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

IQVIA – Policy Analysis Project – Health Economic Evaluation Of Genetic Testing: How Is The Link Between Genetic Testing And Patient-Quality Of Life Captured In Cost-Effectiveness Analyses?

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03-10-2022

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);

This work used infrastructure and resources funded by Fundação para a Ciência e a Tecnologia (UID/ECO/00124/2013, UID/ECO/00124/2019 and Social Sciences DataLab, Project 22209), POR Lisboa (LISBOA-01-0145-FEDER-007722 and Social Sciences DataLab, Project 22209) and POR Norte (Social Sciences DataLab, Project 22209).

Acknowledgements: We thankfully acknowledge the support we received from IQVIA and from our advisor Professor Pedro Pita Barros during the course of our dissertation.

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.

1) How is genetic testing currently used by healthcare systems and providers?

Based on our research we were able to get a perspective on the genetic diseases that are more often tested. Cost-effectiveness analyses were systematically conducted to assess the effects of genetic testing on a restricted number of genetic disorders. More specifically, we found 7 studies regarding colorectal cancer, 2 regarding breast cancer, 3 regarding cardiovascular disorders, and 2 on neonatal diabetes. The remaining studies targeted other conditions that are relatively uncommon among genetic testing evaluations: nephropathy, trisomy 18, 21 and 13, familial hypercholesterolemia, metastatic gastrointestinal tumours, neovascular macular degeneration, and lymphocytic leukaemia. We also found 2 studies regarding the effect of the HLA-B*5801 allele variant in the human leukocyte antigen B.

Disease	Nº of Studies	Paper
Colorectal cancer	7	(8), (12), (13), (15), (18), (19), (23)
Cardiovascular disorders	3	(4), (5), (22)
Breast cancer	2	(3), (10)
Neonatal diabetes	2	(1), (6)
Trisonomy 18, 21 and 12	2	(11), (14)
Nephropathy	1	(2)
Familial hypercholesterolemia	1	(16)
Mestastic gastrointestinal tumors	1	(17)
Neovascular M. degeneration	1	(20)
Lymphocytic leukaemia	1	(21)
HLA-B*5801 allele	2	(7), (9)

Regarding the prevailing purposes for carrying out a genetic test in healthcare systems, we discovered that they are more likely to be performed because of diagnostic screening or pharmacogenetics. In fact, we concluded that 9 of the selected cost-effectiveness analyses were drawn to combine both purposes. These analyses revolved around the cost-effectiveness of screening for a certain gene mutation in people with a genetic disease at an early stage or age (diagnostic screening) in order to target specific drugs or treatments to those who carry that mutation (pharmacogenetics), instead of using a baseline therapy for all population. The rationale behind this is that many diseases can occur either due to a genetic mutation or a non-genetic reason, and the use of a specific drug or therapy in genetic-related diseases may prevent the progression of the disease or even the outbreak of the disease itself. Furthermore, people who carry a gene mutation may manifest adverse reactions to some therapies, and the same with those who do not carry it. Therefore, the cost-effectiveness analysis aims to find the best treatment for each case and target them to the right population.

Studies that focus only on the cost-effectiveness of diagnostic genetic tests were also found to be relevant, although there appears to be a wide range of specific purposes for which diagnostic tests are performed. During our research we found 5 diagnostic tests' studies on the cost-effectiveness of implementing a genetic test to identify a certain disease, as opposed to either no testing or usual screening methods. Additionally, 3 studies were on the cost-effectiveness of optimizing the scope of the genetic test itself, based on a person's risk to develop a certain genetic disease (which simply means that these articles aimed to restrict genetic treatment to high-risk patients), compared to universal screening.

Additionally, 2 articles that hinge only on pharmacogenetic analyses were included in our final selection. These studies' purpose was to detect possible adverse drug reactions that may result from a given genetic treatment. These analyses are relevant because the use of certain drugs may generate unexpected side-effects in the presence of non-apparent gene mutations. By

screening for specific gene mutations, adverse reactions may be contained. Both pharmacogenetics evaluations were targeted to HLA-B*5801 allele detection. Patients with an HLA-B*58:01 allele have an increased risk of developing severe cutaneous adverse drug reactions when treated with allopurinol. The first study evaluated the cost-effectiveness of HLA-B*58:01 screening compared with using other available urate-lowering agents (ULA). The second one analysed the cost-effectiveness of universal testing for HLA-B*5801 compared to no testing prior to the initiation of allopurinol per major ethnicity groups, since HLA-B*5801 prevalence and allopurinol sensitivity risk vary by ethnicity.

Moreover, we found 2 pre-symptomatic predictive studies that addressed the impacts of implementing cascade genetic testing in medical practice. Cascade genetic testing or cascade screening can be defined as the process of extending genetic testing to individuals at risk within a family for inheriting a pathogenic variant previously identified in a biologic relative (National Cancer Institute 2022). In the first article we included, the authors aimed to evaluate the cost-effectiveness of cascade screening in comparison to periodical clinical surveillance, in asymptomatic relatives of patients who carried a genetic disease. The second study focused on determining the cost-effectiveness of disease detection based on cascade genetic testing as opposed to no screening at all. Cascade genetic testing is becoming a common object of interest among the existing literature due to the fact that it will likely be one of the most effective ways to mitigate the costs generated by genetic diseases. Preventing or addressing hereditary genetic conditions at an early stage can drastically reduce the expenditure that would be allocated to treatment.

Lastly, 1 study regarding cost-effectiveness of prenatal screening and another about preimplantation were also included in our SLR.

2) How is genetic testing perceived and evaluated by healthcare payers/ Health Technology Assessment (HTA) agencies?

As previously mentioned, genetic testing is currently perceived as a health technology. As such, it is evaluated through the HTA process.

The papers analysed - some of which followed guidelines published by agencies whose role is to conduct this type of evaluation – are in line with this, since they assess genetic tests through cost-effectiveness analyses in order to consider economic consequences. The CEA is, as already mentioned, one of the three economic evaluations that support HTAs.

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

Some official bodies have already conducted either HTAs of genetic testing or elaborated some guidelines on how to evaluate it. However, based on our literature findings, there was only one study ((8)) that adopted a similar approach to the one applied by the UK Health Technology Assessment report. This paper's authors based their analysis on published parameters to develop their disease natural history model and were thus able to conduct a cost-effectiveness analysis in line with official recommendations.

Even though almost every other study included in our SLR also obtained their data from existing literature, none of them state clearly that their work is based on a genetic testing specific HTA.

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

As previously stated, we only found one article that adopted a similar approach to that applied by a UK Health Technology Assessment report. However, there was no indication that the HTA

framework had even been modelled specifically for the assessment of a genetic testing technology.

6) How is the link between genetic testing and patient quality of life captured in cost-effectiveness analyses?

When a genetic test is performed, it aims to change the clinical pathway that an individual usually follows, and therefore improve his subsequent health states. Since every health state is associated with a determined utility level, this alteration caused by the genetic test execution, will create utility gains for each patient, as opposed to not screening or treating with a different method.

In most of the studies we analysed, we found that QALYs was the most prevalent method used to evaluate the effect that performing a genetic test had on the health states of a population. This also applies to pharmacogenetics. Hence, we can say that the link between genetic testing and patient quality of life is captured in cost-effectiveness analyses through the utilities that are assumed and used to calculate QALYs. The utilities were not calculated by the authors of the studies we evaluated. Instead, the researchers retrieved their utility estimates from the available literature on their specific subject, just like they did with costs.

Additionally, we found 3 studies that were not able to calculate QALYs due to the lack of information on utility weights for the health states they were using. In those, in order to evaluate the clinical outcomes of a strategy when compared to no testing, the researchers used LYS (Life-years saved) instead of QALYs as a mean of measuring the utility gains associated with the new health state made possible due to genetic testing. Nevertheless, LYS only accounts for the utility increment associated with the additional number of years that one person may live due to genetic testing and does not include the life quality associated with those extra years. Thus, the link between quality of life and genetic testing could not be assessed here.

In the following table we present an overview of the QALYs gained with the implementation of genetic testing in all the 23 studies we examined. Some studies presented their QALYs results

as a QALY increment without specifying before and after values (regarding genetic test implementation).

For evaluations that considered more than two possible scenarios, we compared the control group's utility with the genetic testing strategy that accrued higher QALY increment since our aim with this table is simply to show how the link between genetic testing and patient quality of life is addressed in the literature.

We can conclude that most of the analyses indeed address patient's quality of life in their evaluations use QALYs as the preferred system to estimate it. Nevertheless, some studies used ICER instead to display their results. Although the ICER calculation encompasses the estimation of QALYs, meaning that the researchers accounted for quality-of-life increases associated with genetic testing, they did not provide the separated values. Therefore, we were not able to retract information from those.

In general, we found that introducing genetic testing as a common practice in healthcare systems can generate QALY increase.

	QALYs			
	No Genetic Test	Genetic Test	Difference	Notes
1	7.320	7.640	0.320	
2	4.250	4.260	0.010	
3				ICER
4	7.616	7.629	0.013	
5	14.659	14.525	-0.134	
6	17.053	17.079	0.026	
7	13.214	13.226	0.012	
8	14.092	14.318	0.226	LYS
9			0.0109	QALYs Gained
10			0.170	QALYs Gained
11				ICER
12	18.669	18.747	0.078	
13	23.507	23.805	0.298	LYS
14				ICER
15				ICER
16	61.408	62.175	0.767	
17			0.100	QALYs Gained
18	0.669	0.703	0.034	
19	19.912	19.922	0.010	LYS
20			0.121	QALYs Gained
21	7.450	7.630	0.180	
22	14.920	14.960	0.040	
23	17.847	17.902	0.055	

4. Discussion

The Lack of HTA's of Genetic Testing

Our research suggests that the current body of literature shows that HTAs performed for genetic tests is a lot more complex that the theory suggests, as they are not able to fulfil the requirements to effectively and accurately analyse a new technology that might be developed in this field. Although there are some HTAs conducted for genetic diagnostics and pharmacogenetics tests, their number is not comparable to that of those conducted for other technologies. HTAs on genetic tests are rare due to the challenges they pose, and the existing reports are incomplete and do not provide robust results, as we will explain further.

The reasons behind this lack of genomic HTAs are: (1) the lack of systematic literature reviews on the subject generated by issues related to the retrieval of the necessary data on costs and benefits; (2) the difficulties in finding comparable studies, since studies that consider similar assumptions and unitarian measures in their economic evaluations are scarce; and (3) the low methodological quality of the existing evidence, as there is no consensus on the requirements for genomic test evaluation (Nurchis, Riccardi, and Damiani 2022).

(1) Firstly, genetic testing is still a grey area in medicine in the sense that it is hard to evaluate and to efficiently retrieve costs and benefits associated to it. As previously explained, the costs of performing a genetic test are very distinct, ambiguous and hard to measure (at least in comparison to those associated with another type of medical technology), primarily because they must take into account the ELSI (Ethical, Legal and Social Implications) related with them.

The issue with ELSI goes beyond traditional measures - it has to do with the possible violation of people's rights and with the potential emotional damage caused to a patient. Researchers prefer to ignore ELSI because of how sensitive that topic is. Researchers find it simpler to

perform their analyses without weighing in ELSI, even though their existence and importance is fully established in the literature.

In theory, HTAs are multidisciplinary reports which encompass all the social and psychological effects related to a given health technology. In practice however, it is uncommon to see these aspects considered (Nurchis, Riccardi, and Damiani 2022). Even though they are a sensitive topic, ELSI are crucial when it comes to genetic testing, and it is impossible to accurately determine utility and effectiveness if these aspects are not accounted for. Additionally, there is a huge lack of information on tangible costs of genetic testing, leading to analyses based on assumptions or to the exclusion of certain costs for which data cannot be found, ending up in biased results.

(2) Secondly, the few existing articles on genetic testing do not follow any standard framework that incorporates recommended costs, units in which economic outputs should be expressed, or preferable and reliable data sources from which to extract information. With no common ground on which cost-effectiveness analysis should be based, there is no way to amass relevant comparable studies on which HTAs could be developed.

(3) Thirdly, the main aim of producing an HTA is to provide relevant information that can be used to inform policymakers and help them formulate valuable recommendations. This is not feasible if the methodological quality of the primary studies and the quality of evidence is not assured and does not fulfil the requirements presented in legitimate frameworks, such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the Cochrane risk-of-bias scale tools (Nurchis, Riccardi, and Damiani 2022). Since there is no agreement on the requirements for an efficient genomic test evaluation and since there are no HTA guidelines to assess the quality of existing studies, it becomes arduous to come up with unbiased and rigorous results. Some researchers, for example, accept the findings of

observational studies or even biological plausibility of potential benefits, whereas others insist on randomized controlled clinical trials (Khoury et al. 2008). Evidence derived from RCTs is hard to come by because some genetic disorders are too rare to justify the cost of conducting an RCT.

In the absence of sufficient and trustworthy information regarding cost-effectiveness and cost-utility analysis of risk assessment and pharmacogenetic tests, conducting an HTA that effectively evaluates genetic tests is impractical. In order to overcome this gap, it is crucial that some efforts be made.

Guidelines on how to conduct a cost analysis specifically for genetic testing, which include recommended (1) decision models, (2) study designs, (3) timeframes, (4) measure units, (5) population characteristics, (6) costs, and (7) databases must be established. This would not only make the conduct of cost analyses on genetic testing clearer, but it would also make the comparison between different studies used in an HTA easier (and conclusions more accurate).

Also, it is important to ensure that an analysis that does not consider the ethical, legal and psychological dimensions that arise from genetic testing, cannot be included in an HTA. It is essential to encourage critical and rational thinking during report development so that all fundamental HTA domains are encompassed. A process designed to check article and evidence quality is also needed (so that HTAs are properly informed).

Contribution of Our Research

With all the limitations we highlighted in mind, we think our research can be useful in that it could contribute to the improvement of the productive process for genetic testing cost-effectiveness analysis. First, we talked about how there isn't an HTA framework expressly made to analyse genetic tests despite the unique qualities that identify them. Furthermore, we demonstrated the large gap that exists between HTAs for this technology and HTAs for most

other technologies. This gap results from the absence of analyses that inform HTAs for genetic testing and is directly related to the absence of a recognized method to carry out those analyses.

Secondly, we were able to provide information on which models are typically adopted, costs and utilities that are taken into account, typical methods of measuring clinical outcomes and economic results, as well as how to assess whether an analysis is in fact cost-effective by closely examining how evaluations are frequently conducted in the literature. Our research may therefore shed light on the data that should be made accessible in databases so that researchers have the necessary data to conduct evaluations. Additionally, we addressed the issue of some aspects of the existing research not adhering to a predetermined pattern, such as adopted population characteristics, and we suggested it as a potential barrier to cost assessments and HTA reporting.

Moreover, our research made it clear how critical incorporating ELSI costs and benefits is when conducting cost-effectiveness analyses on genetic tests. Only then will HTAs for genetic testing be as accurate as possible. We also showed how HTAs specific for genetic testing are lacking in the current literature, and how this has hampered progress when it comes to the acknowledgement of genetic testing's advantages and to it being treated as a common clinical practice.

Recommendations

Based on our findings regarding the prevailing methods used to conduct cost-effectiveness analyses on genetic testing, we recommend that a detailed framework for their assessment should be designed using modified Markov Models that consider patients' individual characteristics and medical history.

Both the healthcare system perspective and the societal perspective should be used to incorporate costs and benefits, and the data on those costs and utilities should be retrieved from recognized databases.

However, in the future, the calibre of these research needs to be carefully assessed to make sure that they are mostly based on field investigations, rather than infinite literature chains that may have unrecognized mistakes at their roots and continue to taint every new study. Additionally, we support the creation of a small number of databases from which researchers should gather the necessary data in order to ensure consistency across evaluations. These databases should also be updated frequently and consider the costs and utilities that we mentioned as being frequently required (in sections (3) and (4), respectively).

Data regarding QALYs and costs (the two main outcomes of cost-effectiveness analyses) should be used to calculate a final ICER. We again emphasize that it is imperative that ELSI costs and benefits are included in the calculation of these results. Otherwise, a report that truly depicts reality will never be accomplished.

We do not possess enough information concerning population characteristics and we are aware that different genetic tests target different populations. Nevertheless, we highly reinforce the need to settle common ground on this matter so that the modelled population are accurately depicted. This would certainly be a good starting point for further research.

Lastly, we think sensitivity analyses should be included in the framework created for assessing the cost-effectiveness of genetic tests in order to strengthen the reliability of the results. These should be carried out automatically using a Monte Carlo simulation because the results are more accurate.

5. 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.

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