Themed Section: Assessing the Value of Next-Generation Sequencing

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

Kathryn A. Phillips, PhD1*, Patricia A. Deverka, MD, MS2, Deborah A. Marshall, PhD3, Sarah Wordsworth, PhD4, Dean A. Regier, PhD5, Kurt D. Christensen, PhD6, James Buchanan, DPhil4

1Department of Clinical Pharmacy; Center for Translational and Policy Research on Personalized Medicine (TRANSPERS); UCSF Philip R. Lee Institute for Health Policy; and UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; 2American Institutes for Research, Chapel Hill, NC, USA; 3Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada; 4Nuffield Department of Population Health, Medical Sciences Division, University of Oxford, Oxford, UK; 5Cancer Control BC, School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada; 6Bigham and Women’s Hospital, Harvard University, Boston, MA, USA

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.

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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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* Address correspondence to: Kathryn A. Phillips, Department of Clinical Pharmacy, 3333 California Street, Room 420, P.O. Box 0613, San Francisco, CA 94143.

E-mail: kathryn.phillips@ucsf.edu.

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tests that complicate 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 identified the top challenges as those with the highest median scores. 

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).

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

NGS tests can produce 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 rations 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...
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>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Country</th>
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<th>Outcome measure</th>
<th>Results summary</th>
<th>Conclusion summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennette et al. [19]</td>
<td>Clinical/economic impact of returning IFs</td>
<td>United States</td>
<td>Cardiomyopathy, colorectal cancer, healthy individuals with genetic FHx</td>
<td>WGS/ not disclosing WGS IFs</td>
<td>Cost/QALY</td>
<td>Cost/QALY = $44,800 (patients with cardiomyopathy), Cost/QALY = $41,000 (patients with CRC), Cost/QALY = $458,600 (healthy individuals with genetic FHx)</td>
<td>Likely cost-effective for certain populations, Unlikely cost-effective in general population unless NGS &lt; $500</td>
</tr>
<tr>
<td>Gallego et al. [20]</td>
<td>Economic evaluation of NGS panels for CRC</td>
<td>United States</td>
<td>Colorectal cancer</td>
<td>NGS panel/ current standard of care</td>
<td>Cost/QALY</td>
<td>Cost/QALY = $36,500 (highly penetrant CRCF syndrome), Cost/QALY = $77,300 (panel includes low-penetration genes)</td>
<td>First-line NGS panel (genes associated with highly penetrant CRCF syndromes + Lynch syndrome genes) cost-effective</td>
</tr>
<tr>
<td>Kaimal et al. [26]</td>
<td>Decision-analytic model to assess comprehensive outcomes of prenatal genetic testing strategies among women of varying ages</td>
<td>United States</td>
<td>Fetal aneuploidy</td>
<td>NIPT cell-free DNA testing strategies in combination or in sequence</td>
<td>Cost/QALY</td>
<td>Cost = $120,022 (gene sequencing panel), QALYs = 0.721 (gene sequencing panel), Cost = $128,965, QALYs = 0.704 (single-site mutation test strategy)</td>
<td>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</td>
</tr>
<tr>
<td>Li et al. [21]</td>
<td>Is NGS panel (34 genes) for melanoma treatment selection cost-effective?</td>
<td>United States</td>
<td>Metastatic melanoma</td>
<td>NGS panel/ single-site BRAF V600 test only</td>
<td>Cost/QALY</td>
<td>Cost = $120,022 (gene sequencing panel), QALYs = 0.721 (gene sequencing panel), Cost = $128,965, QALYs = 0.704 (single-site mutation test strategy)</td>
<td>NGS panel is the dominant strategy over single-site mutation test strategy (reduced costs and increased QALYs)</td>
</tr>
<tr>
<td>Walker et al. [27]</td>
<td>Determine optimum MSS risk cutoff for contingent NIPT Compare cost-effectiveness of optimized contingent NIPT to universal NIPT and conventional MSS</td>
<td>United States</td>
<td>Fetal aneuploidy</td>
<td>Universal NIPT cell-free DNA/ MSS and optimized contingent NIPT</td>
<td>Cost/diagnosis</td>
<td>Cost/diagnosis universal NIPT = $263,922 (vs. contingent NIPT, payer perspective), Universal NIPT dominated both contingent NIPT and MSS (societal), Contingent NIPT dominated MSS (government/payer)</td>
<td>Most cost-effective policy depended on perspective; universal NIPT dominated (societal perspective), contingent NIPT dominated (government and payer perspective)</td>
</tr>
<tr>
<td>Azimi et al. [28]</td>
<td>Evaluate cost-effectiveness of carrier screening using NGS vs. genotyping for 14 recessive disorders for which guidelines recommend screening</td>
<td>United States</td>
<td>14 recessive disorders in carrier screening</td>
<td>NGS panel/ genotyping</td>
<td>Cost/LY gained</td>
<td>Cost/LY gained = $29,498 (NGS) and cost/affected birth avoided = $1.14 million, Cost/LY gained = $31,812 (carrier screening by genotyping) and cost/affected birth avoided = $1.33 million</td>
<td>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</td>
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### Table 3 – continued

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<th>Study</th>
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<tbody>
<tr>
<td>Fairbrother et al. [29]</td>
<td>Estimate CEA of fetal aneuploidy screening in general pregnancy population using NIPT vs. FTS with serum markers and NT ultrasound</td>
<td>United States</td>
<td>Fetal aneuploidy</td>
<td>NIPT cell-free DNA screening using FTS</td>
<td>Cost/diagnosis</td>
<td>Cost/diagnosis = $497,909 (cost per trisomy case identified with FTS)</td>
<td>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</td>
</tr>
<tr>
<td>Sabatini et al. [23]</td>
<td>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</td>
<td>United States</td>
<td>Advanced non-small cell lung cancer, sensorineural hearing loss, and neurodevelopmental disorders of unknown genetic etiology</td>
<td>Targeted gene panel for three conditions/ current standard of care</td>
<td>Cost/diagnosis, management, treatment, or intervention mix before and after GSP testing</td>
<td>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</td>
<td>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)</td>
</tr>
<tr>
<td>Doble et al. [30]</td>
<td>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</td>
<td>Australia</td>
<td>Metastatic lung adenocarcinoma</td>
<td>MTS/no further testing (chemo or supportive care)</td>
<td>Cost per LY/QALY</td>
<td>Cost/LY = $489,338 (MTS vs. chemo)</td>
<td>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</td>
</tr>
<tr>
<td>Li et al. [22]</td>
<td>Investigate whether a seven-gene test to identify women who should consider risk-reduction strategies could cost-effectively increase life expectancy</td>
<td>United States</td>
<td>Breast cancer</td>
<td>Seven-gene test (BRCA1, ESR2, TP53, PTEN, CDH1, STK11, and一对1/BRCAl/2)</td>
<td>Cost/QALY</td>
<td>Cost/LY = $42,067</td>
<td>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</td>
</tr>
<tr>
<td>Saito et al. [31]</td>
<td>To determine CEA of comprehensive molecular profiling before initiating anti-eGFR therapies for metastatic colorectal cancer</td>
<td>Japan</td>
<td>Metastatic colorectal cancer</td>
<td>Comprehensive molecular profiling/RAS mutation screening</td>
<td>Cost/QALY</td>
<td>Cost/LY = $4,260,187 ¥ (50 y old)</td>
<td>Comprehensive screening more cost-effective than RAS screening</td>
</tr>
<tr>
<td>Schofield et al. [16]</td>
<td>Evaluate economic value for panel or WES of neuromuscular disease</td>
<td>Australia</td>
<td>Neuromuscular disorders</td>
<td>WES and panel/muscle biopsy and protein assays (traditional)</td>
<td>Cost/additional diagnosis</td>
<td>Panel most cost-effective and WES second most vs. traditional diagnostic pathway</td>
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of four different studies (Table 4). The findings were consistent with previous studies indicating that NGS technologies are too expensive for most health care payers.

Interestingly, despite the concern that NGS technologies are too expensive for most 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 described in the literature and increased understanding of variants by focusing on important results.

The specific solutions were as follows:

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<tr>
<td>Stark et al. [18]</td>
<td>Evaluation of three strategies to include WES in current testing pathway</td>
<td>Australia</td>
<td>Pediatric monogenetic disorders</td>
<td>WES after exhaustive standard investigation; WES to replace some investigations; WES to replace most investigations; standard of care</td>
<td>Cost/additional diagnosis; Cost/additional diagnosis; Cost/additional diagnosis; Cost/additional diagnosis; Cost/additional diagnosis</td>
<td>Early WES triples diagnostic rate for one-third of cost per diagnosis</td>
<td></td>
</tr>
<tr>
<td>Tan et al. [32]</td>
<td>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</td>
<td>Australia</td>
<td>Monogenic disorders in children</td>
<td>Singleton WES/standard diagnostic pathway (no single-gene or panel testing)</td>
<td>Cost/additional diagnosis</td>
<td>Savings/additional diagnosis; Savings/additional diagnosis; Savings/additional diagnosis; Savings/additional diagnosis</td>
<td>Singleton WES in children with suspected monogenic conditions; Savings/additional diagnosis; Savings/additional diagnosis; Savings/additional diagnosis; Savings/additional diagnosis</td>
</tr>
<tr>
<td>Tsiplova et al. [17]</td>
<td>Comparison of CMA to WES/WGS in autism spectrum disorder</td>
<td>Canada</td>
<td>Autism spectrum disorders</td>
<td>WES, WGS/CMA (additional positive finding)</td>
<td>Cost/diagnosis</td>
<td>Cost/diagnosis; Cost/diagnosis; Cost/diagnosis; Cost/diagnosis</td>
<td>Incremental cost was less for CMA than for WES</td>
</tr>
</tbody>
</table>

Note. All studies were CEA 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 aneuploids. 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:

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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 findings. They then generated a summary cost-effectiveness ratio for returning a secondary finding that could be compared to the cost-effectiveness of returning a primary diagnosis.
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.

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