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Cost-effectiveness frameworks for comparing genome and exome sequencing versus conventional diagnostic pathways: A scoping review and recommended methods

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Ethics Declaration

This study did not include human subjects or animal research.

Conflict of Interest

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Additional Information

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Abstract

Purpose: Methodological challenges have limited economic evaluations of genome sequencing (GS) and exome sequencing (ES). Our objective was to develop conceptual frameworks for model-based cost-effectiveness analyses (CEAs) of diagnostic GS/ES.

Methods: We conducted a scoping review of economic analyses to develop and iterate with experts a set of conceptual CEA frameworks for GS/ES for prenatal testing, early diagnosis in pediatrics, diagnosis of delayed-onset disorders in pediatrics, genetic testing in cancer, screening of newborns, and general population screening.

Results: Reflecting on 57 studies meeting inclusion criteria, we recommend the following considerations for each clinical scenario. For prenatal testing, performing comparative analyses of costs of ES strategies and postpartum care, as well as genetic diagnoses and pregnancy outcomes. For early diagnosis in pediatrics, modeling quality-adjusted life years (QALYs) and costs over ≥20 years for rapid turnaround GS/ES. For hereditary cancer syndrome testing, modeling cumulative costs and QALYs for the individual tested and first/second/third-degree relatives. For tumor profiling, not restricting to treatment uptake or response and including QALYs and costs of downstream outcomes. For screening, modeling lifetime costs and QALYs and considering consequences of low penetrance and GS/ES reanalysis.

Conclusion: Our frameworks can guide the design of model-based CEAs and ultimately foster robust evidence for the economic value of GS/ES.

Keywords

Cost-effectiveness analysis; Decision modeling; Economic evaluation; Exome sequencing; Genome sequencing

Introduction

Advances in genomic technologies have enabled clinical implementation of genome-wide diagnostic tests based on genome sequencing (GS) or exome sequencing (ES). For various suspected genetic disorders, GS and ES can improve diagnostic yield, potentially replacing conventional diagnostic tests including single-gene and gene panel tests.[1] In addition, GS or ES may also inform clinical management and improve subsequent health outcomes for some patients when test results are closely tied to therapeutic choices,[2] eg, regarding decisions

for supportive/palliative care in critically ill infants with diseases of unknown etiology.[3] Yet, clinicians and policy makers face medical and reimbursement decisions for implementing these new and potentially more expensive genetic tests. Comprehensive assessment of clinical benefits and harms as well as economic implications, as compared with conventional diagnostic pathways, are needed to inform such decisions. Model-based cost-effectiveness analyses (CEAs) can serve as a powerful tool to quantify clinical and economic trade-offs.

Because cost-effectiveness outcomes for GS and ES strategies are highly dependent upon the clinical setting and perspective of the analysis (eg, patient/family, health care system, or society), it is difficult to draw broad conclusions about the incremental value of these technologies. Previous reviews of CEAs of GS/ES have identified various methodological, technical, practical, and implementation challenges for evaluation of cost-effectiveness.[4–7] Key issues identified include lack of consistent nomenclature, definition of appropriate analytical perspective and time horizon, accurate cost estimation, identification of appropriate comparators, proper modeling of the population of interest, and incorporation of treatment effectiveness.

To address these challenges, we developed conceptual frameworks for model-based CEAs that compare GS and ES approaches with conventional diagnostic pathways in several key clinical scenarios relevant to clinical guidelines and health policy. These frameworks can provide guidance for teams designing CEAs, help researchers prioritize data collection efforts intended to inform policy decisions, and establish a benchmark for policymakers considering economic value.

Materials and Methods

Overview

For the development of conceptual frameworks, we selected the following scenarios: (1) prenatal testing in fetuses with suspected congenital anomalies, (2) early diagnosis in newborns and infants with suspected genetic disorders, (3) diagnosis in children with a suspected genetic disorder with delayed onset, (4) tumor or germline genetic testing in cancer, (5) screening of healthy newborns, and (6) screening of healthy adults. Clinical diagnostic scenarios were selected on the basis of research questions evaluated within projects conducted by the National Institutes of Health-funded Clinical Sequencing Evidence-Generating Research (CSER) consortium.[8] The screening scenarios were based on whether they pose emerging medical decision problems studied by other research groups.[9–11]

Development of cost-effectiveness frameworks

We constructed the frameworks using the following steps: (1) conducting a scoping review of published economic evaluation studies of GS/ES following Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines, (2) identifying content and drafting graphical representations of each conceptual framework, and (3) obtaining expert consensus. As a basis for our review, we used 5 previously published systematic reviews on economic studies of next-generation sequencing technologies.[4,5,12–14] We integrated the

search syntaxes from each review to construct a novel PubMed search syntax (Supplement 1) and verified its comprehensiveness by ensuring relevant citations contained in the published reviews were all identified. We then ran the PubMed search covering a period from January 1, 2016 through July 23, 2021 to identify new publications that could not have been included in the 5 previous reviews, given publication dates covered by their reported search strategies.

Study selection and data extraction

In brief, study inclusion criteria (Supplement 2) were (1) economic evaluation of 1 or more of the applicable clinical scenarios, (2) high-income country setting, (3) evaluation of clinical sequencing tests, and (4) evaluation of downstream health care and/or non–health care costs beyond the costs of the genetic testing itself, and/or modeled downstream health consequences beyond assessment of genetic diagnosis alone. Newly identified systematic reviews were included to screen their reference lists for additional citations. Narrative reviews/commentaries, editorials, and letters were excluded. Three reviewers (B.S.F., P.M., and Z.B.) screened titles and abstracts for eligibility, with 1 reviewer vote required for inclusion. Two reviewers (B.S.F. and Z.B.) selected articles for inclusion on the basis of duplicate full-text review. Discrepancies were discussed and resolved by consensus. Authors with topic-specific expertise (F.C., H.V.R., H.S.S., B.D.G., K.M.) verified full-text inclusion before data extraction. Finally, one reviewer (B.S.F. or Z.B.) extracted relevant information from each included study using the online platform Covidence and the other reviewer verified extracted data for completeness. The patient population, intervention, comparator, outcomes, timing, and setting (PICOTS) framework was used for designing the data extraction form (Supplement 3).[15] In brief, we extracted information on (1) study design (for definitions see Supplement 4) and setting, (2) target population, (3) sequencing and test application method, (4) comparators, (5) costs and health outcomes, (6) analytical time horizon, and (7) perspective (eg, health care sector, societal). We chose to conduct a scoping review, rather than a systematic review, given the heterogeneity across decision contexts, target populations, specific interventions, and outcomes that we aimed to synthesize.

Data synthesis and analysis

The writing group involved in the development of initial conceptual frameworks was formed by members from the Clinical Utility, Health Economics and Policy working group of the CSER consortium. The Clinical Utility, Health Economics and Policy working group consists of clinicians and researchers with specific expertise in medical genetics, decision science, health services research, and health economics. The lead author (B.S.F) developed schematic drafts of each framework on the basis of a summary of the literature review. The drafts captured attributes deemed relevant for model-based CEAs organized according to the PICOTS framework. Similarities and differences among the clinical scenarios were highlighted. For each clinical scenario, the group provided feedback on the draft graphical representations of the conceptual frameworks during 1 or two 1-hour online meetings.

Finally, frameworks for each clinical scenario were tabulated in a matrix and presented to the broader CSER community. Feedback was requested for face validity, including

understandability, clinical relevance, and completeness. The frameworks were then further refined and final versions were derived by consensus.

Results

Selected studies

Of the 2089 citations, 57 studies were eligible for data extraction (Figure 1). Scenarios for early-onset pediatric disorders and cancer were subdivided by indication. Four studies concerned diagnosis in an acute pediatric care setting vs 7 in a nonacute care/outpatient setting. Because of the similarity, the latter scenario was grouped with the delayed-onset scenario. A total of 13 studies concerned tumor sequencing (tumor profiling) and 4 studies concerned testing for hereditary cancer syndromes. Multiple economic studies of prenatal testing and screening of healthy newborns were not found. Thus, the group's own expertise was used for developing frameworks, supplemented by relevant reviews.[16–18]

Table 1 summarizes the characteristics of the 57 included studies. Most studies were conducted in the United States ($N = 19$) or Australia ($N = 18$). Four studies were designed as descriptive cost analyses of clinical sequencing without comparison to alternative testing strategies. Nine discrete choice experiments and 1 contingent valuation study were included. The remaining 43 economic evaluations included comparative cost analyses. Of these, 13 were literature-based modeling studies. Most however used participant-level data obtained from study subjects enrolled in a single ($N = 20$) or multicenter ($N = 10$) academic setting. Of these, 4 studies used matched controls to account for confounding, and 8 studies performed counterfactual modeling based on a decision tree.

Of the comparative analyses, 32 were designed to formally assess cost-effectiveness; 14 of these considered quality-adjusted life years (QALYs) as the effectiveness measure (ie, were cost-utility analyses), whereas 18 used cost per additional diagnosed patient or molecular diagnosis as the outcome measure. In 24 of 32 studies, a bootstrap or probabilistic sensitivity analysis was performed informed by distributions for uncertain parameters, and in 27 of 32, uncertainty was explored by 1- or 2-way deterministic sensitivity or scenario analysis of key parameters including, eg, cost of sequencing, diagnostic yield, and wait times (Supplement 5).

In 39 studies, the analytical perspective was the national health care sector, whereas 4 studies evaluated outcomes from a commercial payer perspective. Only 4 studies took a societal perspective. A total of 7 preference elicitation studies determined utility from a patient/parent perspective and 3 elicited preferences in a general population sample. In total, 47 studies were solely funded by governmental agencies and/or foundations, and 10 were supported by industry (Supplement 5).

Cost-effectiveness frameworks

A general conceptual structure, following the PICOTS framework, is shown in Figure 2 to outline our recommendations for the design of model-based CEAs per clinical scenario (Table 2). In the following section, we first describe common modeling concepts that were found to be important across multiple clinical scenarios. Subsequently, recommendations

deemed specifically relevant and unique to the clinical scenario are highlighted with a rationale.

Common modeling concepts

Modeling diagnostic pathways—For modeling prenatal testing and diagnosis in pediatrics, differences in the number of performed tests across strategies (clinical sequencing vs conventional testing) should be estimated over a relevant fixed short-term diagnostic pathway horizon (eg, 1 year for diagnosis in pediatrics). Modelers should then incorporate the expected timing and type of sequential tests (eg, first, second, third tier) per strategy. Timing of sequential tests may depend on the time to return of results of previous tests and their findings. By ignoring the timing of tests, for example, when using a cross-sectional diagnostic decision tree analysis as done in most studies evaluating time to diagnosis (Supplement 5), it is difficult to evaluate the comparative cumulative costs over the analytical time horizon for different diagnostic pathways, as well as their effect on families in ending the disutility of having no diagnosis. For estimating costs of delivery of genomic technologies, costs of sample collection, laboratory testing, data analysis, disclosure of genetic test results, and genetic counseling should be incorporated, using gross or micro-costing approaches.[20]

For simulating primary genetic findings and differences in diagnostic yield, the modeler can decide to categorize findings at the patient level or at the molecular diagnosis level using genetic variant interpretations.[21] The latter would potentially allow for multiple diagnoses in a single patient. Modeling of inconclusive findings, including variants of uncertain significance, should be additionally considered because these may affect rates of reanalysis and, thus, the costs and yield of the overall diagnostic pathway (see subsection Reanalysis).

Although rates of medically actionable secondary findings are generally low,[22] we recommend including these when rates are expected to be different across diagnostic strategies because consequences of secondary findings may alter conclusions about cost-effectiveness. However, evaluating implications of secondary findings is complex, and we found only 3 studies[23–25] that considered them. One method might vary estimates of aggregated costs and QALYs from existing economic studies of returning secondary findings within uncertainty analyses. Models can permit potential correlation between primary, inconclusive, and secondary findings within the same patient using bootstrap analysis when participant-level data are available. Given the multitude of competing health outcomes to potentially consider, it makes sense to focus the modeling on outcomes that are relatively common and/or have extreme consequences for survival, quality-of-life, and costs.

Traditionally, decision models that evaluate diagnostic problems include explicit model inputs for underlying disease prevalence and the conditional distribution of diagnostic test results (or vice versa). However, for modeling diagnostic testing for suspected genetic disorders, the likelihood of true genetic disease is sometimes unknown (latent), even though it can be assumed to be very high in a diagnostic setting (eg, on the basis of family history, early-onset, or disorder severity).[26] Therefore, it can be oftentimes sufficient to model genetic findings obtained via more comprehensive strategies (eg, GS or ES and

chromosomal microarray analysis [CMA]), with the counterfactual being more targeted detection within alternative options.

Reanalysis—Reanalysis of clinical sequencing results to identify variant reclassification (eg, once at 18 months or periodically)[27] and its immediate costs were explicitly modeled in only 1 study.[28] However, the potential effect of reanalysis on long-term health outcomes and costs was not considered. Improvements in diagnostic yield with reanalysis and consequences for future health and costs are highly uncertain, especially in the context of discounting based on time preference. We therefore recommend varying rates of improved diagnostic yield with reanalysis assuming different frequency (only once vs every 6–24 months) and its long-term outcomes within credible ranges by sensitivity analyses. As such, the potential effect of increased knowledge for the incremental cost-effectiveness of GS/ES strategies can be assessed in the context of reanalysis costs.

Family-focused outcomes—Except for modeling tumor profiling, when taking a health care sector or societal perspective, modelers generally need to consider including costs and consequences of testing of parents (duo/trio GS and ES in pediatrics), selective testing of additional family members to establish variant causality (also referred to as segregation analysis), and cascade testing of potentially affected family members. When applicable, implications for the diagnostic yield in the proband after family testing need to be accounted for. For modeling costs and health outcomes in family members of the proband, rates of genetic services, specialist referrals, and changes in clinical management should be based on estimates of the number of these relatives. Modelers should determine the relevance of expanding modeling of outcomes in relatives more distant than first-degree relatives and the effect of including cascade screening for making decisions about cost-effectiveness.[29]

Reproductive-focused outcomes—Modelers could consider modeling reproductive-focused outcomes in persons who can become parents including probands and their relatives. Outcomes to consider include decisions about terminating pregnancy, future pregnancy, use of reproductive genetic counseling and technologies, and additional prenatal and carrier-status testing. Modeling life years or QALYs upon live birth, as well as future pregnancy and offspring is possible.[30] However, ethical considerations need to be assessed in the context of explicitly linking these outcomes to long-term costs and benefits (see subsection Prenatal testing), especially when a patient or family perspective is taken.[31]

Societal outcomes—Adding a societal perspective is recommended as a reference case for CEA.[32] Depending on the relevance for the decision problem, it is possible to include patient time and unpaid caregiver time costs, transportation costs, productivity costs, and special education costs. In 2 of the reviewed CEAs,[33,34] such informal health care and non–health care sector costs were deemed important and feasible for inclusion within an analysis from a societal perspective.

Recommendations per clinical scenario

Prenatal testing

Recommendations

- Sequencing strategies for clinical diagnosis in fetuses with congenital anomalies identified through ultrasound scan should be preferably ES-based, with or without testing using CMA. ES-based strategies can be compared with genetic testing using CMA alone. GS may be considered within a scenario analysis for early cost-effectiveness assessment when evidence for its incremental diagnostic value is unclear.
- For determining incremental cost-effectiveness of alternatives, counterfactuals of the cumulative costs of diagnostics and postpartum care should be modeled, as well as rates of genetic diagnoses and pregnancy outcomes.
- Although health outcomes and costs can potentially be extrapolated to a time horizon beyond pregnancy and the postpartum period, we refrained from making recommendations about such long-term cost-effectiveness modeling given the ethical concerns (Table 2).

Rationale: We identified 1 CEA[35] that compared 3 clinical sequencing strategies (ES alone, CMA followed by ES, and CMA and ES combined) vs 1 conventional strategy (CMA alone) in pregnant women undergoing invasive diagnostic testing for an identified congenital anomaly in the fetus (Supplement 5). Although this study did not consider explicit modeling of health outcomes beyond the genetic diagnosis, we recommend modeling of short-term pregnancy outcomes such as live birth, elective termination, and fetal loss because these are more informative for decision-making. However, long-term economic evaluations including modeling of future lives and pregnancies is hampered by complex ethical and preference-sensitive issues, such as elective termination of pregnancy after a positive finding, uncertain outcome after birth, and future reproductive decisions.[31] Depending upon the jurisdiction, legal considerations should also be taken into account.

Diagnosis in pediatrics

Recommendations

- Rapid turnaround GS/ES strategies should be compared with standard turnaround times and traditional workflows for early-onset complex, presumed monogenic disorders that require intensive care (early-onset, acute care setting).
- GS/ES strategies should be modeled and compared with conventional diagnostics, including other forms of genetic testing.
- GS/ES strategies implemented at different stages in the diagnostic pathway should be evaluated.
- When long-term differences are expected, QALYs and costs should be modeled conditional on genetic findings over a time horizon of at least 20 years and these outcomes should be evaluated in the proband as well as parents and siblings (Table 2).

Rationale: A unique aspect of modeling GS/ES in suspected genetic disorders in acutely ill newborns or infants (younger than 1-year old) or older children (younger than 2 years old) is consideration of the effect of rapid turnaround GS/ES vs standard turnaround times. Disorders in which rapid or early GS/ES are relevant include complex, likely monogenic disorders with involvement of multiple organ systems for which intensive care is required or management decisions are critical. As such, resource utilization associated with intensive care should be accounted for in the analysis. In addition, GS/ES can determine a diagnosis when conventional genetic testing is nondiagnostic in a nonacute care/outpatient setting. Target patient populations could include children with unexplained neurodevelopmental disorders, children with epilepsy, and those diagnosed with presumed type 1 diabetes mellitus (Supplement 5). For both early and late-onset diagnostic scenarios in pediatrics, we deemed a 20-year horizon to be sufficient for estimating relevant cost and health outcomes in the context of discounting. QALYs and costs should be estimated in the proband, but also in parents and siblings to account for consequences of family testing (see subsection Family-focused outcomes). We call for collection of more data on the downstream costs and health outcomes in parents and siblings to adequately model the long-term cost-effectiveness.

Genetic testing in cancer

Recommendations

- A lifetime horizon should be used in modeling health and costs for strategies with exome panels for genetic testing in cancer.
- Modeling of cumulative costs and QALYs in first-degree, second-degree, and third-degree relatives should be performed for CEAs (hereditary cancer syndrome testing) (Table 2).

Rationale: For modeling strategies of tumor profiling with exome panels vs conventional molecular profiling in advanced-stage cancers, in the absence of evidence about the efficacy of targeted therapies, modelers can decide to use intermediate outcomes such as initiation and time on targeted vs standard therapy, or therapeutic response over a shorter time horizon (1–5 years). Such analyses of short-term intermediate outcomes, however, have the limitation that changes in costs of treatments cannot be easily compared to changes in health. As such, modelers should estimate disease-specific (or progression-free) survival times, overall survival time, and QALYs. Lifetime cumulative costs from a health care sector perspective can be determined by costs related to cancer screening and surveillance, cancer treatments, and palliative care. From a societal perspective, informal caregiver costs are relevant in this setting and should be included.[36]

For economic evaluation of hereditary cancer syndrome testing with exome panels vs conventional genetic tests such as targeted gene panel and single-gene tests, decision modeling groups should consider simulating lifetime rates of cancer incidence and recurrence, costs and uptake of prophylactic treatments and surveillance, and costs of cancer treatments and palliative care for the proband and their potentially affected relatives (see subsection Family-focused outcomes).

Screening of healthy populations (newborns and adults)

Recommendations

- Lifetime costs and QALYs of GS/ES should be modeled including the uncertain consequences of detecting low-penetrance pathogenic variants and the uncertain costs and health benefits of storing sequencing data for reanalysis.
- For modeling lifetime health outcomes, preference weights for QALY estimation cannot be directly assessed for the childhood health states and these should be either based on assessment of utility in parents or the general population depending on the analytical perspective (screening in healthy newborns).
- Modeling of screening for adult-onset disorders in newborns was considered controversial and recommended to be only included within secondary (scenario) analyses (Table 2).

Rationale: For modeling cost-effectiveness of newborn sequencing, detectable disorders including structural abnormalities with onset at early childhood that can potentially be treated early or even prevented after diagnosis should be included in the decision model. However, incidence rates of these disorders are generally very low, inadequate sensitivity and false positive rates of sequencing become relevant,[37] and the evidence for the effectiveness of immediate and preventive treatments after screen-detected findings using GS/ES is not well-established.[38] There are certain upfront costs associated with the use of GS/ES that include laboratory costs, costs of follow-up tests and monitoring for possible disease, and costs of genetic services delivered to parents. Furthermore, the additional, more uncertain long-term costs and benefits of storing data and reanalysis should be considered. Without modeling long-term consequences appropriately, upfront costs may receive too much weight in the analysis and net benefits may be underestimated. In addition, there are limited data on the efficacy and logistics of longitudinal use of genomic data across the lifespan. Screening and/or returning results for adult-onset disorders in newborns can be evaluated as done for adults, but discussion regarding ethical considerations such as the child's future decision-making rights are ongoing and the topic warrants additional research on public preferences and follow up after GS/ES.[39]

For modeling screening of healthy adults, the consequences of detection of pathogenic variants with low penetrance (overdiagnosis) and testing of relatives need to be considered. The analysis for this scenario easily becomes very complex, because numerous clinical conditions need to be simulated over a lifetime horizon, within different populations (individual tested and relatives), whereas various comparator strategies of conventional screening and preventive measures can be defined, eg, periodic and/or opportunistic cancer screening. In addition, uncertainties exist regarding heterogeneity in the analytical performance of GS/ES and variant misclassification in understudied populations.[38]

Discussion

We developed recommendations for the design of model-based CEAs of diagnostic strategies based on GS and ES compared with conventional testing across a set of

relevant clinical scenarios. We identified several unique features for CEAs of these clinical sequencing applications that should be accounted for in decision modeling such as modeling of outcomes in relatives, modeling a multitude of competing health outcomes, and modeling of health outcomes with low and/or uncertain rates and uncertain consequences.

Quantification of both clinical and economic value is deemed important when deciding whether conventional test strategies should be replaced by new, potentially more effective but also more expensive clinical sequencing approaches. For example, in a qualitative study on payer decision-making considerations for coverage of GS, payers conveyed concern about extra costs and suggested model-based CEA as a useful tool in addressing this concern.[40] Yet, as mentioned earlier, several challenges have been identified for such model-based economic evaluations. Generally, a call is made for more robust study design and analysis to increase the validity and generalizability of expected cost-effectiveness outcomes after GS and ES when implemented within routine clinical care.[4,5,12–14] For comparing different health outcomes across technologies, use of the QALY is recommended.[32] Yet, it can be difficult to translate differences in diagnostic yield to QALYs when differences in survival and health-state preferences are less salient. In addition, the value of knowledge or reassurance gained from diagnostic findings may be difficult to measure. In addition, measuring health-state preferences in pediatric populations is a complex task,[41] especially when patient utility scores are preferred above community-based and when spillover effects to caregivers are relevant. Hence, to evaluate sensitivity of cost-effectiveness to uncertain parameters, uncertainty analysis is considered essential. When its results are presented in the context of policy options, these can be useful for guiding further research and strengthening the evidence base for reimbursement decisions.

For the development of our recommendations, we used a comprehensive scoping literature review of previously published economic evaluations and expertise from a diverse group of experienced researchers and clinicians. The resulting set of recommendations may help decision modeling research groups with developing more rigorous CEAs for the selected clinical scenarios. They may also be perceived as useful by genetic researchers in the design of clinical studies that aim to evaluate clinical utility of these novel technologies. Some limitations should be acknowledged. First, we focused our recommendations on a selection of clinical scenarios, whereas other decision problems that are potentially also eligible for use of GS and ES were not considered. For example, we did not review applications of GS and ES in contexts where they have not yet been considered for routine use in clinical practice (eg, cell free DNA sequencing for screening for fetal chromosome abnormalities).[42] Moreover, we restricted our recommendations to a high-income country setting. GS/ES applications are generally limited in low- and middle-income countries, and moreover, it is challenging to generalize cost-effectiveness analysis methods to these countries. Second, we used published economic evaluations on the basis of a scoping review as a starting point for group discussions, and therefore, we may have missed some important concepts for the design of model-based CEAs. However, independent clinical experts assessed our recommendations for face validity and completeness. Third, our search strategy focused on sequencing tests including GS, ES, gene panels, and multigene tests, whereas at least conceptually, economic evaluations evaluating more conventional smaller gene panels and single-gene tests may have been useful as well. Expanding our review to

such economic evaluations was not feasible given the large body of published literature. However, researchers who aim to perform an evaluation of these other genomic applications may still apply our recommendations. Finally, GS/ES technologies and technologies of alternative tests such as commercial gene panels and their application for clinical practice rapidly evolve over time. It can be expected that our work will need to be updated periodically.

For further research, some innovative modeling techniques and analysis types may be tested as potential solutions to the challenges for conducting economic evaluation of GS/ES strategies. For example, when cohorts linked by their pedigree should be modeled, agent-based modeling approaches may overcome some of the limitations of using the conventional state-transition models. In addition, value of information analysis can be used to determine and prioritize research agendas for future empirical studies, better informing model parameters that are considered essential for making more definitive conclusions about cost-effectiveness. Finally, the conduct of equity-informative CEA has been suggested to inform decision-makers about trade-offs between cost-effectiveness and health disparities.[43] Most genomic research databases used to verify variants are based on participants of European ancestry and do not capture the global diversity in human genomic variation. As such, determining cost-effectiveness of GS/ES technologies across all genomic backgrounds or ancestral populations remains a challenge, potentially leading to decisions that are less favorable for underserved and/or disadvantaged populations. In this context, the CSER consortium, now in its second funding cycle,[8] is expected to provide useful information by providing data about the integration of GS and ES in clinical care across over 6100 participants including diverse and medically underserved individuals in a variety of health care settings and disease states.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Raw study data extraction details can be obtained from the corresponding author upon request.

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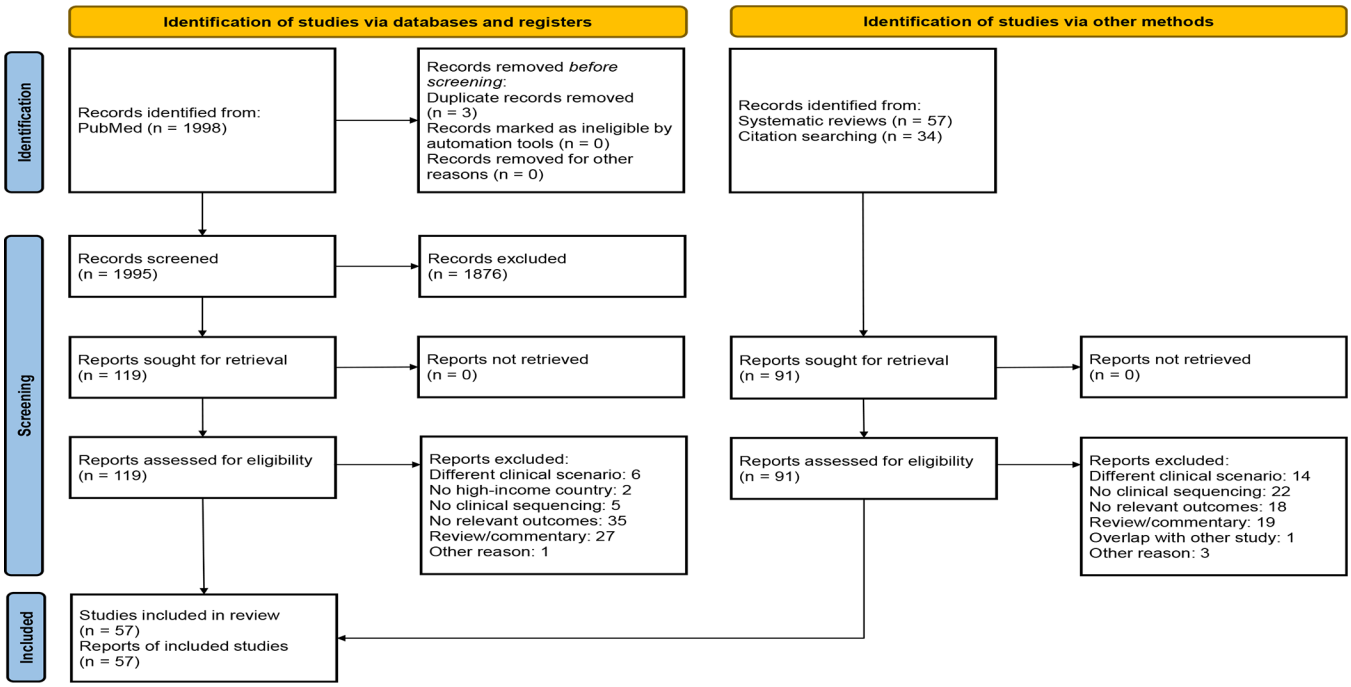

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection process.

Numbers of articles of each step of the review process are indicated. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for study inclusion flow diagrams, reasons for exclusion of records after preliminary screening, ie, screening of titles and abstracts were not tracked.

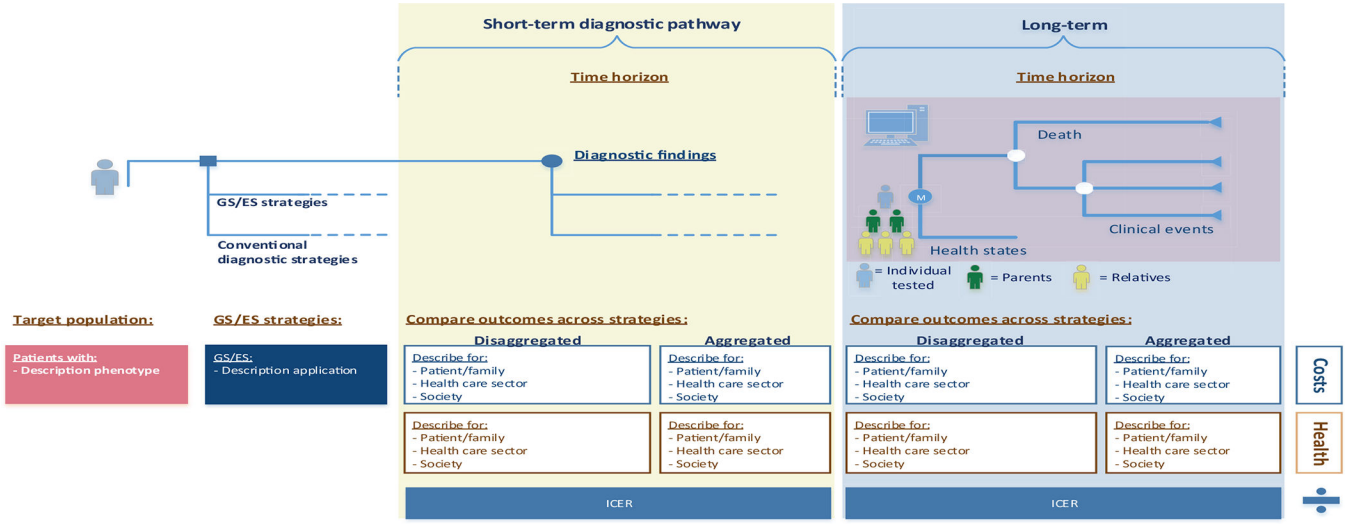

Figure 2. Graphical representation used for development of conceptual frameworks.

ES, exome sequencing; GS, genome sequencing; ICER, incremental cost-effectiveness ratio.

Table 1

Characteristics of the 57 economic studies on clinical sequencing per clinical scenario

Clinical Scenario	Country	Study Design	Analysis Type
Prenatal testing (*N* = 1)	1 United Kingdom	1 single center	1 CEA
Diagnosis in pediatrics			
Early-onset, acute care setting (*N* = 4)	2 Australia, 2 United States	1 literature-based, 3 multicenter	1 cCA, 2 CEA, 1 CUA/CCA/BIA
Early-onset, nonacute care setting (*N* = 7)	6 Australia, 1 Canada	1 multicenter, 6 single center	1 CCA, 3 CEA, 1 CEA/CBA, 1 CEA/CUA, 1 CUA
Delayed-onset (*N* = 22)	7 Australia, 6 Canada, 1 France, 4 Netherlands, 1 United Kingdom, 3 United States	4 literature-based, 2 national survey, 3 online survey, 4 multicenter, 9 single center	1 cCA, 1 CCA, 8 CEA, 1 CEA/BIA, 1 CEA/CBA, 4 dCA, 5 DCE, 1 CUA
Genetic testing in cancer			
Tumor profiling (*N* = 13)	1 Australia, 3 Canada, 1 Japan, 1 Singapore, 2 United Kingdom, 5 United States	5 literature-based, 1 literature-based and multicenter, 1 multicenter, 1 online survey, 4 single center, 1 trial data	3 BIA, 1 cCA, 1 CCA, 1 CEA, 1 CEA/CUA, 5 CUA, 1 DCE
Hereditary cancer syndrome testing (*N* = 4)	4 United States	1 literature-based, 1 literature-based and single center, 1 multicenter, 1 online survey	2 CUA, 2 DCE
Unselected screening[a]			
Adults (*N* = 7)[b]	2 Australia, 5 United States	2 literature-based, 1 national survey, 1 online survey, 3 single center	1 cCA, 2 CCA, 2 CUA, 1 CV, 1 DCE

BIA, budget impact analysis; *CBA*, cost-benefit analysis; *cCA*, comparative cost analysis; *CCA*, cost-consequences analysis; *CEA*, cost-effectiveness analysis; *CUA*, cost-utility analysis; *CV*, contingent valuation; *dCA*, descriptive cost analysis; *DCE*, discrete choice experiment.

[a]Published reviews and group member expertise informed the framework on screening of healthy newborns.

[b]With respect to total study counts, study by Goranitis et al[19] is counted twice for both diagnosis in delayed-onset pediatrics and adult screening. For links to references, see Supplement 6.

Table 2

Comparison of important attributes for model-based cost-effectiveness analysis by clinical scenario

Clinical Scenario	Target Population: Description	GS and ES Strategies	Comparator Strategies	Short-term Outcomes: Disaggregated	Short-term Outcomes: Aggregated	Long-term Outcomes: Disaggregated	Long-term Outcomes: Aggregated
Prenatal testing	Fetuses with suspected congenital anomaly	(1) ES, (2) ES combined with CMA (or after negative CMA); GS may be considered as an emerging strategy within a scenario analysis for early cost-effectiveness modeling	CMA alone	Cross-sectional: Costs: diagnostic costs, postpartum costs; Health: percentage diagnostic findings, live birth, elective termination, fetal loss	Cross-sectional: Costs: total costs; Health: diagnostic yield	Lifetime: Health: possible (fetus, mother, future pregnancies, reproductive outcomes in relatives), but ethical concerns make long-term modeling challenging	Lifetime: Ethical concerns make modeling of long-term cost-effectiveness outcomes, ie, cumulative costs and QALYs challenging
Diagnosis in pediatrics							
Early-onset, acute care setting	Acutely ill neonates/infants aged 0–2 y with suspected genetic disorder	Rapid and standard turnaround GS or ES: (1) replacing standard tests at different tiers, (2) as last resort	Standard care	1 y: Costs: diagnostic costs, costs of genetic services, ICU costs; Health: time to return of results, primary and secondary genetic findings, diagnostic test count, changes in medical care, ICU duration	1 y: Costs: total costs; Health: diagnostic yield	20 y (critically ill neonates) or lifetime: Health: clinical events, reproductive outcomes in proband, parents, other FDRs	20 y (critically ill neonates) or lifetime: Costs: cumulative costs in proband, parents, and other FDRs; Health: QALYs in proband, parents, and other FDRs
Early or delayed-onset, nonacute care setting	Children/young adults with suspected genetic disorder	GS or ES: (1) replacing standard tests at different tiers, (2) as last resort; if ES, combined with/followed by CMA (or after negative CMA results)	Depending on phenotype: (1) targeted gene panel +/− CMA, (2) single-gene tests +/− CMA, (3) standard nongenetic tests	1 y: Costs: diagnostic costs; Health: primary and secondary genetic findings, diagnostic test count, changes in medical care in proband	1 y: Costs: total costs; Health: diagnostic yield	20 y-lifetime: Health: clinical events, reproductive outcomes in proband, parents, other FDRs	20 y-lifetime: Costs: cumulative costs in proband, parents, and other FDRs; Health: QALYs in proband, parents and other FDRs
Genetic testing in cancer							
Tumor profiling	Patients with cancers potentially eligible for targeted therapies	Comprehensive tumor genomic profiling replacing standard single-gene and smaller genomic panel tests; comprehensive tumor genomic profiling after negative standard tumor profiling test results	(1) Standard tumor single-gene tests, (2) smaller tumor genomic panel tests	1–5 y: Costs: costs of biopsies, diagnostics, therapeutics, ADEs, best supportive care; Health: genetic findings, percentage and time on targeted and standard therapy, percentage therapeutic response, percentage palliative treatment in patient	1–5 y: Costs: total costs; Health: percentage or time on targeted and standard therapy, percentage therapeutic response in patient	Lifetime: Health: progression-free and overall survival in patient	Lifetime: Costs: cumulative costs in patient; Health: QALYs in patient
Hereditary cancer	Patients or family members at risk of	Germline large exome panels replacing standard	(1) Standard germline single-gene tests, (2)	6 mo: Costs: diagnostic costs, costs of counseling, costs of approaching	6 mo: Costs: total costs; Health: number of tested	Lifetime: Costs: costs of surveillance/ screening, prophylactic surgery, cancer	Lifetime: Costs: cumulative costs in tested individuals,

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Clinical Scenario	Target Population: Description	GS and ES Strategies	Comparator Strategies	Short-term Outcomes: Disaggregated	Short-term Outcomes: Aggregated	Long-term Outcomes: Disaggregated	Long-term Outcomes: Aggregated
syndrome testing	hereditary cancer syndrome	single-gene and smaller targeted gene panel tests	smaller germline targeted gene panel tests	relatives; Health: primary and secondary genetic findings	individuals and diagnostic yield	treatment; Health: cancer-free and progression-free survival in tested individuals, FDRs, SDRs, TDRs	FDRs, SDRs, TDRs; Health: QALYs in tested individuals, FDRs, SDRs, TDRs
Unselected screening							
Newborns	Healthy newborns	GS or ES as screening test: added to established newborn screening program, either in parallel or after other screening tests	(1) Established newborn screening program alone, (2) established newborn screening program + screening with single-gene or smaller targeted gene panel tests	Early childhood: Costs: diagnostic costs including follow-up testing, costs of storage, reanalysis, counseling, immediate and preventive interventions, monitoring for possible disease; Health: genetic findings	Early childhood: Costs: total costs; Health: parent-reported utility outcome	Lifetime: Costs: costs of immediate and preventive interventions, screening, surveillance; Health: (disease-free) survival, reproductive outcomes in tested newborns and FDRs (if disclosed adult-onset findings)	Lifetime: Costs: cumulative costs in tested newborns and FDRs (if disclosed adult-onset findings); Health: QALYs in tested newborns and FDRs (if disclosed adult-onset findings)
Adults	Healthy adults	GS or ES as screening test	(1) No genetic screening, (2) screening with single-gene or smaller targeted gene panel tests	6 mo: Costs: diagnostic costs, costs of counseling; Health: genetic findings	6 mo: Costs: total costs; Health: individual-reported utility outcome	Lifetime: Costs: costs of risk-reducing interventions (chemoprevention/risk-reducing surgery), screening, surveillance; Health: (disease-free) survival, reproductive outcomes in tested individuals and FDRs	Lifetime: Costs: cumulative costs in tested individuals and FDRs; Health: QALYs in tested individuals and FDRs

ADE, adverse drug event; *CMA*, chromosomal microarray analysis; *ES*, exome sequencing; *FDR*, first-degree relative; *GS*, genome sequencing; *QALY*, quality-adjusted life year; *SDR*, second-degree relative; *TDR*, third-degree relative.