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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 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

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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?

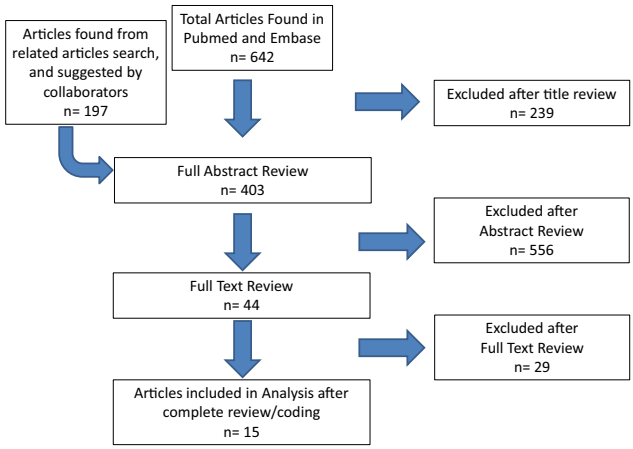

Figure 1 – PRISMA diagram of included and excluded studies.