Comparative Effectiveness Approaches to Evaluate Pharmacogenomic Technology

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Abstract

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Background

Recent advances in genomic science present opportunities to "personalize" pharmaceutical treatments and improve health outcomes. However, such improvements are impeded by sparse evidence assessing pharmacogenomic technology clinical utility. This uncertainty constrains stakeholder decision-making, and has resulted in both sub-optimal and premature clinical translation. Timely assessment of health outcomes and clinical utility is critical to overcoming these translational issues. Comparative effectiveness research (CER) can meet this need by applying epidemiologic, health economic, and bio-statistical methods to generate timely evidence in "real world" conditions.

Objective

To demonstrate the utility of CER methods to evaluate pharmacogenomic technology in case studies in warfarin therapy, lung cancer, and breast cancer.

Methods

First, I utilize a case-control design to evaluate the association between genetic variants and risk of major bleeding in warfarin therapy patients. Second, I conduct a value of information (VOI) analysis to assess the value of a future trial investigating the clinical utility of *ERCC1*-guided adjuvant chemotherapy in lung cancer. Third, I explore the potential application of benefit-risk modeling to inform regulatory review of pharmacogenomic technology, with a specific demonstration in gene-expression profiling in early-stage breast cancer.

Results

In the evaluation of warfarin pharmacogenomics, I demonstrate the first association between *CYP4F2* variants and decreased risk of major bleeding, and provided exploratory evidence suggesting differential *CYP2C9* variant bleeding risk based on geographic setting. In the *ERCC1* VOI analysis, I demonstrate that a trial is expected to cost $30m, create value of $80m, and thus provide $50m in societal net-benefit. In my evaluation of regulatory benefit-risk modeling for pharmacogenomic technology, I examine a range of insights that can be gained through incorporation of systematic and quantitative evaluative methods in regulatory review processes.

Conclusions

In each case study, CER methods provide key evidence about health outcome impacts of pharmacogenomic technologies. These results have direct implications for clinical utility, and can inform stakeholder decision-making. These types of CER applications will likely play an important role in future assessment and translation of pharmacogenomic technologies due to accelerating research and development, and inability of traditional controlled trial designs to provide timely, adaptable, and readily applicable evidence.

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DEDICATION

To Meghann, Kopi, and our future adventures.

INTRODUCTION

The rapid advancement in understanding of genomics over the past decade presents a significant opportunity to "personalize" therapy and improve pharmaceutical outcomes by ascertaining disease prognosis and likelihood of treatment response using pharmacogenomic technology.(1, 2) However, the realization of these improvements in outcomes is impeded by a lack of evidence assessing the clinical utility of pharmacogenomic technologies, defined as the technology's impact on health outcomes. (2-4) Because the pace of evidence generation continues to lag behind the rapid rate of genomic technology development, there is sub-optimal translation of new technologies into clinical practice.(1, 4-6)

Evidence of the clinical utility of pharmacogenomic technologies is limited for many related reasons, including: lack of financial incentives for private industry to invest in costly prospective studies, lack of a clear development pathways, and low regulatory hurdles for marketing pharmacogenomic technologies.(1, 7-10) Collectively, these factors create considerable uncertainty about which pharmacogenomic technologies have clinical utility, as well as which technologies are appropriate for translation into clinical practice. (4, 6, 10, 11) For these reasons, stakeholders such as clinicians, patients, payers, regulatory authorities, and developers continue to have constrained decision-making capacity.

The translation of pharmacogenomic technologies is also complicated by the different evidence requirements both within and between stakeholder groups. (1, 4, 12) While some stakeholders are willing to adopt technologies based on the findings of observational studies or modeling analyses, others expect direct evidence from randomized clinical trials. (8, 13, 14) The lack of

consensus on this issue, coupled with the limitations noted above, creates a translational environment that is not conducive to consistent or timely evaluation of promising technologies.

The ability to assess the clinical utility of pharmacogenomic technology in a timely manner is critical to overcoming these translational roadblocks. In this sense, traditional approaches based on direct evidence obtained from controlled trials is not likely to meet the rapid and ongoing decision-making needs of stakeholders.(4, 10, 15, 16) If these conditions persist, and if alternative approaches are not developed, promising pharmacogenomic technologies may fail to advance in the translational pathway, or may be prematurely integrated into clinical practice.(5)

Three examples of pharmacogenomic technologies subject to these conditions are warfarin pharmacogenomics, *ERCC1* expression testing in non-small cell lung cancer, and gene-expression profiling in early-stage breast cancer.(1, 8, 17) Each of these technologies has limited evidence of clinical utility, and has consequently been stuck in a state of translational stagnation due to varied evidence expectations of stakeholders and unresolved uncertainty. Despite these current conditions, each technology has the potential to exhibit clinical utility, and may be appropriate for translation to clinical practice pending generation of evidence that demonstrates sufficient comparative effectiveness and satisfies the decision-making needs of stakeholders.
A number of comparative effectiveness research (CER) approaches have the potential to provide evidence that meets the decision-making needs of stakeholders within the translational context described above. These approaches include observational studies, value of information analysis, and benefit-risk modeling. Each of these analytic approaches can provide evidence to reduce uncertainty about clinical utility in a flexible and rapid manner aligned with the pace of the

current pharmacogenomic technology marketplace. The objective of my dissertation is to apply these approaches in three cases studies to demonstrate how CER methods can be utilized to generate evidence and facilitate appropriate translation of pharmacogenomic technologies. In chapter I, I utilize a case-control design to evaluate the association between genetic variants and risk of major bleeding in warfarin therapy patients. In chapter II, I conduct a value of information (VOI) analysis to assess the value of a future trial investigating the clinical utility of *ERCC1*-guided adjuvant chemotherapy in lung cancer. In chapter III, I explore the potential application of benefit-risk modeling to inform regulatory review of pharmacogenomic technology, with a specific demonstration in gene-expression profiling in early-stage breast cancer. Lastly, in chapter IV, I review the overall implications of my findings, and reflect on the broader role of comparative effectiveness research in evaluation of pharmacogenomic technology.

CHAPTER I

Genetic Risk Factors for Major Bleeding in Warfarin Patients in a Community Setting

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Abstract

Objective

To assess the association between *CY2C9*, *VKORC1*, and *CYP4F2* genetic variants and major bleeding in warfarin therapy patients undergoing monitoring across a range of geographic and care settings, and explore effects of setting on these associations.

Design

Case-control study, with cases defined as patients who experienced major bleeding while receiving warfarin therapy

Setting

Group Health Cooperative, a non-profit integrated healthcare system providing coverage and medical to more than 660,000 residents in 22 counties throughout Washington State and Northern Idaho

Patients

251 patients with major bleeding events while receiving warfarin therapy, and 134 patients on warfarin therapy not experiencing major bleeding frequency matched to cases on duration of therapy

Measurements

We obtained clinical and demographic exposures from automated databases, surveyed patients for supplementary exposure information, and collected buccal swabs to ascertain *CYP2C9*2* and

3, *VKORC1 1173*, and *CYP4F2*3 status*. The key measures are major bleeding, genotype, and potential confounders. Multivariate logistic regression models were utilized to evaluate the association between genetic variants and major bleeding, as well as interaction with care and geographic setting.

Results

Cases and controls differed significantly in gender (p=0.02), heart valve replacement indication (p<0.01), acetaminophen use (p=0.01); and diagnosis of congestive heart failure (p<0.01) and hypertension (p<0.01). There were not significant differences in other clinical and demographic exposures. *CYP4F2* variants were independently associated with decreased risk of major bleeding (HR: 0.54, 95% CI: 0.29-0.97), while *CYP2C9* variants were independently associated with increased risk of major bleeding (OR: 1.92, 95% CI: 1.02-3.59). *VKORC1* variants showed a trend for increased risk of major bleeding (HR: 1.60, 95% CI: 0.88-2.90). Exploratory analyses of major bleeding risk interactions with care and geographic setting suggested potential increased risk among *CYP2C9* variants in non-metropolitan geographic settings (ratio of OR: 5.63, p=0.06).

Limitations

The generalizability of our findings may be limited by the fact that the study cohort was recruited from a single integrated healthcare system in the Pacific Northwest

Conclusions

In the largest evaluation of warfarin pharmacogenomics and major bleeding to date, we demonstrated the first reported association between *CYP4F2* and major bleeding, supported the

previously reported *CYP2C9* association, and found a major bleeding trend in *VKORC1* variants. These findings expand understanding of genetic major bleeding risk factors, have potential to inform warfarin dosing and monitoring practices, and may have different implications for patients in different geographic settings.

BACKGROUND

The anticoagulant warfarin (Coumadin®) is highly effective in reducing the rate of thromboembolic events in patients with atrial fibrillation, myocardial infarction, joint replacement, and other conditions that confer increased clotting risk.(18-21) However, warfarin therapy initiation and monitoring is complicated by a 20-fold inter-patient variation in therapeutic dose requirement, and a related high rate of serious adverse bleeding events. (22-30) These events are a source of considerable morbidity and mortality, and have been noted as a barrier to use of an otherwise highly effective thromboembolic prophylaxis agent.(30-33)

The genomic advances of the past decade have led to the discovery of three genes that influence warfarin therapeutic dose requirements and have implications for major bleeding outcomes.(2, 34) The cytochrome P450 2C9 (*CYP2C9*) gene encodes a hepatic drug-metabolizing enzyme in the CYP450 family that is the primary metabolizing enzyme of S-warfarin, and the most active isomer. (35-37) Patients who are homozygous for the wild type *CYP2C9* allele (*CYP2C9**1) are considered "normal" metabolizers of warfarin, and those with one or more single-nucleotide polymorphisms (SNPs), are considered "slow" metabolizers.(37-41) Patients with the most common variants, *CYP2C9**2 (rs17998523) and *CYP2C9**3 (rs1057910), have been demonstrated to require significantly lower therapeutic warfarin doses, and have significantly increased risk of major bleeding relative to wild type patients. (2, 26, 39, 42) The vitamin K epoxide reductase complex subunit 1 (*VKORC1*) gene encodes the target enzyme of warfarin. (37, 38, 43, 44) Patients with a variant *VKORC1* allele (1173G>A, rs9934438), have also been demonstrated to require significantly lower therapeutic warfarin doses, and may be at increased risk of major bleeding relative to wild type patients, though here has been no definitive

association established to date.(2, 40, 43, 44) Lastly, the cytochrome P450 4 F2 (*CYP4F2*) gene is involved in metabolizing vitamin K, and is the most recent genetic discovery associated with warfarin therapeutic dose. (37, 44-46) Patients with the *CYP4F2**3 variant (rs2108622) have been demonstrated to require higher warfarin doses relative to wild type patients, and may be at decreased major bleeding risk.(44-47) However, no studies to date have investigated the association between *CYP4F2* and major bleeding.(47)

Despite the evidence above, and 2007 change of the warfarin label to include *CYP2C9* and VKROC1 genetic testing, few clinicians utilize pharmacogenomic testing to inform warfarin dosing and monitoring in practice today. (48, 49) These circumstances are in part due to ongoing uncertainty about the magnitude of genetic variant and major bleeding associations, and related questions about clinical utility and cost-effectiveness.(14, 49-52) Generation of more precise evidence about the role of genomics in warfarin outcomes will be a critical factor in determining if pharmacogenomic strategies take the final translational steps toward widespread clinical application.(8, 14, 53) With these considerations in mind, we conducted a case-control study to evaluate the association between *CYP2C9*, *VKORC1*, and *CYP4F2* genetic status and major bleeding risk. Our objective was to evaluate the independent association between variants and major bleeding in warfarin outpatients in a community setting. We also hypothesized increased strength of variant-bleeding associations in care and geographic settings with expected lower monitoring intensity, and evaluated these effects in exploratory interaction analyses.

METHODS

Study Design & Data Sources

We conducted a case-control study of patients enrolled in Group Health Cooperative (GHC) and receiving warfarin therapy between January 1, 2005 and April 1, 2011. GHC is a non-profit integrated healthcare system based in Seattle, Washington that insures and provides medical care for approximately 660,000 residents of Washington State and Northern Idaho. This study was approved by the Group Health and University of Washington institutional review boards.

Key exposures were ascertained from GHC automated databases (inpatient, outpatient, cancer, demographics, pharmacy, lab, vital signs, census, and death) and a supplemental self-report survey, and mailed buccal swabs were utilized to ascertain *CYP2C9* (*2 and *3), VKROC1 (1173), and *CYP4F2* (*3) genotype. Major bleeding events were identified using a previously validated ICD-9 algorithm and automated inpatient records, and were validated through full medical chart review.(54, 55)

Cohort Definition

Our cohort was comprised of patients who were GHC members and received one or more warfarin prescriptions between January 1, 2005 and April 1, 2011. To be eligible for the study, patients required to: be 18 years or older, maintain continuous GHC enrollment for 2-years prior to the index date, have pharmacy fill records indicating warfarin supply on the index date, have no record of major bleeding in the 12-months prior to the index date, and be capable of completing the self-report survey.

Case Patients

Within the cohort of warfarin users, we defined cases as patients who experienced a major bleeding event while receiving warfarin. Potential major bleeding events were initially identified using a validated International Classification of Diseases, Ninth Edition (ICD-9) algorithm, with a demonstrated positive predictive value of 87% (Full algorithm provided in Appendix A).(54) Events were then validated through full medical chart review using an established "major bleeding" definition. (54, 55) Specifically, events were classified as "major bleeding" if they were clinically overt, and met one or more of the following criteria: a) the patient was hospitalized for the bleeding event; b) hemoglobin dropped more than 2 mg/dl at the time of the event; or c) two or more units of packed red blood cells were transfused to treat the event.(54) Additionally, events were evaluated for strength of supporting evidence. Only "definite" bleeding events were included, defined as: 1) documented direct visualization of blood by a physician; b) documented imaging demonstrating bleeding (such as CT scan showing intracranial hemorrhage); or c) documented imaging of bleeding source in addition to physician documented evidence of bleeding.(54, 56)

Control Patients

From the cohort of warfarin users who did not experience major bleeding events, we randomly selected one control for each case. To do so, potential controls were randomly assigned an index date meeting the inclusion criteria above, and were frequency matched to case index years to attempt to balance potential time-dependent exposures.

Warfarin Exposure Ascertainment

Warfarin use was ascertained from GHC automated pharmacy records. Extracted automated data points included the date of the prescription, date of the pharmacy fill, days supplied, and dose. A prior study has noted excellent agreement of GHC automated records with medical charts for warfarin use ascertainment. (57)

Genetic Exposure Ascertainment

All included cases and controls provided a buccal swab (Epicentre, All-Mailer) for analysis of *CYP2C9*, *VKORC1*, and *CYP4F2* polymorphisms. Polymorphism detection assays were designed and performed in the Functional Genomics Laboratory, Center for Ecogenetics and Environmental Health at the University of Washington, Seattle, WA. DNA was extracted from the buccal cell collection brushes using Qiagen kits and standard methods (Qiagen, Valencia, CA). DNA samples were then genotyped using pre-designed 5'-nuclease SNP Genotyping Assays (Applied Biosystems, Foster City, CA), which employ specific fluorogenic probes, as follows. All probes are 3'-labeled with the TAMRA quencher dye. In addition, the specific wild type and variant probes are 5'-labeled with the 6-FAM reporter dye and the VIC reporter dye, respectively.

The fluorescent 5'-nuclease assays were performed and analyzed on an ABI 7900HT Fast Real-Time PCR System (Applied Biosystems). The specific PCR reaction conditions were based on the general guidelines provided by the manufacturer and incorporated 10-25ng of genomic DNA template. Thermocycling parameters consisted of an initial incubation at 95°C for 10 minutes, followed by 50 cycles of 92°C for 15 seconds and 60°C for 1:30.

Testing for deviation of genotype frequencies from Hardy-Weinberg equilibrium was calculated by applying the Hardy-Weinberg model to our data.(58, 59) The chi-squared goodness-of-fit test was utilized to compare expected versus actual prevalence of each *CYP2C9*, *VKORC1*, and *CYP4F2* allele frequency.(59)

In our regression analyses to evaluate the association between genetic variants and major bleeding, we grouped heterozygous and homozygous variant patients in a single "variant" category. This approach was taken due to the small number of homozygous variants, and is consistent with methods from prior studies.(2, 26, 39, 40, 47, 60)

Clinical, Demographic, and Behavioral Exposures

Clinical and demographic features of case and control patients were extracted from GHC automated data records. Specific variables included: age, gender, height, weight, potential warfarin therapy indications, international normalized ratio (INR) results, Charlson comorbidity index, history of diagnosed hypertension, congestive heart failure, diabetes mellitus, cancer; and selected concomitant medications.

Geographic setting at index date was ascertained using patient residence zip codes, and the Index of Relative Rurality (IRR). The IRR is a continuous measure of degree of rurality derived from: population size, population density, extent of urbanized area, and distance to nearest metropolitan area.(61) The IRR was intended as a proxy for warfarin monitoring intensity under the assumption that the factors that are used to derive IRR are also associated with the average frequency of INR testing and dose adjustments.

A 44 item self-report survey was administered to all participants to obtain supplemental information about clinical, demographic, and behavioral, exposures that were not available in automated records. The survey was focused on average exposures in the one-year period prior to the index date. Both case and control survey questions were anchored to the index date (e.g. "in the year prior to [index date], did you ____"). Surveys were initially mailed to patients, but a phone-based survey approach was later implemented to enhance response rate. The self-report survey variables were primarily intended to be utilized in exploratory analyses, however the analyses reported herein utilize self-reported care setting (anticoagulation clinic, primary care, cardiology, or other), warfarin indication, over-the-counter concomitant medication use, distance to monitoring services, race/ethnicity, and household income. Survey responses were cross-validated with automated records in sub-sets of patients where both sources were available.

Statistical Analysis

Case and control patients were compared using chi-square tests and the Fisher exact test, where appropriate, for categorical variables and the Student t-test for continuous variables.

The primary analysis used logistic regression to estimate the risk of major bleeding associated with genetic variant status, expressed as both univariate and multivariate odds ratios (OR) with 95% confidence intervals (CI). Specifically, standard logistic regression methods were used to evaluate the binary outcome of case/control status (i.e. major bleeding or no major bleeding) for each genetic variant exposure. We also used this model to evaluate independent associations for previously reported clinical and demographic risk factors.(25, 62-66)

Potential Confounders

Few known exposures are associated with both our genetic variants of interest and major bleeding, a necessary condition for confounding.(67)Thus, included potential confounders were race/ethnicity and duration of warfarin therapy. Duration of warfarin therapy is a potential confounder because variants may discontinue therapy earlier than wild type patients due to unstable INR, and there is an established increased risk of major bleeding during the initial year of treatment.(2, 25, 39, 62)

Precision Variables

We assessed inclusion of factors reported to be associated with major bleeding and therapeutic dose requirements, as well as several variables hypothesized to be associated with major bleeding. Specific covariates obtained from GHC automated records were: index date age (≥80 vs. <80), gender, body mass index (≥30 vs. <30), index of relative rurality score (continuous); and diagnosis of congestive heart failure, diabetes, or hypertension (in 2 years prior to index date). Specific covariates obtained from the self-report survey were: care setting (anticoagulation clinic, primary care, cardiology, other), heart valve replacement indication, acetaminophen use, distance to warfarin monitoring provider (>10 miles vs. ≤10 miles), and household income (<$50,000 vs. ≥$50,000).

Exploratory Interaction Analyses

Standard logistic regression models were used to evaluate the binary outcome of case/control status for interactions between care and geographic setting with each genotype. Each analysis adjusted for genetic status, in addition to the covariates discussed above. In the analysis of care

setting interaction, care setting was a binary variable (anticoagulation clinic care vs. other care setting). In the analysis of geographic setting interaction, we created a binary variable (metropolitan vs. not metropolitan) based on the IRR score (<0.265=metropolitan). (61)

In post-hoc analyses, we also evaluated variant-bleeding interaction with self-reported distance to monitoring clinic. This analysis was conducted because we believe this variable may be a better proxy for barriers to accessing monitoring services, and monitoring intensity, relative to the IRR score, which may lack sensitivity due to it's county-level scoring.(61)

Throughout the model specification process, model fit was assessed using Akaike Information Criterion (AIC). (68, 69) Selected models demonstrated less information loss through lower AIC scores

All analyses were performed in STATA version 12.0 (STATA Inc., Austin, Tx).

Role of the Funding Source

This study was supported by a grant from the National Institute of General Medical Sciences (1UO1 GM092676-01) and the PhRMA Foundation pre-doctoral fellowship in health outcomes. The funding sources had no role in the design or conduct of the study; collection, analysis, and interpretation of the data; preparation or review of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

An automated record query of all GHC patients meeting inclusion criteria identified a total of 11,738 patients. Among these patients, 702 had evidence of major bleeding with warfarin supply overlap. All 702 of these patients were contacted for potential study participation as cases. From among these patients, 267 (38.0%) were enrolled and 435 (62.0%) refused to participate or never responded to our mailed recruitment letter and calls. We randomly selected 702 control patients from the remaining cohort without evidence of major bleeding by generating random index dates and frequency-matching with case index dates. Among these patients, 308 (43.9%) were enrolled and 394 (56.1%) refused to participate or never responded to our mailed recruitment letter and calls. At the time of this analysis, 245 case and 134 control results were available for inclusion. Participants and non-participants did not differ significantly by age ($p=0.98$), gender ($p=0.82$), duration of GHC enrollment ($p=0.93$), geographic setting ($p=0.50$), or Charlson comorbidity index ($p=0.88$).

Among cases and controls enrolled in this study, significant differences in clinical and demographic exposures included: gender ($p=0.02$), heart valve replacement indication ($p<0.01$), acetaminophen use ($p=0.01$); and diagnosis of congestive heart failure ($p<0.01$) and hypertension ($p<0.01$). Case and control patients did not differ significantly by other clinical, demographic, and behavioral exposures (Table 1).

When analyzed by case and control status, genotype results did not significantly deviate from Hardy-Weinberg equilibrium (Table 2).(59) Analyses that examined deviation from Hardy-Weinberg equilibrium in cases and controls stratified by care (anticoagulation clinic vs. other

settings) and geographic setting (metropolitan vs. non-metropolitan) also did not deviate from Hardy-Weinberg equilibrium.

Univariate Analyses

In univariate logistic regression analyses of the association between the genetic exposures of interest and major bleeding, *CYP4F2* was the only gene with a significant association, demonstrating a 46% reduction in risk of major bleeding in variants relative to wild type patients (OR: 0.54, 95% CI: 0.35-0.82). The full results of the univariate analyses are shown in Table 3.

In univariate analyses of the association between clinical and demographic risk factors and major bleeding, a heart valve replacement indication for warfarin therapy was the strongest risk factor, with an approximate 2.6-fold increased risk of major bleeding (OR: 2.56, 95% CI: 1.24-5.28). Significant associations with major bleeding were also demonstrated for non-specialist care, initial year of warfarin therapy, history of congestive heart failure, body mass index less than 30, and female gender (Table 4).

Multivariate Analyses

After assessment of model fit using AIC to compare different model parameterizations, the covariates that were retained in the multivariate model were: *CYP2C9*, *VKORC1*, and *CYP4F2* status; race (white/other), duration of therapy (<1 year), age (>80), gender, warfarin indication (categorical variable), care setting (4 category variable), obesity (BMI ≥30), distance to warfarin provider (>10 miles), acetaminophen use, household income (<$50,000); and diagnosis of hypertension, diabetes, or congestive heart failure. These covariates all represent established or

potential risk factors for major bleeding among warfarin therapy patients. (62, 64, 70)

In the multivariate logistic regression model, *CYP4F2* remained a significant independent genetic risk factor for major bleeding, demonstrating a 46% reduction in risk of major bleeding in variants relative to wild type patients (OR: 0.54, 95% CI: 0.29-0.97). (Table 5). After adjusting for covariates, *CYP2C9* was also demonstrated to be a significant independent risk factor for major bleeding, with an approximate 2-fold increase in risk of major bleeding among variants relative wild type (OR: 1.92, 95% CI: 1.02-3.59). The *VKORC1* strength of association with risk of major bleeding was increased in the multivariate model, but remained non-significant (OR: 1.60, 95% CI: 1.02-3.59).

In multivariate logistic regression models evaluating of the association between clinical, demographic, and behavioral risk factors and major bleeding, the strength of the heart valve replacement association was increased, with a 4.5-fold increased risk of major bleeding (OR: 4.51, 95% CI: 1.61-12.63). Additionally, patients with diagnosis of hypertension demonstrated a 2.2-fold increased risk of major bleeding (OR: 2.22, 95% CI: 1.14-4.32), and female patients demonstrated a 3-fold increase in risk of major bleeding (OR: 3.0, 95% CI: 1.59-5.66) (Table 4).

Exploratory Interaction Analyses

In exploratory analyses of interactions between *CYP2C9* status and care setting (defined as anticoagulation clinic care or other care), adjusting for the covariates noted above, there was not evidence of additional bleeding risk among variants in anticoagulation care relative to those in other care settings (OR: 1.05, 95% CI: 0.29-3.79). Likewise, there was not evidence of

interaction between care setting and *VKORC1* variants (OR: 1.02, 95% CI: 0.30-3.40) or *CYP4F2* variants (OR: 0.99, 95% CI: 0.30-3.30).

In analyses of interactions between *CYP2C9* status and geographic setting, adjusting for the covariates noted above, there was a non-significant trend toward additional major bleeding risk among variants in non-metropolitan areas relative to those in metropolitan areas (OR: 5.63, 95% CI: 0.96-33.16). There were also highly uncertain trends toward additional risk of major bleeding among *VKORC1* variants (OR: 1.54, 95% CI: 0.37-6.36) and *CYP4F2* variants (OR: 2.24, 95% CI: 0.54-9.21) in non-metropolitan areas relative to metropolitan areas.

In post-hoc exploratory analysis of interaction between *CYP2C9* status and distance to warfarin monitoring provider, we found significant additional major bleeding risk for variants residing more than 10 miles from their warfarin monitoring provider relative to variants residing 10 or fewer miles from their warfarin monitoring provider (OR: 5.69, 95% CI: 1.06-30.72) (Table X). There was highly uncertain evidence of attenuated major bleeding risk among *VKORC1* variants (OR: 0.73, 95% CI: 0.16-3.33) and additional major bleeding risk among *CYP4F2* variants (OR: 1.77, 95% CI: 0.38-8.37) residing more than 10 miles from their warfarin monitoring provider relative to those residing 10 or fewer miles from their monitoring provider.

DISCUSSION

Summary

We used a case-control study design to investigate the association between *CYP2C9*, *VKORC1*, and *CYP4F2* variants and major bleeding in warfarin outpatients from a large integrated

healthcare system. We were able to identify and validate 245 case patients who experienced major bleeding events while receiving warfarin therapy, potentially the largest such group in a warfarin pharmacogenomics study to date. Our analysis demonstrated an independent association between *CYP4F2* variants and major bleeding, as well as an independent association between *CYP2C9* variants and major bleeding. Exploratory analyses of interactions of variant-bleeding associations by geographic setting demonstrated that there may be further increased major bleeding risk for *CYP2C9* variant patients in non-metropolitan areas, or residing more than 10 miles from their warfarin monitoring provider.

The validity of our findings is supported by our replication of many of the clinical and demographic risk factor associations demonstrated in prior observational and randomized study designs.(39, 62, 64) Additionally, our results are supported by consistent allele frequency distributions within Hardy-Weinberg equilibrium across cases and controls, as well as the care and geographic settings evaluated in exploratory analyses.(59) Lastly, our finding that the major bleeding rate in our sampling frame is approximately 5 per 100 patient years, suggests that the incidence odds ratios reported herein should approximate incidence risk ratios, as has been previously discussed in the epidemiology literature. (71, 72)

Implications

This study contributes additional evidence to the growing body of literature evaluating associations between genetic variants and warfarin outcomes. Our findings are important within this context this is the first study we are aware of to establish an association between *CYP4F2* variants and decreased risk of major bleeding. This finding is conceptually consistent with prior

studies that demonstrated increased therapeutic dose requirements in *CYP4F2* variants, and have suggested involvement of *CYP4F2* in vitamin K metabolism.(44-47, 73) Additionally, our findings support the previously established association between *CYP2C9* variants and increased risk of major bleeding, and are consistent with prior studies that have demonstrated a non-significant trend toward increased bleeding in *VKORC1* variants.(2, 26, 39, 74) Collectively, our results reinforce the influence of genetic risk factors on major bleeding outcomes, and imply that if warfarin pharmacogenomic testing strategies are able to successfully reduce major bleeding rates, those reductions may be larger than previously proposed.(41, 74)

Our exploratory analyses of variant-bleeding interactions by geographic setting suggested that there may be even greater risk of major bleeding among *CYP2C9* variants that reside in non-metropolitan areas, or more than 10 miles from their warfarin monitoring provider. These analyses were driven by the hypothesis that patients living in less densely populated areas and/or further from their warfarin monitoring provider, may face barriers to accessing monitoring services that can modify the variant-bleeding association. These findings should be interpreted with caution as they were strictly for exploratory purposes, and were poorly powered. Nonetheless, these findings could have important implications for the clinical validity and utility of warfarin pharmacogenomic testing in different geographic settings, and warrant investigation in future studies with adequate power to examine interaction. In planning this study, our power calculations suggested that to have 80% power to detect a ratio of odds ratios of 2.0, we would require approximately 2,500 patients, which was beyond our scope and resources.

Our results have particular importance in the context of several new oral anticoagulants entering the market (e.g. dabigatran, apixaban, rivaroxaban**)**. In large randomized Phase III trials comparing outcomes with warfarin, these agents were demonstrated to have superior or non-inferior thromboembolism prophylaxis efficacy, and reduced bleeding risk at selected sites.(75-81) Additionally, the fixed dose and more predictable pharmacokinetic and pharmacodynamic properties of these agents has been touted as reducing the need for frequent monitoring, as with warfarin.(75, 77, 78, 82) Consequently, these new agents appear poised to gain increasing oral anticoagulant market share in the years to come. However, a growing number of comparative effectiveness research studies and clinical reviews have urged caution in this transition due to uncertainty about bleeding risks in community settings, poorly defined monitoring needs, lack of established reversal agents for patients with over-anticoagulation, and questionable cost-effectiveness relative to warfarin.(79, 83-89) This uncertainty about comparative and cost-effectiveness could be even greater if the clinical utility of warfarin pharmacogenomic testing is definitively established, and the benefit-risk balance is enhanced.(87-89) For this scenario to be realized, substantial supplementary evidence will need to be generated through well-powered study designs answering meaningful comparative effectiveness questions.(2) It remains unclear if investing in generating such evidence to maintain use of a relative inexpensive and similarly efficacious agent, is favorable to gradual market shift toward more expensive agents with uncertain effectiveness in community settings.

Limitations

The primary limitation of our study was the low and unbalanced number of cases and controls available at the time of this analysis. This resulted in a low number of control variants, and

reductions in statistical power to evaluate variant-bleeding associations. If this analysis had included our enrollment of 267 cases and 308 controls, our power to evaluate the association between *CYP2C9* and *VKORC1* variants and major bleeding risk would have increased from approximately 70% to 90% and 40% to 60%, respectively. Another limitation of this study is that we enrolled prevalent warfarin users, rather than restricting to patients initiating therapy. Prior studies have shown the risk of major bleeding events is highest in the first year of therapy, and particularly high in the first 90 days of therapy. (25, 39, 65) Accordingly, power to investigate variant-bleeding associations is expected to be greatest during this period. Unfortunately, it was not possible to assemble an inception cohort of adequate size in the GHC warfarin therapy population due to low numbers of major bleeding events (approximately 100 from 1/1/2005 to 4/1/2011 vs. 835 events in prevalent users). Future evaluations of warfarin bleeding outcomes should note the potential for attenuated bleeding risk in prevalent users to ensure appropriate statistical power to investigate major bleeding associations. The retrospective approach of our study design was also problematic because it limited our ability to precisely ascertain exposures unavailable in automated records. We utilized a self-report survey to collect additional clinical, demographic, and behavioral exposure data, but there is strong potential for exposure misclassification due to the older age of the cohort (mean age 74), and recall periods that were as long as 5-years. To mitigate potential exposure misclassification issues, we derived our analysis variables from automated records when possible. However, we did rely on self-reported care setting, geographic setting, warfarin indication, race, and distance to warfarin monitoring provider. We felt that these exposures were not as subject to misclassification relative to more changeable exposures like diet and behavior. Lastly, because we recruited patients from a single healthcare system in Washington and Idaho comprised of predominately white patients, it is

possible that our findings are not representative of outcomes in alternative healthcare systems or patient populations.

CONCLUSION

We utilized a case-control study design to assemble what we believe is the largest pharmacogenomic evaluation of major bleeding in warfarin patients conducted to date. We leveraged a considerable number of bleeding events to demonstrate an association between *CYP4F2* variants and decreased risk of major bleeding, potentially the first such finding to date. Our findings also supported prior reports of increased risk of major bleeding among *CYP2C9* variants, and a trend toward increased major bleeding risk in *VKORC1* variants. These findings expand understanding of genetic major bleeding risk factors, have potential to inform warfarin dosing and monitoring practices, and may have different implications for patients in different geographic settings.

Variable	Cases	Controls	p-value
Variables Extracted from Automated Records			
Total Patients	251	134	-
Age in Years at Index Date, Mean (SD)	75.1 (12.4)	74.3 (10.9)	0.96
Male, N (% Col)	120 (49.0%)	81 (61.8%)	**0.02**
Race, N (% Col)			
American Indian or Alaska Native	3 (1.2%)	1 (0.8%)	0.70
Asian	3 (1.2%)	3 (2.3%)	0.45
Black/African American	7 (2.9%)	1 (0.8%)	0.11
Native Hawaiian or Other Pacific Islander	1 (0.4%)	0 (0%)	0.32
White/Caucasian	224 (92.2%)	124 (95.4%)	0.20
Other	2 (0.8%)	0 (0%)	0.16
BMI, Mean (SD)	29.8 (6.9)	30.5 (6.6)	0.94
Duration of GH Enrollment at Index Date (Years), Mean (SD)	16.0 (5.9)	15.2 (6.1)	0.92
Group Health Plan Type, N (% Col)			
Integrated Group Plan	204 (83.3%)	107 (81.7%)	0.81
Network Plan	41 (16.7%)	24 (18.3%)	
Duration of Warfarin Therapy at Index Date, N (% Col)			
<6 Months	46 (18.3%)	13 (9.7%)	
6 Months to 1 Year	13 (5.2%)	5 (3.7%)	0.06
>1 Year	192 (76.5%)	116 (86.6%)	
Geographic Setting of Patient Residence^*, N (% Col)			
Metropolitan Sphere (≤0.265)	204 (81.3%)	104 (77.7%)	0.39
Non-Metropolitan Area (>0.265)	47 (18.7%)	30 (22.3%)	
Reside >10 Miles from Warfarin Monitoring Provider, N (% Col)	44 (20.0%)	27 (22.0%)	0.65
Concomitant Medications, N (% Col)			
Losartan	27 (10.8%)	10 (7.5%)	0.27
Amiodarone	5 (2.0%)	5 (3.7%)	0.36
Torsemide	1 (0.3%)	2 (1.5%)	0.28
Comorbidities, N (% Col)			
Cancer	8 (3.3%)	8 (6.1%)	0.24
Diabetes	52 (21.2%)	39 (29.8%)	0.07
Hypertension	181 (73.9%)	78 (59.5%)	**<0.01**
Congestive Heart Failure	96 (39.2%)	28 (21.4%)	**<0.01**
Charlson Comorbidity Index, Mean (SD)	1.6 (1.7)	1.4 (1.6)	0.93
Self-Report Survey Variables			
Survey Completed by Phone, N (%)	191 (78.0%)	94 (71.8%)	0.19
Survey Gap From Index Date (Years), Mean (SD)	3.7 (1.7)	3.7 (1.9)	>0.99
Warfarin Indication, N (% Col)			
Atrial Fibrillation	74 (31.6%)	52 (41.3%)	0.06
DVT	19 (8.1%)	11 (8.7%)	0.84
PE	23 (9.8%)	11 (8.7%)	0.72
Stroke	22 (9.4%)	10 (7.9%)	0.61
Heart Valve Replacement	43 (18.4%)	10 (7.9%)	**<0.01**
Myocardial Infarction	11 (4.7%)	6 (4.8%)	0.97
Joint Replacement	12 (5.1%)	7 (5.6%)	0.84
Other Clot	9 (3.8%)	6 (4.8%)	0.65
Other (Non-Clot)	5 (2.1%)	5 (4.0%)	0.32

Don't Know	16 (6.8%)	8 (6.3%)	0.85
Care Setting, N (% Col)			
Anticoagulation Clinic	110 (52.1%)	75 (63.3%)	**0.03**
Primary Care	76 (39.0%)	30 (30.9%)	0.11
Cardiologist	18 (9.4%)	7 (7.4%)	0.50
Other	18 (9.3%)	6 (6.4%)	0.30
Concomitant OTC Medications, N (% Col)			
NSAID	20 (8.6%)	6 (4.7%)	0.13
Acetaminophen	68 (32.9%)	27 (21.1%)	**0.01**
Aspirin	61 (26.6%)	36 (27.9%)	0.79
Smoking Status, N (% Col)			
Every Day	15 (6.1%)	5 (3.9%)	
Some Days	4 (1.6%)	2 (1.6%)	0.66
Not at All	226 (92.3%)	121 (94.5%)	
How Often Had 1+ Drinks Containing Alcohol, N (% Col)			
4+ Days Per Week	36 (14.8%)	19 (14.8%)	
2-3 Days Per Week	29 (11.9%)	14 (10.9%)	0.47
2-4 Days Per Month	34 (14.0%)	14 (10.9%)	
Less Than Monthly	62 (25.5%)	26 (20.3%)	
Never	82 (33.7%)	55 (43.0%)	
Household Income <$50,000/Year, N (% Col)	128 (59.5%)	65 (54.6%)	0.36
Genetic Status Variables			
Genetic Variant Status, N (% Col)			
CYP2C9 (*2 or *3)	91 (37.1%)	42 (31.3%)	0.25
VKORC1 1173	160 (63.7%)	77 (57.5%)	0.24
*CYP4F2**3	105 (42.0%)	77 (57.5%)	**<0.01**
Note: Bold p-values indicate statistically significant differences between cases and controls			

Table 1: Clinical, demographic, behavioral, and genetic exposures by cases and control status

Variable	Observed in Cases		H-W Expected in Cases	χ2, p-value	Observed in Controls		H-W Expected in Controls	χ2, p-value	Observed Overall		H-W Expected Overall	χ2, p-value
	N	%	%		N	%	%		N	%	%	
All Patients	251	64.7%	-		137	35.3%	-		388	100.0%	-	
***CYP2C9**2 Status**												
C:C	185	75.5%	75.2%	χ2=0.15	106	80.9%	79.8%	χ2=1.89	299	77.7%	77.1%	χ2=1.16
C:T	55	22.4%	23.0%	p=0.70	22	16.8%	19.1%	p=0.17	78	20.3%	21.4%	p=0.28
T:T	5	2.0%	1.8%		3	2.3%	1.1%		8	2.1%	1.5%	
***CYP2C9**3 Status**												
A:A	217	88.6%	88.9%	χ2=0.9	114	87.0%	86.7%	χ2=0.27	338	87.8%	87.9%	χ2=0.19
A:C	28	11.4%	10.8%	p=0.34	16	12.2%	12.8%	p=0.60	46	11.9%	11.7%	p=0.66
C:C	0	0.0%	0.3%		1	0.8%	0.5%		1	0.3%	0.4%	
***CYP4F2**3 Status**												
G:G	88	35.9%	35.8%	χ2=0.03	57	43.5%	41.6%	χ2=1.13	1	38.4%	37.6%	χ2=0.14
G:A	117	47.8%	48.0%	p=0.86	55	42.0%	45.8%	p=0.29	2	45.7%	47.4%	p=0.71
A:A	40	16.3%	16.2%		19	14.5%	12.6%		1	15.8%	15.0%	
***VKORC1* 1173 Status**												
G:G	143	58.6%	58.4%	χ2=0.01	55	42.0%	44.1%	χ2=0.91	202	52.6%	53.0%	χ2=0.51
G:A	87	35.7%	36.0%	p=0.92	64	48.9%	44.6%	p=0.34	155	40.4%	39.6%	p=0.48
A:A	14	5.7%	5.6%		12	9.2%	11.3%		27	7.0%	7.4%	

H-W=Hardy-Weinberg Equilibrium

Note: No chi-squared two-sided test at alpha=0.05 was significant for difference between observed and expected counts

Table 2: Observed Vs. Expected Prevalence of SNPs Based on Hardy-Weinberg Equilibrium

Genetic Status Exposure	Cases		Controls		Odds Ratio (95% CI)	
	N Variant (% of Cases)	N Wild Type (% of Cases)	N Variant (% of Controls)	N Wild Type (% of Controls)	Univariate Model	Multivariate Model*
***CYP2C9**2 or *3**	88 (35.1%)	163 (64.9%)	40 (29.9%)	94 (70.1%)	1.26 (0.79-2.05)	**1.92 (1.02-3.59)**
***VKORC1* 1173**	160 (63.7%)	91 (36.3%)	77 (57.5%)	57 (42.5%)	1.30 (0.84-2.00)	1.60 (0.88-2.90)
***CYP4F2**3**	105 (42.0%)	145 (58.0%)	77 (57.5%)	57 (42.5%)	**0.54 (0.35-0.82)**	**0.54 (0.29-0.97)**

*Multivariate model adjusted for: Genetic status, race (white/other), duration of therapy (<1 year), age (>80), gender, warfarin indication, care setting, obesity, index of relative rurality score (continuous), distance to warfarin provider (>10 miles), acetaminophen use, household income (<$50,000/year); and diagnosis of hypertension, diabetes, or congestive heart failure

Note: Bold values indicate statistical significance at α=0.05

Table 3: *CYP2C9*, *VKORC1*, and *CYP4F2* genetic status and risk of major bleeding in warfarin therapy patients

Exposure	Odds Ratio (95% CI)	
	Univariate Model	Multivariate Model*
Anticoagulation Care Setting	**0.63 (0.40-0.99)**	1.40 (0.35-5.56)
Hypertension	**1.92 (1.22-3.02)**	**2.22 (1.14-4.32)**
Female Gender	**1.69 (1.10-2.60)**	**3.0 (1.59-5.66)**
1st Year of Warfarin Therapy	**1.98 (1.11-3.52)**	1.64 (0.67-4.05)
Heart Valve Replacement	**2.56 (1.24-5.28)**	**4.51 (1.61-12.63)**
Congestive Heart Failure	**2.37 (1.45-3.87)**	1.84 (0.91-3.69)
BMI >30	**0.65 (0.42-0.99)**	0.52 (0.27-1.02)

*Multivariate model adjusted for: Genetic status, race (white/other), age (>80), warfarin indication, care setting, obesity, index of relative rurality score (continuous), distance to warfarin provider (>10 miles), acetaminophen use, household income (<$50,000); and diagnosis of diabetes, and the other covariates listed above

Note: Bold values indicate statistical significance at α=0.05

Table 4: Clinical and demographic exposures and risk of major bleeding in warfarin therapy patients

	CYP2C9 Wild Type		*CYP2C9* Variants (any *2 or *3)		OR (95% CI) for *CYP2C9* Wild Type (Reference) vs. *CYP2C9* Variants Among Strata of Geographic Setting
	N	OR (95% CI), p	N	OR (95% CI), p	
Metropolitan Geographic Setting	133 Cases 70 Controls	1.0 (Reference)	71 Cases 34 Controls	1.48 (0.74-2.95) p=0.27	1.48 (0.74-2.95) p=0.27
Non-Metropolitan Geographic Setting	30 Cases 24 Controls	0.64 (0.26-1.58) p=0.33	17 Cases 6 Controls	5.30 (0.93-30.05) p=0.06	1.97 (0.33-11.57) p=0.45
OR (95% CI) for Metropolitan Geographic Setting (Reference) vs. Non-Metropolitan Geographic Setting Within Strata of *CYP2C9* Status		0.64 (0.26-1.58) p=0.33		5.97 (0.79-45.29) p=0.08	

Measure of interaction on multiplicative scale: Ratio of ORs (95% CI), p=5.63 (0.96-33.16), p=0.06

Multivariate model adjusted for: Genetic status, race (white/other), duration of therapy (<1 year), age (>80), gender, warfarin indication, care setting, obesity, distance to warfarin provider (>10 miles), acetaminophen use, household income (<$50,000/year); and diagnosis of hypertension, diabetes, or congestive heart failure

Table 5: Interaction of *CYP2C9* genetic status and geographic setting on the risk of major bleeding in warfarin therapy patients

Appendix A

Major Bleeding ICD-9 Algorithm From Arnason et al., 2006 (40)

423.00 hemopericardium	535.51 gastritis/duodenitis NOS with hemorrhage
430.00 subarachnoid hemorrhage	535.61 duodenitis with hemorrhage
431.00 intracerebral hemorrhage	537.80 gastroduodenal dis nec
432.00 Nontraum extradural hem	562.02 diverticula sm intestine w hemorrhage
432.1 Subdural hemorrhage	562.03 diverticulitis sm intestine w hemorrhage
432.9 Intracranial hemorr NOS	562.12 diverticula of colon w hemorrhage
455.20 int hemrrhoid w comp nec	562.13 diverticulitis of colon w hemorrhage
455.50 ext hemrrhoid w comp nec	568.81 hemoperitoneum
455.80 hemrrhoid NOS w comp nec	569.30 rectal and anal hemorrhage
459.00 hemorrhage NOS	569.85 angiodysplasia with hem nec
456.00 esophag varices w bleed	578.00 hematemesis
456.20 esoph varices in oth dis	578.10 blood in stool
530.70 mallory—weiss syndrome	578.90 Gastrointest hemorr NOS
530.80 esophageal disorder nec	593.81 renalvascular disorder
531.00 ac stomach ulcer w hem	599.70 hematuria
531.01 ac stomach ulcer w hem-obst	623.80 noninflam dis vagina nec
531.20 ac stomach ulc w hem/perf	626.20 excessive menstruation
531.21 ac stomach ulc w hem/perf-obst	626.60 metrorrhagia
531.40 chr stomach ulc w hem	719.10 hemarthrosis-unspec
531.41 chr stomach ulc w hem-obst	719.11 hemarthrosis-shoulder
531.60 chr stomach ulc hem/perf	719.12 hemarthrosis-up/arm
531.61 chr stomach ulc hem/perf-obst	719.13 hemarthrosis-forearm
532.00 ac duodenal ulcer w hem	719.14 hemarthrosis-hand
532.01 ac duodenal ulcer w hem-obst	719.15 hemarthrosis-pelvis
532.20 ac duodenal ulc w hem/perf	719.16 hemarthrosis-l/leg
532.21 ac duodenal ulc w hem/perf-obst	719.17 hemarthrosis-ankle
532.40 chr duoden ulcer w hem	719.18 hemarthrosis-jt, nec
532.41 chr duoden ulcer w hem-obst	784.70 epistaxis
532.60 chr duoden ulc w hem/perf	784.80 Hemorrhage from throat
532.61 chr duoden ulc w hem/perf-obst	786.30 hemoptysis
533.00 ac peptic ulc w hemorr	
533.01 ac peptic ulc w hemorr-obst	
533.20 ac peptic ulc w hem/perf	
533.21 ac peptic ulc w hem/perf-obst	
533.40 chr peptic ulcer w hem	
533.41 chr peptic ulcer w hem-obst	
533.60 chr peptic lc w hem/perf	
533.61 chr peptic lc w hem/perf-obst	
534.00 ac marginal ulcer w hem	
534.01 ac marginal ulcer w hem-obst	
534.20 ac margin ulc w hem/perf	
534.21 ac margin ulc w hem/perf-obst	
534.40 chr marginal ulcer w hem	
534.41 chr marginal ulcer w hem-obst	
534.60 chr marg ulc w hem/perf	
534.61 chr marg ulc w hem/perf-obst	
535.01 acute gastritis with hemorrhage	
535.11 Atrophic gastritis with hemorrhage	
535.21 gastr mucosoal hypertroph with hemorrhage	
535.31 alcoholic gastritis with hemorrhage	
535.41 gastritis nec with hemorrhage	

CHAPTER II

Genetic Testing to Predict Treatment Outcomes in Early-Stage Lung Cancer: The Value of Future Research

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ABSTRACT

Background

Recent observational research has identified numerous biomarkers with the potential to optimize non-small cell lung cancer (NSCLC) treatment decisions and outcomes. Rigorous prospective evaluation will likely be required before candidate markers are utilized in routine clinical practice. However, given resource constraints, such studies are only feasible for a sub-set of promising biomarkers. Value of information (VOI) analysis is an emerging comparative effectiveness method that can be used to prioritize biomarkers for future research under these conditions.

Objective

Assess the value of future research for *ERCC1* expression testing to inform adjuvant chemotherapy decisions in Stage I NSCLC in the United States.

Methods

We developed a decision-analytic model to synthesize current data about morbidity, mortality, and cost for *ERCC1*-guided and non-guided chemotherapy strategies. Model inputs were derived from the International Adjuvant Lung Trial (IALT), SEER, and published and unpublished sources. VOI methods were used to calculate the expected value of a future *ERCC1* testing clinical trial with sample sizes of 125 to 1,000 subjects per arm. The expected net benefit of each sample size was calculated by subtracting trial cost from trial value.

Results

The expected value of the trial with 125, 250, 500, and 1,000 subjects per arm was $57m, $75m, $84m, and $86, respectively. The expected net benefit of each sample size was $50m, $61m, $54m, and $29m, respectively. Reducing uncertainty about the *ERCC1* negative overall survival predictive hazard ratio was particularly high-value.

Conclusions

Considerable societal value could be realized through a clinical trial to evaluate *ERCC1*-guided chemotherapy in stage I NSCLC. At an optimal sample size of 250 subjects per arm, trial value is approximately double trial cost, compares favorably to value for other cancer biomarkers, and has significant upside related to expanding low-dose CT screening, stage shifts, and resulting increases in the *ERCC1* testing affected population. This type of VOI approach to trial evaluation can inform future design and prioritization decisions.

BACKGROUND

Non-Small Cell Lung Cancer Epidemiology

Non-small cell lung cancer (NSCLC) is among the most common cancer sub-groups in the United States, with approximately 192,000 incident cases expected in 2012.(90) Due to the asymptomatic nature of the disease at early stages, only about 15% of cases are diagnosed with Stage I disease. (91) Though Stage I patients have better survival prognosis relative to those with more advanced stages, 5-year survival is approximately 50%. (91-93) In this context, personalized medicine strategies have the potential to optimize health outcomes by identifying patients at high risk of developing disease, enhancing the rate of detection of early disease, and informing treatment selection for those that have diagnosed disease.(17, 94) Successful development and translation of these types of biomarkers can result in meaningful public health impact given the substantial incidence, morbidity, and mortality associated with lung cancer in the United States.(17, 94, 95)

Standard Guideline-Based Adjuvant Chemotherapy Strategies

Standard care for Stage I NSCLC is generally intended to be curative, and often begins with surgery to completely resect the tumor(s).(96, 97) After surgery, patients and clinicians are faced with a decision about whether adjuvant chemotherapy should be utilized to reduce the risk of disease recurrence. This decision is typically informed by a variety of clinical and pathologic factors, with disease stage playing a prominent role.(96, 97) These prognostic factors are intended to provide a sense of the potential risk of recurrence so that the balance of benefits and risks of adjuvant chemotherapy can be weighed. However, a number of large clinical trials have demonstrated a lack of adjuvant chemotherapy survival benefit in Stage I NSCLC, and so

clinical guidelines, like those from the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN), generally recommend against adjuvant chemotherapy for Stage I patients.(96-98)

Biomarker-Informed Adjuvant Chemotherapy Strategies

Though Stage I patients do not derive chemotherapy benefit on average, recent biomarker research has indicated that sub-groups may derive significant benefit.(17, 99-102) One prominent candidate biomarker that has emerged from this line of research is Excision Repair Cross Complementation Group 1 (*ERCC1*) gene expression levels. *ERCC1* is a gene that codes for a protein involved in the DNA damage repair pathway. (17, 103-106) In completely resected patients that do not receive adjuvant chemotherapy, patients with tumors expressing high *ERCC1* levels (*ERCC1* positive) may have favorable survival prognosis relative to those with tumors expressing low *ERCC1* levels (HR: 0.77, 95% CI: 0.56-1.05).(99) Additionally, *ERCC1* negative patients have been demonstrated to have significant platinum-based adjuvant chemotherapy overall survival benefit (HR: 0.73, 95% CI: 0.55-0.96), while *ERCC1* positive do not (HR: 1.01, 95% CI: 0.74-1.38).(99) Despite the growing body of observational evidence supporting these associations, there remains considerable uncertainty about the comparative effectiveness of *ERCC1*-guided strategies relative to standard guideline-based strategies due to the limitations of retrospective designs, and limited statistical power in many of the studies.(17, 106, 107) *ERCC1* testing will likely need to undergo rigorous prospective evaluation to determine if it will take the final translational steps toward routine clinical application.(17, 106, 107) However, given the resource-intensive nature of clinical trials, it is unclear if investing in an *ERCC1* testing clinical trial would be a high-value use of scarce research resources.

Value of Information Analysis to Inform Biomarker Translation

Value of information (VOI) analysis is an emerging comparative effectiveness research method that can be used to assess and prioritize investment in biomarker translation with the objective of maximizing societal return on investment.(108-114), VOI analysis has recently garnered attention from a variety of prominent research funding entities, including the National Heart, Lung, and Blood Institute, National Cancer Institute, Agency for Healthcare Research and Quality, and Patient Centered Outcomes Research Institute.(113-116)

Objective

The objective of this study is to assess the value of future research for *ERCC1*-guided adjuvant chemotherapy in Stage I NSCLC. Specifically, we assessed the value of a future clinical trial, and compared our findings with the value of research in other cancer biomarkers. The results of this analysis can be used to inform research design and prioritization decisions for a variety of stakeholders, including funding agencies, clinical researchers, and biomarker developers.

METHODS

Study Context

This study was conducted in support of the Center for Comparative Effectiveness Research in Cancer Genomics (CANCERGEN), a multidisciplinary consortium including the Fred Hutchinson Cancer Research Center (FHCRC), University of Washington, the Center for Medical Technology Policy (CMTP), and SWOG, one of the largest of the National Cancer Institute-supported cancer clinical trials cooperative groups in the United States.(117-119) The

overall mission of CANCERGEN is to generate high quality evidence regarding the clinical utility and economic value of genomic technology applications compared to standard care.(117) As a part of this project, an External Stakeholder Advisory Group (ESAG) was tasked with creating a priority ranking of six biomarkers in cancer for evaluation in a prospective comparative effectiveness trial to potentially be carried out by SWOG.(117-119) Preliminary analyses of the VOI of *ERCC1* were used to inform the priority ranking, but the results presented herein are more detailed and informative for trial design, including a ranking of the value of individual variables involved in an *ERCC1*-guided adjuvant chemotherapy strategy.

Analytic Framework

Decision Model Structure

We developed a decision-analytic model to simulate health outcomes for a cohort of patients with completely resected stage I NSCLC from the time of adjuvant chemotherapy decision-making until death (Figure 1). Upon entering the model, the cohort is allocated to either *ERCC1* expression testing or a standard guideline-based approach to inform the decision of whether to receive adjuvant chemotherapy. In the *ERCC1* testing strategy, patients that test *ERCC1* positive are not considered indicated to receive adjuvant chemotherapy, and patients that test *ERCC1* negative are indicated to receive adjuvant chemotherapy with cisplatin and vinorelbine. In the standard guideline-based strategy, all patients are not indicated for adjuvant chemotherapy, in accordance with clinical guidelines from the American Society for Clinical Oncology (ASCO).(96) Patients in each strategy can follow the indicated chemotherapy pathway or deviate from the pathway.

All patients are tracked for adverse events, distant recurrence, overall survival, and quality adjusted life years (QALYs) over their lifetime (Figure 1). The quality-adjusted life-year (QALY) is a standard metric from comparative effectiveness research that incorporates a quality of life "utility score" adjustment with life expectancy.(120-122) A utility score of 0 represents the value for death and 1 represents the value for "full" health. Thus, 10 years of life at a utility of 0.5 is equivalent to 5 years of life with full health.(121) Thus, the QALY can be used to compare the morbidity and mortality of strategies in a single measure.

Outcome uncertainty was evaluated using Monte Carlo simulation methods.(123-125) This approach involved specifying the prior distributions of each model input, repeatedly sampling from each input distribution, and propagating the values through the model framework to calculate outcomes. (123, 124)

The decision model was implemented in Microsoft Excel (Microsoft Inc., Redmond, WA).

Decision Model Inputs

Model inputs were derived from the International Adjuvant Lung Trial Surveillance Epidemiology and End Results (SEER) database, published literature, and government sources. (91, 99, 126-129) We derived model inputs from the results of retrospective analyses of the International Adjuvant Lung Trial (IALT) where possible.(99, 128, 129) The IALT was a Phase III randomized controlled trial comparing cisplatin-based adjuvant chemotherapy with monitoring only in 1,867 early-stage (I-III) NSCLC patients across 33 countries. (126, 127) Current understanding of the prognostic and predictive implications of *ERCC1* expression is

largely based on several retrospective analyses of long-term outcomes in the IALT cohort stratified by *ERCC1* expression level.(99, 128, 129)

Mean parameter values and uncertainty ranges were derived directly from source studies when possible. Assumptions were implemented for variables that were not reported in the literature. Our primary assumption was that in the *ERCC1*-guided strategy, the proportion choosing adjuvant chemotherapy would increase slightly relative to standard care, and not all patients who choose adjuvant chemotherapy are indicated by *ERCC1* negative status. Specifically, we assumed that an average of 10% of *ERCC1* positive and 40% of *ERCC1* negative patients decide to receive chemotherapy based on evidence of chemotherapy utilization in 10%-30% of standard care patients.(130-134)

Table 1 provides our model inputs, uncertainty ranges, and data sources. A more detailed discussion of our assumptions, data sources, and rationale for selecting point estimates and uncertainty ranges is provided in Appendix A.

Value of Information Approach

Calculation of Expected Net Monetary Benefit

Using the results generated in our Monte Carlo simulation, we calculated the expected net monetary benefit (NMB) of each strategy. The NMB combines cost and quality-adjusted survival in a single metric to facilitate comparison of strategies in monetary terms, and is derived from the formula: $[\lambda * QALYs] - Cost$, with λ defined as the willingness-to-pay per quality-adjusted life year gained.(108, 135) The NMB expresses how much value a given technology provides in

excess of the given willingness-to-pay threshold. When comparing the NMB of different strategies, the strategy with higher NMB is considered to be optimal. This type of comparison can be made over thousands of Monte Carlo simulations, with the strategy that results in greater NMB on average defined as optimal.

Given the lack of an explicit willingness to pay threshold (per QALY) in the United States, we calculated the value of research over a range of $50,000 to $200,000 per QALY gained.(136-139) We believe that this range reflects the implied willingness-to-pay for cancer treatments in the United States, and is consistent with values used in prior analyses.(114, 136, 140)

Calculation of the Maximum Value of Information

In order to facilitate comparison with previous analyses, we estimated the maximum value of future research (also known as the "Expected Value of Perfect Information"). The maximum value of information was calculated by determining how frequently the non-optimal strategy produced greater NMB, as well as the magnitude of those NMB differences.(141, 142) Accordingly, the maximum value of research is the upper bound of the potential value of future research, and represents a hypothetical scenario where all uncertainty is eliminated and there is no opportunity loss.(141, 142)

Calculation of the Value of an ERCC1 Testing Clinical Trial

To provide a more realistic estimate of the value of information, we also calculated the value of a specific clinical trial design with specific sample sizes. Our hypothetical, future clinical trial enrolls post-operative Stage I NSCLC patients who have not received previous adjuvant

chemotherapy. Included subjects undergo *ERCC1* expression testing, are classified as *ERCC1* positive or negative, and are block-randomization by *ERCC1* status to receive adjuvant chemotherapy (cisplatin+vinorelbine) or monitoring only. The trial endpoints include overall survival, distant recurrence, safety, and health-related quality of life. Using publically available clinical trial cost resources, we approximated the overall cost of the trial per patient per year, and average duration of follow-up (Table 2).(127, 143-146)

To estimate the value of the trial design (also known as the "Expected Value of Partial Sample Information), we calculated the difference between the incremental NMB of the optimal strategy with current information, and the incremental net benefit of the optimal strategy with reduced uncertainty after the trial. (108-110, 147) Thus, value was measured through reduced variance in model inputs and outcomes commensurate with the trial's sample size, and the resulting ability to choose the optimal strategy with greater certainty. This result provides per-patient value that can be scaled to the population level using the affected population, compared with the cost of research, and used to calculate the return on research investment.(112, 142, 148)

Affected Population

The value of information accounts for the affected population over the useful lifetime of the optimal strategy (Table 2). To enumerate the affected population, we first determined the annual affected population through an analysis of Surveillance Epidemiology and End Results (SEER) incidence data for Stage I NSCLC.(91) Next, we summed the annual affected population over the estimated useful lifetime of the optimal strategy, the period of time before the optimal strategy is expected to be displaced by an alternative strategy. This input was informed by expert opinion

given a lack of data sources. We also defined a rate of diffusion into clinical practice to reflect that, if optimal, *ERCC1* testing would be gradually (rather than instantly) adopted by clinicians following the trial. The rate of diffusion was implemented as a linear additive function (Table 2).

Calculation of the Expected Net-Benefit of Conducting the Clinical Trial

To estimate the expected net-benefit of the clinical trial, we subtracted the estimated cost of the trial from the population value of information for the clinical trial. To provide a more realistic estimate of the expected net benefit, we modified the 5-year affected population to account for gradual diffusion of *ERCC1* testing into clinical practice, and discounted the trial value beginning 10 years in the future to account for the time lag between the present and the release of the hypothetical trial results. The resulting expected net benefit the United States societal value that is expected to be realized, in excess of cost, as a result of the information provided by the *ERCC1* clinical trial (i.e. the return on research investment).

Given uncertainty about each of the affected population and trial inputs, we felt it was important to examine uncertainty around the value of information and expected net benefit results. To do so, we specified high and low values for each affected population and trial variable, and conducted a one-way sensitivity analysis for both the value of the trial and expected net benefit of the trial.

Value of Information Calculation Algorithms

Our value of information calculations utilized the two-level Monte Carlo simulation algorithm described by Ades et al., Brennan et al, and others.(108, 149) The theory and procedures involved in this approach are described in detail elsewhere.(108, 110, 111, 150) The algorithm

was implemented in Microsoft Excel (Microsoft Inc., Redmond, WA) and R (R Foundation, Vienna, Austria)/Winbugs (Bugs Project, Cambridge, UK) to allow comparison of results.

Our analyses utilized 2012 United States costs, and discounted value of information at 3% per year.

RESULTS

Maximum Value of Information

In the model simulation, the *ERCC1* strategy was optimal, producing greater net monetary benefit in 74% of simulations at a willingness-to-pay of $150,000 per QALY (Table 3). In the 26% of simulations where the standard care strategy was favored, the opportunity loss was 0.08 life years, 0.05 QALYs, and $7,600 in net monetary benefit. In other words, compared to a scenario with no uncertainty about the optimal strategy, current uncertainty levels resulted decreased survival and quality-adjusted survival, and increased cost. The corresponding maximum value of information was $2,012 per patient. In the base case 5-year affected population of 180,000 patients, the total EVPI was $362 million (Table 4).

Clinical Trial Value of Information

In our analysis of the value of a clinical trial design with 500 patients per arm, the *ERCC1* strategy was still optimal, producing greater net monetary benefit than the standard care strategy in 88% of simulations (14% more simulations than with current uncertainty levels). The resulting average net monetary benefit opportunity loss was $6,450, and the corresponding value of the trial was $207 million for the maximum base case 5-year affected population of 180,000. Thus, compared to current uncertainty levels, the post-clinical trial scenario resulted in gains of value

of approximately $1,150 per affected patient (Table 4). When we examined the value of the clinical trial with alternative sample sizes of 125, 250, and 1,000 per arm, the value of information was $156 million, $199 million, $235 million, and $413 million, respectively for the maximum 5-year affected population of 180,000.

In analyses of the per-patient value of information for the individual variables investigated in the clinical trial, the *ERCC1* negative overall survival predictive hazard ratios had the highest value at $73 million ($406 per patient) at a sample size of 500 patients per arm (Figure 2).

Return on Investment (Net Benefit)

With the value of the clinical trial design with sample sizes of 125, 250, 500, and 1,000 per arm were $57m, $75m, $85m, and $86 million, respectively. When these values were compared with the cost of the trial, the expected net benefit (or return on investment) was $28m, $47m, $54m, and $57m, respectively (Table 5).

In one-way sensitivity analyses of the clinical trial net benefit over plausible ranges of incidence, *ERCC1* testing diffusion, and useful lifetime of *ERCC1* testing, trial designs with 125 to 1,000 subjects per arms ranged from a loss of $39 million to a gain of $232 million (Figure 3). The most influential variable was disease incidence, but the variable that led to negative return on investment was overwhelmingly the useful lifetime of *ERCC1* testing.

DISCUSSION

Summary

The rapid pace of biomarker discovery necessitates new approaches to systematically assess and prioritize biomarkers for prospective evaluation so that research resources generate maximum return on investment. Value of information analysis can meet this need by providing estimates of the value of future research that can be compared between technologies to facilitate priority ranking. We applied this approach to evaluate *ERCC1* expression testing, a promising prognostic and predictive biomarker in Stage I NSCLC. Our VOI analysis demonstrated that *ERCC1* testing research is generally of high value, and that a specific clinical trial designs with a sample size of 125, 250, 500, and 1,000 per arm are expected to result in $57m, $75m. $84m, and $86 in societal value over a 5-year time horizon, respectively. The net benefit of each design, or the value in excess of the trial cost, is expected to be $50m, $61m, $54m, and $29m, respectively.

Implications

Our results have several important implications for the design, sample size, and prioritization of a future *ERCC1* testing trial. First, we find that even a small trial is expected to be of high value, as even a sample size of 125 subjects per arm provides an approximate 50% increase in information about most variables (relative to current information), and results in expected value of $57m and expected net benefit of $50m (Figure 4). Second, this analysis reveals the point of diminishing returns on the clinical trial sample size is approximately 250 subjects per arm. Beyond this sample size, uncertainty about the trial variables is reduced to a degree that opportunity loss is minimal, and further trial cost increases at a faster rate trial than trial value (Figure 4). In one-way sensitivity analyses we found that a sample size of 250 per arm is

expected to result in positive net benefit across variables ranges, and has upside value of up to $222m (Figure 3). This upside value is driven by the assumption that increasingly sensitive screening modalities will be utilized over the 10-year duration of the clinical trial (e.g. low-dose CT), and that by the time trial results are available, as much as 50% of NSCLC will be diagnosed at Stage I.(151, 152) These types of quantitative insights can inform biomarker research stakeholders as they attempt to design and prioritize future studies.

In our analysis of the value of individual variables, the *ERCC1* negative predictive overall survival hazard ratio was of particularly high value. This finding demonstrates that the comparative effectiveness of an *ERCC1*-guided chemotherapy strategy is largely driven by the magnitude of survival benefit in *ERCC1* negative patients who receive adjuvant chemotherapy. The influence of the *ERCC1* predictive hazard ratio is attributable to the highly uncertain magnitude of chemotherapy benefit, and the strong influence of chemotherapy benefit on comparative survival and net-monetary benefit. This finding suggests that future *ERCC1* testing research designs that resolve uncertainty about the effectiveness of platinum-based chemotherapy in *ERCC1* negative patients should be of relatively high priority compared to research that focuses on other *ERCC1* endpoints.

Reducing uncertainty about the *ERCC1* positive predictive hazard ratio, *ERCC1* negative distant recurrence relative risk, and *ERCC1* positive distant recurrence relative risk was also shown to be of moderate value (Figure 2). The value of reducing uncertainty about these variables was lower than the *ERCC1* negative predictive hazard ratio and chemotherapy uptake rate because they had less influence on determining the optimal strategy. For example, the *ERCC1* positive

predictive hazard ratio, was of lower relative value because the prior distribution of the hazard ratio is a null effect (HR: 1.01, 0.74 to 1.38).(99) This type of systemic and quantitative approach to assessing the comparative value of specific variables can prove useful to biomarker stakeholders looking to understand the relative merits and tradeoffs of measuring different endpoints in future research.

Limitations

This study has several limitations that are worth noting. First, we investigated overall survival as the primary endpoint in our future *ERCC1* testing clinical trial, but other endpoints could be selected. Based on endpoint selection, the cost of the trial and value to society could vary considerably relative to the design we evaluate above. Thus, it should be noted that even though *ERCC1* expression testing in Stage I NSCLC is a generally high-value research area, the return on investment could vary significantly based on research design.

Our analyses of the value of information for individual variables demonstrated that reducing uncertainty about chemotherapy uptake in *ERCC1* negative patients is a particularly high value research area. This finding reflects the fact that if *ERCC1* negative patients prefer to receive monitoring only, an *ERCC1*-guided chemotherapy strategy has significantly less potential to be optimal versus standard care, regardless of the magnitude of chemotherapy benefit. These factors were modeled as independent because we believe that patient's adjuvant chemotherapy preferences will be relatively insensitive to the magnitude of the hazard ratio (given that the point estimate is expected demonstrate only a moderate protective effect). However, it is possible that the chemotherapy preferences of some patients may change if future research demonstrates

the average adjuvant chemotherapy benefit to be slightly increased or attenuated. If this scenario were true, it could have implications for the value of research for the *ERCC1* negative hazard ratio, chemotherapy uptake rate, and the overall clinical trial. This anecdote illustrates the complexity of structuring value of information analyses, as well as the limitations of using any mathematical modeling approach to interpret multidimensional phenomena.

Lastly, a general limitation of value of information approach to assessing future research is that it requires specification of the useful lifetime of the technology.(112) This variable is difficult to ascertain even if no market competitors are expected over the given time horizon. However, in an ever-expanding biomarker market, there will certainly be many such competitors. The expected time period before such a competitor renders *ERCC1* testing obsolete is likely a function of the rate of discovery of biomarkers with superior comparative effectiveness, as well as the probability that such a competitor undergoes sufficiently rigorous evaluation to establish market dominance. As discussed in the background, this type of evidence has been generated for extremely few biomarkers to date, and may not be generated in the future, even if there was a successful *ERCC1* trial experience. We have conducted one-way sensitivity analyses to attempt to quantify the impact of these uncertainties on the value of the *ERCC1* clinical trial.

Comparison with Previous VOI Research

When considered in the context of the maximum value of information for alternative cancer biomarkers, *ERCC1* testing research is of relatively high value (Table 6). The comparative value of *ERCC1* testing research is driven by the large affected population, and significant expected opportunity loss associated with *ERCC1* testing uncertainty. We compared biomarkers on the

basis of maximum value of information, the only value of information results reported in the comparator studies.(140, 153, 154) The realistic value of clinical trials (or other research designs) will be much less, and non-proportional in the majority of cases. This is because the value of information for specific designs is driven, in part, by the sample size underlying variable prior distributions. Thus, if current information for different technologies is based on different sample sizes, the specific value of information for future research for each technology will approach the maximum value of information at different rates with increasing sample size.

CONCLUSION

We assessed the value and return on investment for a future clinical trial to evaluate the comparative effectiveness of an *ERCC1*-guided adjuvant chemotherapy strategy in Stage I NSCLC. Our results demonstrate that considerable societal value could be realized through a clinical trial design randomizing *ERCC1* positive and negative subjects to either cisplatin-based adjuvant chemotherapy or monitoring only. The trial design we evaluated is expected to result in $30m to $60m in value in excess of the expected cost of the trial, compares favorably to VOI for other cancer biomarkers, and has significant upside related to expanding low-dose CT screening, stage shifts, and subsequent increases in the *ERCC1* testing affected population. These results can inform investment in future *ERCC1* testing research, and provides a common metric to compare and prioritize designs within and between emerging biomarkers.

Model Inputs	Mean	95% CI Lower	95% CI Upper	Distribution	Reference
***ERCC1* Expression Testing Inputs**					
% Testing *ERCC1* Positive	50%	40%	60%	Beta	(155)
Cost of *ERCC1* Expression Testing	$300	$240	$360	Normal	(156)
***ERCC1* Positive (+) Survival Inputs**					
ERCC1+ Mean OS (No Chemo)	6.78	-	-	Constant	(155)
ERCC1+ OS Predictive HR	1.01	0.74	1.38	Log Normal	(99)
ERCC1+ % Distant Recurrence (No Chemo)	22%	-	-	Constant	(157)
ERCC1+ Distant Recurrence Relative Risk	0.96	0.67	1.25	Log Normal	(99)
***ERCC1* Negative (-) Survival Inputs**					
ERCC1- Mean OS (No Chemo)	5.73	-	-	Constant	(155)
ERCC1- OS Predictive HR	0.73	0.44	1.02	Log Normal	(99)
ERCC1- % Distant Recurrence (No Chemo)	25%	-	-	Constant	(157)
ERCC1- Distant Recurrence Relative Risk	0.81	0.57	1.05	Log Normal	(99)
Common Survival Inputs					
Time from Recurrence to Death (Years)	1.0	0.5	1.5	Normal	Assumption
Adjuvant Chemotherapy Inputs					
ERCC1 Positive % Choosing Chemotherapy	10%	5%	15%	Beta	Assumption
ERCC1 Negative % Choosing Chemotherapy	40%	8%	72%	Beta	Assumption
Standard Care % Choosing Chemotherapy	20%	6%	34%	Beta	(130)
Cisplatin+Vinorelbine Direct Cost	$6,154	$4,308	$8,000	Normal	(158)
Mean Cycles of Cisplatin+Vinorelbine	3.0	-	-	Constant	(146)
Chemotherapy Adverse Event Inputs					
% With Grade 3/4 AE on Cisplatin+Vinorelbine	80%	68%	92%	Beta	(98)
Mean Duration of Grade 3/4 AE (Years)	0.16	0.08	0.24	Normal	Assumption
% of Grade 3/4 AEs Requiring Inpatient Care	20%	10%	30%	Beta	Assumption
Mean Cost of Inpatient Care for AE	$27,150	$19,005	$35,295	Normal	(159)
Mean Cost of Outpatient Care for AE	$140	$70	$210	Normal	(156)
Health State Utility Inputs					
No Evidence of Disease Utility	0.67	0.54	0.80	Beta	(160)
On Chemotherapy Utility	0.58	0.46	0.70	Beta	(161)
Chemotherapy Grade 3/4 Adverse Event Utility	0.46	0.28	0.64	Beta	(161)
Distant Recurrence Utility	0.49	0.39	0.59	Beta	(161)
Other Cost Inputs					
Mean Cost Per Month Before Distant Recurrence	$125	$63	$188	Normal	(156)
Mean Cost Per Month After Distant Recurrence	$5,627	$2,251	$9,003	Normal	(162)

SD=Standard Deviation, OS=Overall Survival, HR=Hazard Ratio, AE=Adverse Event

Table 1: Prior Distributions of Model Inputs. Standard care survival outcomes are calculating using weighted averages of *ERCC1* sub-group outcomes to maintain proper covariance between strategies during Monte Carlo simulation runs.

	Base Case Value	Low Value	High Value	Source
Stage I NSCLC Incidence in the United States	36,000	28,800	113,000	(91, 151)
Useful Lifetime of *ERCC1* Testing (Years)	5	2	8	Expert Opinion
Annual Rate of Diffusion into Clinical Practice	20%	10%	30%	Assumption
Clinical Trial Average Cost Per Subject Per Year	$4,000	$2,400	$6,400	(143, 145)
Mean Duration of Follow-Up Per Patient in Clinical Trial	8	6	10	(127, 146)
Per-Patient Value of the Clinical Trial	$846 ($100,000/QALY) $1,149 ($150,000/QALY) $1,425 ($200,000/QALY)	-	-	Calculated

Table 2: Clinical Trial Expected Net Benefit Inputs

	ERCC1 Testing (95% CI)	Standard Care (95% CI)	Incremental Outcome (95% CI)
Life Years	6.62 (6.05, 7.19)	6.46 (6.14, 6.78)	0.26 (-0.30, 0.74)
QALYs	4.37 (3.45, 5.29)	4.27 (3.42-5.12)	0.14 (-0.20, 0.48)
Cost	$17,641 ($12,140, $23,142)	$16,678 ($11,417, $21,939)	$1,172 (-$1,445, $3,789)
Net Monetary Benefit	$638,364 ($500,379, $776,349)	$624,467 ($496,617, $752,317)	$13,896 (-$28,116, $55,908)

CI=Credible Interval

Table 3: Monte Carlo Simulation Outcomes at a Willingness-to-Pay of $150,000 per QALY

	VOI at $100,000 per QALY ($ Millions)	VOI at $150,000 per QALY ($ Millions)	VOI at $200,000 per QALY ($ Millions)
Maximum Value of Information	$250	$363	$484
Value of Information for Clinical Trial			
Clinical Trial Total	$152	$207	$257
***ERCC1* Negative Predictive OS Hazard Ratio**	$53	$73	$95
***ERCC1* Negative Chemotherapy Uptake**	$0.4	$22	$43
***ERCC1* Positive Predictive OS Hazard Ratio**	$3	$4	$5
***ERCC1* Negative Distant Recurrence Relative Risk**	$23	$35	$48
***ERCC1* Positive Distant Recurrence Relative Risk**	$19	$27	$35

VOI=Value of Information, OS=Overall Survival

Table 4: Value of Information Results at Willingness to Pay of $100k, $150k, and $200k per Quality-Adjusted Life Year. The clinical trial values are for a sample size of 500 subjects per arm, and reflect the full 5-year affected population of 180,000. Variables that are not shown did not demonstrate value associated with reducing uncertainty in the clinical trial. Individual variable values do not sum to the total trial value because of interactions between variables when examined simultaneously.

Year of Analysis	Annual Trial Cost	Cumulative ERCC1 Testing Diffusion	Annual Affected Population	Annual Per-Patient Value of Information	Annual Population Value of Clinical Trial	
0	$4,000,000	0%	0	0	-$4,000,000	Clinical Trial Phase of Analysis
1	$3,883,495	0%	0	0	-$3,883,495	
2	$3,770,384	0%	0	0	-$3,770,384	
3	$3,660,567	0%	0	0	-$3,660,567	
4	$3,553,948	0%	0	0	-$3,553,948	
5	$2,587,826	0%	0	0	-$2,587,826	
6	$2,512,453	0%	0	0	-$2,512,453	
7	$1,626,183	0%	0	0	-$1,626,183	
8	$1,578,818	0%	0	0	-$1,578,818	
9	$1,532,833	0%	0	0	-$1,532,833	
10	$0	20%	7,200	$827	$5,955,641	Clinical Care Phase of Analysis
11	$0	40%	14,400	$803	$11,564,351	
12	$0	60%	21,600	$780	$16,841,289	
13	$0	80%	28,800	$757	$21,801,021	
14	$0	100%	36,000	$735	$26,457,549	
Total	**$28,706,508**	-	**108,000**	-	**$53,913,344**	

Table 5: Calculation of the Expected Net Benefit of an *ERCC1* Testing Clinical Trial. Values presented are for a willingness to pay of $150,000 per QALY, and for a sample size of 500 subjects per arm. Note that we implemented a conservative assumption that no patients receive *ERCC1* testing in routine care until the completion of the clinical trial phase.

Study	Biomarker Technology	WTP Threshold ($USD)	Per-Patient VOI ($USD)	Affected Population (Horizon)	Population VOI ($M USD)
Roth et al. (2012)	*ERCC1* Testing in Stage I NSCLC	$50,000	$669	180,000 (5-Year)	$120.40
		$100,000	$1,338		$240.80
Carlson et al. (2009)	EGFR testing in advanced NSCLC	$100,000	$381	87,480 (5-Year)	$31.40
Hall et al. (2012)*	Gene-Expression Profiling in Node-Positive Early-Stage Breast Cancer	£30,000 (~$50,000)	£3,045 (~$4,800)	79,250 (10-Year)	£212.0 (~$334.9)
Woods et al. (2012)*	CYP2D6 Testing in Early-Stage Breast Cancer	£30,000 (~$50,000)	£540 (~$850)	196,092 (10-Year)	£106.0 (~$167.5)

WTP=Willingness to Pay, VOI=Value of Information, USD=United States Dollars

***Studies utilizing U.K. costs and affected population, so population VOI not directly comparable with Roth (2012) and Carlson (2009)**

*Maximum value of research, discounted at 3% per year, assumes instant 100% diffusion for consistency with comparators
&Maximum value of research, discounted at 3% per year
^Maximum value of research, discounted at 3.5% per year
#Maximum value of a clinical trial, undiscounted

Table 6: Value of Cancer Biomarker Research. All studies are compared in terms of maximum value of information. Our results are presented at willingness to pay thresholds of $50,000 and $100,000 per QALY to allow comparison with the other studies in like terms.

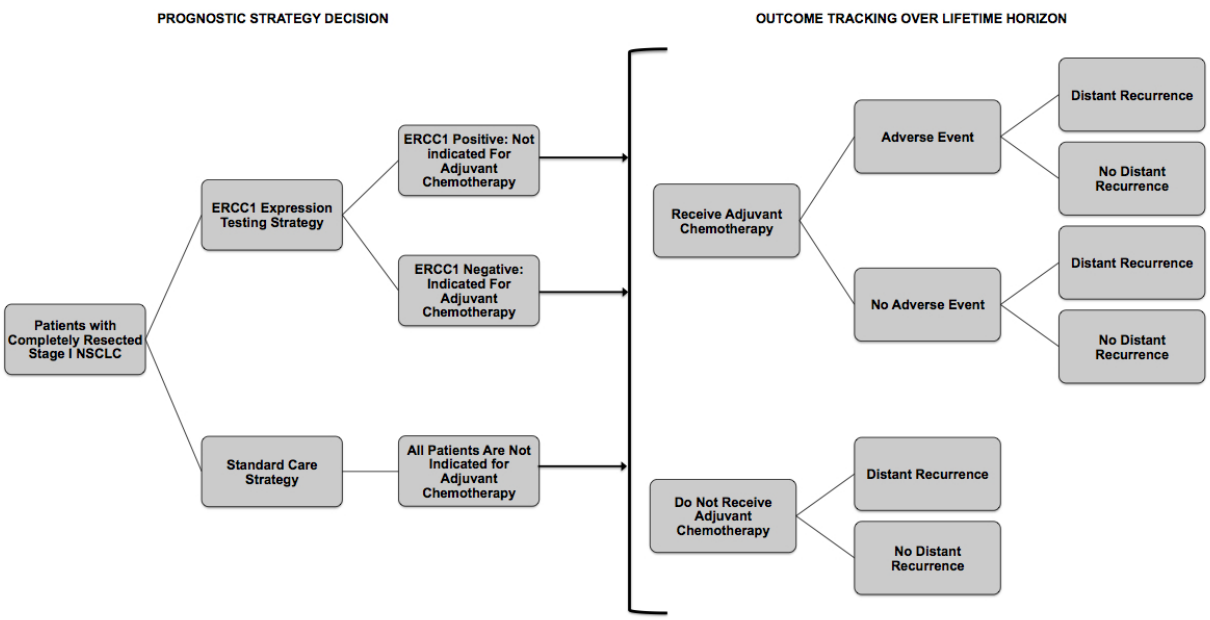

Figure 1: Decision model structure. Patients move from left to right through the model. All patients are tracked until death.

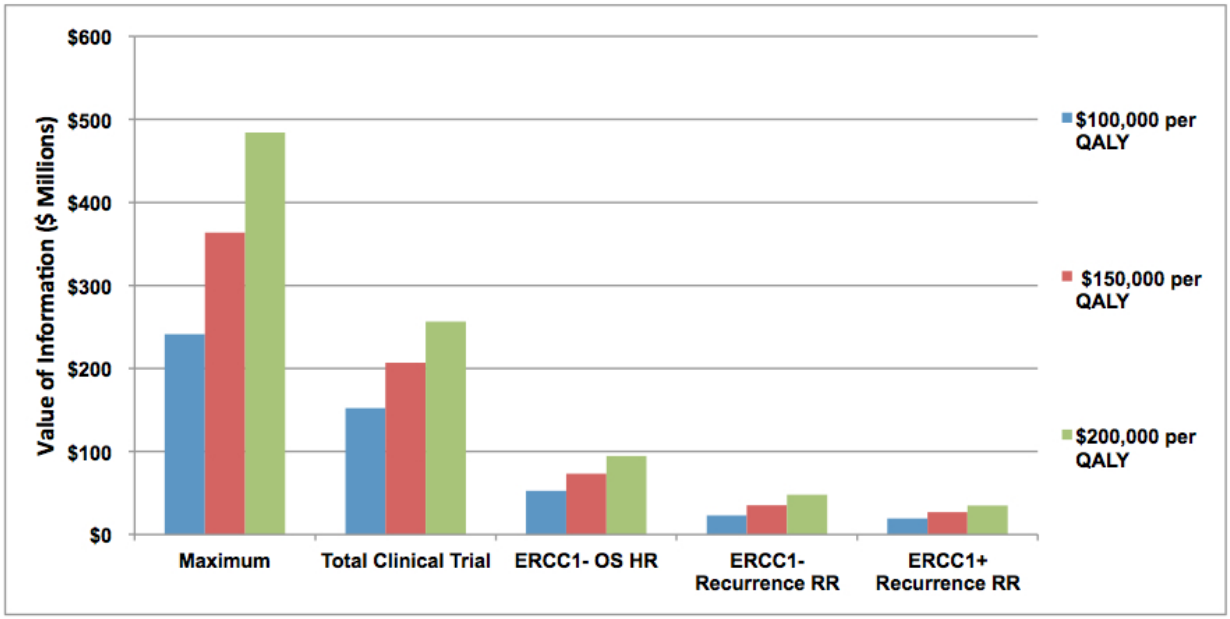

Figure 2: Comparison of maximum, clinical trial, and variable value of information. All clinical trial values are for a sample size of 500 subjects per arm, and reflect the full 5-year affected population of 180,000.

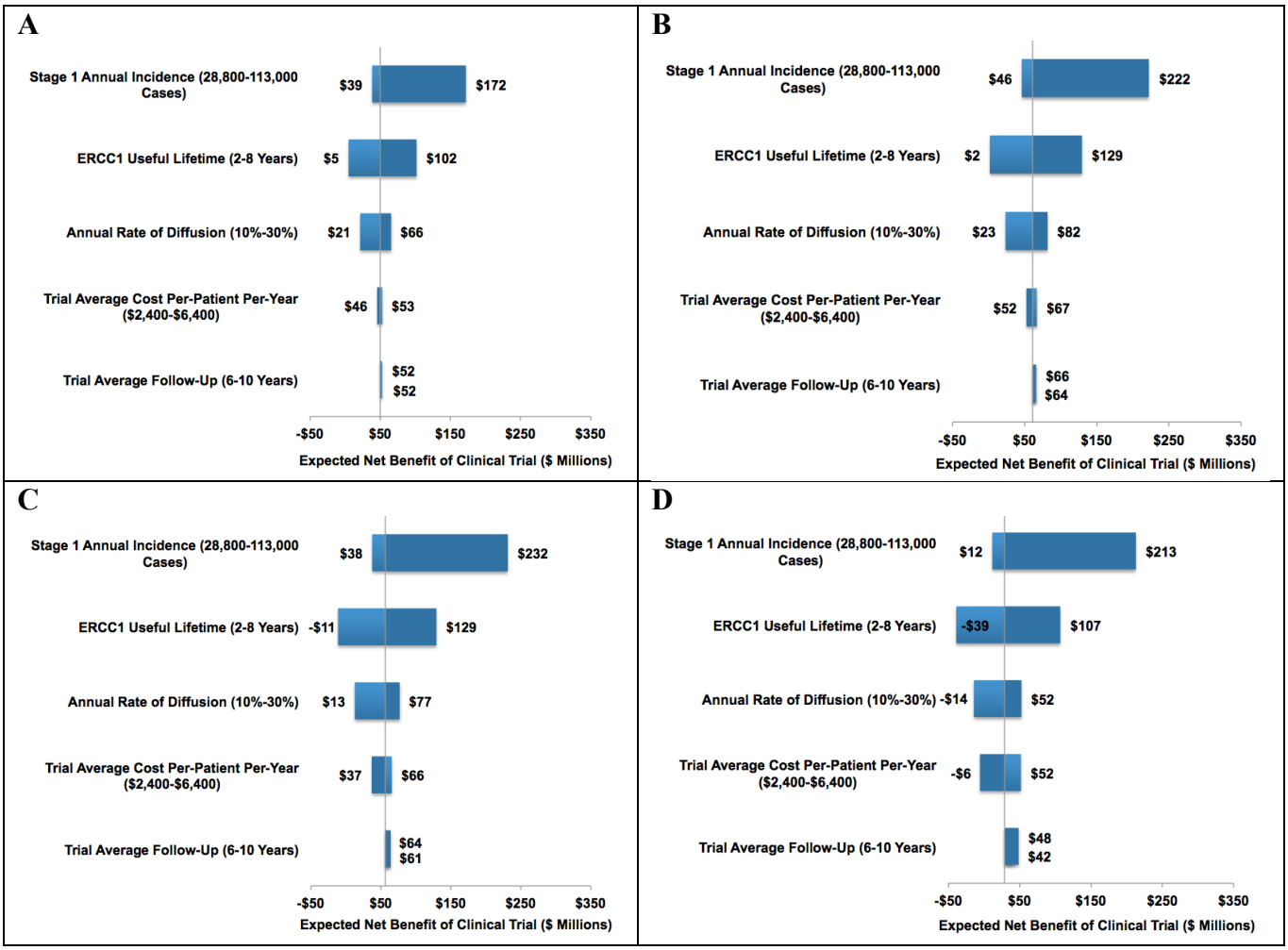

Figure 3: *ERCC1* clinical trial net-benefit one-way sensitivity analysis at sample sizes of (A) 125, (B) 250, and (C) 500, and (D) 1,000 subjects per arm. All analyses are for a willingness to pay of $150,000 per QALY.

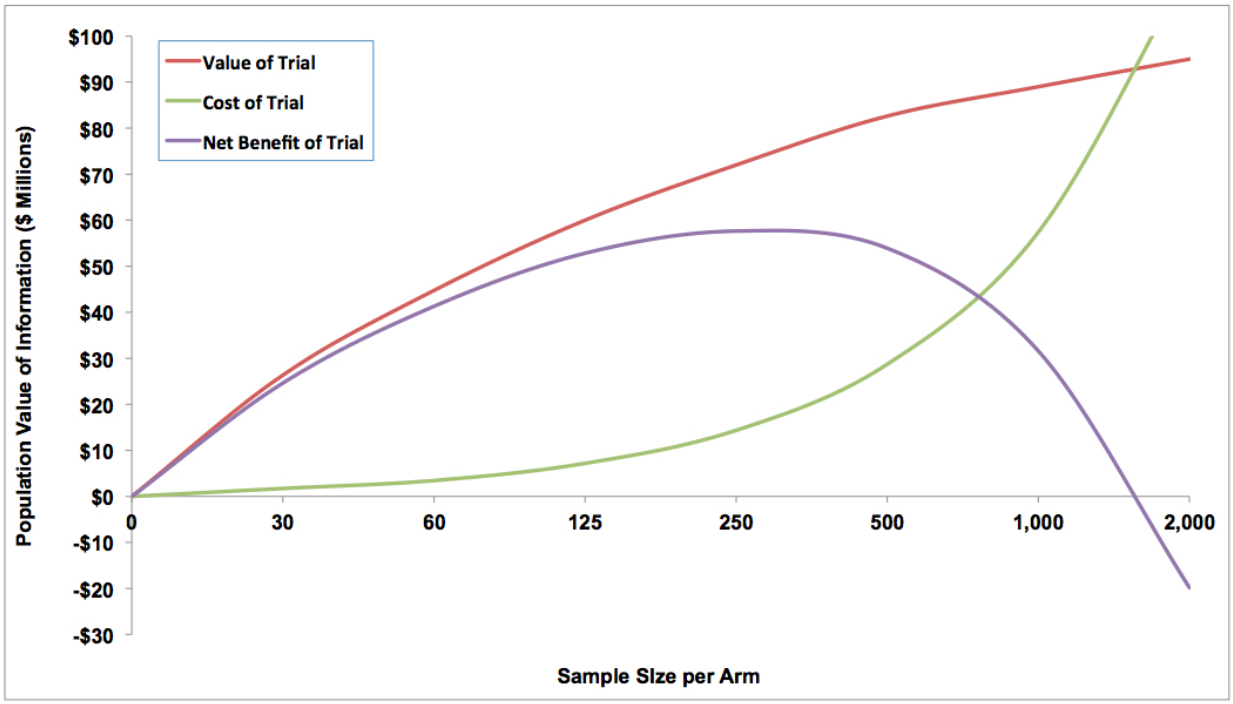

Figure 4: Clinical trial value of information, cost, and net benefit by sample size at a willingness to pay of $150,000 per QALY

APPENDIX A

Data Source Details

ERCC1 Testing in the International Adjuvant Lung Trial

Many of our model parameters were informed by the results of retrospective analyses of the International Adjuvant Lung Trial (IALT). The IALT was a Phase III randomized controlled trial comparing cisplatin-based adjuvant chemotherapy with monitoring only in 1,867 early-stage (I-III) NSCLC patients across 33 countries. (126, 127) The original analysis demonstrated statistically significant adjuvant chemotherapy overall survival benefit in Stage III patients, and small non-significant protective effects in Stage I and II patients.(126) Subsequent retrospective analyses of long-term outcomes the IALT cohort stratified by *ERCC1* expression status have demonstrated *ERCC1*-positive patients to have a better overall survival prognosis (HR: 0.77, 95% CI: 0.56-1.05 vs. *ERCC1*-negative), but *ERCC1*-negative patients to have predictive chemotherapy benefit (HR: 0.73, 95% CI: 0.55-0.96).(99, 128, 129) Our decision model parameters were informed by the IALT results where they appropriately applied to our simulated Stage 1 cohort.

ERCC1 Expression Testing

Model Inputs	Mean	95% CI Lower	95% CI Upper	Distribution	Reference
% Testing *ERCC1* Positive	50%	40%	60%	Beta	Zheng, 2007
Cost of *ERCC1* Expression Testing	$300	$240	$360	Normal	CPT 88361

The prior mean for the proportion of patients testing *ERCC1* positive was derived from a retrospective analysis of 184 patients with Stage I NSCLC that were treated at H. Lee Moffit Cancer Center between 1991 and 2001.(155) In the Zheng et al. analysis, Automated Quantitative in Situ Protein Analysis (AQUA) was used to characterize *ERCC1* expression level,

with the median expression level utilized as the threshold to define *ERCC1* positive (above the median) and negative (below the median).(155) The prior standard deviation for the proportion testing *ERCC1* positive was derived from the variability in the proportion testing *ERCC1* positive across several studies in early-stage NSCLC.(99, 163) These studies have utilized different *ERCC1* testing methods (e.g. IHC) and different expression cut points to define *ERCC1* positive/negative. The cost of *ERCC1* expression testing was based on CPT code 88361 (computer-assisted tumor immunohistochemistry), and was based on the costs of 100 patients.(156)

Overall Survival in Untreated Patients

Model Inputs	Mean	95% CI Lower	95% CI Upper	Distribution	Reference
ERCC1 Positive Mean OS (No Chemo)	6.78	-	-	Constant	Zheng, 2007
ERCC1 Negative Mean OS (No Chemo)	5.73	-	-	Constant	Zheng, 2007

The point estimate for mean overall survival in patients not receiving adjuvant chemotherapy was derived from the Zheng et al. analysis discussed above.(155) In this analysis, 184 patients were followed for up to 10-years, and assessed for all cause death.(155) To obtain mean overall survival values, we utilized the R based algorithm described by Guyot et al. to extract data points from the first 5 years of Kaplan-Meier curves stratified by *ERCC1* expression level.(164) Next, we fit Weibull curves to the Zheng et al. data points to project survival over a lifetime horizon.(165) Mean overall survival was fixed in the model, as we represented comparative overall survival uncertainty through the overall survival hazard ratio. Standard care overall survival was calculated as a weighted average of the proportion testing *ERCC1* positive/negative in order to maintain appropriate correlation in survival outcomes throughout model simulations.

Adjuvant Chemotherapy Overall Survival Hazard Ratios

Model Inputs	Mean	95% CI Lower	95% CI Upper	Distribution	Reference
ERCC1 Positive OS Predictive HR	1.01	0.74	1.38	Log Normal	Bepler, 2011
ERCC1 Negative OS Predictive HR	0.73	0.44	1.02	Log Normal	Bepler, 2011

The point estimates for the adjuvant chemotherapy overall survival hazard ratios (HR) in *ERCC1* positive and negative patients were derived from an analysis of the IALT cohort conducted by Bepler et al.(99) The IALT cohort included 119 Stage I *ERCC1* positive patients and 148 Stage I *ERCC1* negative patients.(128) However, stage-specific results were not reported, so we utilized the all-stage hazard ratio point estimates and standard deviations reported by Bepler et al.(99) It is important to note that the IALC cohort included Stage I-III patients (Stage I=35%, Stage 2=23%, Stage III=42%), so we assumed equivalent relative effectiveness and uncertainty in a uniformly Stage I cohort.(128) This assumption is more easily applied to *ERCC1* positive patients, who have consistently demonstrated a lack of adjuvant chemotherapy benefit across stages, relative to *ERCC1* negative patients who have a more uncertain level of effectiveness and uncertainty. The standard care chemotherapy overall survival outcomes were calculated as weighted averages of the proportion testing *ERCC1* positive/negative in order to maintain appropriate correlation in survival outcomes throughout our model simulations.

Distant Recurrence Inputs

Model Inputs	Mean	95% CI Lower	95% CI Upper	Distribution	Reference
ERCC1 Positive % Distant Recurrence (No Chemo)	22%	-	-	Constant	Goodgame, 2004
ERCC1 Negative % Distant Recurrence (No Chemo)	25%	-	-	Constant	Goodgame, 2004
ERCC1 Positive Distant Recurrence Relative Risk	0.96	0.67	1.25	Log Normal	Bepler, 2011
ERCC1 Positive Distant	0.81	0.57	1.05	Log Normal	Bepler, 2011

Recurrence Relative Risk					
Time from Recurrence to Death (Years)	1.0	0.5	1.5	Normal	Assumption
Mean Cost Per Month After Distant Recurrence	$5,627	$2,251	$9,003	Normal	Yabroff, 2008

The point estimate and standard deviation for the proportion of untreated patients experiencing distant recurrence was derived from a study of Stage I NSCLC outcomes in 429 patients age 70 or younger conducted by Goodgame et al.(157) This study evaluated health outcomes for all patients who underwent surgical resection for stage I NSCLC at Washington University School of Medicine-between 1990 to 2000. (157) Results were not reported stratified by *ERCC1* status, so we used the reported 5-year distant recurrence proportion for patients age 70 or younger to impute distant recurrence proportions for untreated *ERCC1* positive and negative patients based on the relationship between *ERCC1*-specific recurrence and average recurrence in Bepler et al. (99) We calculated the 5-year relative risk of distant recurrence for patients receiving adjuvant chemotherapy by examining the proportions of patients with recurrence at 5-years by *ERCC1* status from Bepler et al. (99) Distant recurrence free survival was modeled by subtracting the mean time from distant recurrence until death from overall survival. The time from distant recurrence to death was assumed to be 1-year, ranged from 6 months to 1.5 years, was common across model sub-groups, and was assumed to be based on results from 100 patients. Standard care distant recurrence outcomes were calculated as a weighted average of the proportion testing *ERCC1* positive/negative. The average monthly cost after distant recurrence was obtained from an economic analysis of lung cancer costs during the final year of life conducted by Yabroff et al.(162) We applied this monthly cost from the time of recurrence until death.

Monitoring Cost

Model Inputs	Mean	95% CI Lower	95% CI Upper	Distribution	Reference

Mean Cost Per Month Before Distant Recurrence	$125	$63	$188	Normal	CMS Costs

An average monthly monitoring cost was applied to all patients prior to distant recurrence. This cost was based on CMS reimbursement rates, assumed an average of 1 office visit per month and routine lab testing, and was assumed to be based on 500 patients.

Chemotherapy Uptake and Cost

Model Inputs	Mean	95% CI Lower	95% CI Upper	Distribution	Reference
ERCC1 Positive % Choosing Chemotherapy	10%	5%	15%	Beta	Assumption
ERCC1 Negative % Choosing Chemotherapy	40%	8%	72%	Beta	Assumption
Standard Care % Choosing Chemotherapy	20%	6%	34%	Beta	Kassam, 2007
Cisplatin+Vinorelbine Direct Cost	$6,154	$4,308	$8,000	Normal	Younnis, 2005
Mean Cycles of Cisplatin+Vinorelbine	3.0	-	-	Constant	Winton, 2005

In reality it is likely that a small to moderate proportion of Stage I patients will decide to receive adjuvant chemotherapy, as is demonstrated by current observational evidence.(130-132, 134) Though the proportion choosing adjuvant chemotherapy may increase in an *ERCC1* testing strategy, those changes are not likely to be large on average (given ~50% indicated by *ERCC1*), and not all patients who choose adjuvant chemotherapy will necessarily be *ERCC1* negative. To capture these nuances of chemotherapy utilization, we first identified several studies that have evaluated adjuvant chemotherapy utilization in Stage I standard care. (130-132, 134) In these studies, the proportion receiving treatment has ranged from approximately 10% to 36%.(130-132, 134) Because we were unable to identify sources that reported utilization by *ERCC1* status, we assumed that, relative to standard care, a slighter greater proportion of *ERCC1* negative patients receive treatment, and a slighter lesser proportion of *ERCC1* positive patients receive treatment, given evidence about differential chemotherapy benefit by *ERCC1* status. (99) Direct

chemotherapy-related costs were derived from an economic analysis of patients with early-stage lung cancer undergoing treatment with cisplatin+vinorelbine conducted by Younnis et al., and assumed to represent a sample of 500 patients.(158)

Adverse Event Rates and Costs

Model Inputs	Mean	95% CI Lower	95% CI Upper	Distribution	Reference
% With Grade 3/4 AE on Cisplatin+Vinorelbine	80%	68%	92%	Beta	Douillard, 2010
Mean Duration of Grade 3/4 AE (Years)	0.16	0.08	0.24	Normal	Assumption
% of Grade 3/4 AEs Requiring Inpatient Care	20%	10%	30%	Beta	Assumption
Mean Cost of Inpatient Care for AE	$27,150	$19,005	$35,295	Normal	HCUP, 2010
Mean Cost of Outpatient Care for AE	$140	$70	$210	Normal	CMS Costs

The average grade 3/4 adverse event rate was derived from the LACE database meta-analysis, which included event rates from five large randomized controlled trials involving the cisplatin+vinorelbine regimen.(98) We only modeled grade 3/4 events, as they are most likely to impact health-related quality of life and cost. These events included neutropenia, neutropenia, febrile neutropenia, thrombocytopenia, neuropathy, nausea/vomiting, and infection. (98) We assumed that 20% of adverse events would require inpatient care. Inpatient adverse event costs were obtained from the Health Care Utilization Project (HCUP) 2010 average inpatient charges, and adjusted using HCUP cost-to-charge ratios.(159) Outpatient adverse event costs were based on Center for Medicare and Medicaid Services (CMS) reimbursement amounts, and assumed treatment to require 2 office visits, a complete blood count, and electrolyte panel.(156) The average grade 3/4 event rate and cost were calculated across the specific event types noted above, and incorporated into the model as single parameters.

Health State Utility Values

Model Inputs	Mean	95% CI Lower	95% CI Upper	Distribution	Reference
No Evidence of Disease Utility	0.67	0.54	0.80	Beta	Manser, 2006
On Chemotherapy Utility	0.58	0.46	0.70	Beta	Nafees, 2008
Chemotherapy Grade 3/4 Adverse Event Utility	0.46	0.28	0.64	Beta	Nafees, 2008
Distant Recurrence Utility	0.49	0.39	0.59	Beta	Nafees, 2008

We derived health state utility values from a study of NSCLC health states preferences in a community sample of 100 U.K. citizens conducted by Nafees et al., and from a study NSCLC health state preferences in a sample of 92 Australian lung cancer patients conducted by Manser et al. (2006).(160, 161) The Nafees et al. study utilized visual analogue scale (VAS) and standard gamble (SG) utility elicitation methods to examine participant's preferences for 19 NSCLC health states, while the Manser et al. study derived health state utility values from Australian SF-36 instrument.

CHAPTER III

Benefit-Risk Modeling to Inform Genomic Test Regulatory Policies: A Case Study in Early-Stage Breast Cancer

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ABSTRACT

The United States Food and Drug Administration (FDA) is under pressure to develop more rigorous approaches to assess the safety and effectiveness of genomic tests. We propose quantitative benefit-risk modeling as a tool to serve this need. We illustrate the utility of this approach in a case study of two gene-expression profiles intended to identify women with early-stage breast cancer for whom adjuvant chemotherapy has a favorable benefit-risk balance. Benefit-risk modeling, if implemented as an adjunct to standard review processes, could provide systematic and quantitative insights about benefit-risk tradeoffs. However, challenges remain including methodological transparency and stakeholder acceptance.

SETTING

Rapid advancements in genomic research over the past decade present opportunities to use genomic testing to optimize medical decisions and improve health outcomes. However, like other medical technologies, genomic tests also have the potential to result in harm if they perform poorly. For example, if a test misclassifies risk, it could lead to sub-optimal treatment, and patients could experience side effects without clinical benefit. Accordingly, the potential benefits and harms of testing need to be evaluated and weighed in order to provide reasonable assurance that testing has a favorable benefit-risk balance. Currently, these factors are not systematically evaluated during the genomic test regulatory review processes in the United States.

Current Genomic Test Regulatory Environment

The United States Food and Drug Administration (FDA) has statutory authority for regulating genomic tests as a sub-category of medical devices, and their responsibilities include assessment of "safety and effectiveness". (166) However, the degree to which the FDA evaluates the benefits and risks of genomic tests varies considerably based on the risk level of the given test's intended use.(166) (21 USC 360c) Class I ("Low Risk") and Class II ("Moderate Risk") tests are not typically evaluated for benefit-risk tradeoffs.(167) Class III ("High Risk") tests require pre-marketing evidence of safety and effectiveness, but there are not well-defined evidence requirements or systematic approaches to evaluate benefit-risk balance.(167)

Uncertainty in the Genomic Test Market

Due to poorly defined regulatory evidence requirements, few tests are supported by high-level (e.g. controlled trial) evidence when they become available to patients, clinicians, and other end

users.(8, 168) This reality often leaves genomic test end users with considerable uncertainty about benefit-risk tradeoffs, and can result in sub-optimal or premature clinical application.(6, 8) Consequently, some useful tests may not be implemented due to uncertain benefit, and other tests may cause harm (relative to standard care) without the knowledge of the patients and clinicians using them.(1, 4, 169) In response to these problematic aspects of the current genomic test market, stakeholders are increasingly calling for reform of regulatory law and review processes to create clear and uniform regulatory pathways, promote evidence generation, and encourage appropriate clinical translation.(1, 167, 170-175)

Benefit-Risk Modeling to Inform Regulatory Evaluation of Genomic Tests

We propose quantitative benefit-risk modeling as an adjunct to current qualitative benefit-risk approaches for evaluating genomic tests. This approach can provide new insights to regulatory review of genomic tests by synthesizing best available evidence about survival, treatment effectiveness, health-related quality of life, adverse events, and patient/provider decisions to simulate a variety of downstream health outcomes.(3, 168) Additionally, benefit-risk modeling can allow systematic evaluation of uncertainty by exploring downstream health outcomes over plausible ranges of model inputs.(3, 10, 168, 176) These results can facilitate quantitative evaluation of genomic test benefit-risk tradeoffs by comparing health outcomes with those of standard care strategies. (3, 10, 168, 177) In turn, regulatory authorities and other stakeholders could utilize model results to better understand the benefit-risk tradeoffs of genomic testing strategies, and to inform decisions about regulatory approval and appropriate translation.

Objective

The objective of this study is to demonstrate the potential utility of quantitative benefit-risk modeling as an adjunct to traditional qualitative FDA regulatory review approaches. The advantages and limitations of this approach are illustrated through a case study of gene-expression profiling to inform adjuvant chemotherapy decisions in early-stage breast cancer.

CASE STUDY

Case Study Rationale

Breast cancer gene-expression profiles were selected as a case study because of significant clinical utilization, limited evidence, and uncertain benefit-risk balance. These conditions provide an ideal case study to examine the utility and implications of benefit-risk modeling to inform regulatory decision-making for genomic tests.

The Role of Prognostic Tools in Breast Cancer Adjuvant Chemotherapy Decisions

Early-stage breast cancer patients are often faced with the question of whether to receive adjuvant chemotherapy after local-regional surgical treatment. This decision is complicated because the potential benefit of reduced recurrence risk must be balanced against the potential risk of substantial chemotherapy-related toxicity. A number of prognostic tools have been developed to estimate recurrence risk in order to identify patients with a favorable adjuvant chemotherapy benefit-risk balance. Standard clinical algorithms, such the National Comprehensive Cancer Network guidelines, estimate disease recurrence risk using clinical and pathological factors like tumor size, age, estrogen-receptor status, lymph-node status, and HER2 status. (178) Another approach is to use genomic testing (called “gene-expression profiling”) to estimate recurrence risk based on the expression levels of genes associated with tumor

proliferation, invasion, and other factors.(179) Several breast cancer gene-expression profiles are marketed in the United States, but there is ongoing uncertainty about whether they improve health outcomes relative to standard clinical algorithms.(10)

The 21-Gene and 70-Gene Profiles

Two of the most common breast cancer gene-expression profiles are the 21-gene profile (Oncotype Dx®) and the 70-gene profile (MammaPrint®).(180-182) The 21-gene profile classifies patients into one of three recurrence risk groups (high, intermediate, or low).(183) Generally, patients classified as high or intermediate-risk are recommended adjuvant chemotherapy, and those classified as low-risk are not.(183, 184) However, there is a degree of uncertainty about the optimal treatment for intermediate-risk patients, as has been previously noted. (184, 185) Alternatively, the 70-gene profile classifies patients into one of two recurrence risk groups (high or low risk).(186) Generally, patients classified as high risk are recommended to receive adjuvant chemotherapy, and those classified as low risk are not. (187, 188)

Current evidence for the 21-gene and 70-gene profiles is primarily derived from retrospective observational studies.(184, 186, 187, 189-197) This type of study design has a number of limitations, including: lack of data about potential confounders; high potential for bias related to patient selection, follow-up, and outcome ascertainment; and limited ability to extrapolate findings to more diverse patient populations.(67, 198) Two large randomized controlled trails are currently being conducted to provide higher levels of evidence about the 21-gene and 70-gene profiles, but results are not expected for several years.(199, 200) Despite these evidence limitations, both profiles are currently marketed in the United States. As of June 30, 2012, the

manufacturer of the 21-gene profile reported that they had provided more than 295,000 test results to more than 10,000 physicians in the United States and other countries.(201) This substantial level of utilization is much greater than 14,000 results that the 70-gene profile reported providing as of that same date.(202)

APPROACH

Stakeholder Outreach

Our benefit-risk modeling process was informed by feedback from a diverse group of genomic test stakeholders over the course of two workshop sessions. The first stakeholder workshop was held in Seattle, WA in December of 2008, and included patient advocates, physicians, nurses, test developers, payers, researchers, and regulatory professionals from around the United States.(12) The regulatory stakeholders included two state-level department of health representatives, and one FDA representative. During this session, we utilized a modified-Delphi process to obtain general feedback about the concept of benefit-risk modeling to assess the safety and effectiveness of genomic tests.(12) The second workshop session was held in Seattle, Washington in July of 2010, and involved a multidisciplinary oncology group from a Seattle-based healthcare system. In this workshop, we presented a draft gene-expression profiling benefit-risk model, and received feedback about how to improve transparency and usefulness. We incorporated feedback from these sessions into our methods and analysis where applicable.

Benefit-Risk Model Structure

Our benefit-risk model simulated long-term health outcomes for a patient cohort with estrogen-receptor-positive, lymph-node-negative, stage I/II breast cancer; in accordance with the

indication for the 21-gene and 70-gene profiles.(182, 203) Patients entered the model's decision tree after mastectomy or lumpectomy and radiation therapy, and all patients were assumed to be receiving tamoxifen in accordance with standard care for estrogen-receptor-positive disease.(178) Patients were tracked for recurrence risk classification and subsequent adjuvant chemotherapy decisions. (Figure 1) After the adjuvant chemotherapy decision, patients were tracked in three health states (no evidence of disease, distant recurrence, and death) over a lifetime horizon. Patients moved through the model based on inputs derived from the validation trials of the 21-gene and 70-gene profiles and the peer-reviewed literature.

Additional details about the model structure, inputs, and outcomes are provided in Appendix A.

Model Outcomes & Clinical Utility

Genomic test "clinical utility" has been defined in different ways by different stakeholder constituencies. In some cases, a test has been viewed as having clinical utility if it provides clinically actionable information that impacts decisions.(204) In other cases, a test has been viewed as having clinical utility if it has a favorable impact on downstream health outcomes.(3, 168, 204, 205) Benefit-risk modeling can accommodate both of these definitions by calculating a variety of outcomes that are meaningful to end-users.

The quality-adjusted life-year (QALY) is a standard metric from comparative effectiveness research, and can also be used to assess clinical utility.(205-208) The QALY incorporates a quality of life "utility score" adjustment with life expectancy. A utility score of 0 represents the value for death and 1 represents the value for "full" health. Thus, 10 years of life at a utility of

0.5 is equivalent to 5 years of life with full health. In this paradigm, a test can be defined to have clinical utility if it results in a favorable number of QALYs compared to standard care.(3, 205)

In our case study analysis, we accommodated all of the approaches described above by examining clinical utility in terms of risk group classification, impact of risk group classification on chemotherapy decisions, and downstream impacts on distant recurrences, life expectancy, and QALYs. We evaluated undiscounted outcomes (reported below), as well as outcomes discounted at 3% per year in a cohort of 100 women.

Evaluation of Uncertainty

We conducted one-way sensitivity analyses to examine health outcomes over plausible ranges of model inputs. In these analyses, low and high values were specified for each model input, and comparative health outcomes were calculated for each value. This method demonstrates the most influential model inputs, and provides an overview of plausible ranges of model outcomes. Additionally, we conducted scenario analyses to evaluate model outcomes when a sub-set of patients did not follow the tests' recommended adjuvant chemotherapy pathway. Specifically, we examined a scenario where 10%, 40%, and 80% of low, intermediate and high-risk patients received adjuvant chemotherapy, respectively. This scenario is consistent with the clinical practice experience noted in a recent meta-analysis.(209)

CASE STUDY RESULTS

The use of chemotherapy was dramatically different across gene-expression profiling and clinical algorithm strategies. The 21-gene profile, 70-gene profile, and clinical algorithm

strategies resulted in 49%, 50%, and 92% of patients receiving chemotherapy, and 32%, 33%, and 60% experiencing grade 3 or 4 chemotherapy adverse events, respectively. In the cohort of 100 women, the 21-gene profile resulted in approximately equal disease recurrence and life expectancy, and 10 more QALYs compared to the clinical algorithm. In contrast, the 70-gene profile resulted in 1 more recurrence, 30 fewer life years, and 20 fewer QALYs relative to the clinical algorithm. The full results of each strategy are shown in Table 1.

Our sensitivity analysis demonstrated a moderate level of uncertainty about the comparative distant recurrences, life expectancy, and quality-adjusted survival of both gene-expression profiles relative to the clinical algorithm. Specifically, the results were sensitive to the chemotherapy relative risk reduction, and quality of life in the no evidence of health state, and quality of life in the on chemotherapy health state (see Appendix A for additional details). However, even though distant recurrences, life expectancy, and quality-adjusted survival varied moderately over plausible ranges of input values, the comparative outcomes never crossed zero (i.e. the base case optimal strategies were still optimal).

The scenario analysis results were also moderately sensitive to the proportion of patients deciding to follow recommended adjuvant chemotherapy pathways. When 10% of low-risk, 40% of intermediate-risk, and 80% of high-risk patients chose to receive chemotherapy, the 21-gene profile resulted in approximately equivalent distant recurrences, life years, and QALYs compared to the clinical algorithm, due to distant recurrences occurring earlier in follow-up. The 70-gene profile again resulted in *more* recurrences, *fewer* life years, and *fewer* QALYs compared to the clinical algorithm (Table 2). These scenario analysis results demonstrate that

chemotherapy uptake levels can impact the comparative effectiveness of gene-expression profiling, but not to a degree that substantially changes conclusions about comparative effectiveness.

DISCUSSION

We found that the 21-gene profile is expected to result in approximately equivalent distant recurrences and survival versus the clinical algorithm, and slight increases in quality-adjusted survival due to fewer patients experiencing chemotherapy toxicity. In contrast, the 70-gene profile is expected to result in small increases in distant recurrences and small decreases in survival and quality-adjusted survival due to less efficient identification of the highest risk patients to receive chemotherapy.

Our results suggest that, based on available evidence, the benefit-risk tradeoffs and clinical utility of gene-expression profiling with the 21-gene and 70-gene profiles are different, and neither has overwhelming evidence of clinical utility. Specifically, the 21-gene profile only demonstrated potential clinical utility in the context of quality-adjusted survival, and the 70-gene profile did not demonstrate clinical utility in any outcome. These findings suggest that additional comparative effectiveness evidence should be generated for both gene-expression profiles before clinical application. These insights could prove valuable adjuncts to standard qualitative benefit-risk review at the FDA.(210)

Benefit-Risk Modeling as an Adjunct to Current FDA Review Processes

As illustrated above, benefit-risk modeling can provide additional systematic and quantitative insights to current FDA review processes. To demonstrate how benefit-risk modeling can be useful as a general adjunct to current processes, Table 3 provides an overview of how modeling can enhance evaluation of the factors that FDA considers in review of medical devices, as explained in a recent guidance document.(210) These potential applications of regulatory benefit-risk modeling come with the caveat that we are proposing this approach as an adjunct to current processes, rather than a prescriptive replacement. We believe that the regulatory considerations described above are complex and dynamic, and can be best addressed though a mixed methods deliberative approach involving both qualitative and quantitative inputs.

Potential Utility of Benefit-Risk Modeling in the Context of U.S. Regulatory Statutes

The use of benefit-risk modeling to evaluate clinical utility could prove particularly useful to regulatory decision-makers seeking to quantitatively evaluate genomic tests in the context of the device requirements of 21 CFR 806.7. (211) For example, 806.7(b) reads "In determining the safety and effectiveness of a device for purposes of classification… the probable benefit to health from the use of the device [should be] weighed against any probable injury or illness from such use". (211) This language could be interpreted to mean that the effectiveness of genomic tests can be demonstrated through a positive impact on net health outcomes relative to standard comparators (i.e. having "clinical utility"). Additionally, a similar interpretation could be utilized to inform what constitutes a "clinically significant result". This could prove useful in relation to 806.7(e)(1), which states "a device is effective when it can be determined [that]…the use of the device for its intended uses…will provide clinically significant results".(211) Here, regulatory authorities could examine clinical significance by looking at the magnitude of comparative

health outcome gains associated with genomic testing strategies, as well as the level of uncertainty around those gains.

Process Advantages

Benefit-risk modeling also has the potential to provide a number of general process advantages to regulatory authorities seeking to evaluate genomic tests. Perhaps the largest advantage is that creating a benefit-risk model requires explicit definition of clinical pathways and chains of evidence for the comparator technologies or strategies.(3, 168, 212) Thus, the act of creating, using, and evaluating such models can deepen understanding of the clinical pathways following testing, the key inputs that influence health outcomes, and areas of uncertainty. All of these factors were noted as key considerations in device benefit-risk determinations at the FDA in a recent guidance.(210)

Additionally, because benefit-risk models can be structured as interactive tools (as in our case study), regulatory authorities could potentially use models to inform and structure discussions in real time. For example, in our case study, a committee's debate about the importance of chemotherapy decisions could be addressed in real time examining the clinical utility of testing at different chemotherapy uptake levels. In doing this, a committee may find that clinical utility changes more or less than was initially postulated, which can inform and focus subsequent deliberation.

Lastly, benefit-risk modeling can highlight the most influential benefits and harms of genomic tests, which can in turn be utilized to inform the design of discrete choice experiments and

standard preference elicitation studies.(169, 213) These types of studies can provide insights about stakeholder relative preferences for benefits and risks, and can also be valuable adjuncts to standard regulatory review processes.(168) Through these mechanisms, benefit-risk modeling can facilitate timely evaluation of uncertainty, provide common reference points to structure deliberations, and increase transparency about the factors and issues underlying regulatory decisions.

Benefit-risk modeling in other contexts

Regulatory application of benefit-risk modeling in has been previously discussed in the context of pharmaceutical review.(176, 177, 214) For example, Hughes et al. illustrated the potential utility of benefit-risk modeling to inform regulatory decision-making about terfenadine, with particular attention to evaluating clinical utility under conditions of uncertainty about serious adverse events.(177) In a response, Temple noted many of the limitations to benefit-risk modeling we discuss below, and concluded that these limitations would need to be addressed before benefit-risk modeling can be implemented as a regulatory tool.(214) We agree with many of the advantages and limitations Hughes et al. and Temple noted in the context of benefit-risk modeling in pharmaceutical review. However, we believe there may be even greater utility and urgency in applying benefit-risk modeling to evaluate genomic tests given the paucity of evidence and consequent high uncertainty about benefit-risk tradeoffs.

Challenges

A major barrier to benefit-risk modeling in regulatory review of genomic tests are the divergent regulatory pathways that exist in the United States. Above, we describe the regulatory pathway

for tests that are marketed as test kits, and regulated as medical devices by the FDA. However, manufacturers can circumvent this pathway by marketing tests as laboratory services (or "laboratory-developed tests") through the Clinical Laboratory Improvement Amendments (CLIA) of 1988.(215-218) In fact, the 21-gene profile entered the market through this regulatory pathway. (203) Laboratory-developed tests are not currently reviewed by the FDA, and are not typically subjected to any formal regulatory evaluation of safety or effectiveness. If these highly variable genomic test regulatory pathways continue to exist, it is plausible that FDA efforts to implement more rigorous evaluation of benefit-risk tradeoffs could be undercut by an increasing number of manufacturers pursuing market access via the less stringent CLIA pathway.

Regulatory benefit-risk modeling also faces several methodological challenges. One challenge will be reaching consensus on model structure, inputs, and relevant health outcomes. For example, it may be unclear which comparator strategies to evaluate, what time horizon to examine, or which data sources are most appropriate for model inputs. (8, 214) The challenge of developing transparent and valid analyses was highlighted in a recent decision-modeling study that compared the benefits, risks, and costs of the 21-gene and 70-gene profiles. (219) In that study, Yang et al. demonstrated the 70-gene profile to result in 0.097 more QALYs (~1 month of full health) relative to the 21-gene profile over a lifetime horizon.(219) The authors concluded that the 70-gene profile is the dominant testing strategy for guiding adjuvant chemotherapy decisions in early-stage breast cancer. However, these model results were likely biased because different patient cohorts (with different risk of recurrence) were used to simulate the 21-gene and 70-gene profile outcomes, as was noted in a subsequent commentary.(220, 221) Additionally, the model did not simulate the relevant policy decision of whether either profile is an effective

alternative to standard care, as is established decision-modeling practice.(208, 222, 223) While these types of methodological issues can be complex and difficult to resolve, they could potentially be addressed through the development of common standards based on systematic stakeholder outreach and peer review.

Another challenge is a lack of consensus on the most appropriate health outcome(s) to inform decision-making. The QALY, for example, offers the advantage of synthesizing measures of benefit and risk in a single metric, but is often criticized for perceived subjectivity in the health state utility values that underlie its calculation.(12, 214, 224) Based on the feedback we have received from stakeholders, it may be most informative to calculate a variety of pertinent health outcomes in addition to QALYs. This approach can allow decision-makers to examine if using different outcome measures to evaluate clinical utility leads to different conclusions, and can highlight the inherent tradeoffs of relying on given outcomes.

CONCLUSION

We propose the consideration of quantitative benefit-risk modeling as an adjunct to standard qualitative benefit-risk assessment in FDA review of genomic tests that have significant potential for clinical trade-offs. Implementation of this type of approach could prove a valuable advancement toward establishing more consistent, transparent, and rigorous regulatory review processes for genomic tests. Future research should seek to systematically apply and evaluate this type of approach to regulatory review. Though it may be challenging to modify existing regulatory processes for evaluating safety and effectiveness, the incorporation of contemporary

decision tools in regulatory decision-making could be a critical step toward incentivizing appropriate genomic test evidence development and translation.

Strategy	Number Receiving Chemotherapy	Number Experiencing Adverse Event	Distant Recurrences	Life Years	Quality-Adjusted Life Years
21-Gene Profile	494	321	10	3,350	2,990
70-Gene Profile	500	325	11	3,320	2,960
Clinical Algorithm	921	599	10	3,350	2,980

Table 1: Base-case model results. The results are for a cohort of 100 women.

Strategy	Number Receiving Chemotherapy	Number Experiencing Adverse Event	Distant Recurrences	Life Years	Quality-Adjusted Life Years
21-Gene Profile	357	232	11	3,320	2,960
70-Gene Profile	450	293	11	3,300	2,940
Clinical Algorithm	745	484	11	3,320	2,960

Table 2: Scenario analysis results. The results are for a cohort of 100 women in a scenario where 10%, 40%, and 80% of low, intermediate, and high-risk women decide to receive adjuvant chemotherapy, respectively.

Benefit-Risk Criteria	Potential Role of Benefit-Risk Models (BRM)
Types of benefit(s)	While structuring the model, stakeholders explicitly define the impacts of genomic testing on clinical flow, health status, and quality of life
Magnitude of the benefit(s)	BRMs can be structured to quantitatively evaluate the magnitude of benefit(s) from standard and genomic testing strategies
Probability of the patient experiencing one or more benefits	BRMs can be structured to calculate the probability of patients experiencing one or more benefits and enumerate these events over a relevant time horizon
Duration of the effect(s)	Duration of effects can be structured as an explicit model input or a calculated model result
Severity, types, number, and rates of harmful events associated with use of the device	BRMs can facilitate quantitative evaluation of a range of harmful events, with varying rates and severity. Impacts of harmful events can be evaluated in terms of health events (e.g. hospitalizations), life expectancy, quality of life, or quality-adjusted survival.
Probability of a harmful event	The probabilities of harmful events can be incorporated as explicit model inputs or a calculated model results
Duration of harmful events	The duration of harmful events can be incorporated as explicit model inputs or a calculated model results
Risk from false-positive or false-negative results	A wide range of outcomes resulting from false-positive or false-negative results can be calculated, including impacts on health events (e.g. hospitalization), life expectancy, quality of life, or quality-adjusted survival
Uncertainty	Uncertainty in all of the factors above can be quantitatively evaluated through sensitivity analysis, allowing users to consider plausible ranges of outcomes
Characterization of the disease	The process of developing the model involves explicit characterization of the disease and patient flow following diagnosis, treatment, and follow-up
Patient tolerance for risk and perspective on benefit	BRMs can be structured to evaluate different scenarios where patients have different levels of tolerance for risk, and best or worst-case scenario outcomes can be calculated and quantitatively compared
Availability of alternative treatments or diagnostics	Any number of alternative treatments can be compared in a BRM. Additionally, hypothetical future treatments can be evaluated based on target product profiles.
Risk mitigation	BRMs can quantitatively inform risk mitigation strategies by stratifying outcomes into different patient sub-groups to evaluate restricted indications, or different levels of adherence to label warnings.
Post-market Data	Post-market surveillance can be informed by updating model inputs with the most current data available, and evaluating if benefit-risk tradeoffs change (relative to pre-market) with new data.
Novel technology addressing unmet medical need	The BRM framework provides a systematic and explicit means to evaluate health outcomes relative to existing technologies.

Table 3: Potential uses of benefit-risk modeling (BRM) to evaluate key factors considered in regulatory evaluation of genomic tests. The factors noted in the table above were stated as key considerations in the benefit-risk evaluation of medical devices in a recent FDA guidance document.(210)

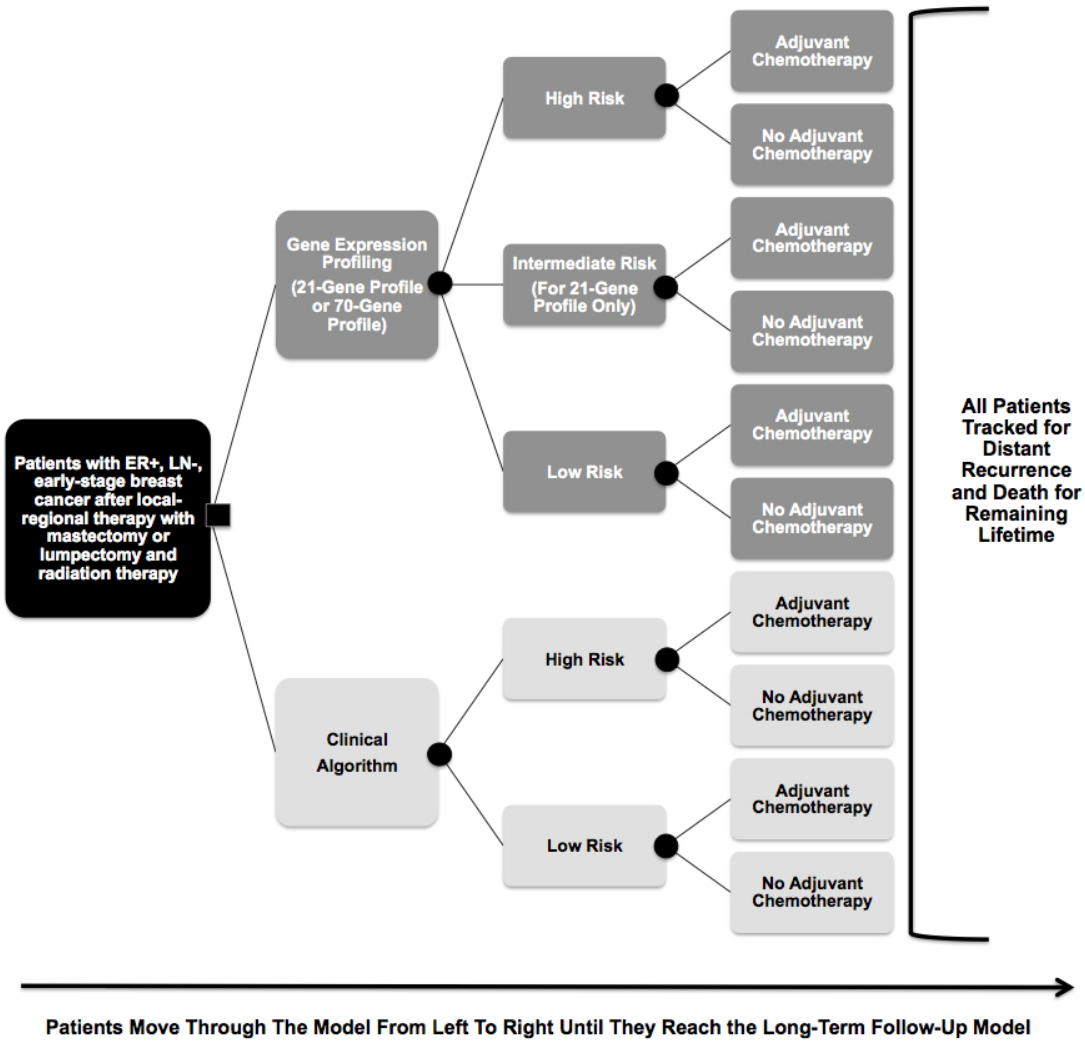

Figure 1: Simplified benefit-risk model schematic

APPENDIX A

This appendix is intended to provide a more detailed overview of the benefit-risk model we discuss in the primary manuscript titled "The Potential Role of Benefit-Risk Modeling to Inform Regulatory Decisions about Genomic Tests: A Case Study in Gene-Expression Profiling in Early-Stage Breast Cancer". The corresponding author will provide the full Microsoft Excel (Redmond, WA) decision model upon request.

General Modeling Approach

Based on stakeholder feedback, we implemented a relatively simple model structure to enhance accessibility for users less familiar with decision-analytic modeling methods. Schematics of the decision tree and long-term outcome simulation model are provided below (Figure A1 and A2)

Our benefit-risk model was developed to simulate long-term health outcomes in a cohort of 100 women with estrogen-receptor-positive, lymph-node-negative, early-stage breast cancer using one of three prognostic strategies to inform their adjuvant chemotherapy decision: 1) gene-expression profiling with a 21-gene profile, 2) gene-expression profiling with a 70-gene profile, 3) a standard NCCN clinical algorithm. Patients entered the decision tree at age 44, after undergoing local-regional therapy with mastectomy or lumpectomy and radiation therapy. All patients were assumed to be receiving tamoxifen, in accordance with standard treatment of estrogen-receptor-positive disease. (178) In all strategies, patients were classified for recurrence risk using the given prognostic tool, and then decided whether to receive adjuvant chemotherapy (Figure A1).

After the adjuvant chemotherapy decision, patients entered a Markov transition model where they were tracked three health states (no evidence of disease, distant recurrence, and death) over a lifetime horizon to simulate long-term health outcomes (Figure A2). Patients entered the Markov model in the "no evidence of disease" state, and were tracked until entry into the absorbing state of "death". This model structure enabled calculation of long-term distant recurrence, survival, and quality-adjusted survival in the simulated cohort.

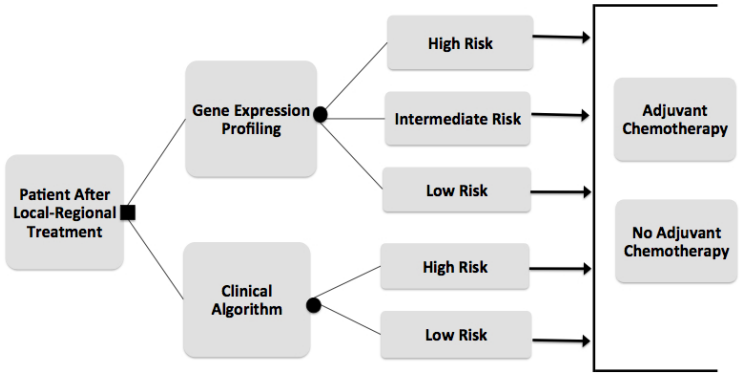

Figure A1: Model decision tree structure. Patients move from left to right until the adjuvant chemotherapy decision is reached. After the decision, patients move to the long-term outcome simulation model.

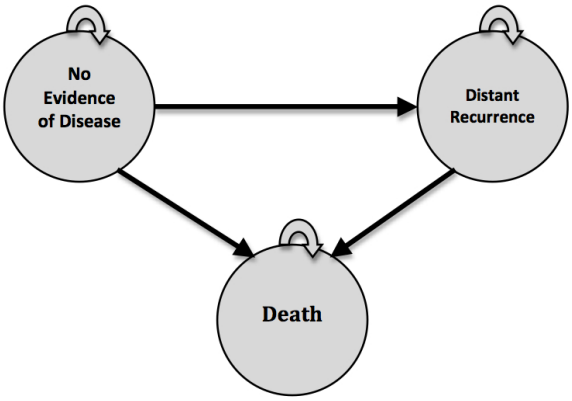

Figure A2: Long-term outcome simulation model structure. Patients are tracked in the no evidence of disease, distant recurrence, and death states from the time of the adjuvant chemotherapy decision until death.

Patient Population

NSABP B-14 was a randomized controlled trial that investigated outcomes in 2,306 women

allocated to either tamoxifen alone; methotrexate, fluorouracil, and tamoxifen (MFT); or cyclophosphamide, methotrexate, fluorouracil, and tamoxifen (CMFT). (225) The study was conducted at centers across the United States and Canada, and included women with primary operable, histologically node-negative, estrogen-receptor-positive breast cancer. Our benefit-risk model simulated outcomes for the tamoxifen-treated patient cohort.(225) Among the B-14 patients randomized to tamoxifen alone, 73% were age 59 or younger, 87% were Caucasian, 45% received lumpectomy, 55% received mastectomy, and 70% had tumors ≤ 2 cm.(225)

Data Sources

Our benefit-risk model was informed by several studies that have reported risk classification and health outcomes in the NSABP B-14 tamoxifen alone cohort. (193, 225-227) For the 21-gene profile strategy, the proportion of patients classified as low, intermediate, and high-risk and 10-year distant recurrence proportions were derived from a retrospective analysis of the cohort conducted by Tang et al. (193) In this study, a total of 668 patients were classified by the 21-gene profile, with 338 classified as low-risk, 149 classified as intermediate-risk, and 181 classified as high-risk. The corresponding proportions of patients with distant recurrence at 10 years of follow-up were 6.8%, 14.3%, and 30.5%, respectively. (193) For the clinical-pathological strategy, the proportion of patients classified as low and high-risk and 10-year distant recurrence proportions were derived from a retrospective analysis of the cohort conducted by Hornberger et al. (226) In this study, a total of 668 patients were classified by NCCN guidelines, with 53 classified as low-risk and 615 classified as high-risk.(226) The corresponding proportions of patients with distant recurrence at 10 years of follow-up were 6.6% and 15.6%, respectively. These proportions were derived from Figure 1 of the paper using Engauge Digitizer,

rather than the paper's input parameters, to remain consistent with the average 10-year distant recurrence proportion that has been reported elsewhere.(193, 226)

We imputed 70-gene profile strategy outcomes for the NSABP B-14 trial cohort, as we were unable to identify any studies that reported risk classification or proportion with distant recurrence by 70-gene profile classification. To impute outcomes for the B-14 cohort, we first derived the proportion of patients classified as low and high-risk from a retrospective analysis of specimens from cancer centers from throughout Europe conducted by Buyse et al.(194). This study included patients with estrogen-receptor-negative disease, but those patients were excluded from the risk group classifications and 10-year distant recurrence rates reported herein. In total, 212 patients with estrogen-receptor-positive, lymph-node-negative early-stage breast cancer were classified by the 70-gene profile, with 106 classified as low-risk and 106 classified as high-risk. (194) The corresponding proportions of patients with distant recurrence at 10 years of follow-up were 8.9% and 27.7%, respectively. (194) To simulate the B-14 patient cohort for the 70-gene profile strategy, we then calculated the ratio of risk group specific 10-year distant recurrence relative to the overall cohort (18.3%). (194) Then, the ratio of 10-year recurrence rates between the high-risk group, low-risk group, and overall cohort were calculated (1.51 and 0.49, respectively) and applied relative to the overall B-14 cohort to estimate 10-year distant recurrence rates for each 70-gene profile risk group. This approach was based on the assumption that the ratio of distant recurrence rates in the risk groups and overall cohort observed in Buyse et al. holds when applied to the B-14 cohort. It is possible that the risk group proportions of the 70-gene cohort would shift slightly in the B-14 cohort relative to the Buyse et al. validation cohort, but this effect would be expected to be very small given that the average baseline 10-year

risk of distant recurrence was 18.6% in Buyse et al., and was 14.9% in the B-14 cohort. (193, 194)

Input Name	Point Estimate	Low Value	High Value	Reference
General Inputs				
Average Proportion with Distant Recurrence at 10 Years	0.15	-	-	NSABP B-14
Average Chemotherapy Relative Risk Reduction	0.35	0.20	0.50	EBCTCG, 2005
Proportion with Grade 3/4 Adverse Event on Chemotherapy	0.65	0.10	0.90	Jones, 2009
No Evidence of Disease Utility	0.90	0.72	1.00	Oestreicher, 2005
Chemotherapy Utility	0.50	0.40	0.60	Oestreicher, 2005
Grade 3/4 Adverse Event on Chemotherapy Utility	0.35	0.28	0.42	Lloyd, 2006
Distant Recurrence Utility	0.30	0.24	0.36	Oestreicher, 2005
Average Duration of Grade 3/4 Adverse Event (Months)	1.00	0.00	3.00	Assumption
21-Gene Profile Inputs				
Proportion High Risk	0.27	-	-	Tang, 2011
Proportion Intermediate Risk	0.22	-	-	Tang, 2011
Proportion Low Risk	0.51	-	-	Tang, 2011
High Risk Proportion with Distant Recurrence at 10 Years (Tamox. Only)	0.07	-	-	Tang, 2011
Int. Risk Proportion with Distant Recurrence at 10 Years (Tamox. Only)	0.14	-	-	Tang, 2011
Low Risk Proportion with Distant Recurrence at 10 Years (Tamox. Only)	0.31	-	-	Tang, 2011
High Risk Chemotherapy Relative Risk Reduction	0	^	^	Tang, 2011
Int. Risk Chemotherapy Relative Risk Reduction	0.39	^	^	Tang, 2011
Low Risk Chemotherapy Relative Risk Reduction	0.74	^	^	Tang, 2011
70-Gene Profile Inputs*				
Proportion High Risk	0.50	-	-	Buyse, 2006
Proportion Low Risk	0.50	-	-	Buyse, 2006
High Risk Proportion with Distant Recurrence at 10 Years (Tamox. Only)	0.09	*	*	Calculated
Low Risk Proportion with Distant Recurrence at 10 Years (Tamox. Only)	0.28	*	*	Calculated
High & Low Risk Chemotherapy Relative Risk Reduction	0.35	#	#	Same Average RRR As Above
Clinical-Pathological Guidelines Inputs				
Proportion High Risk	0.08	-	-	Hornberger, 2005
Proportion Low Risk	0.92		-	Hornberger, 2005
High Risk Proportion with Distant Recurrence at 10 Years (Tamox. Only)	0.07	-	-	Hornberger, 2005
Low Risk Proportion with Distant Recurrence at 10 Years (Tamox. Only)	0.16	-	-	Hornberger, 2005
High & Low Risk Chemotherapy Relative Risk Reduction	0.35	#	#	Same Average RRR As Above

*10-Year distant recurrence is imputed for each risk group using the average distant recurrence rate

^Risk group specific chemotherapy RRR is imputed using the ratio of overall RRR and group RRR noted in the validation study

There is not evidence to support the predictive utility of this strategy in node-negative, ER+ disease, so the chemotherapy RRR is assumed to be uniform across risk groups

Table A1: Model inputs and uncertainty ranges

Distant Recurrence Free and Overall Survival Inputs

Distant recurrence free and overall survival estimates were obtained by calculating transition

probabilities from the 10-year distant recurrence proportions reported in each study noted above. We assumed that all distant recurrences occur by 10 years of follow-up, and the only transition from distant recurrence is to death (annual transition probability 0.35).(184) This transition probability, coupled with non-recurrence related transitions to death based on the 2005 United States life table (variable transition probability with each year of age), allowed calculation of overall survival over the time horizon.

Chemotherapy Relative Risk Reduction Inputs

Average chemotherapy relative risk reduction (RRR) was modeled as a separate input in order to facilitate evaluation of different chemotherapy regimens by varying the effectiveness and adverse event profile. In the base case, we utilized a chemotherapy RRR of 0.35 (0.65 relative risk of distant recurrence by 10 years). (228) The way in which the average chemotherapy RRR was applied to the risk groups within each strategy varied based on evidence from the validation studies of the 21-gene and 70-gene profiles. (184, 194) The 21-gene profile has a moderate level of evidence supporting its predictive utility (i.e. differential chemotherapy benefit between risk groups). (184, 193) However, there is not similar evidence to support the predictive utility of the 70-gene profile or NCCN guidelines in estrogen-receptor-positive, lymph-node-negative early-stage breast cancer. For this reason, in the 21-gene profile strategy, high-risk have a greater RRR than intermediate-risk patients, and intermediate-risk patients have a greater RRR than low-risk patients.(184) This effect was applied by distributing the average chemotherapy RRR in accordance with the ratios noted in the 21-gene profile validation studies.(184, 193) Given a lack of evidence to support differential effectiveness by risk group, the average chemotherapy RRR was applied in all 70-gene profile and clinical algorithm risk groups.

Chemotherapy Uptake Inputs

Chemotherapy uptake inputs were incorporated into the model to allow evaluation of different chemotherapy uptake scenarios. In the base case, we assumed that across strategies, all high and intermediate-risk patients received adjuvant chemotherapy, and all low-risk patients did not receive chemotherapy. However, in scenario analyses, also examined outcomes when different proportions of low, intermediate, and high-risk patients deviated from their suggested clinical chemotherapy pathway, in accordance clinical experience noted in a growing body of observational evidence. (209)

Adverse Event Inputs

Adverse event (AE) rates were derived from the U.S. Oncology 9735 trial, as reported by Jones et al. (229) This trial randomized patients to adjuvant chemotherapy with either docetaxel and cyclophosphamide (TC) or doxorubicin and cyclophosphamide (AC).(229) We derived average grade 3/4 adverse event rates from the 9735 trial, and incorporated this as a model input to represent the proportion who have a grade 3/4 adverse event on chemotherapy (TC=0.65, AC=0.60). This rate was primarily driven by neutropenia, but also included: anemia, febrile neutropenia, infection, deep vein thrombosis, and other thromboembolic events. (229) We restricted our consideration of adverse events to grade 3/4 events because they are most likely to substantially impact health-related quality of life. Adverse events were assumed to occur at the midpoint of the first adjuvant chemotherapy cycle, and were assumed to impact health-related quality of life for one month in the base case analysis. We assumed that no patients died as a result of an adverse event.

It should be noted that chemotherapy effects examined in the majority of the 21-gene and 70-gene profile validation studies involved the cyclophosphamide, fluorouracil, methotrexate, tamoxifen (CMFT) regimen, whereas we modeled the more contemporary TC and AC regimens. (178) Accordingly, there is some degree of uncertainty about the distant recurrence relative risk reduction in the low, intermediate, and high-risk groups of each strategy. Additionally, it is unclear if there would be any differential predictive utility with TC or AC in the 21-gene profile strategy, relative to CMFT.(184, 193) However, our sensitivity analyses were structured to capture the range of outcomes associated with plausible ranges of chemotherapy RRR and grade 3/4 adverse events.

Health State Utility Inputs

Health state utility values were derived from investigations of women with breast cancer in the published literature. (230, 231) We incorporated utilities for no evidence of disease, no evidence of disease on chemotherapy, no evidence of disease and grade 3/4 adverse event on chemotherapy, and distant recurrence health states. Specific health state utility values are shown in Table A1.

Base Case Analysis Outcomes

The model was structured to evaluate three key health outcomes: distant recurrences, life expectancy, and quality adjusted life years (QALYs). These outcomes were intended to reflect factors that are important to a range of stakeholders, and were selected based feedback that has been previously summarized. (12) Distant recurrences were calculated based on baseline recurrence risk and chemotherapy relative risk reduction (when applicable), tracked over the

lifetime horizon of the model, and reported in absolute terms. Life expectancy was calculated based on similar factors as distant recurrences, but also incorporated background mortality from United States life tables. QALYs reflected both duration and quality of life by tracking survival in no evidence of disease, distant recurrence, and death health states, and adjusting the period of time spent in each state by the corresponding health state utility.

Model Calibration and Validation

We calibrated and validated the outcomes of our decision model by examining internal consistency in model results, and then comparing results with those of prior studies. To establish internal consistency, we compared outcomes between strategies in scenarios where all or none of the cohort received chemotherapy. In these scenarios, it would be expected that all model outcomes would be equivalent across strategies, as all patients across all counterfactuals receive the same treatment.

We also evaluated our 70-gene profile simulated outcomes relative to the outcomes of the validation trial that informed our calculations (Table A2). In these comparisons, we found our simulated recurrence and overall survival point estimates to generally fall within the 95% confidence intervals from the source study. (194) The one exception to this finding was the 10-year overall survival proportion for the high-risk group, where our imputed survival proportion of 80.1% slightly exceeded the upper bound of the 95% confidence interval from the source study (75.6%). (194) This simulated outcome is consistent with the lower average baseline 10-year distant recurrence risk in the B-14 cohort (14.6%) relative to the validation study cohort (18.6%), and is likely attributable to our inability to differentiate estrogen-receptor-positive

patients (n=106) from estrogen-receptor-negative patients (n=85) in the high-risk group outcomes reported by Buyse et al.(194) Estrogen-receptor-negative patients are generally at higher risk of recurrence, and so it is plausible that the average high-risk group outcomes reported in Buyse et al. reflected slightly higher risk than would be expected for a uniformly estrogen-receptor-positive cohort. This was not a problem in the low-risk group because 101 of 106 low-risk patients were estrogen-receptor-positive.

	% High Risk	Low Risk Proportion with Distant Recurrence at 10 Years	High Risk Proportion with Distant Recurrence at 10 Years	Low Risk Overall Survival Proportion at 10 Years	High Risk Overall Survival Proportion at 10 Years
Validation Trial	50.0%	8.9% (3.6-14.2)	27.7% (21.4-34.1)	88.5% (82.6-94.4)	69.0% (62.4-75.6)
Simulated Cohort	50.0%	7.3%	22.5%	91.0%	80.1%

Table A2: Comparison of 70-gene profile validation results and simulated results for the B-14 trial cohort

To validate our model simulations, we compared recurrence and survival estimates with a number of prior studies that were not used to inform any of our model parameters. (232-234) All comparisons involved similar estrogen-receptor-positive, lymph-node-negative, early-stage breast cancer patient populations. It is important to note that we would not expect our simulated outcomes to be precisely equivalent to the comparator study outcomes, as our simulated results reflect the average risk of a different patient cohort. However, we would expect our average simulated outcomes to be similar to the comparator studies, as the gene-expression profiles are expected to perform consistently across patients. Across our validation comparisons, we found our simulated results to be generally consistent with the outcomes of the comparator studies (Table A3). This information provides additional assurance that our decision model reasonably reflected "real world" risk and health outcomes.

Comparator Study	Study Design	Comparator Patient Population	Study Finding(s)	Simulated Finding(s)
ATAC Trialists Group (2008)	Randomized Controlled Trial	Average Distant Recurrence for All Strategies	13.7% Distant Recurrence at 9 Years of Follow-Up*	15.7% Distant Recurrence at 9 Years In All Strategies*
Khoshnoud et al. (2008)	Retrospective Cohort Study of Randomized Trials	Average Distant Recurrence for All Strategies	15.5% Distant Recurrence at 10 Years of Follow-Up#	16.5% Distant Recurrence at 10 Years of Follow-Up#
Retel et al. (2010)	Decision-Model	70-Gene Profile Guided Treatment	15.88 Discounted Life Years^	15.30 Discounted Life Years^
Retel et al. (2012)	Decision-Model	21-Gene Profile Guided Treatment	14.76 Discounted Life Years^	14.57 Discounted Life Years^
Retel et al. (2012)	Decision-Model	70-Gene Profile Guided Treatment	14.61 Discounted Life Years^	14.50 Discounted Life Years^

*Hormone-receptor-positive patients, all received chemotherapy, all received tamoxifen
#Estrogen-receptor-positive, no chemotherapy, all received tamoxifen
^20-year time horizon, effects discounted at 1.5% per year in accordance with the comparator study

Table A3: Validation of Simulated Model Outcomes Relative to Comparator Studies

Base Case Analysis Results

We report the average health outcomes of each prognostic strategy in the primary manuscript associated with this appendix. Below, we present outcomes stratified by risk group within each strategy (Figure A3).

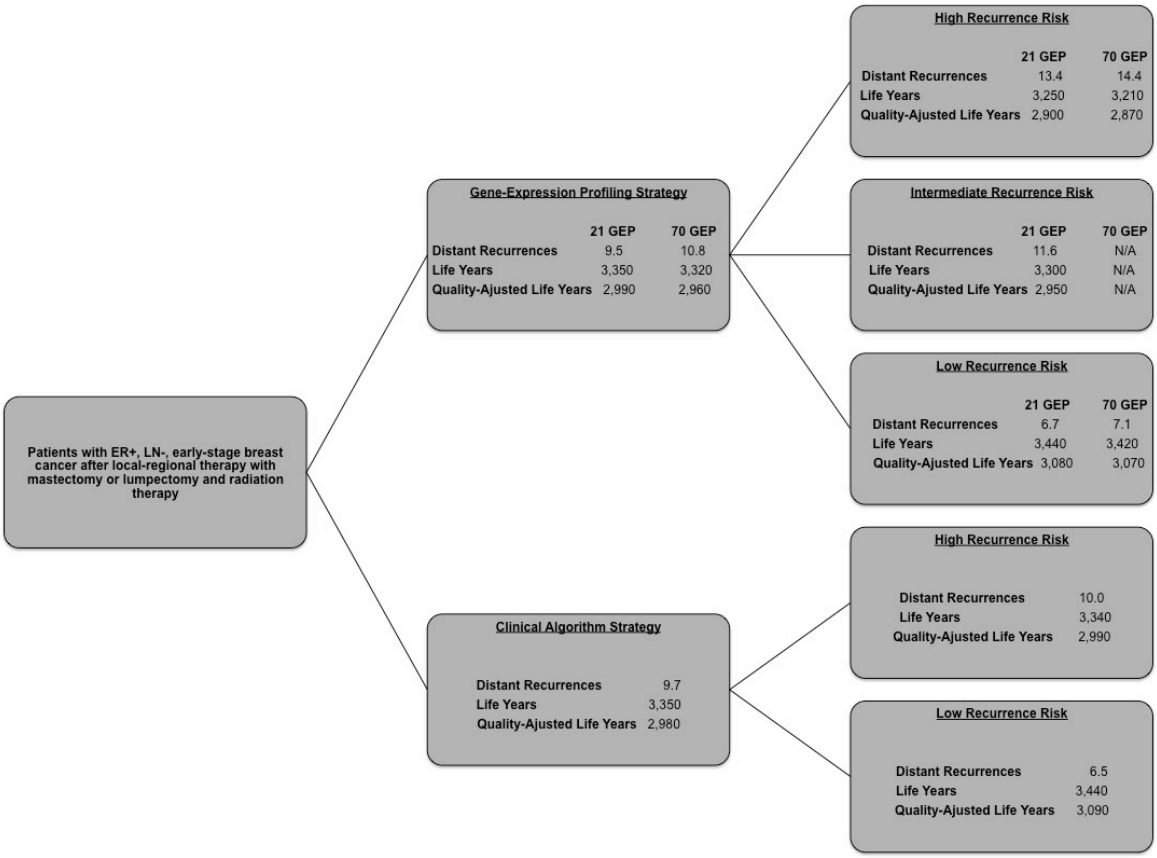

Figure A3: Base case health outcomes by distant recurrence risk sub-groups. Note that patients in the high and intermediate risk groups are assumed to receive adjuvant chemotherapy, while those in the low risk groups are assumed to not receive adjuvant chemotherapy.

Sensitivity Analysis Results

Sensitivity analysis demonstrated that patient adjuvant chemotherapy decisions, baseline 10-year recurrence rate, and chemotherapy relative risk reduction inputs had the greatest influence on health outcomes. Figures A4 and A5 show the range of incremental QALYs for the 21-gene and 70-gene profiles compared with the clinical algorithm over the uncertainty range of model inputs. We do not present sensitivity analysis results for incremental distant recurrences or life years as there are few variable model parameters that impact these outcomes. However, over the range of chemotherapy RRR from 0.20 to 0.50, compared to the clinical algorithm, the 21-gene profile

resulted in 0.2 more to 0.2 fewer recurrences and 6 fewer to 6 more life years, and the 70-gene profile resulted in 0.8 to 1.5 more recurrences and 20 to 40 fewer life years.

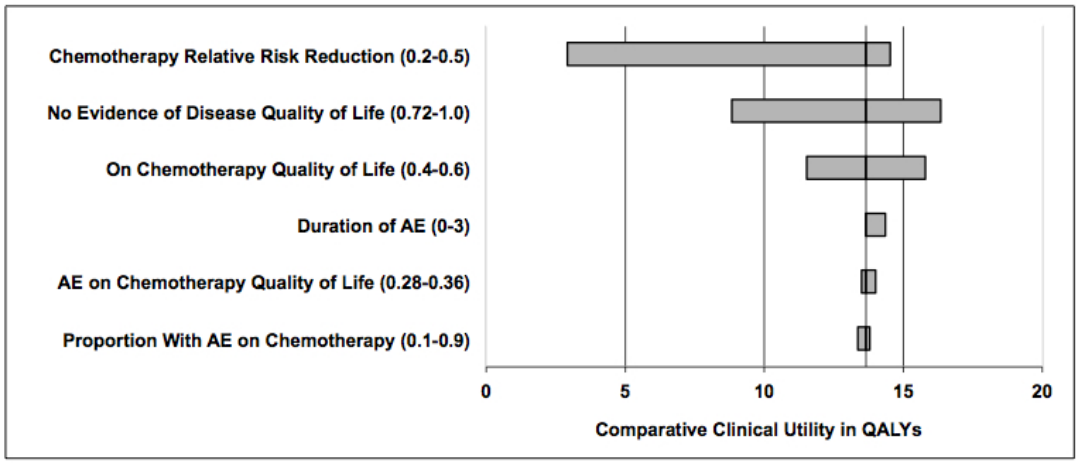

Figure A4: One-way sensitivity analysis results comparing QALYs between the 21-gene profile and the clinical algorithm. The bars in the figure correspond to the difference in QALYs produced by the 21-gene profile and clinical algorithm over the uncertainty range of each model input.

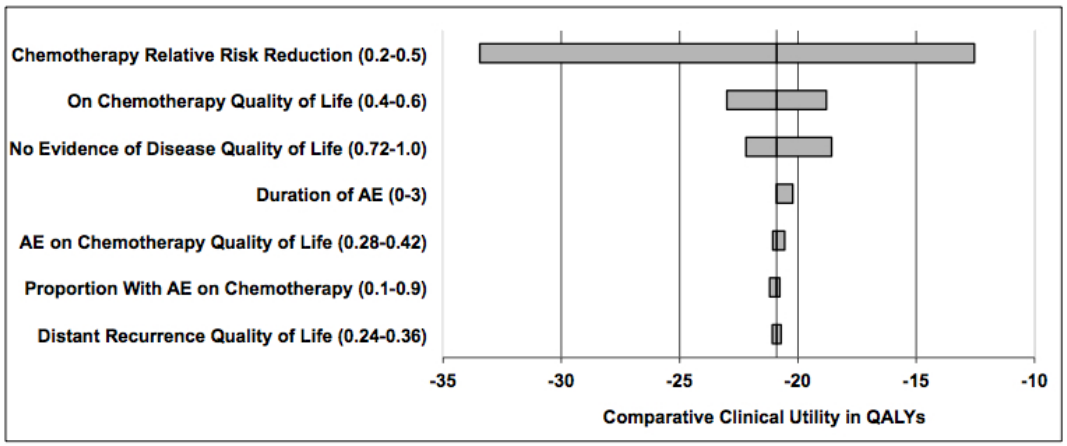

Figure A5: One-way sensitivity analysis results comparing QALYs between the 70-gene profile and the clinical algorithm. The bars in the figure correspond to the difference in QALYs produced by the 70-gene profile and clinical algorithm over the uncertainty range of each model input.

Scenario Analysis Results

A scenario analysis was conducted to evaluate model outcomes with varied chemotherapy uptake levels across the prognostic strategies. In this scenario, we examined outcomes when 10% of low,

40% of intermediate, and 80% of high and-risk patients decided to receive chemotherapy. This scenario was examined to demonstrate the potential impacts on outcomes associated with a plausible proportion of patients not adhering to clinical recommendations, as has been noted in observational studies. (209) The distant recurrence (A), life year (B), and QALY (C) results of this scenario are provided in figure A6 below.

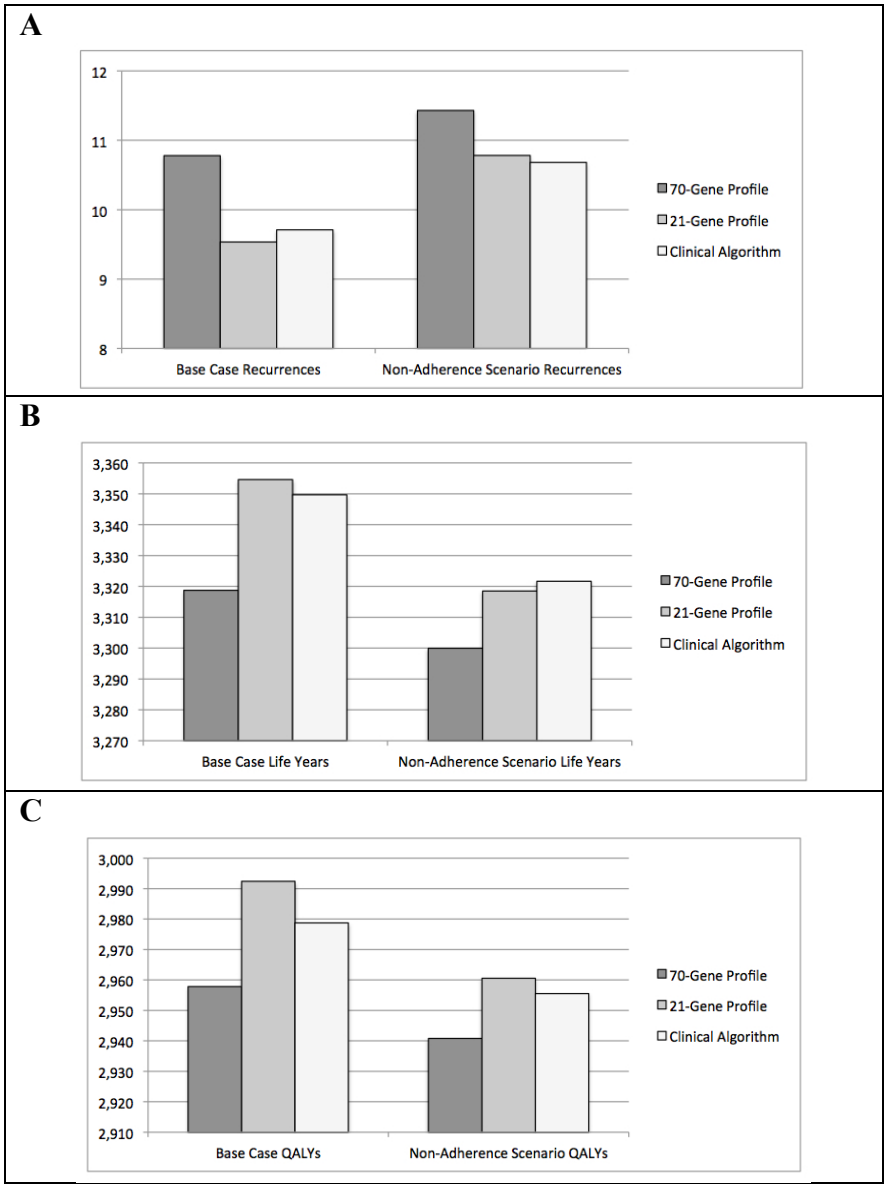

Figure A6: Comparison of base case and non-adherence scenario for (A) distant recurrences, (B) life years, and (C) QALYs.

CHAPTER IV

Overall Conclusions

Summary

In each of the case studies reported above, comparative effectiveness research (CER) methods were applied to provide insights about the health outcomes associated with use of pharmacogenomic technology. In chapter 1, I evaluated the association of genetic variants and major bleeding outcomes in warfarin therapy by leveraging the statistical power provided by a case-control study design to investigate rare health outcomes (e.g. major bleeding). In doing so, I was able to demonstrate the first association between *CYP4F2* variants and decreased risk of major bleeding, support the noted associated association between *CYP2C9* variants and increased major bleeding risk, and provide exploratory evidence suggesting potential additional increases in *CYP2C9* variant major bleeding risk in more rural settings. (26, 39, 47, 73) These findings expand understanding of genetic risk factors for major bleeding in warfarin therapy, have potential to inform warfarin dosing and monitoring practices, and may have different implications for patients in different geographic settings.

In chapter 2, I applied value of information analysis methods to assess the societal economic value of a future clinical trial investigating an *ERCC1*-guided adjuvant chemotherapy strategy in Stage I non-small cell cancer (NSCLC). This analysis demonstrated that such a trial is expected to cost approximately $30m, create societal value of approximately $80m, and thus provide approximately $50m in societal value in excess of trial cost. This value represents a considerable return on investment, compares favorably to the value of information for other pharmacogenomic technologies

reported in the literature, and indicates that research funding stakeholders should consider *ERCC1* testing in Stage I NSCLC a high-priority area for future investment. (140, 153, 154)

In chapter 3, I focused on a regulatory application of a comparative effectiveness method, discussing the potential role of benefit-risk modeling as an adjunct to standard qualitative review processes for pharmacogenomic technologies at the United States Food and Drug Administration (FDA). In this discussion, I demonstrated how benefit-risk modeling can provide systematic and quantitative insights to the review process, enhancing ability to explicitly evaluate potential clinical utility, facilitating assessment uncertainty, and increasing overall transparency.(210)

Collectively, these case studies demonstrate the wide array of applications for CER methods to evaluate pharmacogenomic technology, and provide useful insights to inform future translational decision-making.

Implications

In addition to providing new evidence to inform translational efforts for each of the pharmacogenomic technologies discussed above, each case study raises new questions and suggests areas for future research. In chapter 1, my new finding of an association between *CYP4F2* variants and decreased major bleeding risk raises questions about the biological mechanism underlying the major bleeding effect; whether there is interaction between *CYP4F2* and *CYP2C9*, *VKORC1*, or other genetic variants thought to confer increased risk of major bleeding; and whether this information can have meaningful impact on clinical outcomes in routine medical practice. To address these questions, future studies should evaluate the *CYP4F2*-bleeding association in more

racially and ethnically diverse patient populations and alternative healthcare delivery settings. Additionally, the comparative outcomes of warfarin pharmacogenomic strategies (including *CYP4F2*) warrant evaluation in well-powered future prospective designs. Addressing the aforementioned research questions with new CER evidence can focus pharmacogenomic strategies on patient sub-populations and settings where testing is likely to have maximum impact on health outcomes, can reduce overall uncertainty about the clinical utility of warfarin pharmacogenomics, and can provide stakeholders with actionable information to inform appropriate translation.

In chapter 2, my finding of considerable value in a future *ERCC1* testing clinical trial in Stage I NSCLC raises questions about the optimal pathway forward for prospective evaluation. Though I present evidence that there is high value in an *ERCC1* testing clinical trial, it remains unclear if there is presently the will or ability to conduct such a trial in the United States. Prior work has suggested that there may be barriers to implementation in both respects.(117, 119) Furthermore, due to the scarcity of value of information analyses evaluating pharmacogenomic technologies, it remains uncertain whether an *ERCC1* testing clinical trial would provide high value relative to potential alternative investments of research resources. I did find that trial value compares favorably to three other pharmacogenomic technologies in breast and lung cancer, but there are hundreds of alternative technologies that may provide even greater return on investment. To address this evidence gap, future efforts should be taken to systematically develop value of information evidence for pharmacogenomic technologies to assess and optimize research investment.

In chapter 3, my discussion of the potential role of benefit-risk modeling to inform regulatory review of pharmacogenomic technology highlights a number of opportunities such an approach could

provide, but it remains unclear precisely how this approach would be integrated in regulatory decision-making, and how regulatory stakeholders would utilize such information. These issues should be evaluated through qualitative analyses of regulatory stakeholder perspectives on the potential opportunities and barriers associated with benefit-risk modeling implementation. Additionally, pilot applications of benefit-risk modeling to evaluate selected pharmacogenomic technologies could provide considerable insights about the feasibility and decision-making impacts of incorporating quantitative benefit-risk tradeoff evidence in FDA regulatory reviews.

Conclusion

The Human Genome Project has led to great advances in understanding of the effect of genomics in disease risk and health outcomes over the past decade.(1, 4, 5, 10, 11) As a consequence of these advances, pharmacogenomic tests have increasingly been developed and marketed to consumers to inform clinical decisions. Though these technologies have the potential to improve net health outcomes relative to standard care, they will not always lead to net health benefit, and could potentially have negative net health impacts.(2, 8, 169, 235) Comparative effectiveness research methods can facilitate systematic evaluation of these types of benefit-risk tradeoffs, and can synthesize individual evaluations to provide more comprehensive assessment of clinical utility.(4, 5, 10) However, these methods do have considerable limitations that worth noting. Principally, many such approaches, like value of information analysis, are in need of additional methodological development and explicit standards. Additionally, because many stakeholders are unfamiliar with the relative merits and limitations of many comparative effectiveness research methods, there is noted apprehension about applying CER evidence to inform decision-making.(2, 12, 169) These issues are likely to be resolved over time based on increased outreach, familiarity, and necessity.

Herein, I have discussed the current role and potential future applications of comparative effectiveness research methods in the evaluation of pharmacogenomic technology. I demonstrated three specific applications of these methods through case studies applying an observational design, value of information analysis, and benefit-risk modeling to address meaningful pharmacogenomic questions in warfarin therapy, lung cancer, and breast cancer. These types of comparative effectiveness research methods will likely play an important role in future assessment and translation of pharmacogenomic technologies due to the accelerating pace of research and development, and inability of traditional controlled trial designs to provide evidence that is timely, adaptable, and readily applicable to routine clinical decision-making. Accordingly, lack of comprehensive strategies to develop pharmacogenomic evidence through comparative effectiveness research may result in continued sub-optimal or premature clinical translation, and failure to leverage the utility of personalized medicine strategies to improve public health.

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RESEARCH INTERESTS

My research interests involve application of comparative effectiveness research methods to evaluate the health outcomes of cancer therapeutics and diagnostics, including: randomized controlled trial design, observational study design, decision-analytic modeling, and meta-analysis.

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WORK EXPERIENCE

Federal Regulatory Affairs Coordinator, Swedish Medical Center: Swedish Cancer Institute, Seattle, WA November 2005-July 2008
- Coordinated submissions to federal, state, and institutional regulatory entities in support of ≈150 active investigator-initiated, cooperative group, and commercially sponsored clinical trials.
- Directed the work of research assistants to achieve project objectives

Regulatory Specialist, Quorum Review (Institutional Review Board), July 2005-November 2005
Seattle, WA
- Analyzed IND safety reports, protocol deviations, and serious adverse effect reports to facilitate medical review

RESEARCH & TEACHING ASSISTANTSHIPS

Research Assistant, Grant Titled "Pharmacogenetics in Rural and Underserved Populations", Department of Pharmacy, University of Washington, Seattle, WA July 2010-Present
- Developed survey instrument, participated in study planning, and carried out primary analysis in support of grant objectives

Research Assistant, Grant Titled "Center for Comparative Effectiveness Research in Cancer Genomics (CANCERGEN)", Department of Pharmacy, University of Washington, Seattle, WA — June 2010-October 2011

- Developed decision analytic models to evaluate the value of information associated with a clinical trial to investigate various biomarkers

Research Assistant, Grant Titled "Risk-Benefit Framework for Genetic Testing", Department of Pharmacy, University of Washington, Seattle, WA — October 2008-September 2010

- Developed decision-analytic models, conference presentations, and peer reviewed manuscripts in support of project objectives

Teaching Assistant, Course Titled "Pharmaceutical Law and Ethics", Department of Pharmacy, University of Washington, Seattle, WA — September-December 2007

- Created lecture slides for classroom presentations
- Wrote and edited questions for quizzes, midterm, and final
- Facilitated a 10-week project to analyze regulatory policies

PROFESSIONAL ACTIVITIES

Professional Associations

- International Society for Pharmacoeconomics and Outcomes Research
- Society for Medical Decision Making
- American Society of Clinical Oncology

Journal Reviewer

- Public Health Genomics
- Journal of Gastrointestinal Cancer
- Medical Decision Making
- Value in Health
- Cancer Chemotherapy and Pharmacology
- International Journal of Biological Sciences

Other Activities

- International Society of Pharmacoeconomic and Outcomes Research Oncology Outcomes Research Working Group (2010-Present)
- International Society of Pharmacoeconomic and Outcomes Research Modeling Good Research Practices Task Force (2010-Present)
- Admissions Committee, University of Washington Pharmaceutical Outcomes Research and Policy Program (PORPP), (2009-2010)
- University of Washington Institutional Review Board (2006-2010)

COMPETITIVE FUNDING AWARDS

- Fellow, PhRMA Foundation Pre-Doctoral Fellowship in Comparative Effectiveness (2011)
- Fellow, American Foundation for Pharmaceutical Education Pre-Doctoral Fellowship (2010)
- Recipient, University of Washington Graduate & Professional Student Senate Travel Grant (2010)
- Recipient, University of Washington Graduate School International Travel Grant (2010)
- Recipient, University of Washington: Graduate School Top Student Assistantship (2008)

ACADEMIC HONORS

- Finalist, Best Student Poster Presentation, International Society for Pharmacoeconomics and Outcomes Research Annual Meeting (2011)
- Recipient, Best Student Podium Presentation, International Society for Pharmacoeconomics and Outcomes Research Annual Meeting (2010)

- Recipient, University of Washington Pharmaceutical Outcomes Research & Policy Program Endowed Prize in Health Policy and Economics (2010)
- Member, Alpha Kappa Delta Honor Society (2004)
- Honoree, Union College Dean's List (2002-2004)

STATISTICAL AND ECONOMIC MODELING SOFTWARE PROFICIENCIES

- STATA**,** SPSS, SAS, MS Excel, Tree Age

PEER-REVIEWED PUBLICATIONS

Roth JA, Carlson JJ. The Prognostic Role of *ERCC1* in Advanced Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Clinical Lung Cancer. 2011; 12(6): 393-401.

Roth JA, Carlson JJ. Cost-Effectiveness of Gemcitabine+Cisplatin vs. Gemcitabine Monotherapy in Advanced Biliary Tract Cancer. Journal of Gastrointestinal Cancer. 2011; DOI: 10.1007/s12029-010-9242-0.

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Veenstra DL, **Roth JA**, Garrison LP, Ramsey SD, Burke W. A Formal Risk-Benefit Framework for Genomic Tests: Facilitating the Appropriate Translation of Genomics Into Clinical Practice. Genetics in Medicine. 2010; 12(11): 686-93.

MANUSCRIPTS IN PRESS

Esmail L, **Roth JA**, Rangarao S, Deverka P, Ramsey SD, Carlson JJ, Thariani R, Veenstra DL. Getting our priorities straight: A qualitative study of stakeholders' considerations when prioritizing cancer genomics research. Genetics in Medicine.

Carlson JJ, Thariani R, **Roth JA**, Gralow J, Henry NL, Esmail L, Deverka P, Ramsey SD, Baker L, Veenstra DL. Research Prioritization in Cancer Genomics: Formal Value of Research Analyses within a Stakeholder-Informed Process. Medical Decision Making.

WORKS IN PROGRESS

Roth JA, Ramsey SD, Veenstra DL, Carlson JJ. An Economic Evaluation of First-Line Treatment with Cetuximab in Advanced Non-Small Cell Lung Cancer.

Roth JA, Thariani R, Carlson JJ, Steuten L, Ramsey SD, Veenstra DL. The value of research for *ERCC1* expression testing in Stage I non-small cell lung cancer.

Roth JA, Boudreau D, Wittkowsky A, Blough D, Farin F, Veenstra DL. Association between *CYP2C9* genetic variants and major bleeding in warfarin therapy patients across diverse geographic and care settings.

Carlson JJ, **Roth JA**. The impact of the Oncotype Dx Breast Cancer Assay in clinical practice: systematic review and meta-analysis.

Roth JA, Veenstra DL. Benefit-Risk Modeling to Inform Regulation of Genomic Tests: A Case Study in Early-Stage Breast Cancer.

Ramsey SD, Carlson JJ**, Roth JA,** Berchem G, Schlesser M, Trent J**.** A Value-Based Process for Biomarker Development.

CONFERENCE PODIUM PRESENTATIONS

Roth JA, Carlson JJ. "Accounting for uncertainty in the affected population used in value of information analyses: An application in advanced biliary tract cancer" at the at the Society for Medical Decision Making Annual Meeting, Chicago, IL, October 25, 2011.

Roth JA, Carlson JJ, Steuten L, Ramsey SD, Veenstra DL. "The Value of Research for *ERCC1* Expression

Testing Cinical Trials in Stage I Non-Small Cell Lung Cancer" at the 2011 World Conference on Lung Cancer, Amsterdam, Netherlands, July 6, 2011.

Roth JA, Carlson JJ, Steuten L, Ramsey SD, Veenstra DL. "The Value of Research for *ERCC1* Expression Testing in Stage I Non-Small Cell Lung Cancer" at the International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Baltimore, MD, May 23, 2011.

Roth JA, Veenstra DL. "The Value of Research for *ERCC1* Expression Testing in Stage I Non-Small Cell Lung Cancer" at the Western Pharmacoeconomics Conference, Seattle, WA, April 1, 2011.

Roth JA, Veenstra DL. "Risk-Benefit Framework for Evaluation of Gene Expression Profiling in Women with Early Stage Breast Cancer: A Decision Model Developed in Collaboration with Stakeholders" at the International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Atlanta, GA, May 18, 2010.

OTHER CONFERENCE ABSTRACTS

Carlson JJ, **Roth JA**. "The impact of the Oncotype Dx breast cancer assay in clinical practice: Systematic review and meta-analysis" at the American Society for Clinical Oncology Annual Meeting, Chicago, IL, June 2, 2012.

Roth JA, Carlson JJ, Steuten L, Ramsey SD, Veenstra DL. The influence of patient/provider behavior on the value of *ERCC1* testing research in Stage II non-small cell lung cancer" at the at the Society for Medical Decision Making Annual Meeting, Chicago, IL, October 24, 2011.

Roth JA, Carlson JJ, Steuten L, Ramsey SD, Veenstra DL. "The Value of Research for *ERCC1* Testing in Stage I Non-Small Cell Lung Cancer" at the American Society for Clinical Oncology Annual Meeting, Chicago, IL, June 3, 2011.

Carlson JJ, Thariani R, **Roth JA**, Ramsey SD, Deverka P, Esmail L, Gralow J, Henry L, Veenstra DL. "Value of Research Analyses in Research Prioritization of Cancer Genomic Applications" at the AcademyHealth 2011 Annual Research Meeting, Seattle, WA, June 24, 2011.

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