Themed Section: Assesing the Value of Next-Generation Sequencing

Valuation of Health and Nonhealth Outcomes from Next-Generation Sequencing: Approaches, Challenges, and Solutions

Dean A. Regier, PhD[1,2],*, *Deirdre Weymann, MA*[1], *James Buchanan, DPhil*[3], *Deborah A. Marshall, PhD*[4], *Sarah Wordsworth, PhD*[3]

[1]*Canadian Centre for Applied Research in Cancer Control, Cancer Control Research, BC Cancer, Vancouver, British Columbia, Canada;* [2]*School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada;* [3]*Health Economics Research Centre, University of Oxford, Oxford, United Kingdom;* [4]*Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada*

A B S T R A C T

Background: Next-generation sequencing (NGS) technologies have seen variable adoption in the clinic. This is partly due to a lack of clinical and economic studies, with the latter increasingly challenged to examine patient preferences for health and nonhealth outcomes (e.g., false-positive rate). **Objectives:** To conduct a structured review of studies valuing patients' preference-based utility for NGS outcomes, to highlight identified methodological challenges, and to consider how studies addressed identified challenges. **Methods:** We searched MEDLINE (PubMed), Embase (Ovid), and Web of Science for published studies examining outcomes from health care decisions informed by NGS. We focused our search on direct elicitations of preference-based utility. We reviewed included studies and qualitatively grouped and summarized stated challenges and solutions by theme. **Results:** Eleven studies were included. Most of them (n = 6) used discrete choice experiments to value utility. We categorized challenges into four themes: 1) valuing the full range of NGS outcomes, 2) accounting

for accuracy and uncertainty surrounding effectiveness, 3) allowing for simultaneous multiple and cascading risks, and 4) incorporating downstream consequences. Studies found strong evidence of utility for NGS information, regardless of health improvement. Investigators addressed challenges by simplifying complex choices, by including health outcomes alongside nonhealth outcomes, and by using multiple elicitation techniques. **Conclusions:** The breadth and complexity of NGS-derived information makes the technology a unique and challenging application for utility valuation. Failing to account for the utility or disutility of NGS-related nonhealth outcomes may lead to overinvestment or underinvestment in NGS, and so there is a need for research addressing unresolved challenges.

Keywords: genomic testing, next-generation sequencing, personal utility.

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Introduction

Next-generation sequencing (NGS) is an umbrella term for massively parallel DNA sequencing technologies. The result of the application of NGS is information obtained from simultaneously interrogating multiple genes or the whole genome and their biological inter-relationships. Although NGS shows promise for more accurate patient stratification, the translation of NGS into the clinic has been variable [1,2]. The variability in uptake has been attributed to a lack of evidence base demonstrating clinical effectiveness, clinical utility, and cost effectiveness.

Health technology assessment (HTA) guidelines typically stipulate that off-the-shelf instruments should inform quality-adjusted life-years (QALYs) when answering questions of cost effectiveness. These instruments might not capture all the

benefit-risk trade-offs of NGS health, nonhealth, and process outcomes. Buchanan et al. [3] highlighted that measures informing QALYs do not incorporate preferences for nonhealth outcomes (e.g., false-positive rate) or process outcomes (e.g., time waiting for results). This observation is important in context of the assertion by Marshall et al. [4] that the value of NGS depends on the information that patients receive and the benefits that patients and providers ascribe to NGS information.

Recently, the Second Panel on Cost Effectiveness in Health and Medicine made allowance for an economic evaluation reference case that takes account of nonhealth outcomes. The panel noted that decision makers need a "quantification and valuation of all health and non-health effects of interventions" [5]. In principle, this recommendation supports including preference-based utility in economic evaluation beyond what off-the-shelf instruments usually encapsulate.

The types of outcomes that NGS produces are challenging to value, however. This is because NGS has the potential to uncover a multitude of complex clinically and nonclinically actionable results with far-ranging personal and familial implications. Given the import and complexity of NGS information, our objectives were to 1) conduct a structured review of studies valuing the preference-based utility of NGS health, nonhealth, or process outcomes from consumers' perspectives; 2) highlight the conceptual and methodological challenges these studies encountered when estimating utility; and 3) consider how the included studies addressed the conceptual and stated challenges.
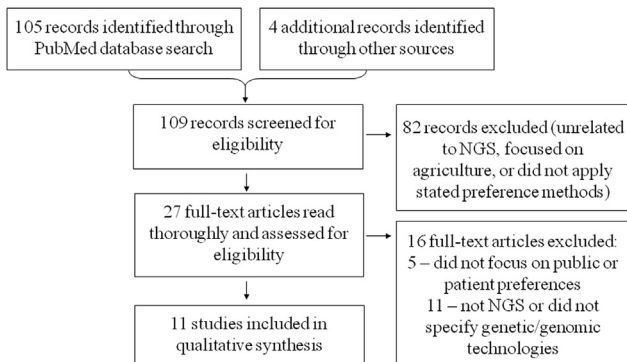
Methods

We conducted a literature search of full-text peer-reviewed articles in MEDLINE (PubMed), Embase (Ovid), and Web of Science. We restricted our search to articles in English published between January 1, 2005, and December 31, 2017. We chose the year 2005 because this was the year that NGS was being implemented in research settings. Our search strategy is outlined in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.010. After initial identification, we imported all articles into EndNote X6. Two of the researchers independently evaluated the title and abstract of all publications to identify articles for inclusion. We limited the search to direct elicitation of preference-based utility. We excluded studies that did not estimate stated preferences, did not focus on patient and/or general public perspectives, or did not focus on NGS. We identified stated challenges through authors' statements on the motivation for estimating utility and in the discussion of study limitations. Using directed content analysis and the study by Marshall et al. [4], we grouped challenges according to categories. Solutions were based on study design and analytic approach, on next steps discussed for research, and on feedback from the working group.

Results

Study Acquisition Flow

Figure 1 presents the flow of the included studies. The PubMed search identified 105 records. Four additional records were identified from searches in Ovid (MEDLINE) and Web of Science, as well as from citations in key articles. After screening titles and abstracts, 82 records were excluded and 27 full-text articles were assessed for eligibility. Of these, 11 studies directly elicited preference-based utility to examine the value of NGS health and nonhealth outcomes. Reasons for exclusion were studies not specifically examining NGS (n = 11) or not focusing on preferences from public or patient perspectives (n = 5).
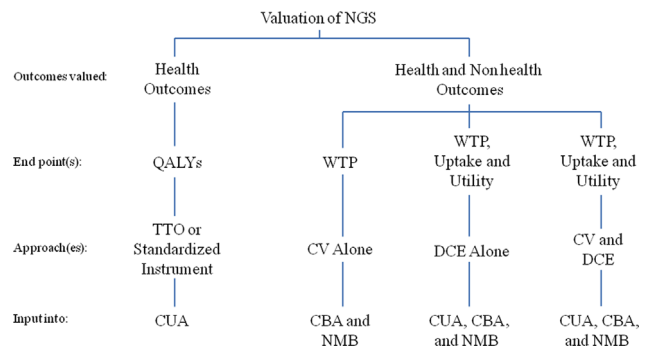
Study Characteristics

Clinical context, end points, and perspective
Detailed characteristics of each study are available in the Appendix in Supplemental Materials. The clinical contexts included NGS for prenatal testing, genomic testing to inform cancer interventions, and return of genomic information irrespective of disease. Of the included studies, 36% examined preferences from the general population's perspective, 46% focused on the perspectives of patients or their families, and 18% examined both perspectives. The studies specified a number of end points, including preference-based utility, predicted uptake, and willingness to pay. These end points were chosen for various reasons. Four studies anticipated that their results would be used as inputs in economic evaluation. Two studies aimed to inform shared decision making, one study aimed to guide policy, two studies sought to inform early-stage technology development and investment, and two studies did not explicitly discuss the reason for preference elicitation.

Methods and approaches to elicit preferences
Figure 2 provides an overview of the applied methods, end points, and their potential uses within economic evaluation. The methods used were discrete choice experiments (DCEs; n = 6), contingent valuation (CV; n = 1), time trade-off (n = 1), as well as a combination of DCE, CV, probability trade-off, and/or ranking exercises (n = 3). Health, nonhealth, and process outcomes were identified through a combination of literature review, focus groups, in-person interviews, pilot testing, and expert opinion (see the Appendix in Supplemental Materials). Two studies did not state how they determined relevant outcomes. Most studies incorporated attributes for health, nonhealth, or process outcomes (n = 9). Attributes pertaining to health-related quality of life were included in four studies and involved likely benefit from treatment, likelihood of treatment side effects, complication rate, or pregnancy-specific outcomes. Health-related attributes described the risk of developing the disease after identifying a variant (n = 8), actionability of the genomic variant (n = 4), severity of the identified disease (n = 4), and/or carrier implications (n = 2). Nonhealth attributes included cost (n = 5),

Fig. 1 – Flowchart describing articles identified and evaluated on the basis of inclusion criteria. NGS, next-generation sequencing.

Fig. 2 – Tree diagram depicting different preference-based approaches to valuation of NGS. CBA, cost-benefit analysis; CUA, cost-utility analysis; CV, contingent valuation; DCE, discrete choice experiment; NGS, next-generation sequencing; NMB, net monetary benefit; QALY, quality-adjusted life-year; TTO, time trade-off; WTP, willingness to pay.