A Work Project, presented as part of the requirements for the Award of a Master's degree in International Development and Public Policy

SYSTEMATIC LITERATURE REVIEW OF PUBLISHED HEALTH ECONOMIC EVALUATIONS OF GENETIC TESTING: WHAT ARE THE PREFERED METHODOLOGICAL APPROACHES WHEN IT COMES TO EVALUATING GENETIC TESTING COST-EFFECTIVENESS AND HOW GENETIC TESTING PERFORMANCE IS CAPTURED IN COST-EFFECTIVENESS ANALYSES

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Abstract

This paper focuses on how cost-effectiveness analyses of genetic testing are conducted. A systematic literature review was performed in order to better understand the characteristics of standard genetic testing health economic evaluations models.

We totalled 1490 initial hits after having inserted the search strategy on the PubMed Advanced Search Builder. After careful screening, only 23 articles were included in our final analysis.

Our article's conclusions highlight some vital aspects researchers should have in mind when elaborating HTA's specific for genetic testing.

Hopefully, our article can contribute to the growing literature body, so that the HTA processes for these health technologies become more rigorous and accurate.

Keywords: Genetic testing; Health Technology Assessment (HTA); Health economic evaluation; Cost-effectiveness analysis; Cost-utility analysis; Cost-benefit analysis; Systematic literature review (SLR);

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1. Introduction

The present work aims to analyze in detail various health economics models regarding genetic testing cost-effectiveness. We seek to gather relevant information on how genetic testing HTAs have been conducted and on how costs, benefits, utilities, and quality of life should be incorporated when conducting the economic evaluations of genetic tests.

This paper is the result of a partnership with IQVIA, which provided us with the research questions and with their continued guidance.

It is appropriate to begin this work by giving some context on genetic testing and its evaluation process.

Genetic testing

It refers to "the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes" (McPherson 2006). In short, genetic testing is a type of test that can identify mutations in our genetic composition: chromosomes, genes, or proteins.

Genetic tests are classified as health technologies, and according to the World Health Organization (WHO 2022) a health technology is the application of organized knowledge and skills in the form of medicines, medical devices, vaccines, procedures, and systems developed to solve a health problem and improve quality of life.

Types and uses of genetic tests

Depending on what is being analysed, the three main types of genetic test are chromosomal, DNA and biochemical (University of Rochester Medical Center 2022):

- Chromosomal tests analyze whole chromosomes or long pieces of DNA to find substantial changes. Anomalies found can consist of extra or missing chromosome copies, duplicate or deleted chromosome pieces, or misplaced chromosome segments.
- DNA tests directly examine the DNA or RNA that composes a specific gene or group of genes. The scope of DNA tests may vary: 1) they can be targeted at single variants that are known to cause disorders in a given gene; 2) they can be targeted at a single gene (these tests search for any uncommon genetic modification in a particular gene); 3) they can target gene panels (these tests analyze variants in more than one gene and are often performed to reach a more specific diagnosis when a person has symptoms that match a wide list of conditions, or when the suspected condition can be caused by modifications in several genes); and 4) they may be focused on whole exome or genome sequencing (these tests analyze the largest portion of an individual's DNA to find genetic variations and are normally used either when the previously mentioned tests don't provide trustable diagnoses or when the suspected condition or genetic cause is unclear).
- Finally, biochemical tests do not directly analyze DNA, but they study the number of proteins or enzymes that are produced from genes, since abnormalities in those amounts can be good indicators that there are changes in the DNA that may be causing a genetic disorder.

Regarding the uses of genetic tests, there are two main purposes for which genetic tests have been used in the medical context: Risk Assessment and Therapy Diagnosis (MedlinePlus 2021), (Testing.com 2021).

Risk Assessment comprises all the tests that are performed with the objective of determining if an individual carries a gene mutation that may result in a genetic disease. The 5 types of tests of genetic Risk Assessment tests are:

- Diagnostic tests, which are DNA-based tests to confirm or rule out a specific genetic disorder in a symptomatic individual and its results may give insight regarding the course of a condition and help deciding the most appropriate treatment.
- Predictive tests, that are the most controversial and involve two subtypes of tests: pre-symptomatic tests which are performed on an asymptomatic individual with family history of a certain disease in order to test for the existence of the gene mutation responsible for that same disease; and pre-disposition tests which target individuals with no family history of a given disease in an effort to better understand his/her pre-disposition to a certain disorder.
- Carrier tests, that identify individuals who may carry autosomal or X-linked recessive mutations and who may be at risk of passing them on to their children, who may develop it (the individual who is tested does not need to exhibit the condition at the time of testing).
- Preimplantation and prenatal tests, which are performed prior to or during a pregnancy to assess the health status of a foetus or embryo.
- New-born screening tests, that take place immediately after birth and whose purpose is to identify genetic disorders that can be treated early in life, thereby avoiding future complications and diseases.

With respect to Therapy Diagnosis purpose, the type of tests that are used are pharmacogenetic tests. These types of tests search for genetic variations that may play a role in over- or under-responsiveness to a therapeutic drug, and most of them aim to look for variants in genes that code for drug-metabolizing enzymes (Testing.com 2021).

There are yet two additional uses for genetic testing within the medical context (Testing.com 2021):

- To identify mutations that cause some cancers in order to provide information on an individual's prognosis and guide targeted therapy.
- Transplantation tests used to tell whether an organ or tissue is a match for the transplant between a donor and recipient.

Health technology assessment

The use of genetic testing has been increasing rapidly over the years worldwide, and with the demand for genetic testing increasing and the pressure on healthcare budgets around the world, it is important that these health technologies are scrutinized, and their effectiveness, benefits, safety and costs understood. For this to happen, as is the case with all health technologies, it is essential that health technology assessments (HTAs) of genetic testing are conducted by agencies/institutions in charge of this type of work (Intelligence 2022), (Xie et al. 2020), (Joore et al. 2020).

An HTA is a multidisciplinary, transparent and accountable process that uses explicit and state-of-the-art methods to determine the value of a health technology at different points in its lifecycle (WHO 2022b). With an HTA it is possible to evaluate whether a new technology works better than the one that is currently being used by summing up the information about medical, economic, social and ethical issues associated with those same health technologies.
HTAs are generally developed through joint efforts that combine the expertise of governments, non-profit institutions, and commercial organizations with the primary aim of providing policymakers with evidence to inform decision-making and develop guidance on the reimbursement and administration of new health technologies in national healthcare systems (Joore et al. 2020).

If recommendations are incorporated soundly into existing healthcare systems, they would become more equitable and would provide more efficient and higher-quality services. HTA is

seen as a link between researchers and policymakers, since it provides the latter with evidence-based information that allows them to implement safe, fair, effective, patient-targeted, and cost-effective health policies (Velasco-Garrido and Busse 2013).

This type of assessment involves multiple steps such as: (1) synthesizing research findings about the effectiveness of different health interventions; (2) evaluating economic implications and analyzing cost and cost effectiveness; (3) appraising the social and ethical implications of the diffusion and use of health technologies as well as their organizational implications; and (4) identifying best practices in health care. An HTA should, therefore, systematically include health economic evaluations which can help national health systems in making decisions on how to better allocate the so often limited healthcare funds to different health technologies (Annemans 2022).

There are different types of economic evaluation, and they can be distinguished by the outcomes that are considered in each. The three main economic evaluations that are addressed in the context of an HTA are cost-effectiveness, cost-benefit and cost-utility analysis (Drummond et al. 2015):

- Cost-effectiveness analyses (CEAs) evaluate whether a given health technology provides as much value for the same cost as a comparable health technology. To assess this, a comparison of costs and consequences (such as health outcomes) associated with all technologies in question is established. CEAs commonly calculate the cost per unit of "natural" health outcomes (deaths prevented or life-years saved per unit of cost) and can provide information regarding whether an intervention maximizes a population's health (considering the available resources) (Joore et al. 2020).
- Cost-utility analyses are essentially cost-effectiveness analyses in which gains in health-related quality of life (HRQoL) are considered and assessed. A commonly used measure of HRQoL is the quality-adjusted life-year (QALY), which has been designed to

combine the quality and quantity of life increases associated with a given medical intervention. Cost-utility analyses commonly result in a relative measure of costs per QALY gained: the incremental cost-effectiveness ratio (ICER). The ICER is then compared to a threshold value below which a technology is deemed a cost-effective use of resources. QALYs are recommended by NICE and by the US Panel on Cost-Effectiveness in Health and Medicine as the preferred measure of health outcome for use in CEAs technology evaluations (Joore et al. 2020).

- The last type of economic evaluation used in HTAs is the cost-benefit analyses. They evaluate both costs and consequences in monetary units. For this, it is necessary to assign a monetary value to any consequences associated with the alternative health technologies (Joore et al. 2020).

Specific HTA processes/frameworks for the assessment of genetic testing

Numerous health-related bodies have attempted to standardize health technology assessment approaches specifically for genetic and genomic medicine. To this end, they have made their evidence publicly available so that a significant body of literature is amassed. However, genetic tests possess distinct and unique features when compared to traditional health technologies, and this results in additional challenges to health care providers and institutions who aim to develop standardized health technology assessments. Due to this fact, genetic testing specific HTAs must be adapted and should not simply be replicated from existing HTAs (Xie et al. 2020).

In an effort to create a framework that could help evaluate genetic tests, the ACCE framework was developed between 2000 and 2004 with the support of the CDC's Office of Public Health Genomics. Named after the four main criteria for evaluating a genetic test (analytic validity, clinical validity, clinical utility and associated ethical, legal and social implications (ELSI)), the ACCE is a model process that includes collecting, evaluating, interpreting, and reporting data about DNA testing for disorders with a genetic component in a format that allows policymakers

access to up-to-date and reliable information for decision making. The ACCE model process is composed of a standard set of forty-four targeted questions that address disorders, testing, and clinical scenarios, as well as analytic and clinical validity and associated ethical, legal, and social issues (CDC 2010).

The first country to produce a framework specifically for evaluating both clinical outcomes and cost-effectiveness of diagnostic tests was Australia in 2005, as detailed by Merlin et al. (2013): "The framework consists of five components: context, clinical benefit, evidence translation, cost-effectiveness, and financial impact; and a checklist of seventy-nine items. To determine whether the new technology should be subsidized, he considered it crucial to identify whether it is a treatment effect modifier or a prognostic factor" (Merlin et al. 2013).

In 2010, Veenstra et al. presented a formal risk-benefit framework for assessing the health-related utility of genomic tests. Their approach relies on combining methods from the fields of decision science, outcomes research, and health technology assessment. Their framework involves: 1) using decision analysis to synthesize data, project incidence of health outcomes, and assess uncertainty; 2) defining health-related utility of genomic tests as improvement in health outcomes as measured by QALY; and 3) exhibiting results in a risk-benefit matrix to simplify the interpretation of findings from these analyses. The matrix leads to a classification of genomic tests based on the risk-benefit profile and the amount of uncertainty, which could aid decisions about use of genetic tests in practice (Veenstra et al. 2010).

Additionally, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG), an independent panel established in 2005, was tasked with developing a systematic process for evidence-based assessments specifically for genetic tests and other applications of genomic technology. According to the panel, the construction of a chain of evidence is necessary. This chain should begin with the technical performance of genetic tests

(analytic validity) and with the associative relevance between a given genotype and a disorder of interest (clinical validity). The final chain portion is related to the effects that test results can have on patient management decisions and on improvements in net health outcomes (clinical utility). To address some unique aspects of genetic test evaluation, the EWG incorporated several aspects of the ACCE model process, including: 1) formal assessment of analytic validity; 2) the use of unpublished literature in some evaluation components when published data was either lacking or of low quality; 3) consideration of ethical, legal, and social implications as integral to all components of evaluation; and 4) inclusion of questions from the ACCE analytic framework in order to organize information collection (Teutsch et al. 2009).

The last relevant attempt to establish standardized frameworks for the analysis of genetic tests we opted to single out was the EuroGenTest initiative aimed at ensuring the widespread use of Clinical Utility Gene Cards (CUGCs). CUGCs were disease-specific guidelines regarding the clinical utility of genetic testing and covered all relevant elements for assessing the risks and benefits of genetic testing. Due to their clear and concise format, they provided efficient guidance to all stakeholders, including clinicians, geneticists, referrers, service providers and payers. Over 100 CUGCs are publicly available, finalized, and many have been published in the European Journal of Human Genetics. Although CUGCs covered all elements relevant to assessing risks and benefits of genetic test applications, the approach did not include health economics studies or measures of the budget impacts of testing (Genomicspolicy 2022).

Following the EuroGentest initiative's lead and combining with the domains of the ACCE evaluation process, the Medical Services Advisory Committee (MSAC) in Australia developed a Clinical Utility Card (CUC) Proforma for applications related to genetic testing for heritable mutations. Pilots were arranged to assess the utility of germline genetic testing for broad disease areas, such as cancer, cardiovascular or mental illness. The approach is modelled after the CUGCs but is constructed from a clinical perspective of disease management rather than a

single gene by gene approach. Furthermore, a completed CUC provides both economic evaluations related to testing clinically affected individuals and the marginal cost effectiveness of testing diagnosed patient's family members (cascade testing). It also assesses the budgetary implications of testing (Norris et al. 2021).

2. Methodology and Research Questions

In order to achieve our aims, we opted for a Systematic Literature Review (SLR) approach. This way, we would be able to provide an accurate, informed, and near bias-free representation of cost-effectiveness and economic implications analyses of genetic testing, as well as a depiction of the current state of genetic testing HTAs employed by healthcare providers.

To conduct our SLR we decided to follow the Handbook published by the Centre for Research Dissemination (CRD) and Cochrane.

The standard methodology outlined by Cochrane is based on five broad stages: 1) Protocol (in which the research questions and the PICO (Population, Intervention, Comparison(s) and Outcome) criteria are defined); 2) Search (in which researchers look through selected databases in order to perform their literature selection); 3) Selection (which comprises the actual selection process). In this phase, titles and abstracts are double screened independently based on the exclusion criteria and PICO framework outlined by the researchers. The included articles are then full-text double-screened to ensure maximum compatibility between selected literature and the PICO criteria informed by the research questions; 4) Data mark-up (in which the data extraction portion of the SLR is conducted); and 5) Reporting (in which the extracted data is summarized, and a findings report is elaborated).

For additional insight into some concepts and for the Introduction and Discussion portions of our article we consulted various other sources that weren't included in the selected articles.

Research questions

The research questions on which we based our analysis reflect a need to address gaps in knowledge related to the lack of structured HTAs specific for genetic testing. The research questions IQVIA defined, and on which we based our SLR were the following:

1. How is Genetic Testing currently used by healthcare systems and providers?
2. How is genetic testing perceived and evaluated by healthcare payers/ Health Technology Assessment (HTA) agencies?

2.a) Are there any Health Technology Assessments of genetic testing technologies?

2.b) Are there any specific HTA processes/frameworks for the assessment of genetic testing medical technology?

3. What are the health economics modelling methods/approaches used to evaluate the cost-effectiveness of genetic testing technologies?

3.a) Are there any preferred modelling methods consistently used for genetic testing technologies?

4. What are the main cost components used in genetic testing cost-effectiveness analyses?
5. What are the preferred methods to incorporate genetic testing performance cost-effectiveness analyses?
6. How is the link between genetic testing and patient quality of life captured in cost-effectiveness analyses?

PICO criteria

With the research questions in mind, we defined a PICO criteria that would lead to the selection of a broad array of articles. Our priority was to keep the PICO criteria as expansive as possible in an attempt to consider literature that focused on different populations, different interventions, and different outcomes. This way, we could be better informed on the different characteristics

genetic testing specific HTAs should have (in terms, e.g., of what costs health providers should consider).

With this goal in mind, the PICO criteria we defined was the following:

P – Population wide.

I – Health economics modelling methods/approaches for genetic testing.

C – (we defined no Comparison branch because our focus was not on how genetic testing fared against other forms of treatment but rather on the components of a complete cost-effectiveness analysis for genetic tests/treatments. As such, it was of no interest to the present article to define a specific treatment to which genetic testing should be compared to).

O – Cost-effectiveness of genetic testing technologies.

Search Strategy

For our analysis, we decided to search the bibliographical database PubMed. The MeSH (Medical Subject Heading) terms we defined in order to retrieve as much relevant information as possible are displayed below:

("genetic testing"[All Fields] OR "genetic tests"[All Fields] OR "genetic test"[All Fields] OR "DNA test*"[All Fields] OR "DNA testing"[All Fields] OR "genetic screening*"[All Fields]) **AND** ("cost benefit analysis"[All Fields] OR "cost benefit analyses"[All Fields] OR "cost benefit analysis"[All Fields] OR "cost benefit analysis economics"[All Fields] OR "cost benefit analysis evaluations"[All Fields] OR "cost benefit analysis cost effectiveness"[All Fields] OR "cost benefit analysis framework"[All Fields] OR "cost benefit analysis methods"[All Fields] OR "cost benefit analysis model"[All Fields] OR "cost effectiveness"[All Fields] OR "cost effective"[All Fields] OR "cost effect analysis"[All Fields] OR "cost effect analyses"[All Fields] OR "cost effective analyses"[All Fields] OR "cost effective analysis"[All Fields] OR "cost effective analysis methods"[All Fields] OR "cost effectiveness"[All Fields] OR "cost effectiveness analyses"[All Fields] OR "cost effectiveness analysis"[All Fields] OR "cost utility

analysis"[All Fields] OR "cost utility and cost effectiveness"[All Fields] OR "cost-utility analysis"[All Fields] OR "economic evaluation"[All Fields] OR "economic evaluations"[All Fields] OR "evaluation, economic"[All Fields] OR "cost benefit"[All Fields] OR "costs and benefits"[All Fields] OR "benefits and costs"[All Fields]) .

To capture the "genetic testing" portion of our analysis, we searched the MeSH database for all relevant synonyms for "genetic testing". The second string of our search strategy focused on the "cost-effectiveness" component of our study. Again, we searched the MeSH database in order to find all relevant synonyms for "cost-effectiveness". Finally, we restricted our analysis to the 2010 – 2022 time period. By narrowing our search to more recent articles, we were able to collect a more relevant selection of articles.

Articles Retrieved and Exclusion Criteria

After inputting our search strategy into the PubMed Advanced Search Builder, we totaled 1498 hits (1490 after initial removal of duplicates). After the double-screening process 388 articles were selected. To narrow this number down before the full-text screening we conducted a second title and abstract double-screening process which reduced the number of articles further to 140. Of the 140 articles submitted for full-text screening, 23 were selected for final inclusion. One reviewer screened approximately one third of the total articles (at each step of the screening process). Those same studies were then double screened by one of the two other reviewers. This procedure was repeated until all articles were screened.

The exclusion criteria defined included the following parameters:

- Articles that did not conduct cost-effectiveness analyses were excluded. Many articles mentioned cost-effectiveness without constructing cost-effectiveness models. Naturally, these studies were not included in our final analysis (1,223 articles were excluded for this reason).

- Articles that conducted cost-effectiveness analyses but that did not focus on genetic testing were excluded (89 articles were excluded for this reason).
- Cost-saving analyses were excluded because they tended to overlook the clinical efficiency component of cost-effectiveness models (88 articles were excluded for this reason).
- Articles that provided no abstract and/or full text were excluded (59 articles were excluded for this reason).
- Articles that focused on animal populations were excluded (3 articles were excluded for this reason).
- Duplicate articles that were included after the first screening process were excluded (5 articles were excluded for this reason).

Data extraction

The data we aimed to obtain from the selected articles revolved around the optimal cost-effectiveness approach health economics researchers should consider when designing HTAs specific for genetic testing. To this end, we retrieved the main features of the economic models present in the articles submitted for final analysis. This included how costs were aggregated (and what costs should be considered), how clinical efficiency should be calculated to accurately reflect reality, or how the link between clinical efficiency and QALY (Quality-Adjusted Life Years) considerations is captured.

Note on the references

Whenever we mention one of the included papers, we use the following notation: (1) (for paper 1, for example). In order to make mentioning the included articles easier, papers (1) through (23) are mentioned in that order in the References. Papers mentioned in parentheses

The remaining references use the following notation: (Author Date). Articles mentioned using this notation represent external data sources and are numbered from 24 to 55 in the References.

3. Results

The results presented below are the answers to the research questions. They are based on the analysis of the 23 papers included in our SLR. It was occasionally necessary to seek information from other sources to complete definitions and relevant concepts.

3) What are the health economics modelling methods/approaches used to evaluate the cost-effectiveness of genetic testing technologies?

To better understand how researchers address matters regarding cost-effectiveness in genetic testing health economics models, we decided to focus on the various steps of the diverse methodologies researchers employed to conjugate clinical efficiency and utility and cost considerations.

The health economics models that supported the articles we chose may shape future HTAs specific for genetic testing. So, to better understand how genetic testing specific HTAs should incorporate utility, cost considerations and cost-effectiveness analysis results, a careful analysis of the health economics models selected is warranted.

Before addressing the characteristics of the models presented in our selected articles, we believe it necessary to define some relevant concepts:

Decision Tree – Tool to model probable events by defining all potential transition states. Its name derives from the shape it is generally presented in – An initial node defines the starting point of disease progression and the subsequent branches contain all of the possible ways in which a patient introduced into the model can evolve.

Markov Probabilistic Model/Cohort Model – Mathematical model based on a decision tree that simulates "lifetime" events for the patient population based on the transition probabilities

associated with disease progression/regression in each of the branches. A Markov model is based on stochastic processes, meaning that for a given patient the transition state they will find themselves in does not depend on anything that happened to that same patient before. This means that progression along the decision tree branches is solely dependent on the probabilities associated to that specific branch.

Monte Carlo Simulation – Method used to model the likelihood of certain outcomes that depend on random variables. This method is generally used in the sensitivity analysis (robustness check) portion of health economics models and its purpose is simply to account for the fact that probabilities associated with each branch are often presented in ranges and not fixed values. Due to this, a Monte Carlo simulation runs the same scenarios for as many times as instructed while altering uncertain probabilities in an attempt to produce more reliable results.

Bayesian Decision Analytical Framework/ Modified Markov Model – This concept refers loosely to probabilistic models based on Bayes' theorem ($P(A|B) = [P(B|A) \cdot P(A)] / P(B)$). These models differ from standard Markov models in the sense that a future event's probability depends on previous occurrences.

Decision Model – Model based on action axioms (if "this", then "that"). From a health economics modelling perspective, these models consider the optimal course of action for a diagnosed patient when comparing outcomes between all relevant strategies (science direct 2022).

Microsimulation Model – These models attempt to correct some of the flaws of traditional cohort models. One of these shortcomings (mentioned before) is the fact that future health states depend only on the transition probabilities, with no regard for previous medical history. By generating outcomes for each patient in the model allows for more reliable results. The downside to microsimulation models is the fact that they can easily become immensely

complex, which generally means the use of programming languages becomes a requirement (Krijkamp et al. 2018).

TreeAge Software – "TreeAge Pro is the leading tool for building decision trees, Markov models and event-based simulations" (TreeAge Software 2022).

Modelling Approaches and Outputs

After careful examination of each article, we were able to outline the main characteristics of each of the models researchers used.

Of the 23 papers included in our SLR, 17 of them revolved around standard Markov Models ((1), (2), (5), (6), (7), (9), (10), (11), (12), (13), (14), (16), (17), (18), (19), (21), (22)). Some are distinct in the way they conduct the sensitivity analysis portion of the model, but that matter will be addressed in a later subsection.

Of the 23 papers included, only 2 of them used a Microsimulation model ((8), (15)) to estimate disease progression in the target population.

The remaining papers used either a Decision Model ((4)), a Modified Markov Model ((3)), or the established MISCAN-COLON ((23)), which is a Modified Markov Model specially designed to auto-generate transition cycles (by doing so, it assures that the events a simulated patient experiences are as unique as possible).

Lastly, it is worth noting that (20) didn't specify, as far as we could gather, what method was used. The data used by those paper's researchers was, however, extrapolated from a Markov Model published by a third party.

Model	N of Studies	Paper
Standard Markov Model	17	(1), (2), (5), (6), (7), (9), (10), (11), (12), (13), (14), (16), (17), (18), (19), (21), (22)
Microsimulation Model	2	(8), (15)

Decision Model	1	(4)
Modified Markov Model	1	(3)
MISCAN-COLON	1	(23)
No Info	1	(20)

All the included papers utilize Decision Trees. (2) and (23) were outliers in the sense that the researchers opted to not present their Decision Tree in a conventional manner. The former did not use a graph because only three transition states were considered and the latter outright excluded the Decision Tree from their paper (it is well-established, however, that the MISCAN-COLON is based on a Decision Tree).

The various models present in the included papers were built by one or by a combination of the following programs/software: Excel (all versions), TreeAge Software, @Risk software (all versions) and Microsoft Visual Studio (all versions). The use of a given program depends on the researchers' choices and aims.

All the models included quantitative methods for determining clinical outputs and economic costs (currency depends on researcher discretion). Clinical outputs were measured either in terms of QALY, LYS (Life Years Saved) or in terms of Life Expectancy.

To present the results of their cost-effectiveness analysis, all the models used some form of ICER expressed in Cost per QALY/LYS. To determine whether a strategy was cost-effective, researchers compared the ICER obtained with a WTP (Willingness-To-Pay) threshold established by published literature (WTP is also expressed in terms of Cost per QALY/LYS).

Parameter and Utility Values

In order to conduct their independent analysis, the researchers whose work we included in our SLR retrieved data from a combination of published literature, ongoing trials (at the time of writing) and reports/statistics published by governmental institutions, health providers or other associated agencies.

The data obtained was used to inform the Decision Trees (which were the starting point for all models) and the utility values used to calculate QALYs and ICERs. Different articles focused of different genetic conditions and those that addressed the same genetic disorders adopted different means of expressing relevant results. This meant that the probabilities used to simulate patient lifetime events drawn from external sources were different between the various included articles. However, the models we analyzed followed similar patterns when selecting relevant data, and most obtained values pertaining to:

- Probabilities associated with the presence of the genetic condition in a given patient.
- Probabilities associated with detection/screening of the genetic condition.
- Probabilities associated with the presence of a genetic disorder in relatives who exhibit that same disorder (considering the varying degrees of proximity to the individual who was screened).
- Probabilities associated with treating the genetic condition at each stage of disease progression (for different age groups).
- Probabilities associated with treatment acceptance once the genetic condition is identified.
- Probabilities associated with response to treatment (for the different treatments considered).
- Probabilities of disease progression without screening/surveillance.
- Probabilities of death at each stage of disease progression.
- Probabilities of death due to causes unrelated to the genetic disorder considered.

Data regarding costs was retrieved from the sources previously mentioned, and the researchers again followed similar patterns when selecting relevant data. Cost considerations, however, will be addressed in a later section (in question 4).

Model population (age, size, sex, etc.)

The populations included in the models were either imported from previous literature, from RCT's and other field studies conducted by the researchers or third parties, or they were modelled from information made available by governmental institutions, health providers or other associated agencies.

Model populations can be as diverse as the researchers' necessities dictate. Some of the studies included only one sex, some included both. Some studies included different age groups and some studies restricted the target population to a specific age group. Additionally, populations varied in terms of geographical region and ethnicity.

Lastly, model populations also differed in terms of their size. For example, (2) considered a population of 4,098 individuals, while (15) considered a population of 40 million people. Generally, articles that considered populations obtained from field studies (conducted either by the researchers themselves or by third parties) included far less patients than articles that conducted their research on simulated populations.

Population characteristics are a direct result of the scenario and treatment the researcher aim to analyze. As such, presenting the actual characteristics of each population for each article would serve no relevant purpose because no pattern or rule of thumb was verifiable.

Scenarios considered to assess genetic testing cost-effectiveness

The standard approach researchers followed was to compare a genetic screening approach with a no screening scenario. However, different articles employed different methods and some researchers compare more than one strategy to the base case scenario. It is worth noting that not all strategies compared to the no screening scenario involved genetic testing. Some of the strategies included in the articles we analyzed consisted of conventional forms of treatment (e.g., colonoscopies, aspirin, etc.).

Of the 23 articles included in the SLR, 14 ((1), (2), (3), (6), (7), (10), (11), (14), (16), (17), (19), (20), (22), (23)) compared only two scenarios. These two scenario comparisons established a side-by-side analyses of either a no genetic testing scenario and a genetic testing scenario or of two different genetic testing methods.

Of the 23 articles included, 3 ((5), (9), (18)) analyzed four different scenarios and 2 ((12), (21)) focused on 5 relevant scenarios.

The remaining 4 articles compared either six scenarios ((4)), eight scenarios ((8)), thirteen scenarios ((15)) or seventeen scenarios ((13)).

How robustness checks were conducted (sensitivity analysis)

All the articles included conducted some form of sensitivity analysis. This portion of the article validates the results presented by providing robustness to them by adjusting certain variable values that affect the transition probabilities used to model the patient population.

The 23 articles we included in our SLR conducted either a Monte Carlo simulation or a manual/arbitrary sensitivity analysis.

3.a) Are there any preferred modelling methods consistently used for genetic testing technologies?

After having analyzed each model present in the 23 articles we selected, the preferred modelling methods become apparent.

Most cost-effectiveness analyses that investigate the economic and clinical implications of genetic treatments tend to be based on standard Markov Models (necessarily based on Decision Trees) and on manual sensitivity analyses.

After having addressed the clinical performance of the genetic screening intervention, researchers consistently associated a cost to each transition state so that a final ICER could be calculated.

5) What are the preferred methods to incorporate genetic testing performance cost-effectiveness analyses?

Before addressing the research question, we believe it is appropriate to briefly mention how utility is calculated. Generally, utility can either be calculated directly (by asking patients how much time with a given disease they would be willing to give up if that meant living x time affliction free, e.g.) or indirectly (through surveys focused on perceived pain levels or mobility restriction (among others)). Additionally, the way in which articles consider QALY levels differ in the sense that some researchers introduce discount rates into their analyses (to account for price fluctuation in the future, as per NHS recommendation) while others present their results in undiscounted QALYs.

In order to conduct cost-effectiveness analyses, all researchers needed a comprehensive way to present the effect genetic testing had on the modeled population. To do this, all 23 articles were required to demonstrate that genetic testing resulted in a utility increase for the simulated patients.

To this end, the researchers whose articles we analyzed imported (as stated in section 3) utility values for each transition state from published literature and governmental or health care reports.

The standard approach when it came to incorporating utility was the following:

1. The default utility a patient would receive from a cycle with no noticeable affliction was maximized. For example: If the model cycle was 1 year and a given patient exhibited

no signs of carrying a genetic condition during that same cycle, then he received utility equivalent to 1 year (1 QALY).

2. If a patient is found to exhibit the relevant genetic condition, then two utility pathways are defined (for models who considered only two strategies: one with genetic treatment and one with no genetic intervention). These two pathways are based on the utility a patient would derive at each stage of treatment (at each cycle) if he either was or wasn't subject to screening. The utility at each cycle for a patient with a genetic condition is always assumed to not be maximized. For example: Consider a model with 1-year cycles built to assess the effect of genetic screening on the treatment of CRC (Colorectal Cancer). A patient who is screened beforehand may derive a utility of 0.850 (0.850 QALYs) during the cycle immediately after because of preemptive medical care, while a patient who was not screened may derive a utility of 0.760 (0.760 QALYs) since the affliction exhibited wasn't addressed as rapidly as it could have been.

The utility values discussed above were consistently expressed in QALY or LYS (or both) in the articles we included (except for studies that used life expectancy increases to present their results). The aggregate QALY or LYS values associated with each strategy were then used to elaborate ICERs, which were frequently utilized.

4. Conclusions

The analysis conducted in this work allows to demonstrate that there is an effort from some institutions in developing specific HTAs for genetic tests as they are aware of the special characteristics of these technologies.

However, when analysing the cost-effectiveness analyses that have been conducted for the economic evaluation of genetic tests – an integral part of an HTA process – it becomes clear that these analyses have not taken into consideration the particular features of genetic tests.

This paper demonstrates this problem, highlighting the main limitations and suggesting some recommendations for future evaluations of genetic testing.

We believe that this work is a contribution to this topic and hope that further scientific evidence will be developed on this matter in order to contribute to more refined evaluations of genetic tests.

5. References

1. Greeley, Siri Atma W., Priya M. John, Aaron N. Winn, Joseph Ornelas, Rebecca B. Lipton, Louis H. Philipson, Graeme I. Bell, and Elbert S. Huang. 2011. "The Cost-Effectiveness of Personalized Genetic Medicine: The Case of Genetic Testing in Neonatal Diabetes." *Diabetes Care 34* (3): 622–27. https://doi.org/10.2337/dc10-1616.

2. Guinan, Kimberly, Catherine Beauchemin, Johanne Tremblay, John Chalmers, Mark Woodward, Muhammad Ramzan Tahir, Pavel Hamet, and Jean Lachaine. 2021. "Economic Evaluation of a New Polygenic Risk Score to Predict Nephropathy in Adult Patients With Type 2 Diabetes." *Canadian Journal of Diabetes* 45 (2): 129–36. https://doi.org/10.1016/j.jcjd.2020.06.010.

3. Hall, Peter S., Christopher McCabe, Robert C. Stein, and David Cameron. 2012. "Economic Evaluation of Genomic Test-Directed Chemotherapy for Early-Stage Lymph Node-Positive Breast Cancer." *Journal of the National Cancer Institute* 104 (1): 56–66. https://doi.org/10.1093/jnci/djr484.

4. Hynninen, Yrjänä, Miika Linna, and Eeva Vilkkumaa. 2019. "Value of Genetic Testing in the Prevention of Cardiovascular Events." *Plos One* 14 (1): e0210010. http://dx.plos.org/10.1371/journal.pone.0210010.

5. Jarmul, Jamie, Mark J. Pletcher, Kristen Hassmiller Lich, Stephanie B. Wheeler, Morris Weinberger, Christy L. Avery, Daniel E. Jonas, Stephanie Earnshaw, and Michael Pignone. 2018. "Cardiovascular Genetic Risk Testing for Targeting Statin Therapy in the Primary Prevention of Atherosclerotic Cardiovascular Disease." *Circulation: Cardiovascular Quality and Outcomes* 11 (4): 1–12. https://doi.org/10.1161/CIRCOUTCOMES.117.004171.

6. Johnson, Stephanie R., Hannah E. Carter, Paul Leo, Samantha A. Hollingworth, Elizabeth A. Davis, Timothy W. Jones, Louise S. Conwell, et al. 2019. "Cost-Effectiveness Analysis of Routine Screening Using Massively Parallel Sequencing for Maturity-Onset Diabetes of the Young in a Pediatric Diabetes Cohort: Reduced Health System Costs and Improved Patient Quality of Life." *Diabetes Care* 42 (1): 69–76. https://doi.org/10.2337/dc18-0261.

7. Jutkowitz, Eric, Maureen Dubreuil, Na Lu, Karen M. Kuntz, and Hyon K. Choi. 2017. "The Cost-Effectiveness of HLA-B*5801 Screening to Guide Initial Urate-Lowering Therapy for Gout in the United States." *Seminars in Arthritis and Rheumatism* 46 (5): 594–600. https://doi.org/10.1016/j.semarthrit.2016.10.009.

8. Kang, Yoon Jung, James Killen, Michael Caruana, Kate Simms, Natalie Taylor, Ian M. Frayling, Tristan Snowsill, et al. 2020. "The Predicted Impact and Cost-Effectiveness of Systematic Testing of People with Incident Colorectal Cancer for Lynch Syndrome." *Medical Journal of Australia* 212 (2): 72–81.

9. Ke, Ching Hua, Wen Hung Chung, Yen Hsia Wen, Yaw Bin Huang, Hung Yi Chuang, You Lin Tain, Yu Ching Lily Wang, Cheng Chih Wu, and Chien Ning Hsu. 2017. "Cost-Effectiveness Analysis for Genotyping before Allopurinol Treatment to Prevent Severe

Cutaneous Adverse Drug Reactions." *Journal of Rheumatology* 44 (6): 835–43. https://doi.org/10.3899/jrheum.151476.

10. Klang, Shmuel H., Ariel Hammerman, Nicky Liebermann, Noa Efrat, Julie Doberne, and John Hornberger. 2010. "Economic Implications of 21-Gene Breast Cancer Risk Assay from the Perspective of an Israeli-Managed Health-Care Organization." *Value in Health* 13 (4): 381–87. https://doi.org/10.1111/j.1524-4733.2010.00724.x.

11. Kostenko, Emilia, Frederic Chantraine, Katleen Vandeweyer, Maximilian Schmid, Alex Lefevre, Deanna Hertz, Laura Zelle, Jose Luis Bartha, and Gian Carlo Di Renzo. 2019. "Clinical and Economic Impact of Adopting Noninvasive Prenatal Testing as a Primary Screening Method for Fetal Aneuploidies in the General Pregnancy Population." *Fetal Diagnosis and Therapy* 45 (6): 413–23. https://doi.org/10.1159/000491750.

12. Ladabaum, Uri, and Ajitha Mannalithara. 2016. "Comparative Effectiveness and Cost Effectiveness of a Multitarget Stool DNA Test to Screen for Colorectal Neoplasia." *Gastroenterology* 151 (3): 427-439.e6. https://doi.org/10.1053/j.gastro.2016.06.003.

13. Ladabaum, Uri, Grace Wang, Jonathan Terdiman, Amie Blanco, Miriam Kuppermann, C. Richard Boland, James Ford, Elena Elkin, and Kathryn A. Phillips. 2011. "Strategies to Identify the Lynch Syndrome among Patients with Colorectal Cancer." *Annals of Internal Medicine* 155 (2): 69–79. https://doi.org/10.7326/0003-4819-155-2-201107190-00002.

14. Lee, Malinda, Katherine T. Lofgren, Ann Thomas, Andrea Lanes, Randi Goldman, Elizabeth S. Ginsburg, and Mark D. Hornstein. 2021. "The Cost-Effectiveness of Preimplantation Genetic Testing for Aneuploidy in the United States: An Analysis of Cost and Birth Outcomes from 158,665 in Vitro Fertilization Cycles." *American Journal of Obstetrics and Gynecology* 225 (1): 55.e1-55.e17. https://doi.org/10.1016/j.ajog.2021.01.021.

15. Lew, Jie Bin, D. James B. St. John, Finlay A. Macrae, Jon D. Emery, Hooi C. Ee, Mark A. Jenkins, Emily He, et al. 2018. "Evaluation of the Benefits, Harms and Cost-Effectiveness of Potential Alternatives to IFOBT Testing for Colorectal Cancer Screening in Australia." *International Journal of Cancer* 143 (2): 269–82. https://doi.org/10.1002/ijc.31314.

16. Ademi, Zanfina, Gerald F. Watts, Jing Pang, Eric J.G. Sijbrands, Frank M. Van Bockxmeer, Peter O'Leary, Elizabeth Geelhoed, and Danny Liew. 2014. "Cascade Screening Based on Genetic Testing Is Cost-Effective: Evidence for the Implementation of Models of Care for Familial Hypercholesterolemia." *Journal of Clinical Lipidology* 8 (4): 390–400. https://doi.org/10.1016/j.jacl.2014.05.008.

17. Banerjee, Sudeep, Abhishek Kumar, Nicole Lopez, Beiqun Zhao, Chih Min Tang, Mayra Yebra, Hyunho Yoon, James D. Murphy, and Jason K. Sicklick. 2020. "Cost-Effectiveness Analysis of Genetic Testing and Tailored First-Line Therapy for Patients With Metastatic Gastrointestinal Stromal Tumors." *JAMA Network Open* 3 (9): e2013565. https://doi.org/10.1001/jamanetworkopen.2020.13565.

18. Behl, Ajay S., Katrina A.B. Goddard, Thomas J. Flottemesch, David Veenstra, Richard T. Meenan, Jennifer S. Lin, and Michael V. Maciosek. 2012. "Cost-Effectiveness Analysis of

Screening for KRAS and BRAF Mutations in Metastatic Colorectal Cancer." *Journal of the National Cancer Institute* 104 (23): 1785–95. https://doi.org/10.1093/jnci/djs433.

19. Biltaji, E.; Walker, B.; Au, T. H.; Rivers, Z.; Ose, J.; Li, C. I.; Brixner, D. I.; Stenehjem, D. D.; Ulrich, C. M. 2021. "Can Cost-Effectiveness Analysis Inform Genotype-Guided Aspirin Use for Primary Colorectal Cancer Prevention?" *Cancer Epidemiol Biomarkers Prev*, no. 30: 1106–1113. https://doi.org/10.1158/1055-9965.EPI-19-1580.

20. Brown, Gary C., Melissa M. Brown, Heidi B. Lieske, Philip A. Lieske, and Kathryn S. Brown. 2015. "A Value-Based Medicine Cost-Utility Analysis of Genetic Testing for Neovascular Macular Degeneration." *International Journal of Retina and Vitreous* 1 (1): 1–16. https://doi.org/10.1186/s40942-015-0016-5.

21. Buchanan, James, Sarah Wordsworth, Ruth Clifford, Pauline Robbe, Jenny C. Taylor, Anna Schuh, and Samantha J.L. Knight. 2017. "Using Genomic Information to Guide Ibrutinib Treatment Decisions in Chronic Lymphocytic Leukaemia: A Cost-Effectiveness Analysis." *PharmacoEconomics* 35 (8): 845–58. https://doi.org/10.1007/s40273-017-0519-z.

22. Catchpool, Max, Jay Ramchand, Melissa Martyn, David L. Hare, Paul A. James, Alison H. Trainer, Josh Knight, and Ilias Goranitis. 2019. "A Cost-Effectiveness Model of Genetic Testing and Periodical Clinical Screening for the Evaluation of Families with Dilated Cardiomyopathy." *Genetics in Medicine* 21 (12): 2815–22. https://doi.org/10.1038/s41436-019-0582-2.

23. Cenin, D. R.; Naber, S. K.; de Weerdt, A. C.; Jenkins, M. A.; Preen, D. B.; Ee, H. C.; O'Leary, P. C.; Lansdorp-Vogelaar, I. 2020. "Cost-Effectiveness of Personalized Screening for Colorectal Cancer Based on Polygenic Risk and Family History." *Cancer Epidemiol Biomarkers Prev*, no. 29: 10–21. https://doi.org/10.1158/1055-9965.EPI-18-1123.

24. Annemans, Lieven. 2022. "Do You Know the Difference between Health Economic Evaluations and Health Technology Assessments?" 2022. https://www.celforpharma.com/insight/do-you-know-difference-between-health-economic-evaluations-and-health-technology-assessments.

25. CADTH. 2017. "Guidelines for the Economic Evaluation of Health Technologies: Canada 4th Edition." Canada. https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

26. CDC. 2010. "Genomics & Precision Health - ACCE Model Process for Evaluating Genetic Tests." 2010. https://www.cdc.gov/genomics/gtesting/ACCE/.

27. Drummond, Michael F., Mark J. Sculpher, Karl Claxton, Greg L. Stoddart, and George W. Torrance. 2015. "Methods for the Economic Evaluation of Health Care Programmes." In , edited by Oxford: Oxford University Press, 4th ed. https://books.google.sm/books?id=lvWACgAAQBAJ&printsec=frontcover&hl=pt-PT#v=onepage&q&f=false.

28. Genomicspolicy. 2022. "Evaluation, Reimbursement & Evidence: Evaluation." 2022. https://www.genomicspolicy.org/evaluation.

29. Intelligence, Mordor. 2022. “Europe Genetic Testing Market.” 2022. https://www.mordorintelligence.com/industry-reports/europe-genetic-testing-market-industry.

30. Joore, Manuela, Sabine Grimm, Annelies Boonen, Maarten De Wit, Francis Guillemin, and Bruno Fautrel. 2020. “Health Technology Assessment: A Framework.” *RMD Open* 6 (3): 6–8. https://doi.org/10.1136/rmdopen-2020-001289.

31. Khoury, Muin J, Al Berg, Ralph Coates, James Evans, Steven M Teutsch, and Linda A Bradley. 2008. “The Evidence Dilemma in Genomic Medicine.” *Health Affairs* 27 (6): 1600–1611. https://doi.org/10.1377/hlthaff.27.6.1600.

32. Krijkamp, Eline M., Fernando Alarid-Escudero, Eva A. Enns, Hawre J. Jalal, M.G. Myriam Hunink, and Petros Pechlivanoglou. 2018. “Microsimulation Modeling for Health Decision Sciences Using R: A Tutorial.” *Med Decis Making* 38: 400–422. https://doi.org/10.1177/0272989X18754513.Microsimulation.

33. McPherson, Elizabeth. 2006. “Genetic Diagnosis and Testing in Clinical Practice.” *Clinical Medicine and Research* 4 (2): 123–29. https://doi.org/10.3121/cmr.4.2.123.

34. MedlinePlus. 2021. “What Are the Uses of Genetic Testing?” 2021. https://medlineplus.gov/genetics/understanding/testing/uses/.

35. Merlin, Tracy, Claude Farah, Camille Schubert, Andrew Mitchell, Janet E. Hiller, and Philip Ryan. 2013. “Assessing Personalized Medicines in Australia: A National Framework for Reviewing Codependent Technologies.” *Medical Decision Making* 33 (3): 333–42. https://doi.org/10.1177/0272989X12452341.

36. National Cancer Institute. 2022. “Cascade Genetic Testing.” 2022. https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/cascade-genetic-testing.

37. NICE. 2022. “NICE Health Technology Evaluations: The Manual.” https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.

38. Norris, Sarah, Andrea Belcher, Kirsten Howard, and Robyn L. Ward. 2021. “Evaluating Genetic and Genomic Tests for Heritable Conditions in Australia: Lessons Learnt from Health Technology Assessments.” *Journal of Community Genetics*, no. EUnetHTA 2016. https://doi.org/10.1007/s12687-021-00551-2.

39. Nurchis, Mario Cesare, Maria Teresa Riccardi, and Gianfranco Damiani. 2022. “Health Technology Assessment of Whole Genome Sequencing in the Diagnosis of Genetic Disorders: A Scoping Review of the Literature.” *International Journal of Technology Assessment in Health Care* 38 (1): 1–8. https://doi.org/10.1017/S0266462322000496.

40. OHE - Office of Health Economics. 2022. “The NICE Health Technology Evaluation Manual: A Fresh Perspective Needed?” 2022. https://www.ohe.org/news/nice-health-technology-evaluation-manual-fresh-perspective-needed.

41. PennMedicine. 2022. “Multiple Marker Screening Test (MMS).” 2022. https://www.pennmedicine.org/for-patients-and-visitors/find-a-program-or-service/obstetrics/prenatal-genetic-testing/diagnosis-and-screening-services/multiple-marker-screening-test-mms.

42. Pharmaceutical Benefits Advisory Committee. 2016. “Overview and Rationale of the Economic Evaluation.” 2016. https://pbac.pbs.gov.au/section-3a/3a-1-overview-and-rationale-of-economic-evaluation.html.

43. Sanders, Gillian D., Peter J. Neumann, Anirban Basu, Dan W. Brock, David Feeny, Murray Krahn, Karen M. Kuntz, et al. 2016. “Recommendations for Conduct, Methodological Practices, and Reporting of Cost-Effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine.” *JAMA Network Open* 316: 1093–1103. https://doi.org/doi:10.1001/jama.2016.12195.

44. science direct. 2022. “Decision Model.” 2022. https://www.sciencedirect.com/topics/psychology/decision-model.

45. Testing.com. 2021. “Human Genetic Testing Applications.” 2021. https://www.testing.com/human-genetic-testing-applications/.

46. Teutsch, Steven M., Linda A. Bradley, Glenn E. Palomaki, James E. Haddow, Margaret Piper, Ned Calonge, W. David Dotson, Michael P. Douglas, and Alfred O. Berg. 2009. “The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group.” *Genetics in Medicine* 11 (1): 3–14. https://doi.org/10.1097/GIM.0b013e318184137c.

47. TreeAge Software. 2022. “TreeAge.” 2022. https://www.treeage.com/.

48. UK Health Security Agency. 2021. “Guidance - Economic Evaluation: Health Economic Studies.” 2021. https://www.gov.uk/guidance/economic-evaluation-health-economic-studies.

49. University of Rochester Medical Center. 2022. “Health Encyclopedia - Types of Genetic Testing.” 2022. https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=85&contentid=p07370#:~:text=Types of Genetic Testing 1 Chromosome studies. Chromosomes.

50. Veenstra, David L., Joshua A. Roth, Louis P. Garrison, Scott D. Ramsey, and Wylie Burke. 2010. “A Formal Risk-Benefit Framework for Genomic Tests: Facilitating the Appropriate Translation of Genomics into Clinical Practice.” *Genetics in Medicine* 12 (11): 686–93. https://doi.org/10.1097/GIM.0b013e3181eff533.

51. Velasco-Garrido, Marcial, and Reinhard Busse. 2013. “Policy Brief: Health Technology Assessment. An Introduction to Objectives, Role of Evidence, and Structure in Europe.” *Journal of Health and Social Behavior*, 1–24. http://www.ncbi.nlm.nih.gov/pubmed/24055071.

52. WHO. 2022a. “Health Products Policy and Standards.” 2022. https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/assessment.

53. ———. 2022b. “Health Technology Assessment.” 2022. https://www.who.int/health-topics/health-technology-assessment#tab=tab_1.

54. Xie, Xuanqian, Olga Gajic-Veljanoski, Lindsey Falk, Alexis K. Schaink, Anna Lambrinos, Myra Wang, Vivian Ng, Wendy J. Ungar, and Nancy Sikich. 2020. “Challenges in Health Technology Assessments of Genetic Tests.” *Journal of Hospital Management and Health Policy* 4: 1–10. https://doi.org/10.21037/jhmhp-20-47.

55. York Health Economics Consortium. 2016. “Perspective.” 2016. https://yhec.co.uk/glossary/perspective/.