Methods for reducing uncertainty in personalized medicine

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A Dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2013

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Abstract

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Background. Evidence uncertainty and paternalistic practices in genomic medicine lead to suboptimal decision-making circumstances, and may result in unfavorable patient outcomes. Reducing decision uncertainty, combined with a shared (patient and clinician) decision-making approach, is believed to result in better overall treatment decisions that better meet patients' needs and fewer negative consequences. **Objective.** (1) To demonstrate the use of value of information analysis to estimate the societal value and research priority of a trial studying pharmacogenomic-guided antiplatelet selection, and (2) to obtain key stakeholder opinions on the necessity and feasibility of a shared decision tool for whole genome sequencing. **Methods.** Objective (1) was accomplished using an expected value of sample information (EVSI) approach. Objective (2) was accomplished using qualitative analysis of key informant interview transcripts. See additional abstracts for more information. **Results.** (1) Substantial value could be realized by performing a pharmacogenomic clinical trial, although reducing uncertainty in the pharmacogenomic association was less valuable than reducing uncertainty in adverse event outcomes. (2) Genetic services providers were open to shared decision-making tools and would use the tool if validated. **Conclusions.** Decision tools are potentially useful for helping genetics stakeholders assess uncertain evidence thresholds, make policy choices, or facilitate treatment decisions.

OVERALL INTRODUCTION

The ability of decision tools to create order among the chaos of genomic medicine is appealing, and thus began the journey of this dissertation research. Our first project in this field was a quantitative risk-benefit assessment of clopidogrel, a recently off-patent antiplatelet drug pharmacogenomically associated with poor thrombotic outcomes, versus prasugrel, a new antiplatelet drug without a pharmacogenomic association but packing increased bleeding risk, and versus a hypothetical pharmacogenomic strategy, in acute coronary syndrome patients. We found that the pharmacogenomic strategy was preferred in most model simulations, however uncertainty in the optimal strategy remained, and this analysis did not factor costs.

Building from this analysis, we turned our attention to estimating the potential value of conducting a clinical trial, based on a recent failed randomized controlled trial and our previous risk-benefit model. In **Chapter 1**, we used value of information (VOI) methodology to assess the societal benefit a clinical trial would provide by reducing current decision uncertainty regarding the optimal antiplatelet therapy strategy, and we were able to comment on whether the current evidence base is sufficient to more widely implement pre-therapy pharmacogenomic testing or if a future trial would be worth the substantial investment it would require.

We also previously engaged genetics services stakeholders directly to assess their interest in using decision tools to aid their policy decisions. *(1)* An important finding of this study was the concern genetic services stakeholders have regarding multiplex testing strategies. The implications of these concerns were clear: focusing future decision-analytic modeling efforts on single-gene test interventions was seen as inessential, and stakeholders preferred that our efforts be focused on modeling array-based or whole genome sequencing (WGS) technologies. Unfortunately, modeling multiplex genomic testing for multiple disorders is a significant

challenge for which traditional decision-analytic approaches are ill equipped. Nonetheless, it gave us inspiration to draft a novel tool for assessing WGS that involves assigning clinically relevant categories to genomic loci that allow for a shared decision-making-driven, streamlined approach to return of WGS results. We explored the possibility of further research on this idea in **Chapter 2.** In this study, we conducted a qualitative analysis of 14 key informant genetics services providers (3 clinical geneticists, 4 genetic counselors, 2 molecular geneticists, and 5 cytogeneticists) to investigate the impacts of WGS on genetics services practice, the value of shared decision-making for genomic results, and the utility of a hypothetical decision tool to combine the two.

Overall impressions and concluding statements can be found in the final chapter of this dissertation.

Is it worth investing in a prospective randomized trial to inform pharmacogenomic testing guidelines?

CYP2C19 and clopidogrel as a case study

Gregory F. Guzauskas, MSPH

Dissertation Chapter 1

ABSTRACT

BACKGROUND Mounting retrospective evidence suggests *CYP2C19* genotyping of acute coronary syndrome patients to inform therapeutic indication for antiplatelet treatment is an exciting possibility for the future of personalized medicine. The Pharmacogenomics of Anti-Platelet Intervention-2 (PAPI-2) trial was to be the first prospective clinical trial to study this intervention, however it was terminated and thus unable to deliver crucial evidence for making decisive personalized medicine policy. The clinical utility and economic value of the PAPI-2 trial, relative to other proposed research, remains unknown.

OBJECTIVE To demonstrate the use of value of information analysis to estimate the societal value and research priority of a trial studying pharmacogenomic-guided antiplatelet selection.

METHODS We programmed a value of information decision model comparing pharmacogenomic-guided, clopidogrel-only, and prasugrel-only strategies. Clinical, quality-of-life, and cost inputs were derived from key clinical trials of antiplatelet therapies, pharmacogenomic-focused retrospective studies, and other published sources. Model simulations assessed the expected value of the prospective trial and the societal net benefit of reducing uncertainty in key trial estimates.

RESULTS The expected net societal benefit of the PAPI-2 trial was approximately $150 million, representing a seven-fold return on investment. Reducing uncertainty in bleed event risks for clopidogrel had the greatest potential societal value at $60 million, followed by reducing uncertainty in the relative bleed risk for prasugrel patients ($10 million) and thrombotic event risk for reduced-function *CYP2C19* patients treated with clopidogrel ($8 million). A prospective study attempting to collect data on costs, long-term life expectancy, and/or quality-of-life measures did not appear to offer any additional societal value.

CONCLUSION Our analysis suggests a prospective trial for individualized antiplatelet therapy seems justified based on the potential return on investment. However the greatest expected benefit from reducing uncertainty was seen in improving estimates of the clopidogrel-prasugrel bleed risk differential, therefore a pharmacogenomic focus of future research may not be warranted. The trial's expected benefits should be compared to those of other competing research proposals when prioritizing future research funding.

INTRODUCTION

Retrospective pharmacogenomic analyses of antiplatelet clinical trials suggest loss-of-function alleles in the *CYP2C19* gene result in reduced drug efficacy in a subset of clopidogrel patients. *(2-4)* Subsequently, multiple studies from a wide variety of health industry perspectives have indicated support for developing approaches to individualize antiplatelet therapy, wherein clopidogrel plus aspirin remains the preferred treatment for most patients but carriers of loss-of-function alleles could be prescribed a different antiplatelet such as prasugrel. *(3-10)* Despite pervasive awareness of these findings and the large population of cardiovascular disease patients they impact, the current evidence base has been judged insufficient to instigate decisive population-scale recommendations for a pharmacogenomics approach to antiplatelet selection, and additional evidence collection has been cited as a precondition to reevaluating this position. *(11)* The caution exercised by regulatory and professional bodies is likely due to the facts that no randomized prospective clinical trials studying pharmacogenomic-guided therapy exist, *(12)* and the risk-benefit tradeoff of switching a carrier patient from clopidogrel to prasugrel has been shown to be unremarkable due to the increased bleed risk associated with prasugrel. *(9)*

In addition to uncertainty regarding the clinical utility of pharmacogenomic-guided antiplatelet therapy, a number of practical barriers to widespread adoption of the technology also exist. While the assay is currently offered by many Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories, results may take a week or longer to obtain, greatly reducing their usefulness in acute medical settings such as invasive coronary procedures. *(12)* Point-of-care genotyping assays are in development, but are not currently available in most settings and may be prohibitively expensive to implement. *(13)* Other commonly cited obstacles to various pharmacogenomic interventions include a lack of institutional and clinician acceptance, limited

access to genomic medicine expertise, a lack of standardization for assays, inadequate electronic health record integration, obligations to follow-up genotyped patients, issues of informed consent, and lack of assay reimbursement by insurance companies. *(14)*

Furthermore, a prospective clinical trial to study pharmacogenomics-guided therapy may not even be feasible due to the expense, time, and logistical issues necessary for effective implementation in most real-world settings. *(12)* The Pharmacogenomics of Anti-Platelet Intervention-2 (PAPI-2) study may have been subject to these difficulties, and was recently terminated prior to completion. *(15)* The study was to be the first prospective randomized trial comparing a pharmacogenomic-guided strategy versus standard care (clopidogrel or prasugrel selection by clinician discretion), a potentially crucial evidence base for or against pharmacogenomic testing in acute coronary syndrome (ACS) patients who underwent percutaneous coronary intervention (PCI). The study's termination implies that the practical issues incurred by pharmacogenomic interventions are enough to overwhelm even substantial funding awards and high medical community interest, and that additional research may have to be accomplished through other means.

Additional research may be warranted if the current indecision to implement widespread pharmacogenomic testing results in worse health and economic outcomes than could be achieved if new evidence definitively supports pharmacogenomic testing. However, the optimal study method, scale, and monetary investment needed to reach this evidential threshold are uncertain. The key challenge of deciding whether a new pharmacogenomic study is justified is to gauge the study's expected return on investment prior to performing it. As the health care industry gradually acknowledges the limits of research funding resources, research prioritization processes are moving away from various assemblies of expert panels to more scientific processes that quantitatively measure the potential value of a new study. *(16)*

Value of information (VOI) analysis, based on Bayesian decision theory, is an approach increasingly being used to quantify the societal value of future research, and can also be used to identify optimal designs and sample sizes for study data collection. *(17-20)* A VOI analysis is based on a probabilistic decision model that evaluates the scope of uncertainty arising from current data, and estimates the potential societal value a future trial would provide by reducing this uncertainty. Expected value of sample information (EVSI) analysis is a specific VOI method that estimates the value of reducing the opportunity cost a society incurs by withholding or incorrectly making decisions based on insufficient evidence, using different hypothetical study designs and sizes. The estimated value that society stands to gain from making policy decisions based on the additional evidence is then contrasted with the research costs of obtaining the evidence. If the analysis demonstrates that the cost of performing the study is lower than the study's expected value, it suggests that scarce health care resources could justifiably be allocated to a prospective study, and its potential return on investment can be compared to the same metric for other health care interventions for research prioritization purposes.

While a number of decision model studies have attempted to quantify the costs and health outcomes of antiplatelet strategies, none have used VOI methods to assess the societal value of conducting additional research. *(9, 10, 21-25)* The objective of this study was to quantify the EVSI for a future clinical study comparing pharmacogenomic-guided antiplatelet strategy versus standard care strategies. The findings of this analysis can be useful to policy makers by (1) providing an estimate of the societal value that could have been attained by the PAPI-2 trial had it reached completion, (2) identifying key sources of uncertainty arising from current data, to focus future research on the most relevant study outcomes, (3) demonstrating how the study scope, study cost, and useful lifetime of a technology impact the magnitude of expected societal benefits, and (4) assigning a metric (expected net societal benefit, discussed below) that can be

used to compare the proposed pharmacogenomic study versus alternative health care investments when making research prioritization decisions.

METHODS

Overall Approach

We used a VOI analytical approach to assess the expected value of conducting a study of pharmacogenomic-guided antiplatelet therapy. First, we developed a probabilistic decision model based on the PAPI-2 trial to simulate a prospective trial comparing pharmacogenomic-guided antiplatelet therapy versus standard care in ACS patients who have undergone PCI. *(19)* We populated the model inputs with health outcome probabilities, relative risks, quality-of-life estimates, and costs from multiple published sources of current information. The model tracked simulated patients' health outcomes and associated costs for each prospective trial arm, and extrapolated quality-adjusted life years (QALYs) saved over surviving patients' remaining lifetime following the trial. Second, we conducted probabilistic sensitivity analysis to assess the range of uncertainty (95% credible ranges, analogous to 95% confidence intervals in Frequentist statistics) in our estimates arising from parameter uncertainty. Finally, we programmed the model to synthesize current information with 'new' information generated by simulating the addition of new patients, corresponding to a new study.

Model Structure

We used the PAPI-2 design as a basis for our decision model, and directly compared (1) the pharmacogenomic-guided strategy, (2) clopidogrel-only, and (3) prasugrel-only (Figure 1). Patients in the clopidogrel and pharmacogenomic-guided strategies were classified as being either noncarriers or carriers of the reduced-function *CYP2C19* allele, and we assumed no

pharmacogenomic interactions in patients who received prasugrel. *(26)* Carriers in the pharmacogenomic-guided arm were assigned prasugrel therapy. We used a decision tree to model short-term (1-year) health care costs and outcomes, followed by a long-term (40-year) Markov chain to model subsequent health care costs, health outcomes, and quality-adjusted life expectancy for patients who survived the short-term element.

Patients entering the short-term element could experience one of the following: nonfatal MI, nonfatal stroke, stent thrombosis, cardiovascular death, nonfatal bleeding, bleed death, or no event. Short-term element survivors entered the long-term element in one of three health states, depending on their outcomes in the short-term element: pre-event (stent thrombosis, nonfatal bleed, or no event), MI (nonfatal MI), or stroke (nonfatal stroke); the absorbing health state was all-cause death. We assumed stent thrombosis did not occur beyond the first year of stent placement. *(27)* Pre-event patients could transition to the MI or stroke health states by experiencing a nonfatal thrombotic event, or transition to the all-cause death health state due to a fatal thrombotic event or death from other causes. Patients in the MI or stroke health states remained there until they transitioned to all-cause death.

Population

The modeled patient population was reflective of TRITON-TIMI 38 *(28)* and a pharmacogenomic meta-analysis *(29)* that provided the short-term clinical parameter information (described below). In TRITON-TIMI 38 (N=13,608), patients were evenly randomized to clopidogrel or prasugrel. Both populations had PCI in 99% of patients. The pharmacogenomic meta-analysis included 9,685 ACS/PCI patients from 9 studies evaluating *CYP2C19* genotype and thrombotic outcomes. We modeled 3600 patients per study arm in all VOI calculations based on the intended sample size of the PAPI-2 trial.

Clinical Inputs

Clinical parameters are listed in Table 1. We modeled 22% of patients being carriers of a reduced function *CYP2C19* allele according to estimates from a population genetics study. *(30)* Carriers were at significantly higher risk for thrombotic outcomes (cardiovascular death, myocardial infarction, stent thrombosis, or stroke) than were noncarriers. Prasugrel-treated patients were at significantly higher risk for bleed outcomes (nonfatal or fatal). We derived short-term health outcome probabilities for each trial arm using TRITON-TIMI 38 and meta-analysis estimates; noncarrier clopidogrel patient outcomes were used as the basis of calculations and we used hazard ratios to derive outcome probabilities for carrier patients treated with clopidogrel and patients treated with prasugrel. We estimated long-term element survival probabilities using results from the TIMI-22 study and the American Heart Association annual report of heart disease and stroke statistics. *(31, 32)* We assumed that the probabilities for nonfatal and fatal MI or stroke in pre-event patients declined over time, and that all patients who entered the MI or stroke states had an increased risk of all-cause death for a baseline of five years, then returned to a mortality risk similar to pre-event patients. We derived all-cause annual mortality from U.S. life table age- and sex-adjusted mortality rates. *(33)*

Economic Inputs

Quality of life inputs are listed in Table 2. We incorporated preference-based quality-of-life estimates from a 2006 report of EQ-5D utility scores elicited from several thousand respondents to the U.S. Medical Expenditure Panel Survey. *(34)* The default health state score for all patients was chronic ischemic heart disease, and we employed disutilities (quality-of-life decrements) for each thrombotic or bleed outcome patients experienced. We derived our quality-of-life estimate for bleeding from the prasugrel manufacturer's submission to the National Institute for Health and Clinical Excellence and assumed that bleeding affected quality-of-life for

14 days on average. *(35)* Health-state utilities were assessed at the conclusion of the short-term element and for each 1-year long-term increment.

Cost inputs are listed in Table 3. We assumed a pharmacogenomic assay cost of $500 based on a previous decision model of genetic testing for antiplatelet therapy. *(10)* Costs associated with hospitalizations in both the short-term and long-term model elements were assigned a diagnosis-related group (DRG) defined by the United States Medicare program. Costs for each DRG (year 2012) were estimated from average Medicare reimbursement rates obtained from the Medicare Part A data file. *(36)*

We derived our estimate of the prospective trial cost from public records of funding disbursement to the PAPI-2 trial prior to its termination. *(37)* A total of $11.4 million was allocated and $10.8 million was awarded, with approximately 20% defined as indirect study expenses and the remainder defined as direct expenses. Based on this information, we derived a variable per patient trial cost of $1200 based on the total allocated award for the PAPI-2 trial minus 20% budgeted for indirect study costs. Scenario analyses (described in a subsequent section) of different per patient costs were performed to assess this assumption. We assumed a 10-year lifetime for the current technology, and performed scenario analyses (described in a subsequent section) of different time horizons to gauge the effect of this assumption. We assumed 500,000 PCI procedures are performed on ACS patients in the US per year based on estimates by the American Heart Association. *(32)*

Key Assumptions

A number of retrospective pharmacogenomic studies have pointed toward the possible roles of ultra- and intermediate-metabolizer alleles of the *CYP2C19* gene. However, intermediate metabolizer patients have exhibited wide inter-individual variability in platelet response, *(38)* and

a more recent study of ultra-metabolizers suggests a small (if any) effect on clopidogrel-related traits that is most likely due to genetic linkage with the most common reduced-function allele. *(39)* For simplicity, we assumed patients were carriers or noncarriers of this allele. Additionally, we chose to limit trial outcomes to one thrombotic or bleed outcome per patient due to a lack of patient-level data from our clinical sources. In practice, any one patient may experience multiple such events. Lastly, our model included three arms (pharmacogenomic-guided, clopidogrel, prasugrel) versus the two proposed by the PAPI-2 trial (pharmacogenomic-guided, antiplatelet chosen by clinician) to address potential biases of individual clinicians preferring one drug over another and because clopidogrel therapy is considered to be the standard of care in most clinical settings. The cost of conducting the trial is therefore increased by approximately 50% compared to the PAPI-2 study's actual costs.

Model Analysis

We first performed probabilistic sensitivity analysis using Monte Carlo simulation, wherein all model parameters were jointly varied across a range of possible values over 10,000 simulations, to estimate uncertainty arising from current information. Our subsequent VOI analysis was informed by the methodology outlined by Ades et al. and Koerkamp et al. *(18, 20)* This approach uses Bayesian methods and a two-level Monte Carlo sampling simulation to calculate the EVSI for uncertain model parameters. The EVSI calculation algorithm simulates the results of new data arising from the specified sample size, combining current (prior) evidence with simulated (posterior) data. Combining current and simulated data 'shrinks' the uncertainty ranges of parameters, which has the downstream effect of shrinking the uncertainty ranges surrounding the model results. We performed 1 million simulations in each algorithm to ensure statistical convergence.

We adopted a net monetary benefit (NMB) approach to directly compare the health and economic results of each strategy—net benefit calculations apply a monetary value to health outcomes, creating a single, comparable metric that simplifies the trade-off between cost and health impact. NMB is calculated by applying a presumed society's willingness-to-pay (WTP) threshold per QALY saved and subtracting the cost of the strategy (WTP * Total QALYs of Tx – Total Cost of Tx). *(20)* We assumed a societal WTP threshold of $100,000 in all base case analyses, based on recent publications. *(40)* We discounted all costs and QALYs by 3% per year to reflect the present value of future population health benefits. *(41)*

The difference in net benefit between two strategies is the incremental net benefit (INB), and the uncertainty surrounding this estimate is the basis for EVSI calculations. Specifically, the EVSI is the incremental difference between the NMB of a decision made with new sample information and a decision made without it (current information). If the EVSI for a simulated sample size is greater than the expected total cost of conducting a trial of that size, then the expected net benefit of sampling (ENBS) is positive and signifies a good economic value to the society that is willing to pay for it. *(18)* When planning a prospective clinical trial, the optimal sample size based on EVSI calculations is the sample size at which the ENBS reaches its maximum. *(20)*

The primary outcomes were the expected value of conducting a prospective randomized trial and its ENBS to society, and the expected value of reducing uncertainty in thrombotic and bleed inputs. Secondary outcomes were the expected value of partial sample information (EVPSI) for other groups of similar parameters, such as quality-of-life and acute care cost parameters. When estimating the expected value of conducting a prospective randomized trial, we sampled only from the thrombotic and bleed outcome parameters (the primary and secondary outcome measures of the prospective trial). We multiplied the primary and secondary outcomes by the effective population that stands to benefit from the new information—all present and future

ACS/PCI patients spanning the time horizon for the technology—to estimate the ENBS from a societal perspective.

Scenario Analyses and Model Validation

We implemented a number of scenario analyses to test our model assumptions. First, we performed an expected value of perfect information (EVPI) analysis to evaluate the impact of eliminating all uncertainty rather than merely reducing it. This hypothetical value is the value of information that would be achieved with an infinite sample size, thus it represents the maximum value the EVSI could achieve as sample size increases. Second, we estimated the expected value of conducting a hypothetical study that simultaneously collects data on all model parameters including clinical outcomes, costs, long-term survival, and quality-of-life. Third, we tested the impact of reducing the cost of a pharmacogenomic assay from $500 to $100 to explore a scenario in which future assay costs fall due to technological improvement. Fourth, we evaluated our assumption of a 10-year technology time horizon by evaluating the ENBS for 5-year and 15-year time horizons. Finally, we tested additional trial costs per patient to gauge the impact this value has on optimal sample size.

We verified the two-level Monte Carlo sampling algorithm by testing the mean estimates and 95% CRs of NMB and model parameters, before and after sampling. We also performed sensitivity analyses to examine the influence of uncertainties in the model inputs and to judge the robustness of the findings. Single-variable (one-way) sensitivity analyses of INB between strategies were performed with the value of each input varied over the ranges shown in Table 1. Clinical parameter ranges were obtained from reported (when available) and data-derived confidence intervals. All costs were varied by 25%.

RESULTS

The results of probabilistic sensitivity analysis showed that the pharmacogenomic-guided strategy had the highest overall value in 84% of simulations at the base case WTP threshold. Increasing the WTP threshold effectively increased the percentage of simulations that favored the pharmacogenomic strategy, but also increased the value of the remaining uncertainty. Probabilistic sensitivity analysis results for different WTP scenarios are presented in Figure 2.

Value of Conducting a Prospective Randomized Trial

Primary outcome results are presented in Figure 3. The expected value of conducting a trial based on the PAPI-2 design was approximately $150 million at an expected cost of approximately $21 million. The ENBS was therefore $129 million, representing a seven-fold return on investment. Larger trials, which provide more information and thus further reduce uncertainty, had greater expected value. For example, a study with trial arms the same size as the TRITON-TIMI 38 study ($n \approx 6800$) has an expected value of $200 million at an expected trial cost of $38 million, resulting in an ENBS of $162 million.

Value of Research on Thrombotic and Bleed Inputs

The estimated value of reducing uncertainty in trial outcomes was greatest for clopidogrel patient bleed event probabilities, with a combined expected value of $60 million. The expected value of reducing uncertainty in prasugrel bleed risk compared to clopidogrel bleed risk was $10 million, followed by an expected value of $8 million for reducing uncertainty in thrombotic risk for carrier patients treated with clopidogrel. Reducing uncertainty in prasugrel thrombotic event risk had little to no impact.

Reducing uncertainty in health outcome inputs was more valued at lower WTP thresholds than at higher thresholds. This occurred because uncertainty in quality-adjusted life expectancy had greater potential to change the optimal decision strategy when quality-of-life gains were less valued and the expense of the pharmacogenomic assay made it less optimal than standard care. At greater WTP thresholds, the pharmacogenomic-guided strategy's superior health outcomes become more valued and outweigh its associated cost.

Value of Research on Other Model Inputs

Reducing uncertainty in quality-of-life estimates, long-term survival probabilities, and all acute and long-term costs exhibited little to no additional value, indicating the greatest source of model uncertainty and potential value was to be found in the bleed and thrombotic event inputs.

Scenario Analyses

The EVPI was $146 per patient (equal to total opportunity loss) or $344 million for the effective population. Results from the EVPI analysis are presented in Figure 4. EVPI analysis provided estimates of the potential societal value achieved by eliminating all model uncertainty at various WTP thresholds. At lower WTP thresholds, the superior health outcomes of the pharmacogenomic strategy are not highly valued, thus the additional cost associated with this strategy (mostly due to assay cost) means the strategy is suboptimal compared to standard care. As WTP thresholds increase, the value of the pharmacogenomic-guided strategy's superior health outcomes increases, and the value of remaining uncertainty about the optimal strategy reaches a peak at approximately $37,000 WTP. As WTP continues to increase, uncertainty about the optimal strategy decreases, however the value of the diminishing uncertainty continues to increase at a constant rate. The approximate expected value of simultaneously reducing uncertainty in all model parameters was $170 million, or approximately

half the EVPI. By increasing sample size as demonstrated in Figure 3, this value approaches the EVPI.

We observed modest differences in expected value in a scenario with a lowered pharmacogenomic assay cost (Figure 5). The largest impacts of our assumptions were exhibited by the time horizon for the future use of individualized antiplatelet strategies (Figure 6) and the trial cost per patient (Figure 7).

DISCUSSION

We estimated the expected value of conducting a prospective randomized trial comparing a pharmacogenomic-guided antiplatelet strategy to standard care. Similar to previous decision analyses of antiplatelet strategies, differences between antiplatelet drug strategies were modest; *(9, 10, 22)* specifically, reduced thrombotic event risks in patients assigned to prasugrel were mitigated by increased bleed risk. Nonetheless, the expected value of conducting a prospective pharmacogenomic trial of antiplatelet strategies was approximately $150 million, at an expected study cost of approximately $21 million, representing a seven-fold return on investment. The greatest sources of uncertainty and therefore the study outcomes with the highest potential returns on investment were bleed event estimates for clopidogrel patients at $60 million, followed by bleed relative risk estimates for prasugrel at $10 million and thrombotic relative risk estimates for reduced-function *CYP2C19* carriers treated with clopidogrel at $8 million. Our findings also indicate that additional studies of health economic outcomes such as quality of life and costs in antiplatelet treatment strategies have little to no value.

Our analysis thus suggests, from a theoretical perspective, that a prospective trial studying the impact of pharmacogenomic testing may be justified based on the potential return on investment. However, it appears that the greatest source of current uncertainty of whether to recommend a pharmacogenomic-guided antiplatelet strategy is the differential bleed risk between clopidogrel and prasugrel, not the differential in thrombotic risk among reduced-function carrier and noncarrier clopidogrel patients. Taking this and expected study costs into account, it appears that a future trial to reduce uncertainty in the clopidogrel-prasugrel bleed risk differential is justified based on the potential return on investment, but a trial studying pharmacogenomic thrombotic risk differential may not be. If the expected return on investment specific to the pharmacogenomic aspect of the study does not justify the research cost, then we should assume that current information is in fact sufficient to recommend more widespread *CYP2C19* testing prior to antiplatelet treatment initiation.

The substantial body of available retrospective evidence for clinical utility supports this assertion. Furthermore, the considerable difference in drug cost between the recently off-patent clopidogrel and the newer prasugrel will likely impact clinical decisions to treat with prasugrel for years to come. The adoption of a pharmacogenomic strategy to antiplatelet therapy ensures a place at the table for prasugrel, and appears to be offer better overall health outcomes at marginal additional cost to society.

It is important to mention that the *expected* net benefit is a probabilistic average resulting from a mathematical model. The *actual* net benefit of a prospective trial can only be realized once the trial has been conducted, and the trial may come to different conclusions about the optimal strategy. *(42)* If additional research is performed, the expected societal benefit should be compared with the expected societal benefit of other research proposals. If a different study expects a greater potential net societal benefit, then research funding should prioritize it over

the research priorities identified in our study. Other clinical applications of pharmacogenomics include *HLA-B** testing for HIV therapy, one of the most prominent examples to date of pharmacogenomics being integrated into routine medical practice, and *CYP2C9* or *VKORC1* testing to predict Warfarin responsiveness. If the potential return on investment for obtaining additional information on either of these interventions is greater than the expected return we report in our study, then it deserves research-funding prioritization.

Our study has a number of limitations worth noting. First, our results were sensitive to the magnitude of our assumptions about the time horizon of the proposed technology and the per patient cost of the prospective trial. These parameters are difficult to project because future technology or interventions are mostly unknown, and the cost per patient of a clinical trial is largely dependent on where, when, and whom is conducting it. Ultimately, projecting these variables is a necessary process in the assessment of expected net benefit for future research, and care should be taken to consider the significance of scale when comparing alternative research proposals. *(42)* Reduction of pharmacogenomic assay cost did not significantly alter the expected net benefit of performing the trial or the optimal sample size, perhaps underscoring the priority of reducing uncertainty in bleed and thrombotic event inputs.

Second, our model was limited by the simplifying structural and parameter assumptions required to assemble it. Although the two-level Monte Carlo approach we used in EVSI calculations is intended to minimize correlations among model inputs, our use of noncarrier event probabilities as a basis for calculations and published hazard ratios to estimate relative risks for prasugrel and carrier/clopidogrel patients were nonetheless highly dependent on one another and may obscure the true relevance of these estimates to research prioritization. Third, our trial-based clinical inputs came from only three studies, and only one of these was a prospective clinical trial. Although TRITON-TIMI 38 was a large clinical trial and the *CYP2C19*

meta-analysis we used to model the pharmacogenomics of clopidogrel patients analyzed nine pooled populations (>9,500 patients), the incorporation of data from other studies may provide more precise estimates that result in less model uncertainty. Similarly, our long-term model and quality-of-life estimations were informed by a small number of studies.

Fourth, the results of the meta-analysis used in our study to model pharmacogenetic effects did not incorporate data from all the recent trial and meta-analysis data concerning clopidogrel metabolism. Specifically, we did not model so-called ultra- (*CYP2C19* *17/*17) or intermediate- (*CYP2C19* *1/*2, *1/*3) metabolizers; by not including intermediate metabolizers, we may overestimate the benefit of the pharmacogenomic-guided strategy, while adequate evidence for an independent effect of the *17 allele on clinical outcomes is lacking. *(38)* Also of note, patients could only experience one health outcome during the short-term element when in reality patients may experience multiple outcomes within the first year of antiplatelet therapy. Fifth, our analysis is specific to ACS patients who undergo an invasive procedure such as PCI. Previous clinical trials have demonstrated non-ST-segment elevation MI patients who do not undergo revascularization have poorer long-term cardiovascular outcomes than those who do undergo revascularization, but this population has been underrepresented in Pharmacogenomic studies and we have excluded them from this analysis. *(43-47)*

In conclusion we estimate that, from a theoretical perspective, the current decision uncertainty concerning pharmacogenomic testing for ACS/PCI patients receiving antiplatelet therapy justifies the cost of a prospective clinical trial, however the greatest value of future research lies in better understanding of the clopidogrel-prasugrel bleed risk differential. The termination of the PAPI-2 trial exemplifies the difficulty of conducting a pharmacogenomics-focused clinical trial, however our trial simulation indicates that the evidence threshold for pursuing a pharmacogenomic-guided antiplatelet approach may already be met, and these obstacles may not need to be overcome. The results of our analysis should illustrate the need for a clearer

understanding of pharmacogenomic evidence thresholds, funding priorities within pharmacogenomic translational research, and the value (or lack thereof) of pharmacogenomic translational research in relation to investment in other health areas. Formal quantification of the value of genomics translational research in conjunction with stakeholder engagement to guide and make use of these analyses provides an approach to get us out of this quagmire of needing prospective clinical trials without the ability to successfully fund and/or complete all of them.

Table 1. Clinical Inputs. Noncarrier = clopidogrel patents who are noncarriers of CYP2C19 reduced function allele; MI = myocardial infarction; HR = hazard ratio.

NONCARRIER EVENT PROBABILITIES	Base Case	One-Way Sensitivity Range		Distribution	Reference
Nonfatal MI	0.088	0.071	0.105	Beta	3
Nonfatal Stroke	0.006	0.001	0.011	Beta	3
Cardiovascular Death	0.013	0.006	0.020	Beta	3
Stent Thrombosis	0.016	0.009	0.024	Beta	3
Nonfatal Bleed	0.017	0.009	0.025	Beta	3
Bleed Death	0.001	0.000	0.003	Beta	3
HR: PRASUGREL VS. CLOPIDOGREL	**Base Case**	**One-Way Sensitivity Range**		**Distribution**	**Reference**
Nonfatal MI	0.76	0.67	0.85	Log-Normal	27
Nonfatal Stroke	1.02	0.71	1.45	Log-Normal	27
Cardiovascular Death	0.89	0.70	1.12	Log-Normal	27
Stent Thrombosis	0.48	0.36	0.64	Log-Normal	27
Nonfatal Bleed	1.32	1.03	1.68	Log-Normal	27
Bleed Death	4.19	1.58	11.11	Log-Normal	27
HR: CLOP POOR METABOLIZER	**Base Case**	**One-Way Sensitivity Range**		**Distribution**	**Reference**
Nonfatal MI	1.45	1.09	1.92	Log-Normal	28
Nonfatal Stroke	1.73	0.68	4.38	Log-Normal	28
Cardiovascular Death	1.84	1.03	3.28	Log-Normal	28
Stent Thrombosis	2.81	1.81	4.37	Log-Normal	28
Nonfatal Bleed	1.00	0.75	1.25	Log-Normal	28
Bleed Death	1.00	0.75	1.25	Log-Normal	28

Table 2. Quality of Life Inputs. CVD = cardiovascular disease; MI = myocardial infarction

UTILITY MEASURES	Base Case	One-Way Sensitivity Range		Distribution	Reference
CVD	0.79	0.78	0.81	Beta	33
Nonfatal MI Disutility	0.04	0.04	0.0413	Beta	33
Nonfatal Stroke Disutility	0.05	0.05	0.0526	Beta	33
Stent Thrombosis Disutility	0.02	0.02	0.0202	Beta	33
Major Bleed Disutility	0.25	0.19	0.31	Beta	33

Table 3. Cost Inputs. CVD = cardiovascular disease

DRUG THERAPY COSTS	Base Case	One-Way Sensitivity Range		Distribution	Reference
CYP2C19 Testing	$500	$375	$625	Normal	9
Clopidogrel, Annual	$365	$274	$456	Normal	9
Prasugrel, Annual	$2,500	$1,875	$3,125	Normal	9
ACUTE CARE COSTS	**Base Case**	**One-Way Sensitivity Range**		**Distribution**	**Reference**
Myocardial Infarction	$9,075	$6,806	$11,344	Normal	35
Stroke	$8,119	$6,089	$10,149	Normal	35
Cardiovascular Death	$9,451	$7,088	$11,814	Normal	35
Stent Thrombosis	$5,256	$3,942	$6,570	Normal	35
Major Bleed	$7,038	$5,279	$8,798	Normal	35
Bleed Death	$7,414	$5,561	$9,268	Normal	35
LONG-TERM COSTS	**Base Case**	**One-Way Sensitivity Range**		**Distribution**	**Reference**
CVD Pre-Event	$4,550	$3,413	$5,688	Normal	35
CVD Post-MI	$5,688	$4,266	$7,109	Normal	35
CVD Post-Stroke	$7,454	$5,591	$9,318	Normal	35

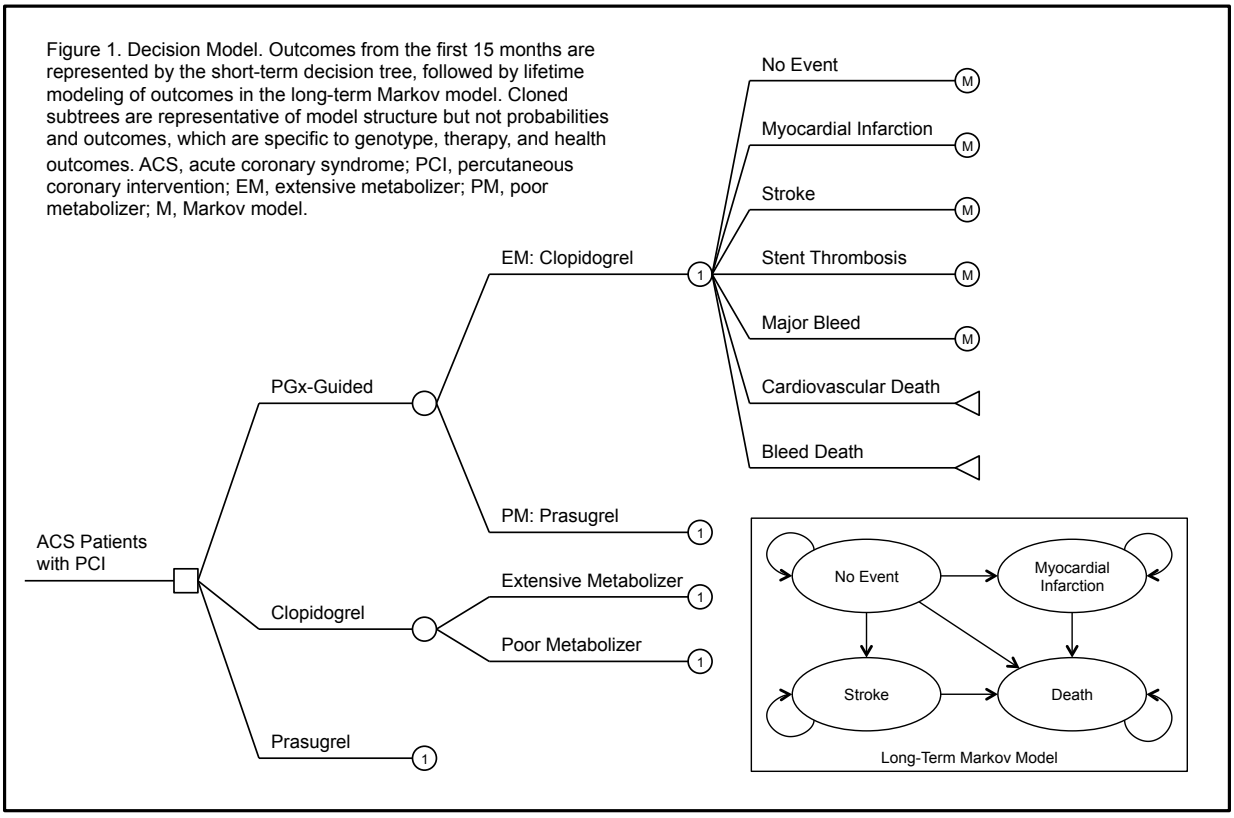


Figure 2. Results of probabilistic sensitivity analysis. The incremental net benefit (INB) for the PGx-guided strategy vs. standard care with 95% uncertainty boundaries, based on 10,000 simulations of patient- level net benefits, across multiple values for the willingness-to-pay threshold (WTP) in US dollars/QALY.

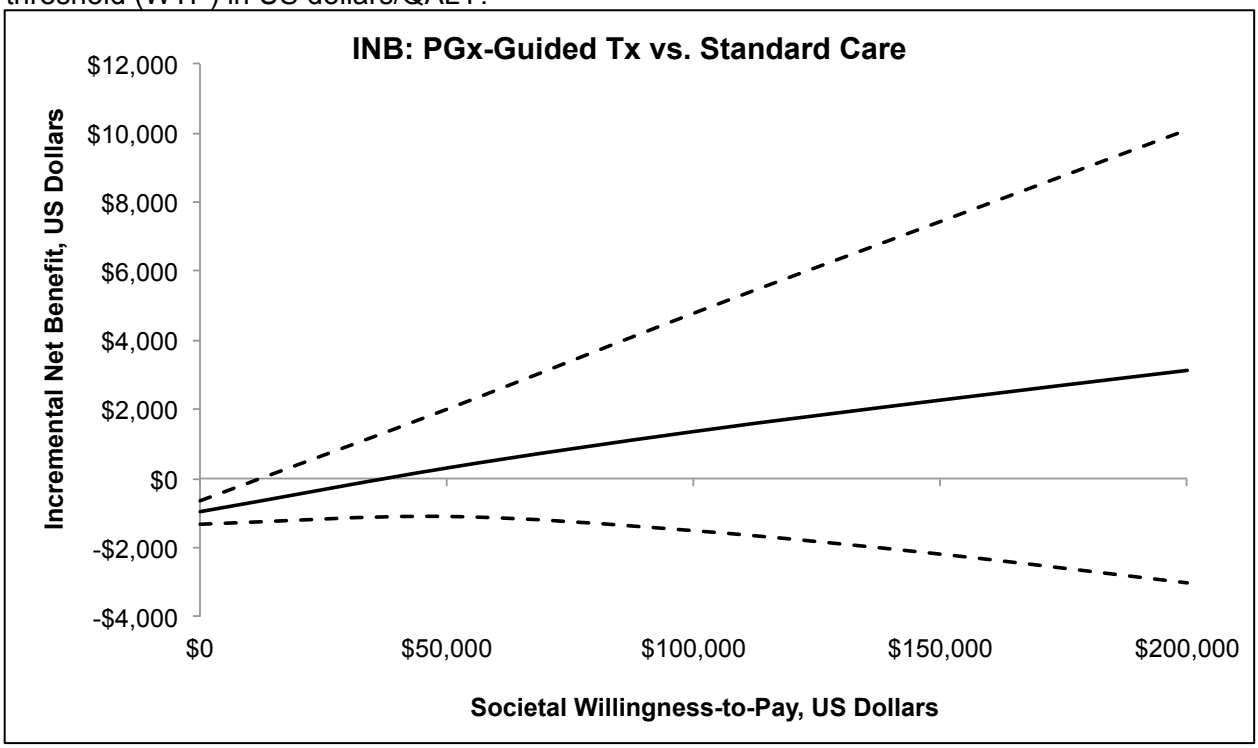


Figure 3. Expected value of a prospective trial studying pharmacogenomic-guided antiplatelet therapy. The proposed study collects data on all thrombotic and bleed event parameters. All values in the graph assume a $100,000 societal willingness to pay (WTP) threshold. Different trial arm sample sizes demonstrate the additional value of more sample information.

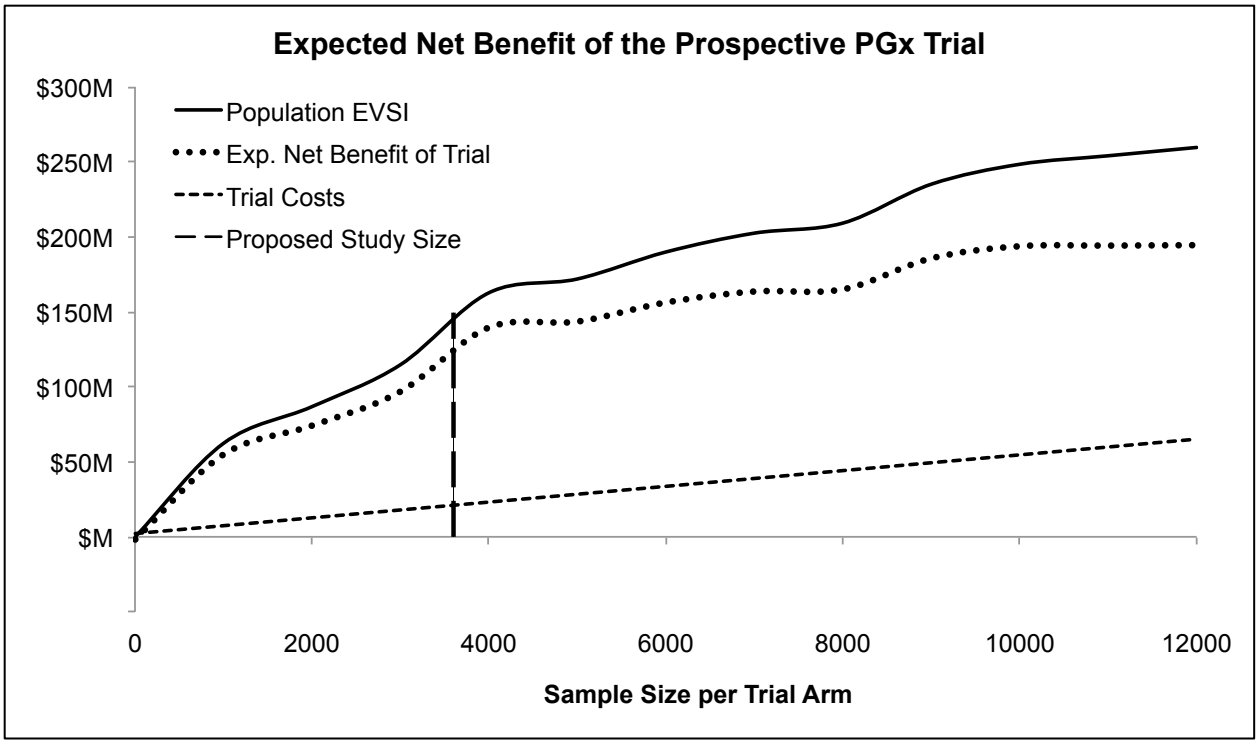


Figure 4. Expected Value of Perfect Information (EVPI). The proposed study collects an infinitely-sized sample, eliminating all uncertainty in model results. The EVPI thus represents a ceiling value for the results of increasing sample sizes in EVSI calculations. At low willingness-to-pay thresholds, the pharmacogenomic-guided strategy's net gain in quality-adjusted life years are not highly valued, thus the greater cost of the strategy makes it less favorable compared to standard care strategies and decision uncertainty (and its value) is low. With increasing WTP, the pharmacogenomic -guided strategy's net gain in quality-adjusted life years is increasingly valuable, and reaches a peak value at the WTP threshold where uncertainty about the optimal strategy among the three is greatest. As WTP continues to increase, uncertainty about the optimal strategy decreases at a diminishing rate, while the value of this decreasing uncertainty increases at a constant rate with each additional dollar of WTP.

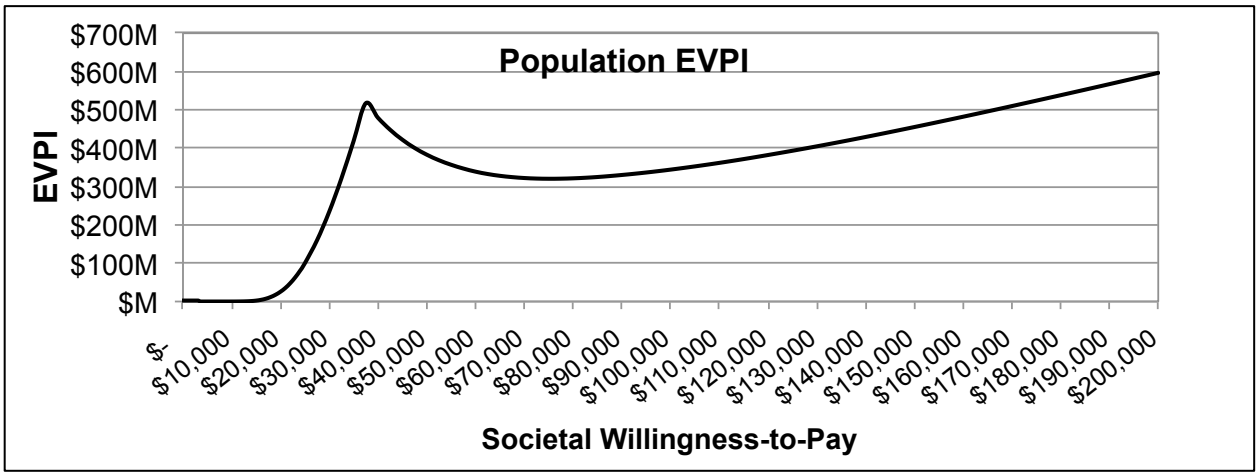


Figure 5. Scenario with reduced pharmacogenomic assay cost. The proposed study collects data on thrombotic and bleed inputs only. Reduced pharmacogenomic assay cost results in decreased trial cost, and reducing uncertainty in trial parameters thus has greater net societal value. All values in the graph assume a $100,000 societal willingness to pay (WTP) threshold. Different trial arm sample sizes demonstrate the additional value of more sample information.

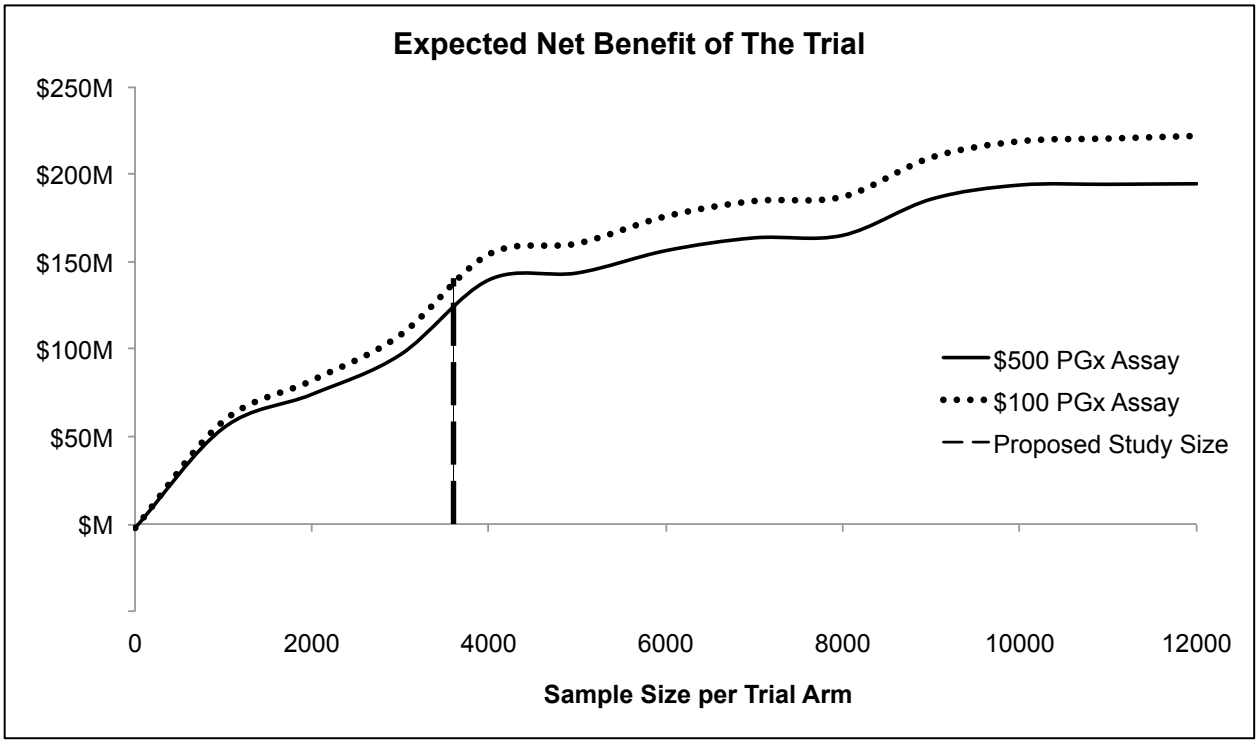


Figure 6. Effect of assumed time horizon for usefulness of technology. The number of years future patients can expect to benefit from the results of the proposed study is uncertain because much depends on unknown improvements in technology and future evidence. The greater the time horizon, the greater the number of patients who can expect to benefit, thus the greater the expected net benefit for society. All values in the graph assume a $100,000 societal willingness to pay (WTP) threshold. Different trial arm sample sizes demonstrate the additional value of more sample information.

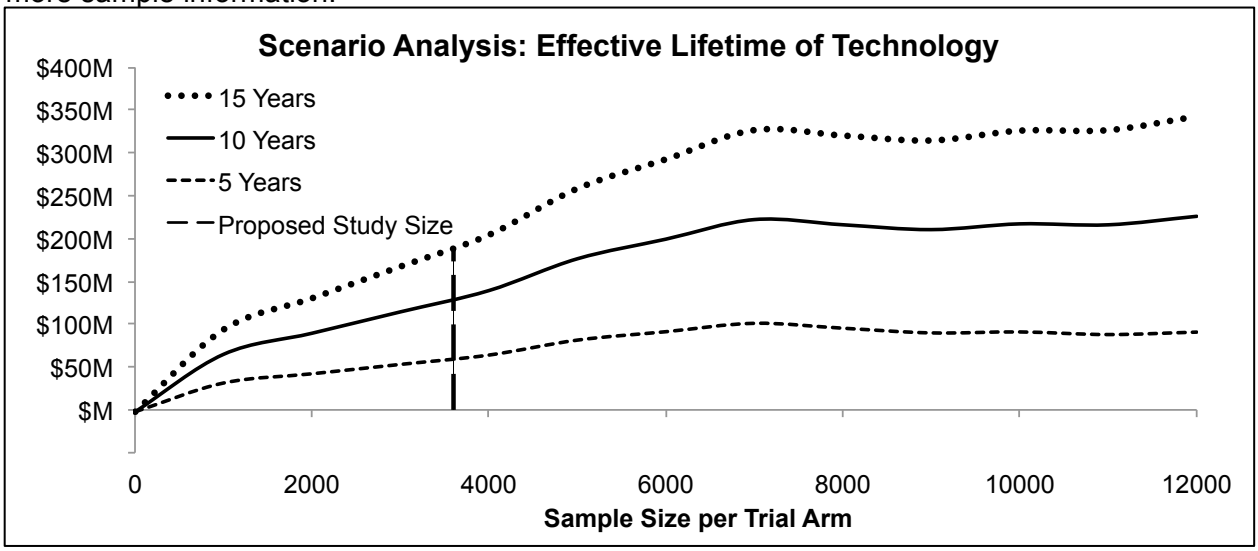
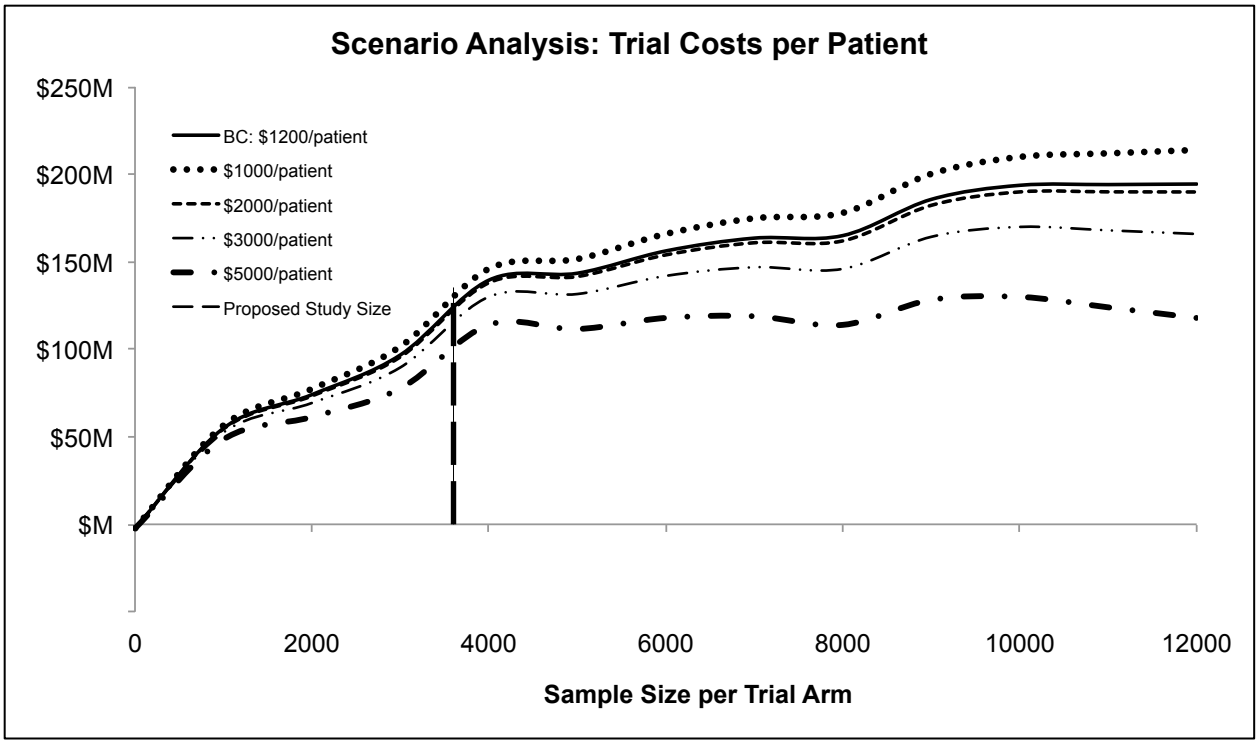


Figure 7. Effect of trial cost per patient. As study costs per patient increases, total trial costs increase such that the expected net benefit of sampling decreases. All values in the graph assume a $100,000 societal willingness to pay (WTP) threshold. Different trial arm sample sizes demonstrate the additional value of more sample information.



Utility of Shared Decision-Making When Returning Whole Genome Sequencing Results: A Directed Content Analysis of Key Informant Responses

Gregory F. Guzauskas, MSPH

Dissertation Chapter 2

ABSTRACT

BACKGROUND Current guidelines advise against considering patient preferences when making decisions about whole genome sequencing return of results. The rationale for this position derives from the enormous practical challenges and clinical and ethical uncertainties that arise from granting patients access to personal data with implications that have long been considered problematic by genetic experts. Concurrently, national emphasis on implementing shared decision-making frameworks in other areas of healthcare is increasing. The utility of a decision tool for facilitating shared whole genome sequencing decision-making between genetics providers and patients is unknown.

OBJECTIVE To obtain key stakeholder opinions on the necessity and feasibility of a shared decision tool for whole genome sequencing.

METHODS We conducted semi-structured interviews with 14 key informant genetics services providers (3 clinical geneticists, 4 genetic counselors, 2 molecular geneticists, and 5 cytogeneticists) to investigate the impacts of whole genome sequencing on future healthcare practices, the value of shared decision-making for genomic results, and the utility of a hypothetical decision tool to combine the two. Interviews were analyzed qualitatively using directed content analysis.

RESULTS Participants expressed reservations about implementing whole genome sequencing on a broader scale, though felt it was inevitable. Participants were uniformly in favor of utilizing patient preferences in shared decision-making frameworks, however their opinions were closely tied to the need to preserve a human element to provider-patient interactions, the need for comprehensive evidence aggregation, and a desire to acknowledge the importance of expert opinion in certain situations. When considering the use of a decision tool to link shared decision-making to whole genome sequencing results, participants felt that any tool that enhanced or eased their professional experience was favorable, provided it was valid, beneficial to the patient, and it addressed their previously stated concerns.

CONCLUSION Genetic services providers are open to considering patients' preferences for the types of genomic results they receive. Development of shared decision tools for this purpose appear to be warranted.

INTRODUCTION

Primary healthcare services are increasingly expected to integrate whole genome sequencing (WGS) technology into patient care. This 'trickle down' in genomic medicine scope is primarily driven by an ever-expanding knowledge base of the genomic foundations of common diseases and the ever-decreasing logistical and cost barriers to performing genomic testing. *(14, 48, 49)* Despite the exciting promise WGS holds for 'personalized' medicine, the extraordinary analytical burden and ethical dilemmas that accompany it have driven the genomics community to largely adopt a paternalistic approach to deciding which results should be reported to patients in current healthcare settings. *(50, 51)* Additional reasons cited for regulating the return of genomic results include: (1) the duty to prevent harm in instances of high disease penetrance and available treatment, (2) low clinical utility in knowledge of slightly elevated disease risks, (3) patients' lack of genetics expertise and/or understanding of risk estimation, (4) clinical skepticism that genetic information promotes healthier lifestyles, and (5) uncertainty about the validity of many genetic associations with disease. *(14, 50-52)* These recommendations acknowledge an intrusion on bioethical standards such as patient autonomy and shared decision-making; *(53-56)* regardless, the ultimate decision by genomics professional organizations is to err on the side of practicality and expert clinical judgment in the face of unprecedented change.

However, an expert-driven approach to the return of WGS results may fall short in realizing the potential clinical utility of taking a more holistic approach to valuing the attributes of genomic testing results. The Institute of Medicine defines shared decision-making as "care that is respectful of and responsive to individual patient preferences, needs, and values" and that ensures "that patient values guide all clinical decisions." *(57)* Since this concept began emerging over a decade ago, shared decision-making has become one of the fundamental approaches to improving the quality of U.S. health care, *(58-63)* though its application to

genomics is problematic. In particular, shared decision-making is best applied in decisions involving an appreciable trade-off of benefit versus risk, *(61)* and the implications of genomic information can range from clinically irrelevant to life-altering. In these circumstances, genetic services professionals are justifiably wary of the workload and potential harm associated with discussing marginally important genetic information or relinquishing their duty to warn patients of imminent danger. *(51)* Nonetheless, a compelling argument can be made for patients' rights to know the contents of their own DNA and have input on clinical decisions stemming from this information.

A novel approach to incorporating shared decision-making into genomic medicine may be the use of decision tools. *(1)* Numerous studies have demonstrated how the use of a computer-based decision aid has a significant impact on how patients perceive and retain complex information in healthcare settings. *(64-68)* If implemented effectively, a decision aid can maximize patient comprehension by presenting difficult concepts in engaging ways, allowing users to obtain information at their own pace and to review material as needed. *(67)* If implemented ineffectively, the patient receives little to no benefit and the healthcare provider's limited consultation time may be needlessly extended. *(69)* Though face-to-face interaction with a clinician or genetic counselor should remain an essential aspect of genetic medicine, a readily accessible decision aid for patients may lessen the "information overload" that sometimes occurs during counseling. *(67)*

We are in the process of developing a platform to facilitate the synthesis of patient preferences for genomic testing results with clinical and policymaker expert opinion. Widespread support of the platform by genetic services professionals, the intended end users, is crucial to implementation. A practical path to gaining this support is to embrace the insights of a representative group of genetic services professionals and invite them to participate in the

development process. To obtain these insights, we sought to apply a formal approach to eliciting these representatives' attitudes and opinions pertaining to the usefulness and feasibility of our goal.

The primary objective of this study was to gauge genetic services professionals' opinions and attitudes toward the need for a computer-based decision tool integrating a shared decision-making approach to return of genomic results. We sought to generate important insights and concepts from anticipated end users of our platform, to clarify potential demand for its services, highlight necessary improvements in design, and foster shared interest among end users and their peers in achieving real-world implementation.

METHODS

We utilized a key informant interview approach to collect the perspectives of a representative stakeholder group of genetics services professionals. Key informant interviewing is a formalized qualitative method for studying agents of a community who are in a position to know the community as a whole, and provides specific insight on the nature of a particular problem as well as informed recommendations for solutions. *(70)* We initially collected a convenience sample *(71)* of individuals from the University of Washington and from a US-based laboratory corporation through a known contact. Initial participants were asked to recommend colleagues for study participation. Candidate participants had advanced graduate degrees and included clinical geneticists, genetic counselors, molecular geneticists, and cytogeneticists. Our study received University of Washington institutional review board approval, and we obtained verbal informed consent from each study participant.

We previously presented an overview of decision-analytic modeling to members of the Western States Genetic Services Collaborative Reimbursement Work Group and state Medicaid representatives and conducted directed content analysis and an anonymous survey to gauge their attitudes toward decision-analytic modeling. *(1)* Based on this prior research, we identified key concepts of interest concerning WGS and shared decision-making. *(72)* The topics we wished to further explore included (1) the current and future use of WGS, (2) shared decision-making, and (3) usefulness and suggested features of a decision tool for aiding shared decision-making following WGS. Next, we developed these concepts into a semi-structured interview guide (Table 2) to facilitate key informant interviews. One investigator (GFG) conducted (via telephone), digitally recorded, and transcribed all in-person interviews. Interviews typically lasted 40–60 minutes. Participants were asked a set of open-ended questions to elicit detailed descriptions of their experiences with the subject matter.

We analyzed interview transcripts using a directed content analysis approach, in which we used the key concepts of interest identified from previous research findings to classify thematic phrases arising from these concepts. *(73)* A directed approach to content analysis allows existing theory to be supported and extended; as research and comprehension in an area grows, the directed approach builds on past conceptions to more explicitly study a phenomenon. *(73)* We uploaded transcribed interviews into Dedoose, an online software program for qualitative data analysis. We used an iterative process to identify themes and develop a coding scheme.

RESULTS

Participant characteristics are summarized in Table 1. We interviewed a total of fifteen genetics services providers and excluded one due to a personal request to withdraw from the study. The

fourteen remaining participants consisted of three clinical geneticists, four genetic counselors, two molecular geneticists, and five cytogeneticists. Half of participants were over the age of 50, three were male, and nine worked for privately owned companies. Clinical geneticists and genetic counselors reported direct contact with patients, whereas molecular and cytogeneticists generally reported genetic testing results to ordering physicians or other go-betweens.

We present qualitative results ordered according to the overall themes targeted for directed content analysis: (1) current and future states of the field of genetics/genomics, (2) shared decision-making, and (3) usefulness and suggested features of a decision tool for aiding shared decision-making following WGS. Statements illustrating each theme, as well as sub-themes identified during our analysis, are presented in Table 2.

Current and Future States of the Field

When participants were asked what they thought would be the biggest challenges on the horizon for genetics services, most began by discussing the complexity involved in genomic analysis, and their belief that the complexity would progressively increase over time. In addition, the majority of participants who dealt directly with patients (primarily clinical geneticists and genetic counselors) felt the limited amount of face time they were allotted per patient was insufficient to properly explain complex genetic results and their implications; for example:

> *I think that some of the technology out there is very complex. It's even hard for me to understand some of this technology and I work in the field. I think that the real communication to the patients from somebody that knows how to communicate these kinds of complex concepts to patients is really going to be the key to making sure the*

patients understand. Because a lot of times, that's not something that takes 15 minutes from a general practitioner or even an internist. It takes a lot of time and a lot of information and a lot of going back and forth between questions from the patient, and time to have them understand really what the testing is all about, what information they can get, and what they can do with that information. (CY-3)

There's such depth of education and understanding to knowing exactly what genomic testing does, what it can't do, and what the results could mean, that there's just no way to get that level of education and understanding to 99.9% of the population. People who don't have a degree in this are just not going to know some of the background. It's impossible to teach all of that in one or two or even three long counseling sessions. (CG-2)

When discussing the transition of genetic services to a more genomics-oriented practice, most participants believed the transition was inevitable. When thinking about how the transition would actually play out, participant attitudes were mixed. One cytogeneticist invoked her/his experience with adapting to past changes in genetic services practices: "*We've had these transitions before. I guess I don't see it as any big jump. It's not any different than when we jumped to arrays. It's just trying to make a complex subject easy enough for the physician so they should be able to communicate it to the patient."* (CY-4) Most other participants were wary of the transition. In particular, two-thirds of participants expressed to varying degrees their concerns regarding the potential volume of information and the resources that would be required to analyze it. For example:

I think many people find it very exciting, with the potential for a lot of helpful information for patients and physicians. I don't see it that way. I see it as a mess. I look at it from the

perspective of 'how are the laboratories going to be able to generate all of this information, manage it, and give it interpretation that people can use? (MG-1)

We had [a patient's test results] the other day that had about 200 genes, one of which we thought was something we should talk about. Something like 212 annotated genes. The counselors walked themselves down the list and they thought we really should talk about each of them. So it makes you crazy because there's too much stuff. And of course the next generation will make it crazier. (CG-1)

Responses to the question of whether or not WGS would ever become a routine part of more generalized healthcare were wide-ranging. Participants aged 50 or older were more likely to express skepticism about the likelihood of WGS making large inroads into primary care. This age group was also more likely than those under 50 to voice concerns about the volume and complexity of genomic results. One participant was highly skeptical of WGS ever playing a large role: "*You get a family history of one person with say, cancer, and then boom get a genetic result that changes the outcome. I think those types of things are going to translate relatively quickly to the front line. But I think other things are going to be not so important. People still get colds and diabetes and asthma, and I think it's unrealistic, it's a university-centric view of the world to think that what's happening on the pages of the New England Journal is what's happening in the clinic."* (CG-3) However, the remainder largely agreed WGS would eventually be utilized in primary care settings: *I think no matter how much you try and hide from it, it's coming. I think it will be hard for primary care. I know a lot of patients are doing their own research on genetics and they're bringing it to their primary care physicians, and a lot of primary care physicians are going to have a hard time dealing with it. Whether they like it or not.* (GC-1)

One genetic counselor suggested her/his profession would become more specialized as

genomic medicine entered primary care: *“I think it will. I think it will become a part of primary care and become part of the medical record. There are different models for genetic services delivery. So a genetic counselor will sit in the neurology clinic, or another genetic counselor will sit in the cardiology clinic, so a patient doesn't have to be referred to an overall genetic counselor.”* (GC-2)

Of note, half of participants from different specialties spontaneously expressed concern regarding the clinical utility of integrating genomics into primary care. Commonly cited themes included evidence thresholds and a lack of treatment options, among others. For instance one cytogeneticist discussed the value of risk adjustment for common diseases: “*If they feel they needed it, but sometimes that's kind of confusing. What kind of testing do you order, you know in terms of genetics? It's not like something that's definite, and you need to deal with that information. Some of the genetic information you get will just adjust the risk, it doesn't say you're going to get that disease. Sometimes it will just say that you are at risk for getting that disease. For folks to understand risk is a difficult concept.”* (CY-3)

Shared Decision-Making

Participants favored shared decision-making, though with caveats. The most frequently cited reason across specialties was a perceived lack of basic genetics education among patients. Possibly related to this sentiment was a hesitancy to relinquish control over access to more esoteric genomic results, such as incidental findings or variants of uncertain significance. These perspectives are represented in the following statements:

I would say yes they should. I'm hesitating though. I think the hesitation is more just

because patients aren't often educated. That doesn't mean that they are not capable of making decisions regarding themselves, it's just that how well-informed is their decision? (CY-1)

Yes and no. I can't answer that without a lot of caveats. It depends on what I perceive my patient's level of comprehension to be. Probably in all honesty if I felt extremely strongly about something, my patient's opinion would count for very little, if I didn't feel very strongly about it probably it would account for a lot. I think that's a situational response not a global response. (CG-3)

When we asked participants to specify the proper balance between expert and patient in a shared decision-making framework, five participants asserted that a patient's preferences were more important than the provider's expert judgment. The remainder of participants reiterated their misgivings about giving patients too much control over information they were not able to understand. Genetic counselors in particular stressed their non-directive approach: "*I think that patients should have a bigger portion as long as you feel like they have a complete understanding of what it is that they are making a decision about. It's your responsibility as the counselor to make sure they actually understand the decisions they are making. I think patients definitely are important. It's their information and they're the ones making the ultimate decisions. It's our job to make sure they understand why we would want them to have the information that we think is important."* (GC-3)

Most participants who expressed misgivings about patients having too much autonomy discussed the role of clinical expertise. One participant implied that expert opinions are fairly standardized across the field, whereas even an individual patient's preferences can demonstrate considerable variation: "*Hopefully everyone is respecting the patient's wishes, but*

I'm sure there are times when physicians will still feel it is in their best interests to go against the patient's wishes. I don't know if that's good or bad, but expertise goes a long way too. Also, preferences change over time, and not even long periods of time but short periods." (MG-1)
Another participant noted that in today's culture of patient empowerment and the internet, a patient who is driven to learn the information a provider is hesitant to provide can successfully obtain it: *"I've certainly seen patients that go off on their own and do their own research and are fairly sophisticated at tracking down people they want to talk to. Most patients I'm guessing aren't that sophisticated and they either take what they get or they go find somebody else that will do what they want."* (CY-4)

Usefulness and Suggested Features of a Decision Tool

Participants were generally in favor of using a decision tool to facilitate shared decision-making with patients. Frequently cited reasons to support a future tool included the increasing complexity and scope of genomic information, a lack of adequate resources and time for analysis per patient, rapid changes in the current genomics knowledge base, increased patient interest in genetic information, and a broad sense that any additional service that made their jobs easier would be welcome so long as it worked. Regarding their characterization of the tool 'working', participants used descriptors such as 'transparency', 'validity', and 'easy to use'. Participants thought a visual component for the patient would be a valuable addition.

Participants mentioned evidence (published literature, online databases, clinical guidelines, etc.) aggregation in a unified interface among the components they would like to see in an eventual decision tool. Most of these participants were thinking this would be of most benefit to their practice, however one participant saw potential benefits of evidence aggregation to patients: *"I think it should include links or access to other resources. If they want to go above and beyond*

just reading the report, they can explore further for more information in the application rather than having to Google it on their own. Have something point them in the right direction. But also be able to communicate directly with the provider, whether a provider or genetics professional, to ask direct questions about things." (GC-1) Another participant thought access to evidence should be differentiated between provider and patient: *"I think they should differ if they're going to deliver the results directly to the patient or deliver the results directly to the physician, because the level of comprehension could be different. They should be customized for the physician or for the patient."* (MG-2) Most agreed that the growing evidence base for the multitude of genomic associations with disease was too much for any one provider to handle: "*That would be good particularly as all of this gets more complicated, because one person cannot possibly really have a handle on every correlating factor. And this new data is coming out, what was right last week can be wrong this week. So you really need rapid updates of present knowledge. As well as a broad-based tool that can bring in new whole genome correlations."* (CY-5)

One genetic counselor thought the greatest benefit of the tool would be enabling patients to be more authentic about their wishes and expectations: *"I think that if this tool would enable a patient to answer questions about what's happening, it helps them be better in their decision-making, because I think when you're speaking with patients sometimes they really… when they're talking to you they may not always be so honest about how they feel about things. Whereas if they're answering questions, then it might be that they answer questions in a way that makes them more honest about how they actually approach things. And then set that up prior to counseling sessions and then be able to show them how they might handle things based on the questions. That might actually be more helpful in utilizing that information concerning counseling sessions."* (GC-4)

Another participant, when considering the primary care future of WGS and what to do with common disease risk findings, felt that the tool needed to do a good job of describing what a particular risk meant to a particular patient and in a way they would understand: *“Even basic risk if that's what the patient actually needs… risk assessment, to have an app that they know what kind of risk they take when they go out and drive down the road, you'll have a risk similar to the risk that we're talking about with this abnormality that they have in their sequence.”* (CY-3)

When we asked participants whether they or their colleagues would actually use a decision tool like the one they were asked to imagine, twelve of the fourteen agreed they would. However, a number of participants were vocal about the need for actual provider-patient interaction and were cautious to state that this process cannot be reduced to something as simple as a computer algorithm: *“If it could do all of that then yes. You would probably want to make sure the patients didn't feel that the whole system was robotic. There should certainly be a person who they get to speak with, a person to shake their hand and meet them and sit down with them in the clinic and get to know that there is a person behind all of that.*” (CG-2) Furthermore, one participant was worried that a computational approach to return of results would lead some providers and/or clinicians to overly rely on the decision tool rather than cultivate their own command of the genomic knowledge base: *“I can think of colleagues who would use this tool for evil and not good. They would use this to pump up their own power.”* (CY-2)

Finally, participants were evenly divided about whether the incorporation of patient preferences for shared decision-making would make the tool more or less valid. For example: *“…it would be wrong for that communication to not happen and those patients’ preferences to not be heard. Because then you end up discussing what they never wanted. So preferences would make me trust it more.* (CG-2) A participant with the opposite view stated: *“Is this a tool that gives me the individual patient's preferences coupled with global provider's expertise? Or average patients? I*

don't know. I think if it has that particular patient's preferences, and somehow there was something that could… You know I don't know the answer to that. In general I don't trust anybody else's opinion but my own. I'm leery of experts, and I don't know the answer." (CG-3)

DISCUSSION

We elicited genetics services providers' perspectives on the impact of WGS technology and their ideas for a platform to return WGS information to patients using a shared decision-making tool. In general, the providers we interviewed expressed reservations about the practicality and clinical utility of WGS in primary care, though admitted that its use was likely inevitable. Taking note of this, participants felt that any tool that enhanced or eased their professional experience and was beneficial to patients was favorable. However, many tethered their favorable opinions to the implementation and components of the decision tool, frequently stipulating the need to preserve a human element to provider-patient interactions, the need for comprehensive evidence aggregation, and a desire to acknowledge the importance of expert opinion in certain situations. Participants were largely in favor of utilizing patient preferences.

Our findings imply that recent recommendations by the American College of Medical Genetics and Genomics (ACMG) *(50)* to exclude patient preferences from decisions to return incidental finding results does not necessarily reflect the views of all of its members. While the practicalities of incorporating patient preferences into these decisions are doubtless easier to overcome when discussing hypothetical scenarios, our participants nonetheless stated that patients' opinions should matter. Furthermore, participants' frequent referrals to the 'education gap' more often than not preceded personal anecdotes about what providers did to improve patient understanding of genetic results, indicating a desire to empower patients to make

informed decisions. Further research of stakeholder attitudes and opinions about shared decision-making in the context of WGS, utilizing a broader array of genetics services stakeholders including policymakers and healthcare payers, may be warranted. Such research would provide a more complete picture of what stakeholders want to achieve with primary care WGS versus what can realistically be achieved, and enable new discussions about the tradeoffs various stakeholders are willing to make for a positive impact on society.

We found that genetics services providers work in a challenging environment and are wary of the changes they face in their field. In particular, the large potential volume of WGS data and the perceived difficulty of interpreting it present challenges that individual providers feel unprepared to meet. Additionally, they are open to new methods for dealing with these problems. Furthermore, we assume that providers and patients have by now passed a supposed threshold of computer literacy, and that both parties are accustomed to the use of computers to aggregate and analyze complex information. In view of these observations, we infer that structured decision processes for aggregating and interpreting genomic information could be useful, widely accepted solutions to the difficult problems presented by the genomic age. Further research into adapting decision-analytic approaches to return of genomic results is currently underway. *(1, 51)*

Our analysis had several limitations. Our study was exploratory in nature and should not be considered representative of genetics services providers as a whole. Participants largely hailed from two geographical regions, although the recommendations for other participants broadened the scope of the study's generalizability. However, generalizability is not an inherent aim of qualitative research; rather, specificity of the views of this study's participants is the ultimate goal. A more quantitative approach using surveys or discreet choice experiments in a larger sample of participants would be better at assessing the representativeness of our findings.

Secondarily, the lead researcher conducted all aspects of the study; therefore our results and interpretation are highly sensitive to the lead researcher's inherent biases in how participants were questioned and how participants' statements were understood. Additional qualitative data coders may have reduced coding bias, however a content analysis study should be considered subjective in nature, thus additional data coders may have provided additional insights but not necessarily reduced subjectivity.

In conclusion, we found that contrary to recent ACMG recommendations, genetic services providers are open to considering patients' preferences for the types of genomic results they receive. The providers are open to solutions to reducing the complexity and uncertainty of integrating WGS into primary care, and shared decision-making tools may be an acceptable approach to these problems. We recommend further consideration of the role patient preferences can potentially play in making WGS technology a positive strategy for improving health outcomes in a manner that satisfies both sides of the provider-patient relationship.

Table 1. Participant Summary

	n	%
Specialty		
Clinical Geneticist (CG)	3	21%
Genetic Counselor (GC)	4	29%
Molecular Geneticist (MG)	2	14%
Cytogeneticist (CY)	5	36%
Gender		
Female	11	79%
Male	3	21%
Age		
Under 50	7	50%
Over 50	7	50%
Employment		
Corporate Employment	9	64%
University Employment	5	36%
Direct Patient Interaction		
Yes	7	50%
No	7	50%

Table 2. Codebook: Themes and illustrative statements pertaining to providers' perspectives of WGS in primary care, shared decision-making, and decision tools.

Theme	Example Statement
Current and Future States of the Field	
Conversations with Patients	
Standard Practices	Usually it's a clinical setting in which the individual is fully disclosed that is not an exam, it's more of a consultative situation, so there's not so much a disempowering situation for the patient. And then we tell them what the results are, what they need, what the limitations are, and if we want to do further testing. (CG-3)
Relay Information	Usually the genetic testing, I'm either talking directly to the ordering physician or occasionally the pathologist who is the intermediate between myself and the ordering physician. The third one would probably be the genetic counselors, so trying to explain what testing would be useful to those three groups. Very rarely do we talk to the patients. (CY-4)
Difficult Information to Explain	I can tell you most of the talks I have with physicians, they're wanting to know - are they interpreting results properly, is there anything further they can do? I'm just thinking how recently I had a conversation with a physician who tested two brothers and we were asked to search for candidate genes for recessive disorders. The list that was generated was sent to the physician, and he wasn't quite sure what he was supposed to do with it. So I had to walk him through that. (CY-1)

Theme	Example Statement
Future Challenges in Genetic Services	
Education Gap	I think that the biggest challenge we face is that people are not educated. They come in and it's part of our job to educate them. So it's a challenge. I think time is a constraint, depending on how much they know coming in it can take longer than expected to go through what it is that we're going to be testing for. We are offering them more and more panel type tests and we have less time to really explain what it is the test is looking for and what the mutations are. (GC-3)
Resource Scarcity	I do think that the challenge is going to be to cover the cost of some of the more expensive testing. For conditions such as miscarriage where that expensive testing, medical dollars should be spent elsewhere. (CY-2)
Complexity	The complexity is the most difficult challenge. The more recent generations of testing. There are so many more possible outcomes, where it used to be fewer possibilities. Of course it wasn't ever terribly simple. (CG-1)
Misconceptions	I think people have preconceived ideas sometimes of what genetic testing is, and we're trained to explain it in a way that makes sense to them. People have ideas about what genetics does, and it's really not what they think it is. So that makes it difficult when you explain it to people. (GC-4)

Theme	Example Statement
Science Dynamism	I also think the ever-changing technology and the new testing options keep changing, and it becomes difficult for everybody to understand new information all the time and what the different options are. (GC-4)
Security Concerns	You've got with regard to generating that data, the sheer amounts of data that have to be stored somewhere. And secured. So there are IT issues, security issues, my goodness it's a lot to deal with. (CY-1)
Volume of Data	For the everyday physician and even the everyday OB/GYN and even some of the maternal fetal medicine doctors that are out there, who have been in the field of genetics for many years, it is just a lot of information to give to patients. (CY-3)
WGS and Primary Care	
Care vs. Information	If they feel they needed it, but sometimes that's kind of confusing. What kind of testing do you order, you know in terms of genetics? It's not like something that's definite, and you need to deal with that information. Some of the genetic information you get will just adjust the risk, it doesn't say you're going to get that disease. (CY-3)
No Won't Happen	I think it's unrealistic, it's a university-centric view of the world to think that what's happening on the pages of the New England Journal is what's happening in the clinic. (CG-3)

Theme	Example Statement
Yes Will Happen	It probably will if costs go down. At this point I still see it being a little bit cost prohibitive. But it is very quickly moving to the point where it may no longer be. I was talking to a newborn screening director, and even newborn screening people feel that in 50 years, newborn screening is probably going to be obsolete because they think that everything is moving towards genomic testing. So literally everyone will be getting this from birth. That's the way some people see it going. (MG-1)
Skepticism for Implementation	As far as primary care, I tend to think about it within the realm of pediatricians not so much in the realm of internists. But you could still have the same issues with internists as well. (CY-1)
Current Method for Returning Results	
Clinical Utility	If you're testing the patient for Marfan syndrome you can explain that we can't cure it but there are surveillance things that would be recommended. There would be more appropriate earlier treatment we would do for the symptoms and signs, and recurrence risks we could give, improve schools, and work in understanding what's going on with you. (CG-2)
Personal Convictions	However that's not to say that if a client calls me back and says this patient had sequencing in this gene and they were thinking that there was a three exon deletion, would you mind looking at this gene, if I can confirm that for them I will but I'm certainly not going to report a three exon, six KB deletion upfront. (CY-1)

Theme	Example Statement
Child vs. Adult Onset	My preference would be to not test for adult onset disorders for pediatric patients. (CG-2)
Practical Concerns	If we do the whole genome sequence and we get back lots of results that we are not looking for, and we've done it because it's cheaper, theoretically I would upfront tell the patient we're going to do this test because it is less expensive for us to do it this way and we will get the answers that we want. (CG-3)
Guidelines and Evidence	There are criteria that we set up ahead of time when we started reporting. The guidelines set up what we report what were not going to report. If something meets the criteria, then you report it, if they don't then you don't. Of course there's always room for discussion if it's a gene that we do feel has clinical implications to the patient. (GC-4)
Shared Decision-Making	
Attitudes Toward Shared Decision-Making	
For Sharing	I do. You're asking if we would want to respect the patient's wishes on whether or not to know something incidental or not? I was thinking about for example prenatal testing. Some of these newer tests that are coming out, like the maternal blood tests, certainly patients should be informed about these types of testing, know what their limitations are, and be able to decide whether or not they want those tests. (MG-1)

Theme	Example Statement
Against Sharing	What results could be given if you want them and what results we shouldn't report at all? That's part of the discussion in a research setting but not so much in a clinical setting. (GC-3)
Sharing: It Depends	Yes and no. I can't answer that without a lot of caveats. It depends on what I perceive my patient's level of comprehension to be. (CG-3)
Proper Balance Between Provider and Patient	
Equal Importance	I think it should be important but on the other hand I think sometimes the clinician has a better overall picture than the patient does. But I think it should be shared decision. (CY-4)
Provider Priority	I don't think parents should be able to come in and say we want our ten-month old checked for Huntington's or whatever in the future. Maybe they think a gene that is associated with homosexuality or something, stuff like that I would not be okay with. So I think there are some particular areas where it is the provider's job to police patient autonomy for children.(CG-2)
Patient Priority	There's a classic answer for that. You always present the data to the patient and let them decide. Sometimes it's very difficult findings you present them, which to me as an individual the decision seems very clear, but they decide something else. But that's the right thing to do. (CY-5)

Theme	Example Statement
Usefulness and Suggested Features of a Decision Tool	
Suggestions for Making a Tool	
Components of Hypothetical Decision Tool	I think it should include links or access to other resources. If they want to go above and beyond just reading the report, they can explore further for more information in the application rather than having to Google it on their own. Have something point them in the right direction. (GC-1)
Process of Hypothetical Decision Tool	A lot of teleconferencing and the sharing of information through the Internet in terms of being able to physically see somebody through a computer to share that information, then to see if they're actually understanding what they're being told, and not have to have somebody right there in an office to sit down with the patient. (CY-3)
Usability/Aesthetics/Transparency	They have to be user-friendly and they definitely have to be comprehensive. I think they should differ if they’re going to deliver the results directly to the patient or deliver the results directly to the physician, because the level of comprehension could be different. They should be customized for the physician or for the patient. (MG-2)
Personal Utility of Having Tool	
Would Use It	Yes. Hopefully it would be something that if I had a question about something, that I could go to it. (CY-3)

Theme	Example Statement
Would Not Use It	Do I want my patient educated before they come in to see me? They've taken genetics in high school, and if they didn't learn it then then they're not going to in five minutes on the computer. I don't have even the slightestt concept of what kind of computer algorithm would be beneficial. (CG-3)
Might Use It If...	As long as the patient's preferences don't contradict what you think the patient hears, so as long as they don't choose to hear about risks or something, you know you got a make sure you get everything in there that they need to know. (CY-4)
Colleague Acceptance	
Would Use It	I think genetic counselors would find it helpful. I think they would really like to see something out there where patients would have direct access to their results and you don't necessarily have to be worried that they're not getting the wrong information from their providers who were not able to provide them with that information correctly. (GC-1)
Would Not Use It	I think it depends. You always have more conservative people or people who like innovation. There's no black and white, there are so many shades of gray. That's why I don't think you will be able to get a straight answer. (MG-2)
Might Use It If...	Cost is always a big deal. And I think the people that are going to have the biggest problems with it are going to be people that have problems with anything like that, you know people who don't even want to do whole exomes now. (CG-2)

OVERALL CONCLUSION

The contents of this dissertation have attempted to shed light on two significant, well-debated topics in genomic medicine from the perspective of decision science techniques. We demonstrated that current evidence thresholds are sufficient for widespread implementation of pharmacogenomic testing to guide antiplatelet therapy, and that future resources aimed at reducing uncertainty in ACS patients may be best spent studying bleed risk differential, not genetic risk for poor drug metabolism. Furthermore, we identified a general appreciation for shared decision-making and the incorporation of patient preferences into genomic results decision-making, a departure from the 'party line' of the American College of Medical Genetics and Genomics, and recognized a need for decision tools to facilitate this integration.

Two divergent, overarching strategies to optimizing modern healthcare are evidence-based guidelines and personalized medicine. *(74, 75)* Evidence-based guidelines often represent enormous efforts of clinical data collection and analysis concerning a particular intervention, rigorously distilled into generalizable recommendations based on real-world findings in real-world patients. Conversely, personalized medicine "refers to the tailoring of medical treatment to the individual characteristics of each patient," *(76)* implying its benefits are most realized by those patients who fall through the cracks of evidence-based medicine. Indeed, a single patient may spend the entirety of her life benefitting from the medical practices honed in the study of the collective, only to suddenly be faced with a medical decision that only her unique genome is qualified to answer.

However the human genome is perhaps the least understood component of clinical health, and the vast uncertainty of the individual human genome is made infinitely complex by the uniqueness of each individual person. Prohibitive testing costs, low prospective financial returns

from genetic testing interventions, tolerant genetic testing regulatory policy, and uncertainty about the clinical utility of genomic associations other than those for rare diseases have resulted in an insufficient clinical evidence base for either a guidelines- or personalized-approach to treating most genetic conditions. *(77-79)* And as long as genomic technology development outpaces most efforts at evidence generation, sub-optimal translation of new technologies into clinical practice will continue to be a challenge. *(80-82)*

Genetic services stakeholders—including patients, clinical geneticists, genetic counselors, guideline developers, and health insurers—do not have the luxury of waiting to find out which genetic tests are recommended to be offered in the clinical setting, which should be covered by insurance, at what level, with what restrictions, and for whom. These tests typically become available to patients and clinicians before their clinical utility is fully understood; *(78, 81, 82)* thus, a key challenge in the decision-making process is assessing the evidence that is available on how genetic testing affects health outcomes. *(83)* Therefore, genetic services stakeholders must often make these decisions in the absence of complete and reliable evidence of clinical utility, and often under budget constraints. These challenges will likely only increase in scope in the era of WGS.

Decision tools are potentially useful for helping genetics stakeholders assess uncertain evidence thresholds, make policy choices, or facilitate treatment decisions. A decision tool is a formal, usually quantitative synthesis of available clinical data relevant to particular health interventions, and is used to better understand the evidence base for comparing two or more courses of action, often in the absence of a comparative clinical trial. *(19)* In addition to data synthesis, decision tools can also be used to aid patient assessment of complex medical choices, while also taking into account their personal values and preferences. In this sense, decision tools are a part of a shared decision making process, encouraging active participation

by patients in healthcare decisions. *(58, 69)* Our future research efforts will focus on additional drug-drug comparisons using VOI analyses, and we intend to take our idea of a shared decision tool for WGS results to next levels of development.

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