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Themed Section: Assesing the Value of Next-Generation Sequencing

Methodological Issues in Assessing the Economic Value of Next-Generation Sequencing Tests: Many Challenges and Not Enough Solutions

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ABSTRACT

Background: Clinical use of next-generation sequencing (NGS) tests has been increasing, but few studies have examined their economic value. Several studies have noted that there are methodological challenges to conducting economic evaluations of NGS tests. **Objective:** Our objective was to examine key methodological challenges for conducting economic evaluations of NGS tests, prioritize these challenges for future research, and identify how studies have attempted solutions to address these challenges. **Methods:** We identified challenges for economic evaluations of NGS tests using prior literature and expert judgment of the co-authors. We used a modified Delphi assessment to prioritize challenges, based on importance and probability of resolution. Using a structured literature review and article extraction we then assessed whether published economic evaluations had addressed these challenges. **Results:** We identified 11 challenges for conducting economic evaluations of NGS tests. The experts identified three challenges as the top priorities for future research: complex model structure, timeframe, and type of analysis and comparators used. Of the 15 published studies included in our literature review, four studies described specific solutions relevant to five of the 11 identified challenges. **Conclusions:** Major methodological challenges to economic evaluations of NGS tests remain to be addressed. Our results can be used to guide future research and inform decision-makers on how to prioritize research on the economic assessment of NGS tests.

Keywords: economics, methods development, next-generation sequencing, personalized medicine, precision medicine.

Introduction

Understanding the economic value of clinical tests that use next-generation sequencing (NGS) is critical to their appropriate implementation. The use of NGS tests (including multigene panel, whole-exome, and whole-genome sequencing) has been increasing [1]. Nevertheless, only a limited number of studies have examined their economic value [2]. Several studies have noted that there are methodological challenges to evaluating NGS tests that may be a barrier to conducting evaluations [3–12].

Our objective was to examine key methodological challenges in conducting economic evaluations of NGS tests, prioritize these challenges for future research, and identify how studies have attempted solutions. The fundamental key characteristic of NGS

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tests that complicates their economic evaluation is that, by definition, they simultaneously examine multiple genes and can produce multiple results, each with distinct short- and long-term clinical and economic trajectories. In contrast, most economic evaluations examine the value of one test conducted for a specific reason, with one defined result, and with a single trajectory of costs and outcomes, and thus this approach may have to be modified for NGS tests. A previous study noted that researchers need to be "creative" about approaches to evaluating the costs and outcomes of NGS tests [13]. Addressing challenges in conducting economic evaluations can facilitate the ability of researchers to conduct such evaluations as well as increase the clarity and transparency of economic analyses for decision makers.

Methods

Overview

We identified challenges for economic evaluations of NGS using previous literature and input from coauthors with expertise in economic methods and NGS. We used a modified Delphi assessment to prioritize these challenges on the basis of their perceived importance and probability of their resolution by methodological consensus. We then used structured literature review and article extraction to assess whether published evaluations had developed and applied solutions to these challenges.

Identifying Challenges for Economic Evaluations of NGS

We developed our list of challenges for economic evaluations of NGS tests in two steps. First, we built on a previous study that defined issues in economic evaluation of personalized medicine more broadly [14]. We then modified the list to include challenges that are particularly relevant to NGS tests, on the basis of studies describing challenges for NGS evaluations [3–12]. Coauthors reviewed the list for accuracy and completeness. We did not restrict the list to only those challenges that are *unique* to NGS, but focused on those for which there was group consensus that NGS testing made them especially challenging. We categorized challenges, but we recognize that there is some overlap among them.

Delphi Method

We used the modified Delphi method [15] with the authors who are health economics experts to rate and rank methodological challenges to economic evaluation of clinical NGS testing. In the first round we described 11 challenges and asked experts to rate them using the following scales:

1. Importance (four-point rating scale from very important to unimportant, including the option to choose "no judgment");
2. Probability of resolution in the next 5 years via methodological consensus (five-point rating scale from very probable to very improbable, including the option to choose "no judgment").

Respondents were also asked to provide a written rationale for each of their ratings. After excluding the "no judgment" ratings, we calculated the median scores for both rating scales and selected the top challenges using a threshold median score of 3. This threshold corresponded to a rating of "important" or "very important" on the importance scale and "either way" (50/50 chance of being resolved), "probable" (better than a 50% chance of being resolved), or "very probable" (almost certain to be resolved) on the probability scale.

The purpose of the second round for the survey was to narrow the list of priority challenges on the basis of the information gathered in the first round. We provided the experts with the subset of challenges that met the aforementioned criteria in round 1 as well as the descriptive rationales for these ratings. We then asked respondents to identify and rank the three top challenges on the basis of their current assessment of importance and probability of resolution and in order of preference for taking action now (1 = most preferred; 3 = less preferred). Respondents provided their rationale for each ranking. We determined the top scoring challenges on the basis of how often each challenge was chosen as either "most preferred" or "preferred."

Structured Literature Review to Identify Published Economic Evaluations and Their Solutions

We systematically conducted searches in PubMed and Embase to identify economic evaluations of NGS tests. We also used manual searching by reviewing article citations and review articles.

We used 10 known relevant articles to identify relevant search terms [16–25] (searches are described in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.017). The PubMed search used specific Medical Subject Headings terms to identify directly relevant articles and used title key words to identify articles not yet indexed. The Embase search was designed to be similar to our PubMed search, but was revised to fit Embase terms. We also had to modify searches to capture studies of noninvasive prenatal tests using NGS because of how they were coded.

We screened articles by their titles and abstracts, with full text reviewed as necessary (Fig. 1). We included studies if they met the following inclusion criteria:

1. empirical economic evaluation (including cost-effectiveness/cost-benefit/budget- impact analyses, but excluding cost/consequence studies that did not calculate a ratio);
2. study of clinical use of NGS tests (i.e., we did not include gene expression profiling panels or tests of a single gene or gene pairs such as *BRCA1/2*); and
3. published in English.

We abstracted study variables using Excel spreadsheets to code study characteristics and solutions used to address challenges. Given that our key objective was to identify solutions to challenges rather than simply identify the challenges, we coded studies as follows:

1. Did the study address any of the identified methodological challenges using a specifically described approach?
2. If yes, what challenge was addressed and what solution was used?

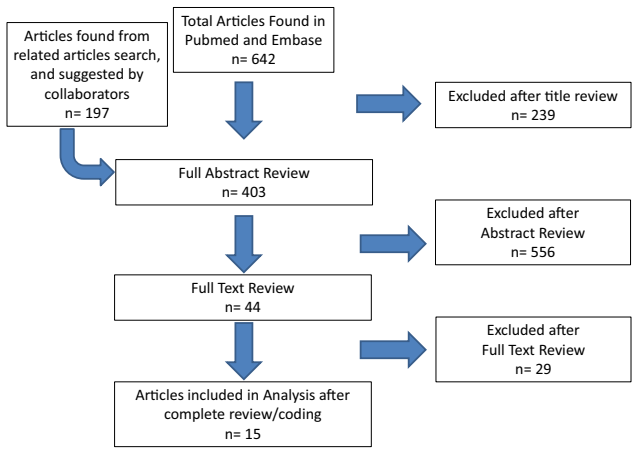

Figure 1 – PRISMA diagram of included and excluded studies.

We then identified how many of the challenges were addressed with specific solutions in the included studies. We did not attempt to define the quality and appropriateness of the methods used by the included studies in terms of whether they identified challenges or not. The challenges were not relevant to all the studies, and thus there was no need for some of the studies to identify challenges or apply solutions. We also did not assess the validity or generalizability of the solutions used.

Results

Challenges in Conducting Economic Evaluations of NGS Tests

We identified 11 challenges, which we grouped into 3 categories (Table 1).

Table 1 – Challenges identified for economic evaluations of NGS tests.

Study questions and model structure
Complex model structure: Modeling multiple pathways, results, and testing uses (as a result of multiple genes being tested); may include modeling potential interactive effects (e.g., of life expectancy across multiple conditions)
Time frame: Modeling upstream (e.g., equipment purchase) and downstream (e.g., recurring testing and storage costs) costs and outcomes specific to NGS when relevant; may include potential savings if doing test upfront with later use of results
Secondary findings: Incorporating possibility of secondary findings and their impact (positive and negative) when relevant
Type of analysis and comparators used: Determining appropriate type of analysis and using approaches other than CEA when relevant; using appropriate comparators that take into account what NGS is being compared with and whether substitution or addition
Directly attributable outcomes: Identifying costs/outcomes directly attributable to NGS when necessary to parse out
Measuring costs and outcomes
Broad measures of patient outcomes: Quantifying range of outcomes for person being tested when relevant (e.g., measuring personal utility to patients because of psychological benefits from having a diagnosis etc.)
Broad measures of health outcomes beyond person tested: Modeling individual outcomes beyond person being tested when relevant (e.g., modeling impact on family members)
Broad measures of societal outcomes: Modeling impact beyond patient outcomes (e.g., education and employment)
Data aggregation: Aggregating data from multiple sources when necessary to measure NGS impact (e.g., combining data from multiple studies)
Data availability and quality
Data availability issues: Examining lack of evidence and data variability as relevant to NGS (e.g., prevalence, penetrance, clinical utility, and race-specific inputs)
Statistical issues: Examining statistical issues as relevant to NGS (e.g., triangulating and integrating data sources and using value of information analysis)

CEA, cost-effectiveness analysis; NGS, next-generation sequencing.

Study questions and model structure (complex model structure, time frame, secondary findings, type of analysis and comparators used, directly attributable outcomes)

NGS tests can provide multiple results, and they have a much greater likelihood of identifying what are called "variants of unknown significance," which are variants of a gene that have been identified through genetic testing, but whose significance to the function or health of an organism is not known. They may also generate secondary findings that are unrelated to the original reason for testing. Each of these findings may have distinct clinical trajectories and thus different costs and outcomes, and modeling every possible result and trajectory is often impractical. Secondary findings and variants of unknown significance can have either positive or negative impacts on costs and outcomes. In addition, findings may have interactive effects such that the sum is greater than the parts. For example, knowledge of the patterns of multiple mutations may provide more information than sequential, single-gene testing, thus requiring complex economic models to reflect these interactions. There may also be interactive effects such as the joint impact of multiple outcomes on life expectancy.

Determining the relevant time frame and costs and outcomes within that time frame can be particularly complex with NGS tests. There may be upstream costs and outcomes that are incurred before testing such as equipment costs; downstream costs and outcomes such as data storage costs; variant re-interpretation; and costs as a result of additional testing or workup due to secondary findings. Of particular relevance is that NGS tests of the individual's genetic makeup (i.e., germline) may provide information that can be used throughout an individual's lifetime, and thus costs and outcomes should be appropriately prorated and discounted.

The choice of the type of analysis and relevant comparator(s) can be challenging. NGS tests can be compared with single-gene tests, sequential single-gene testing, other types of testing, or no testing. In addition, NGS tests may be simultaneously relevant to multiple conditions (e.g., breast and colorectal cancer, or cancer and heart disease), complicating the determination of the appropriate comparator. Of particular relevance is that NGS tests may substitute for other interventions or may supplement them, which increases the complexity of modeling these tests.

Finally, it can be challenging to identify which costs and outcomes are directly attributable to NGS versus those that would have occurred anyway. For example, NGS results may suggest cancer screening, which would have been recommended anyway as a preventive measure.

Measuring costs and outcomes (broad measures of patient outcomes/health outcomes beyond person tested/societal outcomes, data aggregation)

NGS tests can produce outcomes that go beyond clinical outcomes for the patient, such as personal utility (personal rationales for and benefits of testing that go beyond clinical outcomes), impacts on family members, and impacts beyond individuals on education and employment. Although these effects are not unique to NGS, it has been noted that they may be particularly relevant because of the hereditary nature of genetic diseases and the potential lifetime impacts of testing. Many reviews have noted the challenge of fully capturing the costs and outcomes of NGS tests. For example, testing may end a diagnostic odyssey and thus provide "personal utility" even if it does not change health outcomes. In addition, evaluations of NGS tests may need to aggregate data from multiple studies.

Data availability and quality (data availability issues, statistical issues)

Data on key variables such as prevalence of mutations, clinical utility of testing, and race-specific variables may be lacking for

Table 2 – Top priority challenges to address (modified Delphi results).

Top priority challenges to address	Expert working group rationales
Type of analysis and comparators	*Why important?* • Both are critical • Fundamental for measuring value and ensuring most relevant approach; without right parameters may arrive at right conclusion to the wrong question • If using QALYs when not the right approach, then conclusions are flawed *What is feasible?* • More feasible and quick to address than other challenges • Does not really require anything new, just more attention *What is needed?* • Comparator difficult to define as tests change; comparators may not be obvious—condition-specific or broader? • Requires input from both health economics and decision makers
Complex model structure	*Why important?* • Key issue that cannot be overcome with only transparency or simplifying assumptions and cannot just "get around it" *What is feasible?* • Requires different modeling approaches *What is needed?* • Need to generalize previous efforts • Requires methodological considerations regarding interactions specific to NGS
Time frame	*Why important?* • Key/essential benefit of NGS (test results reused) so critical to measure • Time frame always important as need to capture long-term impact *What is feasible?* • Resolvable within next few years *What is needed?* • Analyses need to comprehensively incorporate information on upstream and downstream costs and outcomes • Large sequencing projects worldwide provide opportunity to address

Note. We determined the top scoring challenges on the basis of how often each challenge was chosen as either "most preferred" or "preferred." Each challenge was chosen by two respondents as "most preferred." For the "preferred" designation, one respondent chose the type of analysis and comparator used, one chose the complex model structure, and two respondents chose time frame. Given that the three top-ranking challenges had similar scores, we did not attempt to further rank them. None of the other challenges was chosen as "most preferred."
NGS, next-generation sequencing; QALY, quality-adjusted life-year.

NGS tests. Evaluation of NGS tests may face data challenges that are more complex than found in other analyses, such as the role of penetrance (the proportion of individuals carrying a particular variant of a gene [the genotype] that also express an associated trait [the phenotype]). Another challenge is that needed data are often not triangulated and integrated so that they can inform economic evaluations. Data may have to be combined from multiple data sources such as provider notes, electronic health record data, test results reported in PDF files, patient self-report, and other clinics where patients are referred. Finally, multiple findings also create joint uncertainties that may require complex statistical estimation and may benefit from value of information analyses (i.e., a formal method for quantifying the value of additional evidence).

Priorities for Addressing Challenges

In the first Delphi round, 7 challenges (out of 11) scored above the median score of 3 for both importance and probability of resolution (see the Appendix in Supplemental Materials). These challenges were complex model structure, time frame, secondary findings, type of analysis and comparators chosen, directly attributable outcomes, data aggregation, and data availability. The experts reassessed the challenges on the basis of the results from round 1 and chose the following challenges in terms of priority for taking action now: type of analysis and comparators used, complex model structure, and time frame (Table 2). The experts also explained why they perceived that these challenges were important and feasible to address.

How Studies Have Developed and Applied Solutions to Challenges

We identified 15 studies for inclusion (Table 3). All but one study (Sabatini et al. [23]) were cost-effectiveness analyses. Most of the studies (60%) were US-based followed by studies from Australia (27%). The studies covered various conditions: 47% were on cancer, 27% were on neurodevelopmental disorders in children,

Table 3 – Economic evaluations of NGS tests (N = 15).

Study	Objective	Country	Disease	Test/ comparators	Outcome measure	Results summary	Conclusion summary
Bennette et al. [19]	Clinical/economic impact of returning IFs	United States	Cardiomyopathy, colorectal cancer, healthy individuals with genetic FHx	WGS/not disclosing WGS IFs	Cost/QALY	• Cost/QALY = $44,800 (patients with cardiomyopathy) • Cost/QALY = $115,020 (patients with CRC) • Cost/QALY = $458,600 (healthy individuals with genetic FHx)	Likely cost-effective for certain populations Unlikely cost-effective in general population unless NGS <$500
Gallego et al. [20]	Economic evaluation of NGS panels for CRC	United States	Colorectal cancer	NGS panel/ current standard of care	Cost/QALY	• Cost/QALY = $36,500 (highly penetrant CRCP syndrome genes) • Cost/QALY = $77,300 (panel includes low-penetrance genes)	First-line NGS panel (genes associated with highly penetrant CRCP syndromes + Lynch syndrome genes) cost-effective
Kaimal et al. [26]	Decision-analytic model to assess comprehensive outcomes of prenatal genetic testing strategies among women of varying ages	United States	Fetal aneuploidy	NIPT cell-free DNA/six testing strategies in combination or in sequence	Cost/QALY	• Multiple-marker screening dominant choice for women aged <38 y • Cost/QALY = $73,154 cell-free DNA screening (age >40 y)	Multiple-marker screening most cost-effective option for most women younger than 40 y; for older than 40 y, cell-free DNA as primary screen becomes optimally cost-effective
Li et al. [21]	Is NGS panel (34 genes) for melanoma treatment selection cost-effective?	United States	Metastatic melanoma	NGS panel/ single-site BRAF V600 test only	Cost/QALY	• Cost = $120,022 (gene sequencing panel), QALYs = 0.721 (gene sequencing panel) • Cost = $128,965, QALYs = 0.704 (single-site mutation test strategy)	NGS panel is the dominant strategy over single-site mutation test strategy (reduced costs and increased QALYs)
Walker et al. [27]	Determine optimum MSS risk cutoff for contingent NIPT Compare cost-effectiveness of optimized contingent NIPT to universal NIPT and conventional MSS	United States	Fetal aneuploidy	Universal NIPT cell-free DNA/ MSS and optimized contingent NIPT	Cost/diagnosis	• Cost/diagnosis universal NIPT = $203,088 (vs. contingent NIPT, government perspective) • Cost/diagnosis universal NIPT = $263,922 (vs. continent NIPT, payer perspective) • Universal NIPT dominated both contingent NIPT and MSS (societal) • Contingent NIPT dominated MSS (government/ payer)	Most cost-effective policy depended on perspective; universal NIPT dominated (societal perspective), contingent NIPT dominated (government and payer perspective)
Azimi et al. [28]	Evaluate cost-effectiveness of carrier screening using NGS vs. genotyping for 14 recessive disorders for which guidelines recommend screening	United States	14 recessive disorders in carrier screening	NGS panel/ genotyping	Cost/LY gained	• Cost/LY gained = $29,498 (NGS) and cost/affected birth avoided = $1.14 million • Cost/LY gained = $33,812 (carrier screening by genotyping) and cost/affected birth avoided = $1.33 million	NGS-based carrier screening (most prevalent recessive disorders) cost-effective in averting more affected births, creating more LYs gained, and reducing annual and lifetime treatment costs as compared with genotyping

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Table 3 – *continued*

Study	Objective	Country	Disease	Test/ comparators	Outcome measure	Results summary	Conclusion summary
Fairbrother et al. [29]	Estimate CEA of fetal aneuploidy screening in general pregnancy population using NIPT vs. FTS with serum markers and NT ultrasound	United States	Fetal aneuploidy	NIPT cell-free DNA/ screening using FTS	Cost/diagnosis	• Cost/diagnosis = $497,909 (cost per trisomy case identified with FTS) • NIPT cost <$453 then cost savings vs. FTS	NIPT in general pregnancy population leads to more prenatal identification of fetal trisomy cases vs. FTS and is more economical at NIPT unit cost of $453
Sabatini et al. [23]	Impact of using targeted gene panel in optimizing care for patients with advanced non–small cell lung cancer, use of targeted gene panel in diagnosis and management of patients with sensorineural hearing loss, and exome sequencing in the diagnosis and management of children with neurodevelopmental disorders of unknown genetic etiology	United States	Advanced non–small cell lung cancer, sensorineural hearing loss, and neuro-developmental disorders of unknown genetic etiology	Targeted gene panel for three conditions/ current standard of care	Cost/diagnosis; management, treatment, or intervention mix before and after GSP testing	• For tumor sequencing, total cost of treatment decreases by $2.7 million (from $10.2 million to $7.5 million), but only if patients receive investigational targeted therapies • For hearing loss, analysis revealed both increase in diagnostic yield from 24% 26% and cost savings of $0.24 million for a hypothetical plan of 1 million members • For pediatric neurodevelopmental disorders, analysis suggests selective use of exome sequencing can demonstrate possible cost savings depending on assumptions regarding exome costs and diagnostic yield	Each model demonstrated value by reducing health care costs or identifying appropriate care pathways, depending on assumptions regarding cost and timing of testing (definition of value differs by clinical scenario)
Doble et al. [30]	Compare use of MTS to select targeted therapy on the basis of tumor genomic profiles to no further testing (with chemo or with supportive care) in fourth-line treatment of metastatic lung adenocarcinoma	Australia	Metastatic lung adenocarcinoma	MTS/no further testing (chemo or supportive care)	Cost per LY/QALY	• Cost/LY = A $485,199 (~US $378,000) MTS vs. BSC) • Cost/QALY = A $361,580 (~US $282,000) (chemo vs. BSC) • Cost/QALY = A $489,338 (~US $381,000) (MTS vs. chemo)	MTS not cost-effective; VOI analyses reveal reducing decision uncertainty for cost and resource use parameters, testing parameters and clinical transition probabilities have greatest value
Li et al. [22]	Investigate whether a seven-gene test to identify women who should consider risk-reduction strategies could cost-effectively increase life expectancy	United States	Breast cancer	Seven-gene test (*BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *STK11*, and *PALB2*)/*BRCA1*/ 2	Cost/QALY	• Cost/LY = $42,067 • Cost/QALY = $69,920 (50 y old) • Cost/LY = $23,734 • Cost/QALY = $48,328 (40 y old)	Testing seven breast cancer–associated genes, followed by risk-reduction management starting at either age 40 or 50 y, could cost-effectively improve life expectancy
Saito et al. [31]	To determine CEA of comprehensive molecular profiling before initiating anti-eGFR therapies for metastatic colorectal cancer	Japan	Metastatic colorectal cancer	Comprehensive molecular profiling/RAS mutation screening	Cost/QALY	• Cost/QALY = 4,260,187 ¥(~US $40,000)	Comprehensive screening more cost-effective than RAS screening
Schofield et al. [16]	Evaluate economic value for panel or WES of neuromuscular disease	Australia	Neuromuscular disorders	WES and panel/ muscle biopsy and protein assays (traditional)	Cost/additional diagnosis	• Panel saved $17,075/ additional diagnosis • WES saved $10,204/ additional diagnosis	Panel most cost-effective and WES second most vs. traditional diagnostic pathway

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Table 3 – *continued*

Study	Objective	Country	Disease	Test/ comparators	Outcome measure	Results summary	Conclusion summary
Stark et al. [18]	Evaluation of three strategies to include WES in current testing pathway	Australia	Pediatric monogenetic disorders	WES after exhaustive standard investigation WES to replace some investigations WES to replace most investigations/ standard of care	Cost/additional diagnosis	• Cost/additional diagnosis = $6,327 (WES after exhaustive standard investigation) • Cost/additional diagnosis = $2,045 (WES to replace some investigations) • Savings/ additional diagnosis −$1,702 (WES to replace most investigations)	Early WES triples diagnostic rate for one-third of cost per diagnosis
Tan et al. [32]	Investigate impact of WES in sequencing-naive children suspected of having monogenic disorder and evaluate CEA if WES had been available at different time points in diagnostic trajectory	Australia	Monogenic disorders in children	Singleton WES/ standard diagnostic pathway (no single-gene or panel testing)	Cost/additional diagnosis	• Savings/ additional diagnosis $6,838 (WES at initial tertiary presentation) • Savings/ additional diagnosis $4,140 (WES at first genetics appointment)	Singleton WES in children with suspected monogenic conditions has high diagnostic yield, and CEA is maximized by early application in the diagnostic pathway
Tsiplova et al. [17]	Comparison of CMA to WES/WGS in autism spectrum disorder	Canada	Autism spectrum disorders	WES, WGS/CMA	Cost/diagnosis (additional positive finding)	• Cost/diagnosis rate = $25,458 CAD (~US $20,000) (CMA + WES vs. CMA) • Cost/diagnosis rate = $26,020–$58,959 (~US $20,000–US $47,000) (WGS vs. CMA depending on machine) • Cost/diagnosis rate = $28,300–$195,056 (~US $22,000–US $153,000) (WGS vs. CMA + WES depending on machine)	Incremental cost was >CAD$25,000 per additional positive finding if CMA was replaced by newer technology. Future reductions in material and equipment costs and increased understanding of variants will lead to improved value

Note. All studies were CEAs except for Sabatini et al. [23], which was a cost-impact analysis/budget-impact analysis, and all studies used the payer perspective except Walker et al. [27], which used payer, governmental, and societal perspectives.
BSC, best supportive care; CEA, cost-effectiveness analysis; CMA, chromosomal microarray; CRC, colorectal cancer; CRCP, colorectal cancer and polyposis; eGFR, estimated glomerular filtration rate; FHx, family history; FTS, first trimester combined screening; GSP, genomic sequencing procedure; IFs, incidental findings; LY, life-year; MSS, maternal serum screening; MTS, multiplex targeted sequencing; NGS, next-generation sequencing; NIPT, noninvasive prenatal testing; NT, nuchal translucency; QALY, quality-adjusted life-year; VOI, value of information; WES, whole-exome sequencing; WGS, whole-genome sequencing.

and 20% were on fetal aneuploidies. About half the studies used intermediate outcome measures (e.g., cost per diagnosis; n = 7). Interestingly, despite the concern that NGS technologies are too expensive for health care payers, all the studies except one [30] identified an NGS test scenario that was cost-effective.

Of the 11 challenges, 6 were addressed with specific solutions that were described in four different studies (Table 4). The specific solutions were as follows:

1. Bennette et al. [19] addressed the challenges of complex model structure, secondary findings, and data aggregation. They addressed the modeling complexities introduced by multiple results and conditions and the challenge of modeling secondary findings. Their approach simplified the research question and model to make them manageable and leveraged existing data to make the analyses feasible. They narrowed the research question by modeling three archetypal groups and seven conditions. They also included only those genes that were previously defined as having clinical utility rather than all possible secondary findings. They then leveraged existing cost-effectiveness analyses when possible rather than creating their own models.
Bennette et al. also addressed the challenge of data aggregation by combining data from multiple studies and creating a composite cost-effectiveness ratio. They multiplied the individual-level estimates for costs and quality-adjusted life-years associated with returning a secondary finding by the expected prevalence of identifying and returning those

Table 4 – Specific solutions applied to specific challenges.

Challenges	Studies addressing a specific challenge with a specific solution
	Study questions and model structure
Complex model structure	Bennette et al. [19] addressed complexities of modeling secondary findings through a targeted modeling approach and incorporating previous cost-effectiveness analyses. Gallego et al. [20] analyzed hypothetical panels that included less penetrant mutations to consider how adding these mutations would reduce estimated cost effectiveness, given that panels include most highly penetrant mutations first.
Time frame	Studies did not use explicit solutions to address.
Secondary findings	Bennette et al. [19] focused solely on secondary findings.
Type of analysis and comparators used	Sabatini et al. [23] used budget-impact analysis and three scenarios to address needs of decision makers.
Directly attributable outcomes	Studies did not use explicit solutions to address.
	Measuring costs and outcomes
Broad measures of patient outcomes	Studies did not use explicit solutions to address.
Broad measures of health outcomes beyond person tested	Studies did not use explicit solutions to address.
Broad measures of societal outcomes	Studies did not use explicit solutions to address.
Data aggregation	Bennette et al. [19] combined data from multiple studies and created a composite cost-effectiveness ratio. Sabatini et al. [23] aggregated cost data across laboratories by using representative laboratories and cross-laboratory comparisons.
	Data availability and quality
Data availability issues	Studies did not use explicit solutions to address.
Statistical issues	Doble et al. [30] used value of information analysis to assess where it would be of greatest value for decision makers to reduce uncertainty.

Note. Challenges are not relevant to all studies.

results to estimate the implications of returning secondary findings at the population level.

2. Gallego et al. [20] addressed the challenge of complex model structure by analyzing hypothetical test scenarios as part of their cost-effectiveness analysis of NGS tests for the diagnosis of colorectal cancer and polyposis symptoms. They noted that tests typically include the most highly penetrant mutations first, but then may expand to include less penetrant mutations. Thus, they analyzed four hypothetical tests in order of increasing effectiveness in which each panel was larger than the previous one because of additional, lower prevalence mutations.
3. Doble et al. [30] addressed the challenge of statistical issues by using value of information analysis to assess where it would be of greatest value for decision makers to reduce uncertainty, in their cost-effectiveness analysis of multiplex targeted screening to select targeted therapy for fourth-line treatment of metastatic lung adenocarcinoma. They found that such screening was not cost-effective compared with no testing. Nevertheless, by using value of information analysis, they determined that additional research to reduce uncertainty may be a worthwhile investment, specifically that reducing decision uncertainty for cost and resource use parameters, testing parameters, and clinical transition probabilities would have the greatest value.
4. Sabatini et al. [23] addressed the challenges of data aggregation and the type of analysis and comparators used. They used budget-impact analysis, which is a method that has not been as frequently applied to NGS tests or other tests as cost-effectiveness analysis. They also analyzed three different scenarios. By using these approaches, they addressed what they perceived to be the needs of the relevant decision makers.

Sabatini et al. [23] also addressed the challenge of data aggregation by aggregating cost data across laboratories by using representative laboratories and cross-laboratory comparisons. They noted that one challenge in performing cost analyses for methods with multiple technology platforms and assay steps is the difficulty in determining a representative sample. To address this challenge, several laboratories performing clinical testing that met their definition of a representative laboratory were selected. They also incorporated the full costs of laboratory testing including the costs of bioinformatics and pipeline development, the costs associated with assessing the quality of the run, and the short- and long-term costs of storing data.

We did not find studies that specifically addressed other challenges (Table 4). Some studies mentioned such challenges but did not then attempt to address them with new solutions or with modifications of existing approaches.

Discussion

We identified numerous challenges in conducting economic evaluations of NGS tests and identified three challenges considered by experts to be the highest priorities for future research. We found that some challenges have been addressed using specific solutions but many challenges have not been addressed and solutions have not been generalized beyond specific studies. Of the three highest priority challenges, we found efforts to apply solutions to two of those challenges but we did not find any studies that have addressed one of the high-priority challenges (appropriate time frames).

Study Limitations

Our search may have missed relevant studies. As noted in other reviews [2], the available search terms for identifying NGS panel

studies are incomplete. There are no search terms for gene panels or multigene tests and thus we focused on identifying studies of sequencing tests. We also found that studies may be inconsistently coded; for example, the study by Li et al. [22] was incorrectly coded in PubMed as a "gene expression profiling panel" and thus we located this study using manual searching. To address these limitations, we used a range of data sources (PubMed, Embase, and manual searching) and a range of search terms. The number of studies we included differs from other recent reviews (e.g., Schwarze et al. [2]) because we focused on multigene panels in addition to whole-exome sequencing/whole-genome sequencing tests and we did not include studies focused only on costs.

We cannot ensure that we included all relevant challenges. We thus used a range of sources to identify the most relevant challenges and obtained input from coauthors. Similarly, we also cannot ensure that we identified all solutions used. Our study's scope did not include determining whether studies should have addressed specific challenges or assess the methodological quality of studies. Instead, we focused on examining what challenges were or were not addressed using solutions. Finally, we did not assess the appropriateness and adequacy of the identified solutions and other feasible solutions because this was beyond the scope of this study. Future research should obtain additional expert input on the priority challenges to address and their potential solutions.

Conclusions

Although researchers are starting to consider the challenges in conducting economic evaluations of NGS technologies, a great deal more research effort is required to identify and test potential solutions. It would be helpful if future research could further identify viable solutions in addition to examining the solutions already used in published studies. Questions to be addressed include the following: How generalizable are the identified solutions? What other solutions could be feasible? Can we determine when specific solutions are most relevant? How can economic theory contribute? These questions can be addressed using expert input, case studies, and assessment of ongoing research that has not yet been published.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.06.017.

REFERENCES

[1] Phillips KA, Deverka PA, Hooker GW, et al. Genetic test availability and spending: Where are we now? Where are we going? Health Aff (Millwood) 2018;37:710–6.

[2] Schwarze K, Buchanan J, Taylor JC, et al. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. Genet Med [published online ahead of print February 15, 2018. http://dx.doi.org/10.1038/gim.2017.247.

[3] Fugel HJ, Nuijten M, Postma M, et al. Economic evaluation in stratified medicine: methodological issues and challenges. Front Pharmacol 2016;7:113.

[4] Annemans L, Redekop K, Payne K. Current methodological issues in the economic assessment of personalized medicine. Value Health 2013;16: S20–6.

[5] Lu CY. Economic evaluation of whole-genome sequencing in healthy individuals: What can we learn from CEAs of whole-body CT screening? Genet Med 2016;18:103–4.

[6] Rogowski W, Payne K, Schnell-Inderst P, et al. Concepts of "personalization" in personalized medicine: implications for economic evaluation. Pharmacoeconomics 2015;33:49–59.

[7] Payne K, Eden M, Davison N, et al. Toward health technology assessment of whole-genome sequencing diagnostic tests: challenges and solutions. Per Med 2017;14:235–47.

[8] Joosten SE, Retel VP, Coupe VM, et al. Scenario drafting for early technology assessment of next generation sequencing in clinical oncology. BMC Cancer 2016;16:66.

[9] Basu A, Carlson JJ, Veenstra DL. A framework for prioritizing research investments in precision medicine. Med Decis Making 2016;36:567–80.

[10] Payne K, McAllister M, Davies LM. Valuing the economic benefits of complex interventions: when maximising health is not sufficient. Health Econ 2013;22:258–71.

[11] Phillips KA, Ladabaum U, Pletcher MJ, et al. Key emerging themes for assessing the cost-effectiveness of reporting incidental findings. Genet Med 2015;17:314–5.

[12] Buchanan J, Wordsworth S, Schuh A. Issues surrounding the health economic evaluation of genomic technologies. Pharmacogenomics 2013;14:1833–47.

[13] Christensen KD, Dukhovny D, Siebert U, et al. Assessing the costs and cost-effectiveness of genomic sequencing. J Pers Med 2015;5:470–86.

[14] Husereau D, Marshall DA, Levy AR, et al. Health technology assessment and personalized medicine: Are economic evaluation guidelines sufficient to support decision making? Int J Technol Assess Health Care 2014;30:179–87.

[15] Landeta J. Current validity of the Delphi method in social sciences. Technol Forecast Soc Change 2006;73:467–82.

[16] Schofield D, Alam K, Douglas L, et al. Cost-effectiveness of massively parallel sequencing for diagnosis of paediatric muscle diseases. NPJ Genom Med 2017;2:4.

[17] Tsiplova K, Zur RM, Marshall CR, et al. A microcosting and cost-consequence analysis of clinical genomic testing strategies in autism spectrum disorder. Genet Med 2017;19:1268–75.

[18] Stark Z, Schofield D, Alam K, et al. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement. Genet Med 2017;19:867–74.

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

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

[21] Li Y, Bare LA, Bender RA, et al. Cost effectiveness of sequencing 34 cancer-associated genes as an aid for treatment selection in patients with metastatic melanoma. Mol Diagn Ther 2015;19:169–77.

[22] Li Y, Arellano AR, Bare LA, et al. A multigene test could cost-effectively help extend life expectancy for women at risk of hereditary breast cancer. Value Health 2017;20:547–55.

[23] Sabatini LM, Mathews C, Ptak D, et al. Genomic sequencing procedure microcosting analysis and health economic cost-impact analysis: a report of the association for molecular pathology. J Mol Diagn 2016;18:319–28.

[24] Valencia CA, Husami A, Holle J, et al. Clinical impact and cost-effectiveness of whole exome sequencing as a diagnostic tool: a pediatric center's experience. Front Pediatr 2015;3:67.

[25] Weymann D, Laskin J, Roscoe R, et al. The cost and cost trajectory of whole-genome analysis guiding treatment of patients with advanced cancers. Mol Genet Genom Med 2017;5:251–60.

[26] Kaimal AJ, Norton ME, Kuppermann M. Prenatal testing in the genomic age: clinical outcomes, quality of life, and costs. Obstet Gynecol 2015;126(4):737–46.

[27] Walker BS, Nelson RE, Jackson BR, et al. A CEA analysis of first trimester non-invasive prenatal screening for fetal trisomies in the United States. PLoS One 2015;10(7):e0131402.

[28] Azimi M, Schmaus K, Greger V, et al. Carrier screening by next-generation sequencing: health benefits and cost effectiveness. Mol Genet Genomic Med 2016;4(3):292–302.

[29] Fairbrother G, Burigo J, Sharon T, et al. Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a CEA analysis. J Matern Fetal Neonatal Med 2016;29(7):1160–4.
[30] Doble B, John T, Thomas D, et al. Cost-effectiveness of precision medicine in the fourth-line treatment of metastatic lung adenocarcinoma: an early decision analytic model of multiplex targeted sequencing. Lung Cancer 2017;107:22–35.
[31] Saito S, Kameyama H, Muneoka Y, et al. CEA analysis of the use of comprehensive molecular profiling before initiating monoclonal antibody therapy against metastatic colorectal cancer in Japan. J Cancer Policy 2017;12:61–6.
[32] Tan TY, Dillon O, Stark Z, et al. Diagnostic Impact and CEA of Whole-Exome Sequencing for Ambulant Children With Suspected Monogenic Conditions. JAMA Pediatr 2017;171(9):855–62.