Title: Valuation of health and non-health outcomes from next generation sequencing: Approaches, challenges, and solutions

Running title: Valuation of NGS outcomes: challenges and solutions

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Précis: Genomic information is highly complex and next-generation sequencing (NGS) technologies are a challenging application for valuation of utility. Failing to account for the utility or disutility of NGS-related non-health outcomes may lead to over- or under-investment in health technologies

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ABSTRACT

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 non-health outcomes (e.g., false positive rate).

Objectives: 1) Conduct a structured review of studies valuing patients' preference-based utility for NGS outcomes; 2) highlight identified methodological challenges; and 3) consider how studies addressed identified challenges.

Methods: We searched Medline (PubMed), Embase (Ovid), and Web of Science for published studies examining outcomes from healthcare 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. The majority (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 non-health outcomes, and through using multiple elicitation techniques.

Conclusion: The breadth and complexity of NGS-derived information makes the technology a unique and challenging application for utility valuation. Since failing to account for the utility or disutility of NGS-related non-health outcomes may lead to over- or under-investment in NGS, there is a need for research addressing unresolved challenges.

HIGHLIGHTS

What is already known about the topic?

- Next generation sequencing technologies (NGS) provide large amounts of genomic information with a multitude of implications on patients' and families' preference-based utility and on the healthcare system.
- NGS information has an impact on health, non-health, and process outcomes.
- Researchers are applying several methods with limited guidance when estimating the value of health and non-health outcomes.

What does the paper add to existing knowledge?

- We identify four challenges to eliciting the preference-based value of outcomes from NGS.
- Studies have addressed challenges by simplifying complex choice tasks, by including health outcomes alongside non-health outcomes, and through simultaneously using multiple elicitation techniques.
- There remains considerable scope to comprehensively address challenges for estimating the utility of health and non-health outcomes from NGS.

What insights does the paper provide informing health care-related decision-making?

- It is the breadth and complexity of information obtained from NGS that makes it a unique and challenging context for eliciting preference-based utility.
- Ignoring the utility or disutility of NGS non-health outcomes may lead to over- or under-investment in NGS technologies.

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, non-health and process-related outcomes. Buchanan et al. (2016) highlight that measures informing QALYs do not incorporate preferences for non-health (e.g., false positive rate) or process outcomes (e.g., time waiting for results). This observation is important in context to Marshall et al.'s (2017) assertion 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 non-health 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 into 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 non-clinically 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, non-health, 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 English-language articles published between January 1, 2005 and December 31, 2017. We chose 2005 because this was the year that NGS was being implemented in research settings. Our search strategy is outlined in the Appendix. After initial identification, we imported all articles into EndNote X6.[6] Two researchers (DW and DAR) 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. (2017) we grouped challenges according to categories. Solutions were based on study design and analytic approach, on discussed next steps for research, and on feedback from the working group.

RESULTS

Study acquisition flow

Figure 1 presents the flow of 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 non-health outcomes. Reasons for exclusion were studies not specifically examining NGS (n=11) or not focusing on preferences from public or patients' perspectives (n=5).

Study characteristics

Clinical context, endpoints, and perspective

Detailed characteristics of each study are available in the Appendix. 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 endpoints, including preference-based utility, predicted uptake, and willingness to pay (WTP). These endpoints were chosen for a variety of reasons. Four studies anticipated their results would be used as inputs into 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, endpoints, and their potential uses within economic evaluation. The methods used were discrete choice experiments (DCE; n=6), contingent valuation (CV; n=1), time trade-off (TTO; n=1), as well as a combination of DCE, CV, probability trade-off and/or ranking exercises (n=3). Health, non-health, and process outcomes were identified through a combination of literature review, focus groups, in-person interviews, pilot testing, and expert opinion (Appendix). Two studies did not state how they determined relevant outcomes. Most studies incorporated attributes for health, non-health, 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 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). Non-health attributes included cost (n=5), turnaround time (n=3), type of procedure (n=3), test reliability (n=2), level of physician support or shared decision-making (n=2), and genetic test score (n=1).

Conceptual and methodological challenges

The studies highlighted a number of conceptual and methodological challenges for estimating the outcomes from NGS. The challenges relate to a need for valuing the full range of NGS-related health and non-health outcomes, capturing how preferences change with accuracy of genomic

information, multiple scientific uncertainties, and capturing downstream consequences of NGS-generated information.

Challenge 1: Valuing the range of NGS-related health, non-health and process outcomes

NGS produces genome-wide information with the potential for multiple outcomes. It is the breadth and complexity of information that makes NGS a unique case for preference-based valuation. The studies noted that NGS provides information on one or all of disease diagnosis, prognosis, treatment response, and hereditary risk. The types of information returned become complex to communicate when NGS uncovers variants of uncertain significance (VUS) or secondary findings (SFs). The potential outcomes of SFs include uncovering risk for diseases that may or may not have effective treatment options; availability of early screening strategies for family members; or pharmacogenetic information on response to drugs. The continuing debate is whether patients should be given information on diseases that are not treatable.[7-9] This is because patients may value the information absent of effective treatment and improvement in health status.

How studies conceptually addressed the broad range of outcomes

Researchers in the genetics and health economics literature have labelled the value of non-health outcomes as 'personal utility', which relates to the benefit that patients ascribe to the spectrum of information derived from genomic technologies, regardless of its potential to improve health.[10,11] Articulating the concept in this way was important because it broadened the scope of what the genetics literature considered as beneficial or of value to patients, families, and the healthcare system. The included articles articulated this concept of personal utility in two ways:

(i) as the benefits or harms manifested outside medical contexts; the value of genomic information; or as the value of knowledge that is separate from clinical effectiveness; or (ii) as the worth individuals ascribe to the full range of NGS testing outcomes, including health, non-health, and process outcomes.

The included studies provided evidence that supports the importance of health and non-health outcomes to the valuation of benefit. In all studies, respondents valued informational and process attributes. Regier et al. (2015) found that 27% of the general population would want SF information for disorders with severe quality-of-life consequences, irrespective of whether effective medical treatment was available. Marshall et al. (2016) found that 45% of adult respondents were willing to pay for information on a variant for which there was no effective treatment available. Lewis et al. (2017) determined that parents were interested in the return of highly penetrant non-medically actionable conditions in children, particularly if manifestations were more severe (e.g. earlier age of onset, greater level of disability). Buchanan et al. (2016) and Cuffe et al. (2014) provide evidence of disutility for waiting longer for results of NGS, with the former also finding respondents had a preference for who delivered the results. Marshall et al. (2016) found that women preferred to receive chemotherapy for early stage breast cancer if they trusted their oncologist's opinion, irrespective of NGS estimates of recurrence risk and likely benefit from chemotherapy.

Challenge 2: NGS testing varies in accuracy and has uncertain effectiveness outcomes

Preference-based research has established the importance of accuracy and clinical utility of diagnostic information.[17,18] In the context of NGS, it has been noted that the evidence needed

to support estimates of accuracy and clinical utility requires significant amounts of data. This is apparent in large-scale sequencing initiatives such as the U.K. 100,000 Genomes Project and the U.S. Precision Medicine Initiative.[19,20] On a smaller scale, targetable biomarkers are increasingly sought retrospectively as part of randomized controlled trials not powered to find an effect. Given individual genomic heterogeneity and the requirement of large amounts of data, significant valuation challenges arise because of NGS outcomes are subject to imprecision around health outcomes (including uncertainty around clinical utility) and prediction error (accuracy), which can lead to disease misclassification.[14,21]

How studies addressed accuracy and uncertain effectiveness outcomes

The impact of accuracy has been included through non-health attributes describing sensitivity, specificity, or reliability. In precision oncology, Najafzadeh et al. (2012) addressed sensitivity through describing the proportion of patients who could be cured by a new medication but did not receive the medication because of inaccurate results. Specificity was the proportion of patients who would not benefit from the new medication but would receive it because of incorrect test results. Buchanan et al. (2016) incorporated test reliability into their DCE, defining the attribute in terms of the number of tests that provide an incorrect result. These studies found that respondents could distinguish between attribute levels describing various levels of accuracy. None of the included studies addressed the potential for imprecision around clinical effectiveness, and this remains an important application of future research.

Challenge 3: NGS has simultaneous multiple and cascading uncertainties

NGS information includes a process of patients simultaneously receiving layers of information. The initial decision to undergo genomic testing carries immediate risk-benefit trade-offs, including for example the risk of adverse effects associated with a biopsy, test accuracy, and the probability of identifying a pathogenic variant.

The challenge is to represent these multiple risks and their interdependencies, termed 'multiple cascading uncertainties' by Marshall et al. (2017). From a choice-theoretic perspective, these streams of sequential information and probabilities can be thought of as endogenous to individuals' choices. This type of endogeneity has been termed 'multiple discreteness'.[22] The nature of these probabilities and their influence on choice are not easily incorporated into standard stated preference methods. In terms of econometric estimation, modeling utility without reference to multiple discreteness may result in inconsistent estimators. If these probabilities are included, appropriately presented, and understood by respondents, the econometric model must take into account the interdependence of the attribute levels and their sequential nature with the possibility of diminishing marginal utility as information is returned at various time-points.[23]

How studies have examined simultaneous multiple and cascading risks

Included studies addressed this challenge by simplifying the complexity of the choice process. Regier et al. (2015) focused solely on the return of SFs by describing penetrance (number of people with a genetic variant who actually get the disease), availability of effective interventions, quality of life, return of carrier status, and cost. They did not take into account the upstream choice of undergoing NGS testing for the primary condition. Instead, they asked respondents to imagine they had been diagnosed with an unspecified disease and that SFs may be found.

Marshall et al. (2017) simplified their decision scenario by decomposing the process into two parts. First, respondents were asked to complete a CV task aimed to understand the value of NGS information for a broad set of uncertain outcomes. This was followed by DCE tasks that aimed to understand if respondents would be willing to act on the information they received. The aim of this approach was to reduce the dimensionality of the problem with the authors concluding that the DCE method alone is limited when inferring more realistic decision-making situations. None of the studies identified approaches to deal with the endogeneity associated with multiple discreteness.

Challenge 4 Downstream health and non-health consequences

Downstream outcomes from NGS are contingent on whether information is returned and acted upon.[4] For a hereditary condition, there are downstream outcomes beyond the patient alone because the healthcare system may fund NGS testing for family members. Additional testing and the concomitant risk-benefit outcomes discussed in the previous section will depend on the patient choosing to notify family members. The choice of the patient can also generate a negative or positive externality. This is because patients' decisions can affect future health and non-health outcomes of family members. From a healthcare system perspective, a negative externality can occur in the context of over-diagnosis if the affected individual consumes unnecessary healthcare, potentially incurring the opportunity cost of displacing health from other patients.

In terms of SF, the downstream benefits of identified conditions with effective treatments can be captured by existing preference-based measures. Findings of VUS are potentially associated with treatable conditions that patients are at risk for in the future, but have the added complexity of

uncertainty surrounding whether the variant causes disease. Importantly, a VUS may never be determined as clinically relevant because the numbers of other patients with the same rare variant who both have NGS and who express the phenotype may never be sufficient to establish causality.[24] Conceptually, this is related to the economic idea of Knightian uncertainty. Proposed by economist Frank Knight,[25] this type of uncertainty arises in scenarios where individuals cannot know all the information they need in order to accurately understand the odds of a particular outcome occurring. The implication of Knightian uncertainty is that the odds of an outcome are incalculable and as such both the immediate and long-term preference-based utility for the outcome is impossible for an individual to calculate. Taking a Bayesian perspective, however, individuals may still attach probabilities to these unknown unknowns.

How studies have incorporated downstream consequences

Marshall et al.'s (2017) approach was to first specify a profile of health problems related to a hypothetical gene variant, and then ask individuals to state a preference between possible downstream medical interventions. These interventions would effectively reduce the risk of health problems arising from the variant but would also carry possible adverse side effects and require out-of-pocket costs. The individual could also choose to undergo a watchful waiting scenario. They found that respondents valued NGS information most if there was a noninvasive medical intervention available to reduce their risk of developing a health problem. Preferences for undergoing a preventative medical intervention were greatly impacted by the probability of adverse side effects. Kupperman et al. (2016) applied time trade-off techniques to elicit preferences for potential prenatal testing outcomes, including the identification of a VUS.

Scenarios involving pregnancy termination in the context of a VUS or having a baby with a VUS received low utility scores.

DISCUSSION

We identified 11 studies estimating the preference-based value of NGS outcomes. We found that authors directly elicited preference-based utility for NGS because off-the-shelf instruments do not adequately account for the breadth or types of NGS outcomes that patients or families may value. This hypothesis was empirically supported in the results of the included studies.

The evidence suggests that ignoring the preference-based value for health and non-health NGS outcomes in economic evaluation may lead to over- or under-investment if a system wants to maximize patients' utility from healthcare services. That is, healthcare systems may over-invest if individuals have disutility for aspects of NGS-generated knowledge and under-invest if they place importance on the NGS knowledge.[27] While such analyses will not replace the use of QALYs as the HTA reference case, we believe demand-side approaches to economic evaluation can be used as additional evidence for decision-makers' consideration.[28]

The majority of the included studies used DCEs to directly elicit preferences. However, given the few preference studies of NGS and a lack of HTA recommendations regarding using DCE to inform resource allocation, a crucial area of research is to outline recommendations on which stated preference methods are appropriate for supporting economic evaluation of NGS. We expect these recommendations will also need to consider important equity issues surrounding the use of metrics other than QALYs. This is a critical issue that is beyond the scope of this study.

The included studies outlined several challenges when eliciting the value of the large amounts of complex information obtained by NGS. We found the solutions to challenges were limited and not comprehensive in approach, and were broadly related to discussions of concepts on what constitutes benefit, descriptions of risk and accuracy, simplifying complex choice tasks, or by sequentially using multiple valuation techniques. While important first steps, these solutions are not unique and there remains scope for a comprehensive solution to valuing NGS outcomes.

CONCLUSION

Researchers are facing challenges when estimating the preference-based value of NGS. We conclude that it is the breadth and complexity of information that makes NGS-guided healthcare a unique valuation case study. Indeed, we identified challenges that are a direct result of the types of information that NGS provides. There remains considerable scope regarding providing comprehensive solutions to these challenges. We highlight the problems of incorporating uncertainty around outcomes, endogeneity of choice, and downstream consequences of NGS testing as areas for needed research.

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FIGURES

Figure 1: Flow chart describing articles identified and evaluated based on inclusion criteria

Figure 2: Tree diagram depicting different preference-based approaches to valuation of NGS

NGS: next-generation sequencing, QALYs: quality-adjusted life years, WTP: willingness to pay, TTO: time trade-off, CV: contingent valuation, DCE: discrete choice experiment, CBA: cost-benefit analysis, CUA: cost-utility analysis, NMB: net monetary benefit