handheld IN NHSEED,HTA

OR MeSH DESCRIPTOR Cell Phones IN NHSEED,HTA

OR MeSH DESCRIPTOR Genetic Therapy EXPLODE ALL TREES IN NHSEED,HTA

OR MeSH DESCRIPTOR Molecularly Targeted Therapy EXPLODE ALL TREES IN NHSEED,HTA

OR MeSH DESCRIPTOR Pharmacokinetics EXPLODE ALL TREES IN NHSEED,HTA

OR MeSH DESCRIPTOR Fitness Trackers IN NHSEED,HTA

OR MeSH DESCRIPTOR Artificial Intelligence IN NHSEED,HTA

OR MeSH DESCRIPTOR Machine Learning IN NHSEED,HTA

OR MeSH DESCRIPTOR Algorithms IN NHSEED, HTA

OR MeSH DESCRIPTOR Pharmacogenomic Testing IN NHSEED,HTA

AND * IN NHSEED, HTA WHERE LPD FROM 01/01/2009 TO 13/03/2019

Econlit

AB,TI("biomedical technology assessment" OR "economic evaluation" OR "quality adjusted life year" OR "program cost effectiveness" OR (technology NEAR/3 assessment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*)

AND

AB,TI("economic model" OR "simulation" OR (model AND (economics OR "economic aspect")) OR "decision tree" OR ((model OR modeling OR modelling OR simulation* OR microsimulation*) NEAR/6 (econom* OR pharmacoeconom* OR cost OR costs)) OR (decision NEAR/3 (analy* OR tree OR trees)) OR discrete-event* OR "state transition" OR markov OR ((individual* OR patient-level*) NEAR/3 (sampl* OR simulation*)) OR (dynamic NEAR/3 transmission*) OR probabilistic* OR partition*-survival*)

AND AB,TI("personalized medicine" OR "risk stratification" OR "pharmacogenetics" OR "genetic variation" OR "genetic procedures" OR "genotype" OR "biological marker" OR "mobile application" OR "personal digital assistant" OR "mobile phone" OR "gene therapy" OR "immunotherapy" OR "pharmacogenomics" OR "pharmacokinetics" OR "activity tracker" OR "artificial intelligence" OR "machine learning" OR (("algorithm" OR "genetic algorithm" OR "learning algorithm" OR "classification algorithm") AND (risk OR therapy)) OR "omics" OR "pharmacogenetic testing" OR "self monitoring" OR ((personalized OR personalised OR individualised OR individualized OR precision OR stratif* OR targeted* OR algorithm*) NEAR/6 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration OR decision*)) OR ((genetic OR gene OR genomic) NEAR/3 (variation OR technique OR procedure OR procedures OR test OR testing OR therapy OR sequence OR sequencing OR profile OR profiling)) OR genotype* OR (biologic* NEAR/3 marker*) OR biomarker* OR telemonitor* OR (mobile NEAR/3 (applicat* OR app OR apps)) OR wearable* OR (personal NEAR/3 digital NEAR/3 assistant) OR (handheld NEAR/3 computer*) OR ((mobile OR cell*) NEXT/1 phone*) OR smartphone* OR immunotherap* OR immunetherap* OR pharmacogenomic* OR pharmacogenetic* OR pharmacokinetic* OR (digital NEAR/3 (health OR medicine)) OR mHealth* OR eHealth* OR m-Health OR e-Health OR tracker* OR (artificial NEAR/3 intelligence) OR (machine NEAR/3 learning) OR ((remote OR self) NEAR/3 (monitor OR monitoring)) OR pharmacometabolom* OR metabolom* OR proteomic* OR pharmacoproteomic* OR lipidomic* OR pharmacolipidomic* OR omics OR (model

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NEAR/3 (guided OR based) NEAR/3 (medicine OR therapy OR treatment OR risk OR regimen OR dosing OR duration)) OR (risk NEAR/3 score))

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A.2 – Interview protocol modelling experts

PDF file with PPT of interview protocol

A.3 – Interview protocol end-users

PDF file with PPT of interview protocol

A.4 – Studies included in the systematic literature review

Gene therapies (n=12)

Banken R, Rind D, Cramer G, Synnott PG, Chapman R, Khan S, et al. Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value. 2018.

Ellis AG, Mickle K, Herron-Smith S, Kumar VM, Cianciolo L, Seidner M, et al. Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value. 2019.

Lasser KE, Mickle K, Emond S, Chapman R, Ollendorf DA, Pearson SD, et al. Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. 2018.

Lin JK, Lerman BJ, Barnes JI, Boursiquot BC, Tan YJ, Robinson AQL, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. J Clin Oncol. 2018;36(32):3192-202.

Machin N, Ragni MV, Smith KJ. Gene therapy in hemophilia A: A cost-effectiveness analysis. Blood Adv. 2018;2(14):1792-8.

National Institute For Health And Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]. 2018.

National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]. 2018.

National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. 2018.

South E, Cox E, Meader N, Woolacott N, Griffin S. Strimvelis for Treating Severe Combined Immunodeficiency Caused by Adenosine Deaminase Deficiency: An Evidence Review Group Perspective of a NICE Highly Specialised Technology Evaluation Review. PharmacoEcon Open. 2019;3:151-61.

Tice JA, Walsh JME, Otunoye I, Chapman R, Kumar V, Seidner M, et al. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. 2018.

Whittington MD, McQueen RB, Ollendorf DA, Kumar VM, Chapman RH, Tice JA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients with Relapsed or Refractory Leukemia. JAMA Pediatr. 2018;172(12):1161-8.

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Zimmermann M, Lubinga SJ, Banken R, Rind D, Cramer G, Synnott PG, et al. Cost Utility of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease. Value Health. 2019;22(2):161-7.

Omics profiling-guided interventions

Germline mutations (n=102)

Ademi Z, Watts GF, Pang J, Sijbr, s EJG, Van Bockxmeer FM, et al. Cascade screening based on genetic testing is cost-effective: Evidence for the implementation of models of care for familial hypercholesterolemia. J Clin Lipidology. 2014;8(4):390-400.

Alagoz O, Durham D, Kasirajan K. Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions. Pharmacogenomics J. 2016;16(2):129-36.

Asphaug L, Melberg HO. The Cost-Effectiveness of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer in Norway. MDM Policy Pract. 2019;4(1):2381468318821103.

Bennette CS, Gallego CJ, Burke W, Jarvik GP, Veenstra DL. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. Gen Med. 2015;17(7):587-95.

Berm EJJ, Gout-Zwart JJ, Luttjeboer J, Wilffert B, Postma MJ. A model based cost-effectiveness analysis of routine genotyping for CYP2D6 among older, depressed inpatients starting nortriptyline pharmacotherapy. PLoS ONE. 2016;11(12).

Butzke B, Oduncu FS, Severin F, Pfeufer A, Heinemann V, Giesen-Jung C, et al. The cost-effectiveness of UGT1A1 genotyping before colorectal cancer treatment with irinotecan from the perspective of the German statutory health insurance. Acta Oncol. 2016;55(3):318-28.

Chen CX, Hay JW. Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. Int J Cardiol. 2015;181:417-24.

Chen YE, Kao SS, Chung RH. Cost-effectiveness analysis of different genetic testing strategies for Lynch syndrome in Taiwan. PLoS ONE. 2016;11(8).

Chong HY, Lim YH, Prawjaeng J, Tassaneeyakul W, Mohamed Z, Chaiyakunapruk N. Cost-effectiveness analysis of HLA-B ∗ 58:01 genetic testing before initiation of allopurinol therapy to prevent allopurinol-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in a Malaysian population. Pharmacogenet Genomics. 2018;28(2):56-67.

Chong HY, Saokaew S, Dumrongprat K, Permsuwan U, Wu DBC, Sritara P, et al. Cost-effectiveness analysis of pharmacogenetic-guided warfarin dosing in Thailand. Thromb Res. 2014;134(6):1278-84.

Compagni A, Melegaro A, Tarricone R. Genetic Screening for the Predisposition to Venous Thromboembolism: A Cost-Utility Analysis of Clinical Practice in the Italian Health Care System. Value Health. 2013;16(6):909-21.

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Crespin DJ, Federspiel JJ, Biddle AK, Jonas DE, Rossi JS. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: A cost-effectiveness analysis. Value Health. 2011;14(4):483-91.

Crosland P, Maconachie R, Buckner S, McGuire H, Humphries SE, Qureshi N. Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales. Atherosclerosis. 2018;275:80-7.

de Graaff B, Neil A, Si L, Yee KC, erson K, Gurrin L, et al. Cost-Effectiveness of Different Population Screening Strategies for Hereditary Haemochromatosis in Australia. Appl Health Econ Health Policy. 2017;15(4):521-34.

Ding Y, Thompson JD, Kobrynski L, Ojodu J, Zarbalian G, Grosse SD. Cost-effectiveness/cost-benefit analysis of newborn screening for severe combined immune deficiency in Washington State. J Pediatr. 2016;172:127-35.

Dinh TA, Rosner BI, Atwood JC, Bol, CR, Syngal S, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2011;4(1):9-22.

Djalalov S, Yong J, Beca J, Black S, Saposnik G, Musa Z, et al. Genetic testing in combination with preventive donepezil treatment for patients with amnestic mild cognitive impairment: An exploratory economic evaluation of personalized medicine. Mol Diagn Ther. 2012;16(6):389-99.

Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B 1502 genotyping in adult patients with newly diagnosed epilepsy in singapore. Neurology. 2012;79(12):1259-67.

Eccleston A, Bentley A, Dyer M, Strydom A, Vereecken W, George A, et al. A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer. Value Health. 2017;20(4):567-76.

Eckman MH, Rosand J, Greenberg SM, Gage BF. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. Ann Intern Med. 2009;150(2):73-83.

Folse HJ, Green LE, Kress A, Allman R, Dinh TA. Cost-effectiveness of a genetic test for breast cancer risk. Cancer prevention research. 2013;6(12):1328-36.

Gallego CJ, Shirts BH, Bennette CS, Guzauskas G, Amendola LM, Horike-Pyne M, et al. Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: A cost-effectiveness analysis. J Clin Oncol. 2015;33(18):2084-91.

Gold HT, Hall MJ, Blinder V, Schackman BR. Cost effectiveness of pharmacogenetic testing for uridine diphosphate glucuronosyltransferase 1A1 before irinotecan administration for metastatic colorectal cancer. Cancer. 2009;115(17):3858-67.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Graves JA, Garbett S, Zhou Z, Peterson J. The value of pharmacogenomic information. National Bureau of Economic Research; 2017. Report No.: 0898-2937.

Greeley SAW, John PM, Winn AN, Ornelas J, Lipton RB, Philipson LH, et al. The cost-effectiveness of personalized genetic medicine: The case of genetic testing in neonatal diabetes. Diabetes Care. 2011;34(3):622-7.

Green LE, Dinh TA, Hinds DA, Walser BL, Allman R. Economic evaluation of using a genetic test to direct breast cancer chemoprevention in white women with a previous breast biopsy. Appl Health Econ Health Policy. 2014;12(2):203-17.

Groessl EJ, Tally SR, Hillery N, Maciel A, Garces JA. Cost-effectiveness of a pharmacogenetic test to guide treatment for major depressive disorder. J Manag Care Spec Pharm. 2018;24(8):726-34.

Hagaman JT, Kinder BW, Eckman MH. Thiopurine S-methyltranferase testing in idiopathic pulmonary fibrosis: A pharmacogenetic cost-effectiveness analysis. Lung. 2010;188(2):125-32.

Holland ML, Huston A, Noyes K. Cost-Effectiveness of Testing for Breast Cancer Susceptibility Genes. Value Health. 2009;12(2):207-16.

Hornberger J, Li Q, Quinn B. Cost-effectiveness of combinatorial pharmacogenomic testing for treatment-resistant major depressive disorder patients. Am J Manag Care. 2015;21(6):e357-e65.

Hoskins P, Eccleston A, Hurry M, Dyer M. Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer. A Canadian model. Gynecol Oncol. 2019.

Ingles J, McGaughran J, Scuffham PA, Atherton J, Semsarian C. A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy. Heart. 2012;98(8):625-30.

Janzic A, Kos M. Cost effectiveness of novel oral anticoagulants for stroke prevention in atrial fibrillation depending on the quality of warfarin anticoagulation control. Pharmacoeconomics. 2015;33(4):395-408.

Jiang M, You JH. CYP2C19 LOF and GOF-Guided Antiplatelet Therapy in Patients with Acute Coronary Syndrome: A Cost-Effectiveness Analysis. Cardiovasc Drugs Ther. 2016;31(1):39-49.

Jiang M, You JHS. CYP2C19 genotype plus platelet reactivity-guided antiplatelet therapy in acute coronary syndrome patients: A decision analysis. Pharmacogenet Genomics. 2015;25(12):609-17.

Jiang M, You JHS. Cost-effectiveness analysis of personalized antiplatelet therapy in patients with acute coronary syndrome. Pharmacogenomics. 2016;17(7):701-13.

Kapoor R, Martinez-Vega R, Dong D, Tan SY, Leo YS, Lee CC, et al. Reducing hypersensitivity reactions with HLA-B∗5701 genotyping before abacavir prescription: Clinically useful but is it cost-effective in Singapore? Pharmacogenet Genomics. 2015;25(2):60-72.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Kazi DS, Garber AM, Shah RU, Dudley RA, Mell MW, Rhee C, et al. Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. Ann Intern Med. 2014;160(4):221-32.

Ke CH, Chung WH, Wen YH, Huang YB, Chuang HY, Tain YL, et al. Cost-effectiveness analysis for genotyping before allopurinol treatment to prevent severe cutaneous adverse drug reactions. J Rheumatol. 2017;44(6):835-43.

Kim DJ, Kim HS, Oh M, Kim EY, Shin JG. Cost Effectiveness of Genotype-Guided Warfarin Dosing in Patients with Mechanical Heart Valve Replacement Under the Fee-for-Service System. Appl Health Econ Health Policy. 2017;15(5):657-67.

Kwon JS, Daniels MS, Sun CC, Lu KH. Preventing future cancers by testing women with ovarian cancer for BRCA mutations. J Clin Oncol. 2010;28(4):675-82.

Kwon JS, Gutierrez-Barrera AM, Young D, Sun CC, Daniels MS, Lu KH, et al. Expanding the criteria for BRCA mutation testing in breast cancer survivors. J Clin Oncol. 2010;28(27):4214-20.

Kwon JS, Tinker AV, Hanley GE, Pansegrau G, Sun S, Carey MS, et al. BRCA mutation testing for first-degree relatives of women with high-grade serous ovarian cancer. Gynecol Oncol. 2019;152(3):459-64.

Ladabaum U, Wang G, Terdiman J, Blanco A, Kuppermann M, Boland CR, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med. 2011;155(2):69-79.

Lala A, Berger JS, Sharma G, Hochman JS, Scott Braithwaite R, Ladapo JA. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A cost-effectiveness analysis. J Thromb Haemost. 2013;11(1):81-91.

Lázaro P, Pérez de Isla L, Watts GF, Alonso R, Norman R, Muñiz O, et al. Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia. J Clin Lipidology. 2017;11(1):260-71.

Li Y, Arellano AR, Bare LA, Bender RA, Strom CM, Devlin JJ. A Multigene Test Could Cost-Effectively Help Extend Life Expectancy for Women at Risk of Hereditary Breast Cancer. Value Health. 2017;20(4):547-55.

Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: A cost-effectiveness analysis. Ann Intern Med. 2012;156(4):279-90.

Martes-Martinez C, Mendez-Sepulveda C, Millan-Molina J, French-Kim M, Marin-Centeno H, Rivera-Miranda GC, et al. Cost-Utility Study of Warfarin Genotyping in the VACHS Affiliated Anticoagulation Clinic of Puerto Rico. P R Health Sci J. 2017;36(3):165-72.

McKay AJ, Hogan H, Humphries SE, Marks D, Ray KK, Miners A. Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis. Atherosclerosis. 2018;275:434-43.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Meckley LM, Gudgeon JM, Anderson JL, Williams MS, Veenstra DL. A policy model to evaluate the benefits, risks and costs of warfarin pharmacogenomic testing. Pharmacoeconomics. 2010;28(1):61-74.

Mesrobian HGO. The value of newborn urinary proteome analysis in the evaluation and management of ureteropelvic junction obstruction: A cost-effectiveness study. World J Urol. 2009;27(3):379-83.

Muller D, Danner M, Schmutzler R, Engel C, Wassermann K, Stollenwerk B, et al. Economic modeling of risk-adapted screen-and-treat strategies in women at high risk for breast or ovarian cancer. The European Journal of Health Economics. 2019;20:739-50.

Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. Genetics in Medicine. 2010;12(2):93-104.

Najafzadeh M, Garces JA, Maciel A. Economic Evaluation of Implementing a Novel Pharmacogenomic Test (IDgenetix®) to Guide Treatment of Patients with Depression and/or Anxiety. Pharmacoeconomics. 2017;35(12):1297-310.

Naylor RN, John PM, Winn AN, Carmody D, Greeley SAW, Philipson LH, et al. Cost-effectiveness of MODY genetic testing: Translating genomic advances into practical health applications. Diabetes Care. 2014;37(1):202-9.

Nherera L, Marks D, Minhas R, Thorogood M, Humphries SE. Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart. 2011;97(14):1175-81.

Nshimyumukiza L, Duplantie J, Gagnon M, Douville X, Fournier D, Lindsay C, et al. Dabigatran versus warfarin under standard or pharmacogenetic-guided management for the prevention of stroke and systemic thromboembolism in patients with atrial fibrillation: A cost/utility analysis using an analytic decision model. Thromb J. 2013;11(1).

Okere AN, Ezendu K, Berthe A, Diaby V. An evaluation of the cost-effectiveness of comprehensive MTM integrated with point-of-care phenotypic and genetic testing for U.S. elderly patients after percutaneous coronary intervention. J Manag Care Spec Pharm. 2018;24(2):142-52.

Panattoni L, Brown PM, Ao BT, Webster M, Gladding P. The cost effectiveness of genetic testing for CYP2C19 Variants to Guide Thienopyridine Treatment in Patients with Acute Coronary Syndromes: A New Zealand Evaluation. Pharmacoeconomics. 2012;30(11):1067-84.

Parthan A, Leahy KJ, O'Sullivan AK, Iakoubova OA, Bare LA, Devlin JJ, et al. Cost effectiveness of targeted high-dose atorvastatin therapy following genotype testing in patients with acute coronary syndrome. Pharmacoeconomics. 2013;31(6):519-31.

Pashayan N, Morris S, Gilbert FJ, Pharoah PDP. Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer: A Life-Table Model. JAMA Oncol. 2018;4(11):1504-10.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Patel V, Lin FJ, Ojo O, Rao S, Yu S, Zhan L, et al. Cost-utility analysis of genotype-guided antiplatelet therapy in patients with moderate-to- high risk acute coronary syndrome and planned percutaneous coronary intervention. Pharm Pract. 2014;12(3).

Patrick AR, Avorn J, Choudhry NK. Cost-effectiveness of genotype-guided warfarin dosing for patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes. 2009;2(5):429-36.

Pelczarska A, Jakubczyk M, Jakubiak-Lasocka J, Banach M, Myśliwiec M, Gruchała M, et al. The cost-effectiveness of screening strategies for familial hypercholesterolaemia in Poland. Atherosclerosis. 2018;270:132-8.

Perez MV, Kumarasamy NA, Owens DK, Wang PJ, Hlatky MA. Cost-effectiveness of genetic testing in family members of patients with long-qt syndrome. Circ Cardiovasc Qual Outcomes. 2011;4(1):76-84.

Perlis RH, Patrick A, Smoller JW, Wang PS. When is pharmacogenetic testing for antidepressant response ready for the clinic? A cost-effectiveness analysis based on data from the STAR*D study. Neuropsychopharmacology. 2009;34(10):2227-36.

Phelps CE, O'Sullivan AK, Ladapo JA, Weinstein MC, Leahy K, Douglas PS. Cost effectiveness of a gene expression score and myocardial perfusion imaging for diagnosis of coronary artery disease. Am Heart J. 2014;167(5):697-706.e2.

Pink J, Pirmohamed M, Lane S. Cost-effectiveness of pharmacogenetics-guided warfarin therapy vs. alternative anticoagulation in atrial fibrillation. Clinical Pharmacology …. 2014.

Plumpton CO, Alfirevic A, Pirmohamed M, Hughes DA. Cost effectiveness analysis of HLA-B*58:01 genotyping prior to initiation of allopurinol for gout. Rheumatology. 2017;56(10):1729-39.

Plumpton CO, Yip VLM, Alfirevic A, Marson AG. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. …. 2015.

Ramírez De Arellano A, Coca A, De La Figuera M, Rubio-Terrés C, Rubio-Rodríguez D, Gracia A, et al. Economic evaluation of Cardio inCode®, a clinical-genetic function for coronary heart disease risk assessment. Appl Health Econ Health Policy. 2013;11(5):531-42.

Rattanavipapong W, Koopitakkajorn T. Economic evaluation of HLA-B* 15: 02 screening for carbamazepine-induced severe adverse drug reactions in T hailand. …. 2013.

Reed SD, Scales Jr CD, Stewart SB, Sun J, Moul JW, Schulman KA, et al. Effects of family history and genetic polymorphism on the cost-effectiveness of chemoprevention with finasteride for prostate cancer. J Urol. 2011;185(3):841-7.

Rejon-Parrilla JC, Nuijten M, Redekop WK, Gaultney JG. Economic evaluation of the use of a pharmacogenetic diagnostic test in schizophrenia. Health Policy Technol. 2014.

Rogowski WH. The cost-effectiveness of screening for hereditary hemochromatosis in Germany: A remodeling study. Med Decis Mak. 2009;29(2):224-38.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Rubio-Terres C, Soria JM, Morange PE, Souto JC, Suchon P, Mateo J, et al. Economic Analysis of Thrombo inCode, a Clinical-Genetic Function for Assessing the Risk of Venous Thromboembolism. Appl Health Econ Health Policy. 2015;13(2):233-42.

Saokaew S, Tassaneeyakul W, Maenthaisong R, Chaiyakunapruk N. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. PLoS ONE. 2014;9(4).

Saramago P, Yang H, Llewellyn A, Palmer S, Simmonds M, Griffin S. High-throughput, non-invasive prenatal testing for fetal Rhesus D genotype to guide antenatal prophylaxis with anti-D immunoglobulin: a cost-effectiveness analysis. BJOG Int J Obstet Gynaecol. 2018;125(11):1414-22.

Schackman BR, Haas DW, Becker JE, Berkowitz BK, Sax PE, Daar ES, et al. Cost-effectiveness analysis of UGT1A1 genetic testing to inform antiretroviral prescribing in HIV disease. Antiviral therapy. 2013;18(3):399.

Serretti A, Olgiati P, Bajo E, Bigelli M, De Ronchi D. A model to incorporate genetic testing (5-HTTLPR) in pharmacological treatment of major depressive disorders. The World Journal of Biological Psychiatry. 2011;12(7):501-15.

Severin F, Stollenwerk B, Holinski-Feder E, Meyer E, Heinemann V, Giessen-Jung C, et al. Economic evaluation of genetic screening for Lynch syndrome in Germany. Gen Med. 2015;17(10):765-73.

Sharma P, Boyers D, Boachie C, Stewart F, Miedzybrodzka Z, Simpson W, et al. Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: A systematic review and economic evaluation. Health Technol Assess. 2012;16(17):1-265.

Shiffman D, Perez MV, Bare LA, Louie JZ, Arellano AR, Devlin JJ. Genetic risk for atrial fibrillation could motivate patient adherence to warfarin therapy: A cost effectiveness analysis. BMC Cardiovasc Disord. 2015;15(1).

Shiffman D, Slawsky K, Fusfeld L, Devlin JJ, Goss TF. Cost-Effectiveness Model of Use of Genetic Testing as an Aid in Assessing the Likely Benefit of Aspirin Therapy for Primary Prevention of Cardiovascular Disease. Clin Ther. 2012;34(6):1387-94.

Sluiter RL, Janzing JGE, van der Wilt GJ, Kievit W, Teichert M. An economic model of the cost-utility of pre-emptive genetic testing to support pharmacotherapy in patients with major depression in primary care. Pharmacogenomics J. 2019.

Sluiter RL, Kievit W, Van Der Wilt GJ, Schene AH, Teichert M, Coenen MJH, et al. Cost-Effectiveness Analysis of Genotype-Guided Treatment Allocation in Patients with Alcohol Use Disorders Using Naltrexone or Acamprosate, Using a Modeling Approach. Eur Addict Res. 2018;24(5):245-54.

Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation Review. Health Technol Assess. 2017;21(51):1-238.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C, et al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technol Assess. 2014;18(58):i-xxxviii+1-405.

Van Dyck W, Gassull D, Vértes G, Jain P, Palaniappan M, Schulthess D, et al. Unlocking the value of personalised healthcare in Europe-breast cancer stratification. Health Policy Technol. 2012;1(2):63-8.

van Nguyen H, Finkelstein EA, Mital S, Gardner DSL. Incremental cost-effectiveness of algorithm-driven genetic testing versus no testing for Maturity Onset Diabetes of the Young (MODY) in Singapore. J Med Genet. 2017;54(11):747-53.

Verhoef TI, Redekop WK, De Boer A, Maitland-Van Der Zee AH. Economic evaluation of a pharmacogenetic dosing algorithm for coumarin anticoagulants in the Netherlands. Pharmacogenomics. 2015;16(2):101-14.

Verhoef TI, Redekop WK, Langenskiold S, Kamali F, Wadelius M, Burnside G, et al. Cost-effectiveness of pharmacogenetic-guided dosing of warfarin in the United Kingdom and Sweden. Pharmacogenomics J. 2016;16(5):478-84.

Wang G, Kuppermann M, Kim B, Phillips KA, Ladabaum U. Influence of patient preferences on the cost-effectiveness of screening for lynch syndrome. J Oncol Pract. 2012;8(3):e24s-30s.

Wang VW, Koh PK, Chow WL, Lim JFY. Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary nonpolyposis colorectal cancer in Singapore. Fam Cancer. 2012;11(2):279-89.

Westwood M, Ramaekers B, Lang S, Grimm S, Deshpande S, de Kock S, et al. Risk scores to guide referral decisions for people with suspected ovarian cancer in secondary care: A systematic review and cost-effectiveness analysis. Health Technol Assess. 2018;22(44):V-264.

Woods B, Veenstra D, Hawkins N. Prioritizing pharmacogenetic research: a value of information analysis of CYP2D6 testing to guide breast cancer treatment. Value in Health. 2011;14(8):989-1001.

Wordsworth S, Leal J, Blair E, Legood R, Thomson K, Seller A, et al. DNA testing for hypertrophic cardiomyopathy: A cost-effectiveness model. Eur Heart J. 2010;31(8):926-35.

You JHS. Pharmacogenetic-guided selection of warfarin versus novel oral anticoagulants for stroke prevention in patients with atrial fibrillation: A cost-effectiveness analysis. Pharmacogenet Genomics. 2014;24(1):6-14.

You JHS, Tsui KKN, Wong RSM, Cheng G. Potential clinical and economic outcomes of CYP2C9 and VKORC1 genotype-guided dosing in patients starting warfarin therapy. Clin Pharmacol Ther. 2009;86(5):540-7.

You JHS, Tsui KKN, Wong RSM, Cheng G. Cost-effectiveness of Dabigatran versus genotype-guided management of Warfarin therapy for stroke prevention in patients with Atrial fibrillation. PLoS ONE. 2012;7(6).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Zhao YJ, Khoo AL, Lin L, Teng M, Koh CJ, Lim SG, et al. Cost-effectiveness of strategy-based approach to treatment of genotype 1 chronic hepatitis C. J Gastroenterol Hepatol. 2016;31(9):1628-37.

Somatic mutations (n=78)

Aguiar PN, Perry LA, Penny-Dimri J, Babiker H, Tadokoro H, de Mello RA, et al. The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC. Ann Oncol. 2017;28(9):2256-63.

Balentine CJ, Vanness DJ, Schneider DF. Cost-effectiveness of lobectomy versus genetic testing (Afirma®) for indeterminate thyroid nodules: Considering the costs of surveillance. Surgery. 2018;163(1):88-96.

Bargalló-Rocha JE, Lara-Medina F, Pérez-Sánchez V, Vázquez-Romo R, Villarreal-Garza C, Martínez-Said H, et al. Cost-Effectiveness of the 21-Gene Breast Cancer Assay in Mexico. Adv Ther. 2015.

Blank PR, Filipits M, Dubsky P, Gutzwiller F, Lux MP, Brase JC, et al. Cost-Effectiveness Analysis of Prognostic Gene Expression Signature-Based Stratification of Early Breast Cancer Patients. Pharmacoeconomics. 2015;33(2):179-90.

Blank PR, Moch H, Szucs TD, Schwenkglenks M. KRAS and BRAF mutation analysis in metastatic colorectal cancer: a cost-effectiveness analysis from a Swiss perspective. Clinical cancer research. 2011.

Blohmer JU, Rezai M, Kümmel S, Kühn T, Warm M, Friedrichs K, et al. Using the 21-gene assay to guide adjuvant chemotherapy decision-making in early-stage breast cancer: A cost-effectiveness evaluation in the German setting. J Med Econ. 2013;16(1):30-40.

Bonastre J, Marguet S, Lueza B, Michiels S, Delaloge S, Saghatchian M. Cost effectiveness of molecular profiling for adjuvant decision making in patients with node-negative breast cancer. J Clin Oncol. 2014;32(31):3513-9.

Buchanan J, Wordsworth S, Clifford R, Robbe P, Taylor JC, Schuh A, et al. Using Genomic Information to Guide Ibrutinib Treatment Decisions in Chronic Lymphocytic Leukaemia: A Cost-Effectiveness Analysis. Pharmacoeconomics. 2017;35(8):845-58.

Cai H, Zhang L, Li N, Chen S, Zheng B, Yang J, et al. Cost-effectiveness of Osimertinib as First-line Treatment and Sequential Therapy for EGFR Mutation-positive Non-small Cell Lung Cancer in China. Clin Ther. 2019;41(2):280-90.

Carlson JJ, Garrison LP, Ramsey SD, Veenstra DL. The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer. Value Health. 2009;12(1):20-7.

Chandler Y, Schechter CB, Jayasekera J, Near A, O'Neill SC, Isaacs C, et al. Cost effectiveness of gene expression profile testing in community practice. J Clin Oncol. 2018;36(6):554-62.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Chang EM, Punglia RS, Steinberg ML, Raldow AC. Cost Effectiveness of the Oncotype DX Genomic Prostate Score for Guiding Treatment Decisions in Patients With Early Stage Prostate Cancer. Urology. 2019.

Chen E, Tong KB, Malin JL. Cost-effectiveness of 70-gene MammaPrint signature in node-negative breast cancer. Am J Manag Care. 2010;16(12):e333-42.

Cosler LE, Lyman GH. Economic analysis of gene expression profile data to guide adjuvant treatment in women with early-stage breast cancer. Cancer Invest. 2009;27(10):953-9.

Cressman S, Karsan A, Hogge DE, McPherson E, Bolbocean C, Regier DA, et al. Economic impact of genomic diagnostics for intermediate-risk acute myeloid leukaemia. Br J Haematol. 2016;174(4):526-35.

Cromwell I, Regier DA, Peacock SJ, Poh CF. Cost-effectiveness analysis of using loss of heterozygosity to manage premalignant oral dysplasia in British Columbia, Canada. Oncologist. 2016;21(9):1099-106.

Das A, Callenberg KM, Styn MA, Jackson SA. Endoscopic ablation is a cost-effective cancer preventative therapy in patients with Barrett's esophagus who have elevated genomic instability. Endosc Int Open. 2016;4(5):E549-E59.

de Lima Lopes G, Jr., Segel JE, Tan DS, Do YK, Mok T, Finkelstein EA. Cost-effectiveness of epidermal growth factor receptor mutation testing and first-line treatment with gefitinib for patients with advanced adenocarcinoma of the lung. Cancer. 2012;118(4):1032-9.

Djalalov S, Beca J, Hoch JS, Krahn M, Tsao MS, Cutz JC, et al. Cost effectiveness of EML4-ALK fusion testing and first-line crizotinib treatment for patients with advanced ALK-positive non-small-cell lung cancer. J Clin Oncol. 2014;32(10):1012-9.

Doble B, John T, Thomas D, Fellowes A, Fox S. Cost-effectiveness of precision medicine in the fourth-line treatment of metastatic lung adenocarcinoma: An early decision analytic model of multiplex targeted …: Elsevier; 2017 2017.

Feller-Kopman D, Liu S, Geisler BP, DeCamp MM, Pietzsch JB. Cost-Effectiveness of a Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer. J Thorac Oncol. 2017;12(8):1223-32.

Garrison Jr LP, Lalla D, Brammer M, Babigumira JB, Wang B, Perez EA. Assessing the potential cost-effectiveness of retesting IHC0, IHC1+, or FISH-negative early stage breast cancer patients for HER2 status. Cancer. 2013;119(17):3113-22.

Ghatnekar O, Andersson R, Svensson M, Persson U, Ringdahl U, Zeilon P, et al. Modelling the benefits of early diagnosis of pancreatic cancer using a biomarker signature. Int J Cancer. 2013;133(10):2392-7.

Govers TM, Takes RP, Baris Karakullukcu M, Hannink G, Merkx MAW, Grutters JPC, et al. Management of the N0 neck in early stage oral squamous cell cancer: A modeling study of the cost-effectiveness. Oral Oncol. 2013;49(8):771-7.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Hall PS, McCabe C, Stein RC, Cameron D. Economic evaluation of genomic test-directed chemotherapy for early-stage lymph node-positive breast cancer. J Natl Cancer Inst. 2012;104(1):56-66.

Hall PS, Smith A, Hulme C, Vargas-Palacios A, Makris A, Hughes-Davies L, et al. Value of Information Analysis of Multiparameter Tests for Chemotherapy in Early Breast Cancer: The OPTIMA Prelim Trial. Value Health. 2017;20(10):1311-8.

Handorf EA, McElligott S, Vachani A, Langer CJ, Demeter MB, Armstrong K, et al. Cost effectiveness of personalized therapy for first-line treatment of stage IV and recurrent incurable adenocarcinoma of the lung. J Oncol Pract. 2012;8(5):267-74.

Hannouf MB, Winquist E, Mahmud SM, Brackstone M, Sarma S, Rodrigues G, et al. Cost-effectiveness of using a gene expression profiling test to aid in identifying the primary tumour in patients with cancer of unknown primary. Pharmacogenomics J. 2017;17(3):286-300.

Harty G, Jarrett J, Jofre-Bonet M. Consequences of Biomarker Analysis on the Cost-Effectiveness of Cetuximab in Combination with FOLFIRI as a First-Line Treatment of Metastatic Colorectal Cancer: Personalised Medicine at Work. Appl Health Econ Health Policy. 2018;16(4):515-25.

Heinzel A, Muller D, Behrendt FF, Giovanella L, Mottaghy FM, Verburg FA. Thyroid nodules with indeterminate cytology: molecular imaging with 99mTc-methoxyisobutylisonitrile (MIBI) is more cost-effective than the Afirma gene expression classifier. Eur J Nucl Med Mol Imaging. 2014;41(8):1497-500.

Holt S, Bertelli G, Humphreys I, Valentine W, Durrani S, Pudney D, et al. A decision impact, decision conflict and economic assessment of routine Oncotype DX testing of 146 women with node-negative or pNImi, ER-positive breast cancer in the U.K. Br J Cancer. 2013;108(11):2250-8.

Hornberger J, Degtiar I, Gutierrez H, Shewade A, David Henner W, Becker S, et al. Cost-effectiveness of gene-expression profiling for tumor-site origin. Value Health. 2013;16(1):46-56.

Hörster L, Schlenk RF, Stadler M, Gabriel M, Thol F, Schildmann J, et al. Cost-effectiveness of methods in personalized medicine. Results of a decision-analytic model in patients with acute myeloid leukemia with normal karyotype. Leuk Res. 2017;62:84-90.

Huxley N, Jones-Hughes T, Coelho H, Snowsill T, Cooper C, Meng Y, et al. A systematic review and economic evaluation of intraoperative tests [RD-100i one-step nucleic acid amplification (OSNA) system and Metasin test] for detecting sentinel lymph node metastases in breast cancer. Health Technol Assess. 2015;19(2):I-215.

Ibarrondo O, Alvarez-Lopez I, Freundlich F, Arrospide A, Galve-Calvo E, Gutierrez-Toribio M, et al. Probabilistic cost-utility analysis and expected value of perfect information for the Oncotype multigenic test: a discrete event simulation model. Gac Sanit. 2018.

Kansal AR, Shaul AJ, Stern S, Busam K, Doucet CA, Chalfin DB. Cost-effectiveness of a FISH assay for the diagnosis of melanoma in the USA. Expert Rev Pharmacoecon Outcomes Res. 2013;13(3):371-80.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Katz G, Romano O, Foa C, Vataire AL, Chantelard JV, Hervé R, et al. Economic impact of gene expression profiling in patients with early-stage breast cancer in France. PLoS ONE. 2015;10(6).

Koleva-Kolarova RG, Greuter MJW, Feenstra TL, Vermeulen KM, de Vries EFJ, Parkin D, et al. Molecular imaging with positron emission tomography and computed tomography (PET/CT) for selecting first-line targeted treatment in metastatic breast cancer: A cost-effectiveness study. Oncotarget. 2018;9(28):19836-46.

Ladabaum U, Allen J, Wandell M, Ramsey S. Colorectal cancer screening with blood-based biomarkers: Cost-effectiveness of methylated septin 9 DNA versus current strategies. Cancer Epidemiol Biomarkers Prev. 2013;22(9):1567-76.

Ladabaum U, Alvarez-Osorio L, Rosch T, Brueggenjuergen B. Cost-effectiveness of colorectal cancer screening in Germany: current endoscopic and fecal testing strategies versus plasma methylated Septin 9 DNA. Endosc Int Open. 2014;2(2):E96-E104.

Lee L, How J, Tabah RJ, Mitmaker EJ. Cost-effectiveness of molecular testing for thyroid nodules with atypia of undetermined significance cytology. J Clin Endocrinol Metab. 2014;99(8):2674-82.

Li H, Robinson KA, Anton B, Saldanha IJ, Ladenson PW. Cost-effectiveness of a novel molecular test for cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab. 2011;96(11):E1719-E26.

Li Y, Bare LA, Bender RA, Sninsky JJ, Wilson LS, Devlin JJ, et al. Cost Effectiveness of Sequencing 34 Cancer-Associated Genes as an Aid for Treatment Selection in Patients with Metastatic Melanoma. Mol Diagn Ther. 2015;19(3):169-77.

Lim EA, Lee H, Bae E, Lim J, Shin YK, Choi SE. Economic evaluation of companion diagnostic testing for EGFR mutations and first-line targeted therapy in advanced non-small cell lung cancer patients in South Korea. PLoS ONE. 2016;11(8).

Lobo JM, Trifiletti DM, Sturz VN, Dicker AP, Buerki C, Davicioni E, et al. Cost-effectiveness of the Decipher Genomic Classifier to Guide Individualized Decisions for Early Radiation Therapy After Prostatectomy for Prostate Cancer. Clin Genitourin Cancer. 2016;15(3):e299-e309.

Lu S, Yu Y, Fu S, Ren H. Cost-effectiveness of ALK testing and first-line crizotinib therapy for non-small-cell lung cancer in China. PLoS ONE. 2018;13(10).

Lu S, Zhang J, Ye M, Wang B, Wu B. Economic analysis of ALK testing and crizotinib therapy for advanced non-small-cell lung cancer. Pharmacogenomics. 2016;17(9):985-94.

Marguet S, Mazouni C, Ramaekers BLT, Dunant A, Kates R, Jacobs VR, et al. European cost-effectiveness study of uPA/PAI-1 biomarkers to guide adjuvant chemotherapy decisions in breast cancer. Eur J Cancer. 2016;63:168-79.

Medical Advisory S. KRAS Testing for Anti-EGFR Therapy in Advanced Colorectal Cancer: An Evidence-Based and Economic Analysis. Ont Health Technol Assess Ser. 2010;10(25):1-49.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Narita Y, Matsushima Y, Shiroiwa T, Chiba K, Nakanishi Y, Kurokawa T, et al. Cost-effectiveness analysis of EGFR mutation testing and gefitinib as first-line therapy for non-small cell lung cancer. Lung Cancer. 2015;90(1):71-7.

Nelson RE, Stenehjem D, Akerley W. A comparison of individualized treatment guided by VeriStrat with standard of care treatment strategies in patients receiving second-line treatment for advanced non-small cell lung cancer: A cost-utility analysis. Lung Cancer. 2013;82(3):461-8.

Paulden M, Franek J, Pham B, Bedard PL, Trudeau M, Krahn M. Cost-Effectiveness of the 21-Gene Assay for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer. Value Health. 2013;16(5):729-39.

Raldow AC, Sher D, Chen AB, Recht A, Punglia RS. Cost effectiveness of the Oncotype DX DCIS Score for guiding treatment of patients with ductal carcinoma in situ. J Clin Oncol. 2016;34(33):3963-8.

Reed SD, Dinan MA, Schulman KA, Lyman GH. Cost-effectiveness of the 21-gene recurrence score assay in the context of multifactorial decision making to guide chemotherapy for early-stage breast cancer. Gen Med. 2013;15(3):203-11.

Retèl VP, Grutters JPC, Van Harten WH, Joore MA. Value of research and value of development in early assessments of new medical technologies. Value Health. 2013;16(5):720-8.

Retel VP, Joore MA, Drukker CA. Prospective cost-effectiveness analysis of genomic profiling in breast cancer: Elsevier; 2013 2013.

Retel VP, Joore MA, Knauer M, Linn SC, Hauptmann M, van Harten WH. Cost-effectiveness of the 70-gene signature versus St. Gallen guidelines and Adjuvant Online for early breast cancer. Eur J Cancer. 2010;46(8):1382-91.

Roth JA, Billings P, Ramsey SD, Dumanois R, Carlson JJ. Cost-effectiveness of a 14-gene risk score assay to target adjuvant chemotherapy in early stage non-squamous non-small cell lung cancer. Oncologist. 2014;19(5):466-76.

Roth JA, Ramsey SD, Carlson JJ. Cost-effectiveness of a biopsy-based 8-protein prostate cancer prognostic assay to optimize treatment decision making in gleason 3 + 3 and 3 + 4 early stage prostate cancer. Oncologist. 2015;20(12):1355-64.

Safonov A, Wang S, Gross CP, Agarwal D, Bianchini G, Pusztai L, et al. Assessing cost-utility of predictive biomarkers in oncology: a streamlined approach. Breast Cancer Res Treat. 2016;155(2):223-34.

Saito S, Kameyama H, Muneoka Y, Okuda S, Wakai T, Akazawa K. Cost-effectiveness analysis of the use of comprehensive molecular profiling before initiating monoclonal antibody therapy against metastatic colorectal cancer in Japan. J Cancer Policy. 2017;12:61-6.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Sathianathen NJ, Kuntz KM, Alarid-Escudero F, Lawrentschuk NL, Bolton DM, Murphy DG, et al. Incorporating Biomarkers into the Primary Prostate Biopsy Setting: A Cost-Effectiveness Analysis. J Urol. 2018;200(6):1215-20.

Schremser K, Rogowski WH, Adler-Reichel S, Tufman ALH, Huber RM, Stollenwerk B. Cost-Effectiveness of an Individualized First-Line Treatment Strategy Offering Erlotinib Based on EGFR Mutation Testing in Advanced Lung Adenocarcinoma Patients in Germany. Pharmacoeconomics. 2015;33(11):1215-28.

Shiroiwa T, Motoo Y, Tsutani K. Cost-effectiveness analysis of KRAS testing and cetuximab as last-line therapy for colorectal cancer. Mol Diagn Ther. 2010;14(6):375-84.

Sutton AJ, Lamont JV, Mark Evans R, Williamson K, O'Rourke D, Duggan B, et al. An early analysis of the cost-effectiveness of a diagnostic classifier for risk stratification of haematuria patients (DCRSHP) compared to flexible cystoscopy in the diagnosis of bladder cancer. PLoS ONE. 2018;13(8).

Tsoi DT, Inoue M, Kelly CM, Verma S, Pritchard KI. Cost-effectiveness analysis of recurrence score-guided treatment using a 21-gene assay in early breast cancer. Oncologist. 2010;15(5):457-65.

Vijayaraghavan A, Efrusy MB, Göke B. Cost-effectiveness of KRAS testing in metastatic colorectal cancer patients in the United States and Germany: Wiley Online Library; 2012 2012.

Vriens D, Adang EMM, Netea-Maier RT, Smit JWA, De Wilt JHW, Oyen WJG, et al. Cost-effectiveness of FDG-PET/CT for cytologically indeterminate thyroid nodules: A decision analytic approach. J Clin Endocrinol Metab. 2014;99(9):3263-74.

Walter E, Dellago H, Grillari J, Dimai HP, Hackl M. Cost-utility analysis of fracture risk assessment using microRNAs compared with standard tools and no monitoring in the Austrian female population. Bone. 2018;108:44-54.

Ward MC, Shah C, Adelstein DJ, Geiger JL, Miller JA, Koyfman SA, et al. Cost-effectiveness of nivolumab for recurrent or metastatic head and neck cancer. Oral Oncol. 2017;74:49-55.

Ward S, Scope A, Rafia R, or A, Harnan S, Evans P, et al. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: A systematic review and cost-effectiveness analysis. Health Technol Assess. 2013;17(44):V-302.

Westwood M, Joore M, Whiting P, van Asselt T, Ramaekers B, Armstrong N, et al. Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small cell lung cancer: A systematic review and cost-effectiveness analysis. Health Technol Assess. 2014;18(32):1-165.

Wong IOL, Tsang JWH, Cowling BJ, Leung GM. Optimizing resource allocation for breast cancer prevention and care among Hong Kong Chinese women. Cancer. 2012;118(18):4394-403.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Wu B, Gu X, Zhang Q. Cost-Effectiveness of Osimertinib for EGFR Mutation–Positive Non–Small Cell Lung Cancer after Progression following First-Line EGFR TKI Therapy. J Thorac Oncol. 2018;13(2):184-93.

Wu JX, Lam R, Levin M, Rao J, Sullivan PS, Yeh MW. Effect of malignancy rates on cost-effectiveness of routine gene expression classifier testing for indeterminate thyroid nodules. Surgery. 2016;159(1):118-26.

Yamauchi H, Nakagawa C, Yamashige S, Takei H, Yagata H, Yoshida A, et al. Societal cost-effectiveness analysis of the 21-gene assay in estrogen-receptor-positive, lymph-node-negative early-stage breast cancer in Japan. BMC Health Serv Res. 2014;14.

Yang M, Rajan S, Issa AM. Cost effectiveness of gene expression profiling for early stage breast cancer: A decision-analytic model. Cancer. 2012;118(20):5163-70.

Zhu J, Li T, Wang X, Ye M, Cai J, Xu Y, et al. Gene-guided Gefitinib switch maintenance therapy for patients with advanced EGFR mutation-positive Non-small cell lung cancer: An economic analysis. BMC Cancer. 2013;13.

Germline and somatic mutations (n=1)

Lotan Y, Woldu SL, Sanli O, Black P, Milowsky MI. Modelling cost-effectiveness of a biomarker-based approach to neoadjuvant chemotherapy for muscle-invasive bladder cancer. BJU Int. 2018;122(3):434-40.

A.5 – References identification checklist per topic

Conditionality of test sequences and/or test outcomes

Gene therapies

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Omics-profiling guided interventions: Germline mutations

de Graaff B, Neil A, Si L, et al. Cost-Effectiveness of Different Population Screening Strategies for Hereditary Haemochromatosis in Australia. Appl Health Econ Health Policy. 2017; 15: 521-34.

Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2011; 4: 9-22.

Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B 1502 genotyping in adult patients with newly diagnosed epilepsy in singapore. Neurology. 2012; 79: 1259-67.

Kwon JS, Daniels MS, Sun CC, et al. Preventing future cancers by testing women with ovarian cancer for BRCA mutations. J Clin Oncol. 2010; 28: 675-82.

McKay AJ, Hogan H, Humphries SE, et al. Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis. Atherosclerosis. 2018; 275: 434-43.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Phelps CE, O'Sullivan AK, Ladapo JA, et al. Cost effectiveness of a gene expression score and myocardial perfusion imaging for diagnosis of coronary artery disease. Am Heart J. 2014; 167: 697-706.e2.

Ramírez De Arellano A, Coca A, De La Figuera M, et al. Economic evaluation of Cardio inCode®, a clinical-genetic function for coronary heart disease risk assessment. Appl Health Econ Health Policy. 2013; 11: 531-42.

Rattanavipapong W, Koopitakkajorn T. Economic evaluation of HLA-B* 15: 02 screening for carbamazepine-induced severe adverse drug reactions in T hailand. …. 2013.

Reed SD, Scales Jr CD, Stewart SB, et al. Effects of family history and genetic polymorphism on the cost-effectiveness of chemoprevention with finasteride for prostate cancer. J Urol. 2011; 185: 841-47.

Rogowski WH. The cost-effectiveness of screening for hereditary hemochromatosis in Germany: A remodeling study. Med Decis Mak. 2009; 29: 224-38.

Sharma P, Boyers D, Boachie C, Stewart F, Miedzybrodzka Z, Simpson W, et al. Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: A systematic review and economic evaluation. Health Technol Assess. 2012;16(17):1-265.

Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation Review. Health Technol Assess. 2017;21(51):1-238.

Wordsworth S, Leal J, Blair E, et al. DNA testing for hypertrophic cardiomyopathy: A cost-effectiveness model. Eur Heart J. 2010; 31: 926-35.

Omics-profiling guided interventions: Somatic mutations

Feller-Kopman D, Liu S, Geisler BP, et al. Cost-Effectiveness of a Bronchial Genomic Classifier for the Diagnostic Evaluation of Lung Cancer. J Thorac Oncol. 2017; 12: 1223-32.

Garrison Jr LP, Lalla D, Brammer M, et al. Assessing the potential cost-effectiveness of retesting IHC0, IHC1+, or FISH-negative early stage breast cancer patients for HER2 status. Cancer. 2013; 119: 3113-22.

Paulden M, Franek J, Pham B, et al. Cost-Effectiveness of the 21-Gene Assay for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer. Value Health. 2013; 16: 729-39.

Reed SD, Dinan MA, Schulman KA, et al. Cost-effectiveness of the 21-gene recurrence score assay in the context of multifactorial decision making to guide chemotherapy for early-stage breast cancer. Gen Med. 2013; 15: 203-11.

Yang M, Rajan S, Issa AM. Cost effectiveness of gene expression profiling for early stage breast cancer: A decision-analytic model. Cancer. 2012; 118: 5163-70.

Turnaround time from test or treatment decision until initiation of patient management strategy

Gene therapies

South E, Cox E, Meader N, et al. Strimvelis for Treating Severe Combined Immunodeficiency Caused by Adenosine Deaminase Deficiency: An Evidence Review Group Perspective of a NICE Highly Specialised Technology Evaluation Review. PharmacoEcon Open. 2019; 3: 151-61.

National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. 2018.

Omics-profiling guided interventions: Germline mutations

Ding Y, Thompson JD, Kobrynski L, et al. Cost-effectiveness/cost-benefit analysis of newborn screening for severe combined immune deficiency in Washington State. J Pediatr. 2016; 172: 127-35.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Eckman MH, Rosand J, Greenberg SM, et al. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. Ann Intern Med. 2009; 150: 73-83.

Sluiter RL, Janzing JGE, van der Wilt GJ, et al. An economic model of the cost-utility of pre-emptive genetic testing to support pharmacotherapy in patients with major depression in primary care. Pharmacogenomics J. 2019.

Omics-profiling guided interventions: Somatic mutations

Doble B, John T, Thomas D, et al. Cost-effectiveness of precision medicine in the fourth-line treatment of metastatic lung adenocarcinoma: An early decision analytic model of multiplex targeted …. Elsevier, 2017.

Huxley N, Jones-Hughes T, Coelho H, et al. A systematic review and economic evaluation of intraoperative tests [RD-100i one-step nucleic acid amplification (OSNA) system and Metasin test] for detecting sentinel lymph node metastases in breast cancer. Health Technol Assess. 2015; 19: I-215.

Li H, Robinson KA, Anton B, et al. Cost-effectiveness of a novel molecular test for cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab. 2011; 96: E1719-E26.

Westwood M, Joore M, Whiting P, et al. Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small cell lung cancer: A systematic review and cost-effectiveness analysis. Health Technol Assess. 2014; 18: 1-165.

Methods to compensate for bias in studies with small target population

Gene therapies

South E, Cox E, Meader N, et al. Strimvelis for Treating Severe Combined Immunodeficiency Caused by Adenosine Deaminase Deficiency: An Evidence Review Group Perspective of a NICE Highly Specialised Technology Evaluation Review. PharmacoEcon Open. 2019; 3: 151-61.

Omics-profiling guided interventions: Germline mutations

Rattanavipapong W, Koopitakkajorn T. Economic evaluation of HLA-B* 15:02 screening for carbamazepine-induced severe adverse drug reactions in Thailand. 2013.

Omics-profiling guided interventions: Somatic mutations

Buchanan J, Wordsworth S, Clifford R, et al. Using Genomic Information to Guide Ibrutinib Treatment Decisions in Chronic Lymphocytic Leukaemia: A Cost-Effectiveness Analysis. Pharmacoeconomics. 2017; 35: 845-58.

Methods to compensate for bias in observational studies

Gene therapies

National Institute For Health And Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]. 2018.

National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. 2018.

Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients with Relapsed or Refractory Leukemia. JAMA Pediatr. 2018; 172: 1161-68.

Omics-profiling guided interventions: Germline mutations

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Omics-profiling guided interventions: Somatic mutations

Paulden M, Franek J, Pham B, et al. Cost-Effectiveness of the 21-Gene Assay for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer. Value Health. 2013; 16: 729-39.

Methods to compensate for bias in using a historical cohort for comparator data

Gene therapies

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Omics-profiling guided interventions: Germline mutations

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Omics-profiling guided interventions: Somatic mutations

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For interventions aiming to cure; methods to compensate for potential bias in the extrapolation of outcomes

Gene therapies

Banken R, Rind D, Cramer G, et al. Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value. 2018.

Ellis AG, Mickle K, Herron-Smith S, Kumar VM, Cianciolo L, Seidner M, et al. Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value. 2019.

Lin JK, Lerman BJ, Barnes JI, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. J Clin Oncol. 2018; 36: 3192-202.

National Institute For Health And Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]. 2018.

National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]. 2018.

National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. 2018.

Tice JA, Walsh JME, Otunoye I, et al. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. 2018.

Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients with Relapsed or Refractory Leukemia. JAMA Pediatr. 2018; 172: 1161-68.

Zimmermann M, Lubinga SJ, Banken R, et al. Cost Utility of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease. Value Health. 2019; 22: 161-67.

Omics-profiling guided interventions: Germline mutations

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Omics-profiling guided interventions: Somatic mutations

Bonastre J, Marguet S, Lueza B, et al. Cost effectiveness of molecular profiling for adjuvant decision making in patients with node-negative breast cancer. J Clin Oncol. 2014; 32: 3513-19.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Marguet S, Mazouni C, Ramaekers BLT, et al. European cost-effectiveness study of uPA/PAI-1 biomarkers to guide adjuvant chemotherapy decisions in breast cancer. Eur J Cancer. 2016; 63: 168-79.

Methods to combine expert opinions into a point estimate plus distribution

Gene therapies

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Omics-profiling guided interventions: Germline mutations

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Omics-profiling guided interventions: Somatic mutations

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Deviation from standard discount rates for reasons particularly relevant to PM interventions

Gene therapies

National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. 2018.

South E, Cox E, Meader N, et al. Strimvelis for Treating Severe Combined Immunodeficiency Caused by Adenosine Deaminase Deficiency: An Evidence Review Group Perspective of a NICE Highly Specialised Technology Evaluation Review. PharmacoEcon Open. 2019; 3: 151-61.

Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients with Relapsed or Refractory Leukemia. JAMA Pediatr. 2018; 172: 1161-68.

Omics-profiling guided interventions: Germline mutations

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Omics-profiling guided interventions: Somatic mutations

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Values beyond the current patient

Gene therapies

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Omics-profiling guided interventions: Germline mutations

Ademi Z, Watts GF, Pang J, et al. Cascade screening based on genetic testing is cost-effective: Evidence for the implementation of models of care for familial hypercholesterolemia. J Clin Lipidology. 2014; 8: 390-400.

Asphaug L, Melberg HO. The Cost-Effectiveness of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer in Norway. MDM Policy Pract. 2019; 4: 2381468318821103.

Bennette CS, Gallego CJ, Burke W, et al. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. Gen Med. 2015; 17: 587-95.

Chen CX, Hay JW. Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. Int J Cardiol. 2015; 181: 417-24.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Chen YE, Kao SS, Chung RH. Cost-effectiveness analysis of different genetic testing strategies for Lynch syndrome in Taiwan. PLoS ONE. 2016; 11.

Crosland P, Maconachie R, Buckner S, et al. Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales. Atherosclerosis. 2018; 275: 80-87.

de Graaff B, Neil A, Si L, et al. Cost-Effectiveness of Different Population Screening Strategies for Hereditary Haemochromatosis in Australia. Appl Health Econ Health Policy. 2017; 15: 521-34.

Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2011; 4: 9-22.

Eccleston A, Bentley A, Dyer M, et al. A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer. Value Health. 2017; 20: 567-76.

Gallego CJ, Shirts BH, Bennette CS, et al. Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: A cost-effectiveness analysis. J Clin Oncol. 2015; 33: 2084-91.

Hoskins P, Eccleston A, Hurry M, et al. Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer. A Canadian model. Gynecol Oncol. 2019.

Kwon JS, Daniels MS, Sun CC, et al. Preventing future cancers by testing women with ovarian cancer for BRCA mutations. J Clin Oncol. 2010; 28: 675-82.

Ladabaum U, Wang G, Terdiman J, Blanco A, Kuppermann M, Boland CR, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med. 2011;155(2):69-79.Lázaro P, Pérez de Isla L, Watts GF, et al. Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia. J Clin Lipidology. 2017; 11: 260-71.

McKay AJ, Hogan H, Humphries SE, et al. Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis. Atherosclerosis. 2018; 275: 434-43.

Mvundura M, Grosse SD, Hampel H, et al. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. Genetics in Medicine. 2010; 12: 93-104.

Nherera L, Marks D, Minhas R, et al. Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart. 2011; 97: 1175-81.

Pelczarska A, Jakubczyk M, Jakubiak-Lasocka J, et al. The cost-effectiveness of screening strategies for familial hypercholesterolaemia in Poland. Atherosclerosis. 2018; 270: 132-38.

Perez MV, Kumarasamy NA, Owens DK, et al. Cost-effectiveness of genetic testing in family members of patients with long-qt syndrome. Circ Cardiovasc Qual Outcomes. 2011; 4: 76-84.

Rogowski WH. The cost-effectiveness of screening for hereditary hemochromatosis in Germany: A remodeling study. Med Decis Mak. 2009; 29: 224-38.

Severin F, Stollenwerk B, Holinski-Feder E, et al. Economic evaluation of genetic screening for Lynch syndrome in Germany. Gen Med. 2015; 17: 765-73.

Sharma P, Boyers D, Boachie C, Stewart F, Miedzybrodzka Z, Simpson W, et al. Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: A systematic review and economic evaluation. Health Technol Assess. 2012;16(17):1-265.

Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C, et al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technol Assess. 2014;18(58):i-xxxviii+1-405.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation Review. Health Technol Assess. 2017;21(51):1-238.

Wang G, Kuppermann M, Kim B, et al. Influence of patient preferences on the cost-effectiveness of screening for lynch syndrome. J Oncol Pract. 2012; 8: e24s-30s.

Wang VW, Koh PK, Chow WL, et al. Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary nonpolyposis colorectal cancer in Singapore. Fam Cancer. 2012; 11: 279-89.

Wordsworth S, Leal J, Blair E, et al. DNA testing for hypertrophic cardiomyopathy: A cost-effectiveness model. Eur Heart J. 2010; 31: 926-35.

Omics-profiling guided interventions: Somatic mutations

Ghatnekar O, Andersson R, Svensson M, et al. Modelling the benefits of early diagnosis of pancreatic cancer using a biomarker signature. Int J Cancer. 2013; 133: 2392-97.

Values beyond the QALY

Gene therapies

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Omics-profiling guided interventions: Germline mutations

Asphaug L, Melberg HO. The Cost-Effectiveness of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer in Norway. MDM Policy Pract. 2019; 4: 2381468318821103.

Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2011; 4: 9-22.

Eccleston A, Bentley A, Dyer M, et al. A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer. Value Health. 2017; 20: 567-76.

Holland ML, Huston A, Noyes K. Cost-Effectiveness of Testing for Breast Cancer Susceptibility Genes. Value Health. 2009; 12: 207-16.

Li Y, Arellano AR, Bare LA, et al. A Multigene Test Could Cost-Effectively Help Extend Life Expectancy for Women at Risk of Hereditary Breast Cancer. Value Health. 2017; 20: 547-55.

Muller D, Danner M, Schmutzler R, et al. Economic modeling of risk-adapted screen-and-treat strategies in women at high risk for breast or ovarian cancer. The European Journal of Health Economics. 2019; 20: 739-50.

Sharma P, Boyers D, Boachie C, Stewart F, Miedzybrodzka Z, Simpson W, et al. Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: A systematic review and economic evaluation. Health Technol Assess. 2012;16(17):1-265.

Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C, et al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technol Assess. 2014;18(58):i-xxxviii+1-405.

Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation Review. Health Technol Assess. 2017;21(51):1-238.

Wang G, Kuppermann M, Kim B, et al. Influence of patient preferences on the cost-effectiveness of screening for lynch syndrome. J Oncol Pract. 2012; 8: e24s-30s.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Omics-profiling guided interventions: Somatic mutations

Chandler Y, Schechter CB, Jayasekera J, et al. Cost effectiveness of gene expression profile testing in community practice. J Clin Oncol. 2018; 36: 554-62.

Raldow AC, Sher D, Chen AB, et al. Cost effectiveness of the Oncotype DX DCIS Score for guiding treatment of patients with ductal carcinoma in situ. J Clin Oncol. 2016; 34: 3963-68.

Equity issues particularly relevant to PM interventions

Gene therapies

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Omics-profiling guided interventions: Germline mutations

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Omics-profiling guided interventions: Somatic mutations

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Uncertainty analysis particularly relevant to PM interventions

Gene therapies

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Omics-profiling guided interventions: Germline mutations

Gallego CJ, Shirts BH, Bennette CS, et al. Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: A cost-effectiveness analysis. J Clin Oncol. 2015; 33: 2084-91.

Graves JA, Garbett S, Zhou Z, et al. The value of pharmacogenomic information. National Bureau of Economic Research, 2017.

Holland ML, Huston A, Noyes K. Cost-Effectiveness of Testing for Breast Cancer Susceptibility Genes. Value Health. 2009; 12: 207-16.

Kazi DS, Garber AM, Shah RU, Dudley RA, Mell MW, Rhee C, et al. Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. Ann Intern Med. 2014;160(4):221-32.

McKay AJ, Hogan H, Humphries SE, et al. Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis. Atherosclerosis. 2018; 275: 434-43.

Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C, et al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technol Assess. 2014;18(58):i-xxxviii+1-405.

Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation Review. Health Technol Assess. 2017;21(51):1-238.

Wang G, Kuppermann M, Kim B, et al. Influence of patient preferences on the cost-effectiveness of screening for lynch syndrome. J Oncol Pract. 2012; 8: e24s-30s.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Omics-profiling guided interventions: Somatic mutations

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Managed entry agreement included in cost-effectiveness analysis

Gene therapies

Lin JK, Lerman BJ, Barnes JI, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. J Clin Oncol. 2018; 36: 3192-202.

National Institute For Health And Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]. 2018.

National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]. 2018.

National Institute For Health And Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]. 2018.

Tice JA, Walsh JME, Otunoye I, et al. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. 2018.

Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients with Relapsed or Refractory Leukemia. JAMA Pediatr. 2018; 172: 1161-68.

Omics-profiling guided interventions: Germline mutations

-

Omics-profiling guided interventions: Somatic mutations

Buchanan J, Wordsworth S, Clifford R, et al. Using Genomic Information to Guide Ibrutinib Treatment Decisions in Chronic Lymphocytic Leukaemia: A Cost-Effectiveness Analysis. Pharmacoeconomics. 2017; 35: 845-58.

Zhu J, Li T, Wang X, et al. Gene-guided Gefitinib switch maintenance therapy for patients with advanced EGFR mutation-positive Non-small cell lung cancer: An economic analysis. BMC Cancer. 2013; 13.

Patients' uptake of testing

Gene therapies

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Omics-profiling guided interventions: Germline mutations

Asphaug L, Melberg HO. The Cost-Effectiveness of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer in Norway. MDM Policy Pract. 2019; 4: 2381468318821103.

Bennette CS, Gallego CJ, Burke W, et al. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. Gen Med. 2015; 17: 587-95.

Chen YE, Kao SS, Chung RH. Cost-effectiveness analysis of different genetic testing strategies for Lynch syndrome in Taiwan. PLoS ONE. 2016; 11.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

de Graaff B, Neil A, Si L, et al. Cost-Effectiveness of Different Population Screening Strategies for Hereditary Haemochromatosis in Australia. Appl Health Econ Health Policy. 2017; 15: 521-34.

Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2011; 4: 9-22.

Crosland P, Maconachie R, Buckner S, et al. Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales. Atherosclerosis. 2018; 275: 80-87.

Gallego CJ, Shirts BH, Bennette CS, et al. Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: A cost-effectiveness analysis. J Clin Oncol. 2015; 33: 2084-91.

Kwon JS, Daniels MS, Sun CC, et al. Preventing future cancers by testing women with ovarian cancer for BRCA mutations. J Clin Oncol. 2010; 28: 675-82.

Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med. 2011; 155: 69-79.

McKay AJ, Hogan H, Humphries SE, et al. Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis. Atherosclerosis. 2018; 275: 434-43.

Mvundura M, Grosse SD, Hampel H, et al. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. Genetics in Medicine. 2010; 12: 93-104.

Nherera L, Marks D, Minhas R, et al. Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart. 2011; 97: 1175-81.

Rogowski WH. The cost-effectiveness of screening for hereditary hemochromatosis in Germany: A remodeling study. Med Decis Mak. 2009; 29: 224-38.

Severin F, Stollenwerk B, Holinski-Feder E, et al. Economic evaluation of genetic screening for Lynch syndrome in Germany. Gen Med. 2015; 17: 765-73.

Sharma P, Boyers D, Boachie C, Stewart F, Miedzybrodzka Z, Simpson W, et al. Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: A systematic review and economic evaluation. Health Technol Assess. 2012;16(17):1-265.

Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C, et al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technol Assess. 2014;18(58):i-xxxviii+1-405.

Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation Review. Health Technol Assess. 2017;21(51):1-238.

Wang G, Kuppermann M, Kim B, et al. Influence of patient preferences on the cost-effectiveness of screening for lynch syndrome. J Oncol Pract. 2012; 8: e24s-30s.

Wordsworth S, Leal J, Blair E, et al. DNA testing for hypertrophic cardiomyopathy: A cost-effectiveness model. Eur Heart J. 2010; 31: 926-35.

Omics-profiling guided interventions: Somatic mutations

Djalalov S, Beca J, Hoch JS, et al. Cost effectiveness of EML4-ALK fusion testing and first-line crizotinib treatment for patients with advanced ALK-positive non-small-cell lung cancer. J Clin Oncol. 2014; 32: 1012-19.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Ladabaum U, Allen J, Wandell M, et al. Colorectal cancer screening with blood-based biomarkers: Cost-effectiveness of methylated septin 9 DNA versus current strategies. Cancer Epidemiol Biomarkers Prev. 2013; 22: 1567-76.

Ladabaum U, Alvarez-Osorio L, Rosch T, et al. Cost-effectiveness of colorectal cancer screening in Germany: current endoscopic and fecal testing strategies versus plasma methylated Septin 9 DNA. Endosc Int Open. 2014; 2: E96-E104.

Patients' treatment adherence

Gene therapies

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Omics-profiling guided interventions: Germline mutations

Asphaug L, Melberg HO. The Cost-Effectiveness of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer in Norway. MDM Policy Pract. 2019; 4: 2381468318821103.

Bennette CS, Gallego CJ, Burke W, et al. The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. Gen Med. 2015; 17: 587-95.

Chen CX, Hay JW. Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States. Int J Cardiol. 2015; 181: 417-24.

Chen YE, Kao SS, Chung RH. Cost-effectiveness analysis of different genetic testing strategies for Lynch syndrome in Taiwan. PLoS ONE. 2016; 11.

de Graaff B, Neil A, Si L, et al. Cost-Effectiveness of Different Population Screening Strategies for Hereditary Haemochromatosis in Australia. Appl Health Econ Health Policy. 2017; 15: 521-34.

Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2011; 4: 9-22.

Eccleston A, Bentley A, Dyer M, et al. A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer. Value Health. 2017; 20: 567-76.

Green LE, Dinh TA, Hinds DA, et al. Economic evaluation of using a genetic test to direct breast cancer chemoprevention in white women with a previous breast biopsy. Appl Health Econ Health Policy. 2014; 12: 203-17.

Holland ML, Huston A, Noyes K. Cost-Effectiveness of Testing for Breast Cancer Susceptibility Genes. Value Health. 2009; 12: 207-16.

Hoskins P, Eccleston A, Hurry M, et al. Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer. A Canadian model. Gynecol Oncol. 2019.

Kwon JS, Daniels MS, Sun CC, et al. Preventing future cancers by testing women with ovarian cancer for BRCA mutations. J Clin Oncol. 2010; 28: 675-82.

Kwon JS, Gutierrez-Barrera AM, Young D, et al. Expanding the criteria for BRCA mutation testing in breast cancer survivors. J Clin Oncol. 2010; 28: 4214-20.

Kwon JS, Tinker AV, Hanley GE, et al. BRCA mutation testing for first-degree relatives of women with high-grade serous ovarian cancer. Gynecol Oncol. 2019; 152: 459-64.

Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med. 2011; 155: 69-79.

Li Y, Arellano AR, Bare LA, et al. A Multigene Test Could Cost-Effectively Help Extend Life Expectancy for Women at Risk of Hereditary Breast Cancer. Value Health. 2017; 20: 547-55.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Liu S, Cipriano LE, Holodniy M, et al. New protease inhibitors for the treatment of chronic hepatitis C: A cost-effectiveness analysis. Ann Intern Med. 2012; 156: 279-90.

Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. Genetics in Medicine. 2010;12(2):93-104.

Parthan A, Leahy KJ, O'Sullivan AK, et al. Cost effectiveness of targeted high-dose atorvastatin therapy following genotype testing in patients with acute coronary syndrome. Pharmacoeconomics. 2013; 31: 519-31.

Pashayan N, Morris S, Gilbert FJ, Pharoah PDP. Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer: A Life-Table Model. JAMA Oncol. 2018;4(11):1504-10.

Pelczarska A, Jakubczyk M, Jakubiak-Lasocka J, et al. The cost-effectiveness of screening strategies for familial hypercholesterolaemia in Poland. Atherosclerosis. 2018; 270: 132-38.

Perez MV, Kumarasamy NA, Owens DK, et al. Cost-effectiveness of genetic testing in family members of patients with long-qt syndrome. Circ Cardiovasc Qual Outcomes. 2011; 4: 76-84.

Pink J, Pirmohamed M, Lane S. Cost-effectiveness of pharmacogenetics-guided warfarin therapy vs. alternative anticoagulation in atrial fibrillation. Clinical Pharmacology …. 2014.

Ramírez De Arellano A, Coca A, De La Figuera M, et al. Economic evaluation of Cardio inCode®, a clinical-genetic function for coronary heart disease risk assessment. Appl Health Econ Health Policy. 2013; 11: 531-42.

Reed SD, Scales Jr CD, Stewart SB, et al. Effects of family history and genetic polymorphism on the cost-effectiveness of chemoprevention with finasteride for prostate cancer. J Urol. 2011; 185: 841-47.

Rogowski WH. The cost-effectiveness of screening for hereditary hemochromatosis in Germany: A remodeling study. Med Decis Mak. 2009; 29: 224-38.

Rubio-Terres C, Soria JM, Morange PE, et al. Economic Analysis of Thrombo inCode, a Clinical-Genetic Function for Assessing the Risk of Venous Thromboembolism. Appl Health Econ Health Policy. 2015; 13: 233-42.

Saramago P, Yang H, Llewellyn A, et al. High-throughput, non-invasive prenatal testing for fetal Rhesus D genotype to guide antenatal prophylaxis with anti-D immunoglobulin: a cost-effectiveness analysis. BJOG Int J Obstet Gynaecol. 2018; 125: 1414-22.

Severin F, Stollenwerk B, Holinski-Feder E, et al. Economic evaluation of genetic screening for Lynch syndrome in Germany. Gen Med. 2015; 17: 765-73.

Shiffman D, Perez MV, Bare LA, et al. Genetic risk for atrial fibrillation could motivate patient adherence to warfarin therapy: A cost effectiveness analysis. BMC Cardiovasc Disord. 2015; 15.

Shiffman D, Slawsky K, Fusfeld L, et al. Cost-Effectiveness Model of Use of Genetic Testing as an Aid in Assessing the Likely Benefit of Aspirin Therapy for Primary Prevention of Cardiovascular Disease. Clin Ther. 2012; 34: 1387-94.

Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C, et al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technol Assess. 2014;18(58):i-xxxviii+1-405.

Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation Review. Health Technol Assess. 2017;21(51):1-238.

Wang G, Kuppermann M, Kim B, et al. Influence of patient preferences on the cost-effectiveness of screening for lynch syndrome. J Oncol Pract. 2012; 8: e24s-30s.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Wang VW, Koh PK, Chow WL, et al. Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary nonpolyposis colorectal cancer in Singapore. Fam Cancer. 2012; 11: 279-89.

Omics-profiling guided interventions: Somatic mutations

Garrison Jr LP, Lalla D, Brammer M, et al. Assessing the potential cost-effectiveness of retesting IHC0, IHC1+, or FISH-negative early stage breast cancer patients for HER2 status. Cancer. 2013; 119: 3113-22.

Ladabaum U, Allen J, Wandell M, et al. Colorectal cancer screening with blood-based biomarkers: Cost-effectiveness of methylated septin 9 DNA versus current strategies. Cancer Epidemiol Biomarkers Prev. 2013; 22: 1567-76.

Ladabaum U, Alvarez-Osorio L, Rosch T, et al. Cost-effectiveness of colorectal cancer screening in Germany: current endoscopic and fecal testing strategies versus plasma methylated Septin 9 DNA. Endosc Int Open. 2014; 2: E96-E104.

Ward S, Scope A, Rafia R, et al. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: A systematic review and cost-effectiveness analysis. Health Technol Assess. 2013; 17: V-302.

Clinicians' adherence to protocols/guidelines

Gene therapies

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Omics-profiling guided interventions: Germline mutations

Compagni A, Melegaro A, Tarricone R. Genetic Screening for the Predisposition to Venous Thromboembolism: A Cost-Utility Analysis of Clinical Practice in the Italian Health Care System. Value Health. 2013; 16: 909-21.

Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2011; 4: 9-22.

Graves JA, Garbett S, Zhou Z, et al. The value of pharmacogenomic information. National Bureau of Economic Research, 2017.

Rejon-Parrilla JC, Nuijten M, Redekop WK, et al. Economic evaluation of the use of a pharmacogenetic diagnostic test in schizophrenia. Health Policy Technol. 2014.

Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C, et al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technol Assess. 2014;18(58):i-xxxviii+1-405.

Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation Review. Health Technol Assess. 2017;21(51):1-238.

Omics-profiling guided interventions: Somatic mutations

Bonastre J, Marguet S, Lueza B, et al. Cost effectiveness of molecular profiling for adjuvant decision making in patients with node-negative breast cancer. J Clin Oncol. 2014; 32: 3513-19.

Chandler Y, Schechter CB, Jayasekera J, et al. Cost effectiveness of gene expression profile testing in community practice. J Clin Oncol. 2018; 36: 554-62.

Hornberger J, Degtiar I, Gutierrez H, et al. Cost-effectiveness of gene-expression profiling for tumor-site origin. Value Health. 2013; 16: 46-56.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Yang M, Rajan S, Issa AM. Cost effectiveness of gene expression profiling for early stage breast cancer: A decision-analytic model. Cancer. 2012; 118: 5163-70.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.