Innovation, Value, and Uncertainty in Oncology Precision Medicine

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Abstract

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Background: There is substantial enthusiasm for precision medicine (PM), and its impact is more apparent in oncology as most new oncology drugs and diagnostics approved over the past decade are based on tumor genetics. PM research endeavors and developments have transformed the way we diagnose, prevent, and treat cancer. However, two major issues are yet to be addressed: 1) How the reimbursement policies have impacted the indication subdivisions versus the technological advances, and 2) Given the vast information that comes from current Next-Generation Sequencing (NGS) technologies, how much information should be used in clinical decision-making context. In this dissertation, I, therefore, developed 1) the quasi-experimental design to estimate the impact of insurance coverage expansions (Medicare part D implementation) on the potential indication size for oral oncology drugs; and 2) a decision-analytical modeling approach to estimate the uncertainty of adding the moderate/low risk genes to the targeted hereditary breast cancer screening (HBCS) gene-panels.

Methods: In Chapter 2, I designed a quasi-experimental study design by exploiting the exogenous variation in the age at the cancer diagnosis for various cancer sites. This variation in age at diagnosis for different cancer sites helped us isolate the impact of Medicare part D from

other contemporary developments such as genomics advances. I used several sources to build a unique dataset including the US Food and Drug Administration (FDA) website, Surveillance, Epidemiological, and End Results (SEER) program database, published and gray literature. I used a difference-in-difference approach to estimate the effect of Medicate part D on the indication size. In Chapter 3, I developed a decision-analytic model to estimate the long-term outcomes of using HCBS gene panels for breast cancer screening in high-risk women. I created three hypothetical gene panels and compared them to no testing strategy and amongst each other. I populated the model using clinical and economic inputs from published epidemiological literature, Surveillance, Epidemiological, and End Results (SEER) program website, and other published cost-effectiveness studies. The outcomes assessed were costs, life years gained (LEs), quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER), the incidence of breast cancer, and ovarian cancer. To characterize uncertainty, I performed one-way and probabilistic sensitivity analyses.

Results: In Chapter 2, I demonstrated that the indication size for oral oncology drugs decreased by 37.5% in the post-Medicare part D period. I also estimated that for a one percent increase in the proportion of Medicare-eligible patients for a cancer site, the indication size for oral cancer drugs decreased by 3.28% (p-value=0.001). In evaluating the covariates as potential mediators, I demonstrated that neither the companion diagnostics nor the line of therapy at the time of drug approval contributed significantly to the causal effect. In Chapter 3, I demonstrated that the inclusion of moderate/low risk genes on the targeted panels increased the overall decision uncertainty. Specifically, all three screening strategies (Panel 1-3) dominated the no screening strategy. Both Panel 2 (BRCA1/2 plus other high-risk genes) and panel 3 (panel 2+ moderate/low-risk genes) dominated (better outcomes, lower cost) panel 1 (BRCA1/2 only) in the deterministic analyses. However, in probabilistic analysis accounting for uncertainty, panel 2

(BRCA1/2 and other high-risk genes) was the optimal strategy at a willingness to pay (WTP) threshold of $100,000 or less.

Conclusions: I found that the labeled indication size for oral cancer drugs decreased in the post-Medicare part D period, and the effect was heterogeneous based on the proportion of Medicare-eligible patients for cancer sites at the time of diagnosis. Using the decision-analytical modeling approach, I found that the evidence is likely sufficient for the inclusion of high-risk genes onto the BRCA1/2 gene-panels; however, the evidence is not sufficient for the inclusion of moderate/low risk genes on the BRCA1/2 gene-panels.

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Chapter 1

INTRODUCTION

Precision medicine (PM) has been at the forefront of research initiatives for almost a decade, but the progress of PM from research to clinical practice has been slow in general (1). PM research endeavors and developments have transformed the way we diagnose, prevent, and treat cancer. Cancer is increasingly no longer classified and characterized merely based on the organ system (or anatomical site) affected but is characterized based on its molecular signature. Innovation in the field of oncology is overarching and extends from new technologies used to identify the germline and somatic mutations in asymptomatic patients to new drugs developed to target specific subtypes of cancer based on their molecular signature. I describe below examples specific to the oncology PM to highlight two key issues that are not yet resolved: impact of reimbursement policy on drug development and the addition of genes of higher uncertainty to create the "expanded multigene panels" for hereditary breast cancer screening.

An example of coverage expansion and its potential impact on drug development and approval is a non-small cell lung cancer (NSCLC) drug crizotinib (Xalkori®). NSCLC patients were previously treated with injectable platinum-based chemotherapies, which were covered under Medicare part B, both prior-to and post-MMA enactment. Some (~5%) of patients with NSCLC have a somatic mutation in gene *ALK*, and a small molecule crizotinib (Xalkori®) was approved for patients whose tumors carry the *ALK* mutation, thereby only 5% (US incidence ~9500 patients) of the NSCLC patients were indicated for this new oral chemotherapy. Similarly, on an average, a smaller percent of lung cancer patients is eligible for other oral chemotherapy drugs approved post-MMA. It should be noted that in clinical trials crizotinib was used as three formulations; capsules, tablets, and intravenous solutions, but it was later developed and marketed as capsule formulation for oral use, and 100% of Medicare Part D plans cover it. In contrast, Miglustat (Zavesca®), the only oral medication for treatment of Gaucher's disease (US incidence ~7500 patients), is covered by only by ~50% of insurance plans (2).

A second example I would like to highlight is the addition of low/moderate risk genes to commercially available hereditary breast cancer screening (HBCS) gene panels to create expanded panels. HBCS gene panels range from 2 genes to more than hundreds of genes sequenced to identify susceptible disease-causing pathogenic variants. All HCBS gene panels include high-risk genes *BRCA1/2,* a pathogenic variant in these two genes may substantially increase the lifetime risk among the variants carriers (3). However, most commercially available HBCS gene panels also include low or unknown risk genes such as *APC, PALLD, and VHL*, which do not have any published evidence/evaluation of breast cancer-related risk. Variants in these low-risk genes may not increase the breast cancer risk above that of the general population. Several published manuscripts and editorials have debated on some key issues of expanded multi-gene panels (4-7):

- If the information from the gene(s) on multigene panels is not providing any "credible" information to alter the clinical course for the patient, why to include such gene(s) on the multigene panel?
- Does the addition of low risk and low/no information gene(s) on the panel reduce the overall clinical and economic value of the multigene panels?
- Do the addition of lower/no information genes on multigene panels has the potential to harm to the patients?

In my dissertation, I focused on innovation, value, and uncertainty in healthcare technologies (drugs and diagnostics) in oncology. My first aim focused on the impact of insurance coverage expansion on innovation in oncology marketplace by using a case study of the impact of Medicare Part D (under MMA 2003) on the development of oral oncology drugs. The second aim of my dissertation focused on estimating the clinical and economic value of next-generation sequencing (NGS) based multi-gene panels for hereditary breast cancer screening (HBCS).

Both oral oncology drugs and multi-gene hereditary cancer panels have shown tremendous growth in a short period and have important clinical and economic significance. In my dissertation research I identified whether the Medicare part D based coverage expansion has moved oncology drug development toward more “precision”, i.e. whether the indication sizes for newly developed oral oncology drugs have decreased since the promulgation of Medicare Part D. My research on the NGS-based hereditary multigene panels I estimated the clinical and economic impact of adding other high-risk and moderate-risk genes to BRCA 1/2, i.e., whether and how does the clinical and economic value of the multigene panels change when other high/moderate-risk genes are added to BRCA1/2.

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Chapter 2

Medicare Part D and Innovation in Oral Oncology Drugs: Pursuit of Smaller Indications?

ABSTRACT

Introduction: Medicare part D, created under the Medicare Modernization Act (MMA) of 2003, was one of the biggest coverage expansions of publicly funded insurance in the US. Previous studies have shown that innovation follows larger markets for greater return on investments. We hypothesized that innovation in oral oncology drugs followed smaller markets if firms' returns on investments are hedged by guaranteed coverage. The objective of our study was to estimate the impact of Medicare part D on the labeled indication size (market size) in oral oncology drugs using a quasi-experimental study design to isolate the effect from other effects such as genomics advances that happened during the same time. [approach]

Methods: We used the quasi-experimental study design by exploiting the exogenous variation in the age at the cancer diagnosis for various cancer sites. This variation in age at diagnosis for different cancer sites helped us isolate the impact of Medicare part D from other contemporary developments such as genomics advances. We used several sources to build a unique dataset including the US Food and Drug Administration (FDA) website, Surveillance, Epidemiological, and End Results (SEER) program database, published and gray literature. We utilized the fixed effects Poisson regression to estimate the impact of Medicare part D on our count outcome of indication size in oral oncology drugs and used injectable cancer drugs as a control group. We controlled for year of approval, line of therapy, companion diagnostic on the label, and cancer site incidence rates as time-varying covariates and included the cancer site and time fixed effects. We used a difference-in-difference approach to estimate the effect of Medicate part D on the indication size.

Results: We identified 261 unique drug-indication pairs, and after excluding the drug-indication pairs based on exclusion criteria we used 237 drug-indication pairs for our final analyses. The

indication size for oral oncology drugs decreased by 37.5% in the post-MMA period. For a one percent increase in the proportion of Medicare-eligible patients for a cancer site, the indication size for oral cancer drugs decreased by 3.28% (p-value=0.001). In our analysis, the companion diagnostics or the line of therapy did not contribute significantly to the indirect effect of Medicare part D on the potential indication size (<5% of the change in coefficients of the main effect after inclusion of potential mediators).

Conclusions: The labeled indication size for oral cancer drugs decreased in the post-MMA period, and the effect was heterogeneous based on the proportion of Medicare-eligible patients for cancer sites at the time of diagnosis. These findings indicate that insurance coverage expansions can incentivize pharmaceutical firms to innovate in smaller markets provided that the drugs being developed for such markets are provided with guaranteed coverage.

INTRODUCTION:

Medicare part D (created under the Medicare Modernization Act (MMA) of 2003) was one of the biggest insurance coverage expansion of a publicly funded insurance in the US after the inception of Medicare (1). Medicare part D covers oral oncology drugs, which were not previously covered, whereas intravenous (IV) oncology drugs were covered by Medicare part B before and after Medicare Part D came into effect (2). Medicare part D was created to provide coverage of prescription drugs for the Medicare enrollees. Expanding the insurance coverage through government subsidies can also provide incentives to pharmaceutical manufacturers to alter their research and development investments focus and drug development programs. Previous research has demonstrated that pharmaceutical manufacturers increase investments in those therapeutic classes of drugs that were newly included in insurance coverage. How the increase in coverage of prescription drugs impacts innovation can be measured using different proxies – number of new drugs approved, number of new clinical trials mounted, and the survival benefits of the newly approved drugs. However, the firms have little incentive to innovate in the smaller markets with limited market potentials, such as neglected tropical diseases and personalized medicine that tailors the drugs for a specific subgroup of patients. Government incentives and subsidies can help motivate for the private firms to innovate and develop drugs in such smaller markets. We hypothesize that the Medicare part D coverage expansion under MMA induced pharmaceutical firms to innovate and increase their R&D investments in such smaller markets in the oncology. The smaller indications, which may have been otherwise not profitable because of smaller market size, provided enough return on investments to the manufacturers of oral oncology drugs, which were provided “mandated” coverage under Medicare part D following MMA implementation. If the Medicare part D provided incentives to firms to develop drugs for smaller indications in oncology, then we should see a decrease in indication size in oral oncology drugs post-Medicare part D, and this effect should

be more pronounced in those cancer sites with higher proportions of Medicare-eligible population.

Impact of Medicare part D on the oncology drugs is a unique natural experiment because oral oncology drugs were not covered before Medicare part D and were covered under part D, but the injectable oncology drugs were covered before, and after Medicare part D. An evaluation of indication size in oral oncology drugs presents an interesting opportunity for the following reasons: 1) a large number of oral oncology drugs approved post MMA providing a sufficient sample size to perform analysis, 2) oncology drugs could have been approved both as oral and IV dosage forms, and 3) oncology drugs are in one of the six protected categories mandated to be on the Medicare part D formularies.

A key challenge in evaluating the impact of Medicare part D are contemporaneous developments; for example, technological advancements in genomics were unfolding, which could confound the impact of Medicare part D on innovation. However, the prevalence of cancer among the general population is age-dependent, i.e., some cancers (e.g., lung and prostate) are more prevalent among older patients whereas other cancers (e.g., leukemia and lymphoma) are less prevalent among the older patients (3). This variability enabled us to address the confounding due to other contemporaneous developments.

While previous studies have demonstrated that Medicare part D creation increased research and development (R&D) investments for therapeutic classes with higher Medicare market share and the increase was not significant for drugs already covered by Medicare part B (4, 5), another study demonstrated that post-Medicare part D, the number of drugs developed in oncology via oral route was higher and the survival gains compared to the standard of care were lower for the oral oncology drugs (6). None of the existing studies focused on the impact of insurance coverage expansions had on firms developing drugs for smaller markets.

The objective of this study was to estimate the independent impact of expanded and mandated prescription drug coverage under MMA on the size of the labeled indication (indication size) in oral oncology drugs. We hypothesized that post-Medicare part D, the indication size for newly approved oral oncology drugs decreased for cancer sites with greater exposure to Medicare. Isolating the effect of Medicare part D on incentives for the development of oral cancer drugs from technological advances and other factors is critical. We overcame this challenge by incorporating following strategies in our design: 1) using the cancer site-specific fixed effects regression models and utilizing different cancer sites with varying proportions of the Medicare-eligible population (e.g., lung cancer vs. childhood leukemias) and 2) inclusion of IV cancer drugs as a negative control.

METHODS:

Study design:

We used the quasi-experimental design to isolate the impact of Medicare part D on indication size in oral oncology drugs. We utilized the variation in prevalence of the Medicare-eligible population for each cancer site. We used the time-series data collected for all oncology drugs approved by the Food and Drug Administration (FDA) between 1994 and 2016. We collected data for all the drugs approved from various sources including FDA website, Surveillance, Epidemiology, and End Results (SEER) program website, published epidemiological literature and mygenome.org website. Our outcome of interest was indication size, which is a count data. Therefore, we utilized the count data Poisson regression for our analysis and included the fixed effects at the cancer site level to absorb any confounding due to any observed or unobserved time non-varying covariates. We included the injectable oncology drugs as a negative control in our analysis.

Study data collection:

We developed a data set of oncology drug approved by the FDA between January 1, 1994, and December 31, 2016. Our dataset included the dates each drug was approved, including the first approved indication and all supplemental approval, route of administration, line of therapy of approved indication. We included all the drugs that were oral or injectables, and the drugs that were topical routes were excluded from the study sample. We also excluded the drugs that were used for chemoprevention or used as palliative therapies.

Approved Drugs and Indications

We used the Food and Drug Administration's (FDA's) website to identify all new drugs that were approved for marketing in the US from January 1, 1994, to December 31, 2016. We then identified all approved oncology indications of each drug approved from 1994-2016. Therefore, for drugs approved for more than one indication, more than one entry is present in our dataset. Apart from the name of the approved label indication, we also extracted other variables, such as companion diagnostic on the label and line of therapy at the time of approval, from the publicly available FDA database. We then classified each of the approved label indication to a "potential indication," i.e., indication which the manufacturer targeted for approval, e.g., a drug which was approved as a 2nd line non-small cell lung cancer (NSCLC) was classified under NSCLC, and a drug which was approved for 3rd line treatment of castration-resistant prostate cancer was classified under castration-resistant prostate cancer.

The rationale for classifying labeled indications under the "potential indications" was twofold: 1) it is difficult to precisely estimate the indication size for specifically defined indication on the label and 2) our research question is about the potential indication targeted by the manufacturer at the time of FDA filing for approval. FDA may limit that potential indication based on its review

of underlying benefits and risks. If a drug was first approved as third-line therapy and later on approved for the first line, we counted it as two different drug-indication pairs.

Cancer Site Specific Incidence and mortality

We used the annual publication of Cancer Statistics published by the American Cancer Society (ASCO) to estimate the yearly cancer site-specific incidence and mortality (3, 7-29). Since 1979, ASCO estimates the number of new cancer cases and expected deaths in a given year, and compiles the data on cancer incidence, mortality, and survival. The site-specific incidence and mortality estimates are based on incidence data from Surveillance, Epidemiology, and End Results (SEER) program of National Cancer Institute (NCI) and mortality data (only from the early 1990s onwards) from the National Center for Health Statistics. For each label indication, we used the cancer site-specific incidence for the year of approval. Using the SEER data, we estimated the proportion of Medicare-eligible patients for each cancer site at the time of diagnosis.

Estimation of indication size

We estimated the size of the potential indication approved by using a systematic approach. First, we used the estimates of the annual incidence to estimate the indication sizes. Second, for all the broader indications, e.g., acute lymphoblastic leukemia, breast cancer, melanoma, etc. we used the site-specific data from the Cancer Statistics for the year of approval. Third, for advanced and metastatic cancer indications, we estimated the indication size based on the reliable scientific sources, such as Cancer Statistics, SEER database, NCI's cancer trends progress report, and published epidemiological articles in peer-reviewed journals. Fourth, for indications which had genetic subtypes listed on the label, (e.g. HER2 negative breast cancer) we used the following sources in order of preference: scientific information provided in the

medical reviews summary by FDA (publicly accessible) for each drug approved, peer-reviewed epidemiological literature, mycancergenome.org website, which provides molecular profiles of site-specific cancers along with estimates of percent of cancers with the genetic marker. For more complex indications such as HER2+ metastatic breast cancer, we estimated the indication size by using the cancer site incidence for the year of approval, and then multiplying it by the proportion of patients who were metastatic that year (Cancer statistics or NCIs Cancer Trends Progress Report) and proportion of breast cancer patients who are HER2+. In cases where more than one source reported a different proportion, we estimated proportion by taking an average of two values. Similarly, in instances where a range of proportion was specified rather than a point estimate, we chose the midpoint of the range to come at the proportion of patients, e.g. for some genetic markers mentioned in label indications, epidemiological literature only reports a range of cancer patients expressing that marker, we chose the midpoint of the range provided in the literature to come at one number to be used in the calculation of indication size.

Statistical Analysis

We used the fixed effects Poisson regression with robust standard errors to estimate the impact of Medicare part D on the potential indication size (incidence in the year of approval). Cancer sites were entered as the fixed effects, which allowed us to: 1) control for any non-time varying observed and unobserved confounding for each cancer site; 2) estimate the within-cancer changes over time in the indication size. We also included the year of approval as the fixed effects to address confounding (e.g., technological advances) that may be common across all cancer sites due to time. We adjusted for the following observed time-varying covariates: line of therapy, annual cancer incidence for the cancer site, companion diagnostic on the label. In our base model, we included the dummy variable for pre-MMA (pre-Medicare part D) vs. post-MMA (post-Medicare part D) time-period and interacted it with a dummy variable of the route of administration (oral vs. IV) to have a difference-in-difference estimation of indication size for oral

vs. injectable drugs in the pre- vs. post-MMA period. The coefficient of this interaction term is a ratio (oral vs. IV) of ratios (pre-MMA vs. post-MMA periods). The model specification is as follows:

$$Y_{it} = \beta_1 * PostMMA + \beta_2 * PostMMA * (Oral\text{-}IV) + \beta_3 * year_t + \beta_4 Z_{it} + \alpha_i + u_i$$

Where i indexes the indication size (count outcome) for cancer site i in year t. PostMMA is a dummy variable for the time-period and was zero for drugs approved before 2003 (passage of MMA) and was coded as 1 for drugs approved after 2006 (after the implementation of MMA). The Oral-IV is the dummy variable for the route of administration for the approved drugs. It was zero for drugs approved for injectable route and was coded as 1 for drugs approved for the oral route. The coefficient of interest in the base model was β_2 (coefficient for the double interaction term between the PostMMA and Oral-IV), which reveals what happened to the indication size of oral drugs in the post-Medicare part D period. Based on our hypothesis we expect that the coefficient of the double interaction term will be significant and negative, showing that the indication size for the oral drugs in the post-MMA implementation period was lower compared to that of injectable cancer drugs.

We then wanted to test the hypothesis that the indication size was smaller for the cancer sites with a higher proportion of the Medicare-eligible patients. To perform this analysis, we included in the mode a triple interaction term between the dummy variables of Oral-IV and postMMA and the continuous variable of the proportion of the Medicare-eligible population for the cancer sites. This analysis highlights the effect of MMA implementation on the oral cancer drugs based on the proportion of the Medicare-eligible population for the cancer sites. Proportion≥65 is the continuous variable for the Medicare-eligible population for a cancer site i. In the “differences-in-differences-in differences” analysis, the coefficient of interest is β_2 (the coefficient for the triple interaction term), which reveals what happened to the indication size of the oral drugs in the

post-MMA period with one percent increase in the Medicare-eligible population for a cancer site. Based on our hypothesis of the oral cancer drugs in the post-MMA period, we expect this coefficient to be negative and significant. The equation with triple interaction terms is shown below:

$$Y_{it} = \beta_1 * PostMMA + \beta_2 * PostMMA * Oral\text{-}IV * (proportion \geq 65)_i + \beta_3 * year_t + \beta_4 Z_{it} + \alpha_i + u_i$$

All analyses were conduction in STATA 15 (Stata Corp., College Station, TX)

Sensitivity and Mediation Analyses

We wanted to see if companion diagnostic and line of therapy at the time of approval mediated some of the causal effect of the MMA (Medicare part D) on the potential indication size. We followed the published methods of mediation analysis(30, 31). To test the mediation effects, we ran the regression model with and without potential mediators and estimated the differences in the coefficients of the main effect (double and triple interaction coefficient terms). We also ran an analysis by to estimate the probability of having a companion diagnostic on the label for the oral and intravenous cancer drugs in the pre- and post-Medicare part D implementation. To estimate the probability of choosing different line of therapies in the pre- and post-Medicare part D era, we ran a multinomial logit models with line of therapy as the outcome variable.

RESULTS:

Our sample dataset included a time-series data for 261 drug-indication approval pairs (Appendix 1). We excluded 24 drug-indication pairs from our analyses because either the route of administration was neither oral or injectable, or we could not estimate the labeled indication size due to lack published epidemiological data in the public domain. Our final dataset included 237 drug-indication pairs approved across 27 unique cancer sites, including acute lymphoblastic

leukemia(ALL), acute myeloid leukemia (AML), bladder, breast, chronic lymphoblastic leukemia (CLL), chronic myeloid leukemia (CML), central nervous system (CNS), cervical, colorectal, gastrointestinal stromal tumor (GIST), gastric, head and neck (H&N), Hodgkin's lymphoma, kidney, lung, melanoma, myeloma, non-Hodgkin's lymphoma (NHL), ovarian, prostate, thyroid, liver, neuroendocrine tumor (NET), neuroblastoma, pancreatic, and sarcoma. We had a complete date on all the included variables for these 237 drug-indication pairs.

The descriptive results of the number of drugs approved by year are presented as Fig. 2. The number of drug approvals was highest for breast cancer followed by lung cancer and NHL and lowest for liver cancer followed by bladder cancer and Hodgkin's Lymphoma (Fig. 3). The proportion of Medicare-eligible patients was lowest for ALL followed by Hodgkin's lymphoma and was highest for bladder cancer followed by lung and CLL (Fig. 4).

Table 1 presents the summary statistics for all the time-varying variables included in our analyses. The estimation results from the difference-in-difference experiment (with double interaction only) using the Poisson conditional fixed effects regression are present in Table 2. The variable of interest for Oral-IV*Post-MMA, which reveals the impact of the post-MMA period on indication size for oral oncology drugs, had the expected negative sign and was significant at 10% significance levels. The indication size for oral oncology drugs decreased by 37.5% in the post-MMA period (Model 4). Thus, we can conclude that the Medicare part D creation (MMA implementation) was associated with an independent decrease in the indication size for the oral cancer drugs in the post-MMA period.

Table 2 also presents the estimation results from model 5 which included the triple interaction term Post-MMA*Oral-IV*Pct>65, which reveals the impact of MMA on the indication size for oral oncology drugs by Medicare-eligible population prevalence. The coefficient of the triple interaction term was negative as expected and was significant at 5% significance levels. From

the coefficient term, we can interpret that for each percent increase in the Medicare-eligible population for a cancer site, the indication size for oral drugs was 3.28% smaller. The differential effect of MMA on the indication size of oral oncology drugs based on the different percent of the Medicare-eligible population is shown in Figure 5. We can see that for cancer sites which had a lower proportion of the Medicare-eligible population, the indication size was increased for oral cancer drugs (e.g., ALL and Hodgkin's Lymphoma). However, for the cancer sites for which the proportion of the Medicare-eligible population was higher (greater than 45%), the indication size for oral cancer drugs decreased significantly in the post-MMA implementation period.

In Fig 6 we have shown how the impact of MMA on the indication size changed with the time following the post-MMA implementation. We see that the highest impact of the MMA on indication size was in the 2006-2009 period. The trend in the other two periods (2010-2013 and 2014-2016) was downward, but the difference in the trend was not statistically significant.

Sensitivity and Mediation Analyses

The results of the analysis for mediation effects of companion diagnostics (on the label at the time of approval) and line of therapy (at the time of approval) are shown in Table 2. Specifically, the inclusion of either of the two variables did not significantly alter the coefficient of the triple interaction term (postMMA*Oral-IV*pct65). Similarly, the estimated indirect effect due to companion diagnostics and line of therapy on the effect of Medicare part D implementation on indication size of oncology drugs was minimal (less than 5% of the total effect).

When we used the companion diagnostics as the outcome variable, the predicted probability of having companion diagnostic on the label of oral cancer drugs was on average 6.9% higher than the that of the intravenous cancer drugs (95% CI: -1.8%, 15.5%). The average predicted probability of having a companion diagnostic on the label at the time of approval in the post-

Medicare part D implementation era was on average 9.4% higher compared to the pre-Medicare part D era (95% CI: 1.2%, 17.8%). The difference in the predicted probability of having a companion diagnostic on the label at the time of approval in the post- vs. pre-Medicare part D era was 4.2% higher (95% CI: -2.1%, 10.4%) for oral cancer drugs compared to the difference for intravenous cancer drugs.

The results of the multinomial analysis for choice of line of therapy is shown in Appendix Table 2. Specifically, the on average the oral cancer drugs were on average 5.6% more likely to be approved as first-line compared to their intravenous drug counterpart. The oral cancer drugs on average were 3.5% and 2.8% less likely to be approved as second- and third-line treatment compared to the intravenous cancer drugs. The difference in the predicted probability of getting approved as a first-line treatment in the pre- vs. post-Medicare part D era was 8.2% higher for oral cancer drugs compared to the difference of intravenous cancer drugs in pre- vs. post-Medicare part D era.

DISCUSSION:

We estimated the impact of MMA implementation (drug insurance coverage expansion) on the indication size of oral cancer drugs. Our study is the first study to estimate the elasticity of indication size of cancer drugs to the proportion of the Medicare-eligible population for cancer sites. We exploited the variation in indication size of cancer drugs in the pre- and post-MMA implementation period and the variation in the proportion of the Medicare-eligible population for different cancer sites. We found that post-MMA implementation (post-2006), the indication size for oral oncology drugs decreased compared to the pre-MMA period and that the effect was more prominent in the cancer sites which had higher (above 45%) proportion of Medicare-eligible patients.

Our study has important implication that the insurance coverage expansions not only provide the expanded coverage for the patients but also provides incentives for the private pharmaceutical firms to innovate and develop drugs for smaller indications, which are otherwise less profitable for firms to focus their R&D investments. The results of our study when combined with results of a previously published study (6), which demonstrated that the number of drugs developed in the oral oncology class was higher in the post-MMA period, demonstrates that the innovation (number of drugs approved as proxy) in the oral oncology drugs was increased post-MMA, and this innovation was for smaller markets (potential indication size as proxy).

Our results are contrary to the bulk of traditional literature which shows that innovation follows the drug classes that have higher market size. In the US, because of Medicare, Social Security Act (SSA), and pharmaceutical policies, oncology is one of the six drug classes which were provided a protected status by the government (32). Guaranteed coverage of oral oncology drugs may explain that the smaller but protected market size may also provide a good return on investment for the pharmaceutical manufacturers. Our results show that as the Medicare-eligible population for cancer site increase, a greater proportion of the “market size” comes under the ambit of a protected class. The market-size hypothesis for innovation in the field of pharmaceutical is not new, and several researchers have demonstrated that larger the market-size more the number of drugs approved (33).

Contrary to the traditional hypothesis in other therapeutic areas, in oncology, increasing anecdotal evidence from academicians and the US Governmental Accountability Office (GAO), points towards a relatively recent trend of pharma companies opting for “narrow-indications” (34). The for-profit private firms choose their portfolio of projects based on their future return on investment; larger the potential returns larger the projects. Narrow-indications although offer smaller market-size (target population) bring several advantages for the firms (35): 1) Possibility of first in market (sometimes only in market) advantage and can dictate the pricing because of

only available drug for an unmet need; 2) Reduced degree of competition from other branded drug entrants; 3) Reduced motivation of generic manufacturers' entry due to smaller target population; 4) Increased profitability and higher margins due to relatively lower development and marketing costs compared to larger indications.

Previously, researchers have demonstrated that the insurance coverage expansions result in increased number of clinical trials mounted and increased number of drugs approved in the newly covered classes (4, 5, 33). Researchers have also shown that post-Medicare part D creation, oral cancer drugs produced smaller survival benefits over existing therapies (6). Previous researchers have also shown that the firms' incentives are in the pursuit for larger markets. Our study demonstrates that firms invest in smaller markets too if their return on investments is hedged by the insurance coverage expansions that provide guaranteed coverage for the smaller markets (indications).

Our study has several limitations. First, indication size of approved labeled indication does not exist in the public domain in the epidemiological literature. Therefore, we had to estimate the indication size for each labeled indication, and in some cases, we had to exclude drug indication combinations for which we could not find any reliable source to estimate the indication size. This may have induced some bias in our results, but since the excluded indications were only less than 10% of all approved indications, the extent of bias may be limited. Second, we estimated the potential indication size, e.g., if the labeled indication was for 2nd line castration-resistant prostate cancer drug, we estimated the size of the indication as that for castration-resistant prostate cancer. We understand this approach of estimating the indication size may introduce some bias, and we addressed this bias by including a covariate of the line of therapy in our models. Third, we used the fixed effects Poisson regression to estimate the impact of MMA on the indication size of the oral cancer drugs, and although the fixed effect approach absorbs the bias due to observed and unobserved non-time varying variables, bias due to the unobserved

time-varying variables not captured in our dataset may still be possible. We tried to collect data for several time-varying covariates in our dataset but there may still be time-varying covariates such as technological advances, which were not captured in our dataset and it may bias our study results. To address this issue, we included the injectable cancer drugs as a negative control. We assume that any effect due to most of the unobserved time-varying covariates that may affect the oral cancer drugs should also affect the injectable cancer drugs.

In conclusion, we found that labeled indication size for oral cancer drugs in the US was smaller after the implementation of Medicare Modernization Act (MMA) and the effect was more pronounced in the cancer sites which had a higher proportion of Medicare-eligible patients. Our findings imply that smaller market sizes observed over time in oral oncology are not due solely to technological innovation such as genomics and that insurance coverage policies may have independently fueled and sustained the creation of such smaller niche markets.

Tables and Figures

Table 1. Poisson regression estimates of indication size of oral cancer drugs in the post-Medicare Modernization Act

Covariates	Model 1 Mean (s.e.) [p-value]	Model 2 Mean (s.e.) [p-value]	Model 3 Mean (s.e.) [p-value]	Model 4 Mean (s.e.) [p-value]	Model 5 Mean (s.e.) [p-value]
Post-MMA[a]	1.78 (0.48) [<0.001] **	2.13 (0.38) [<0.001] **	1.59 (0.44) [<0.001] **	3.22 (0.13) [<0.001] **	1.95 (0.34) [<0.001] **
Oral-IV[b]	-0.98 (0.31) [0.002] *	-1.15 (0.01) [<0.001] **	-0.99 (0.31) [0.001] *	-0.08 (0.14) [0.55]	-1.15 (0.30) [<0.001] **
Pct>65	0.12 (0.06) [0.029]	0.04 (0.05) [0.374]	0.11 (0.07) [0.097]	0.03 (0.05) [0.518]	0.03 (0.05) [0.562]
Cancer site incidence rate	0.05 (0.16) [0.004] *	0.04 (0.02) [002] *	0.05 (0.02) [0.004] *	0.04 (0.015) [0.009] *	0.04 (0.02) [0.006] *
PostMMA*Oral-IV	1.04 (0.62) [0.023] *	1.29 (0.55) [0.018] *	1.47 (0.66) [0.026] *	-0.47 (0.27) [0.089] †	1.35 (0.58) [0.020] *
PostMMA*Pct>65	0.02 (0.01) [0.001] *	0.02 (0.01) [0.002] *	0.02 (0.01) [<0.001] **		0.02 (0.01) [0.001] *
Oral-IV*Pct>65	0.02 (0.01) [0.004] *	0.02 (0.01) [<0.001] **	0.02 (0.01) [0.004] *		0.02 (0.01) [<0.001] **
PostMMA*Oral-IV*Pct>65	-0.034(0.01) [0.053] †	-0.033(0.01) [0.010] *	-0.034(0.01) [0.015] *		-0.033 (0.01) [0.010] *
Companion-Dx		-0.38 (0.08) [<0.001] **		-0.41 (0.08) [<0.001] **	-0.38 (0.09) [<0.001] **
Line of therapy			0.07 (0.09) [0.441]	0.05 (0.09) [0.564]	0.07 (0.09) [0.474]
Cancer site fixed effects	Yes	Yes	Yes	Yes	Yes
Year fixed effects	Yes	Yes	Yes	Yes	Yes
Number of observations	222	222	222	222	222
Chi-squared	1.18e+05	1.05e+06	4.36e+12	1.57e+06	5.35e+11
Number of cancer sites	22	22	22	22	22

***Note:* * represents that the results are significant at 5% significance levels, **represents that results are significant at 1% significance levels, and † represents that results are significant at 10% significance levels.**

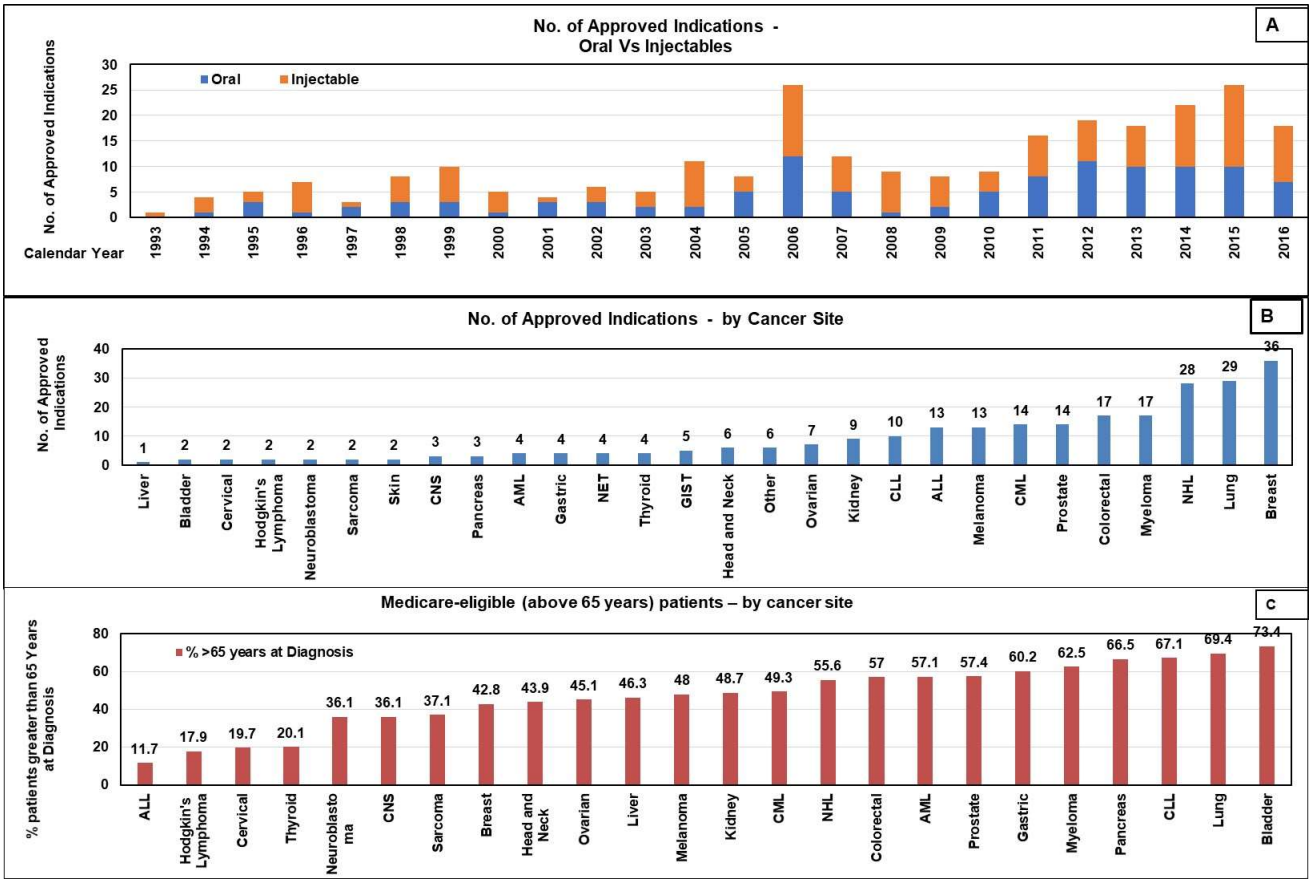

Figure 1: A) Number of approved oncology drug-indication pairs in the US between 1994 to 2016; B) Number of approved drug-indication pairs by cancer site; C) Proportion of Medicare-eligible (age ≥ 65 years) patients by cancer site.

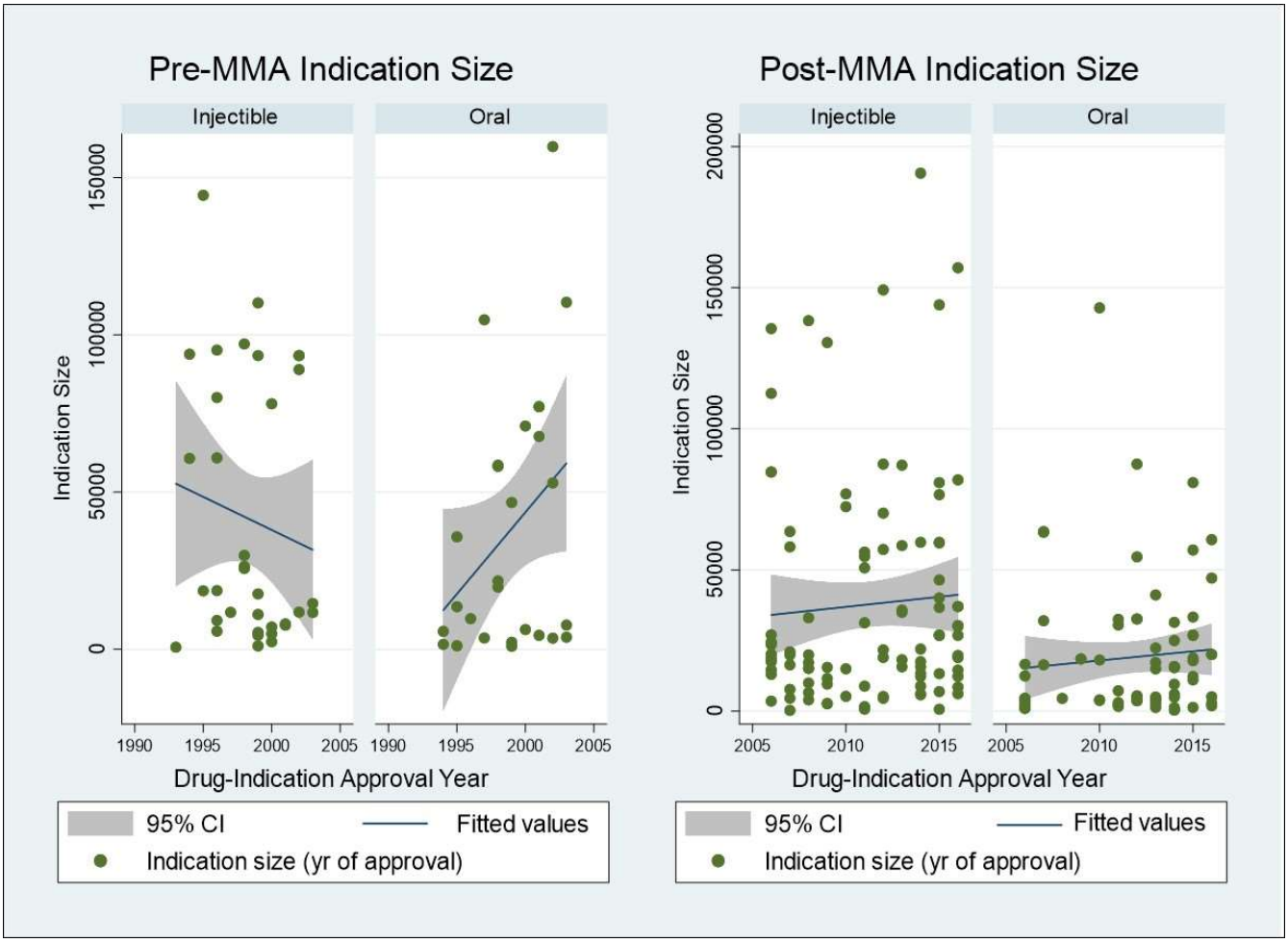

Figure 2: Indication size in the pre-Medicare Modernization Act (MMA) and post-MMA period for oral and injectable drugs.

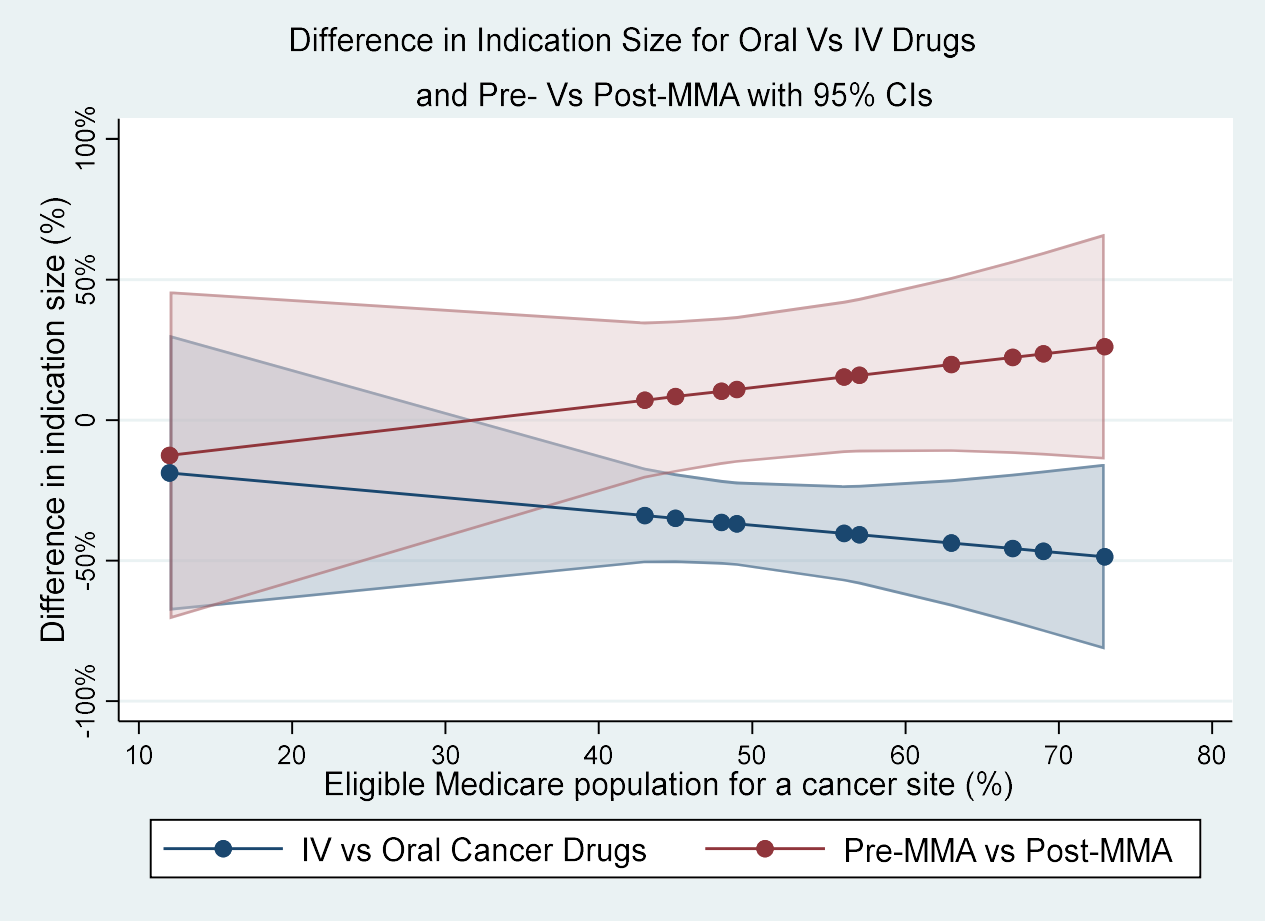

Figure 3: Difference in the indication size for Oral vs. Injectable drugs and Pre-MMA vs. Post-MMA periods

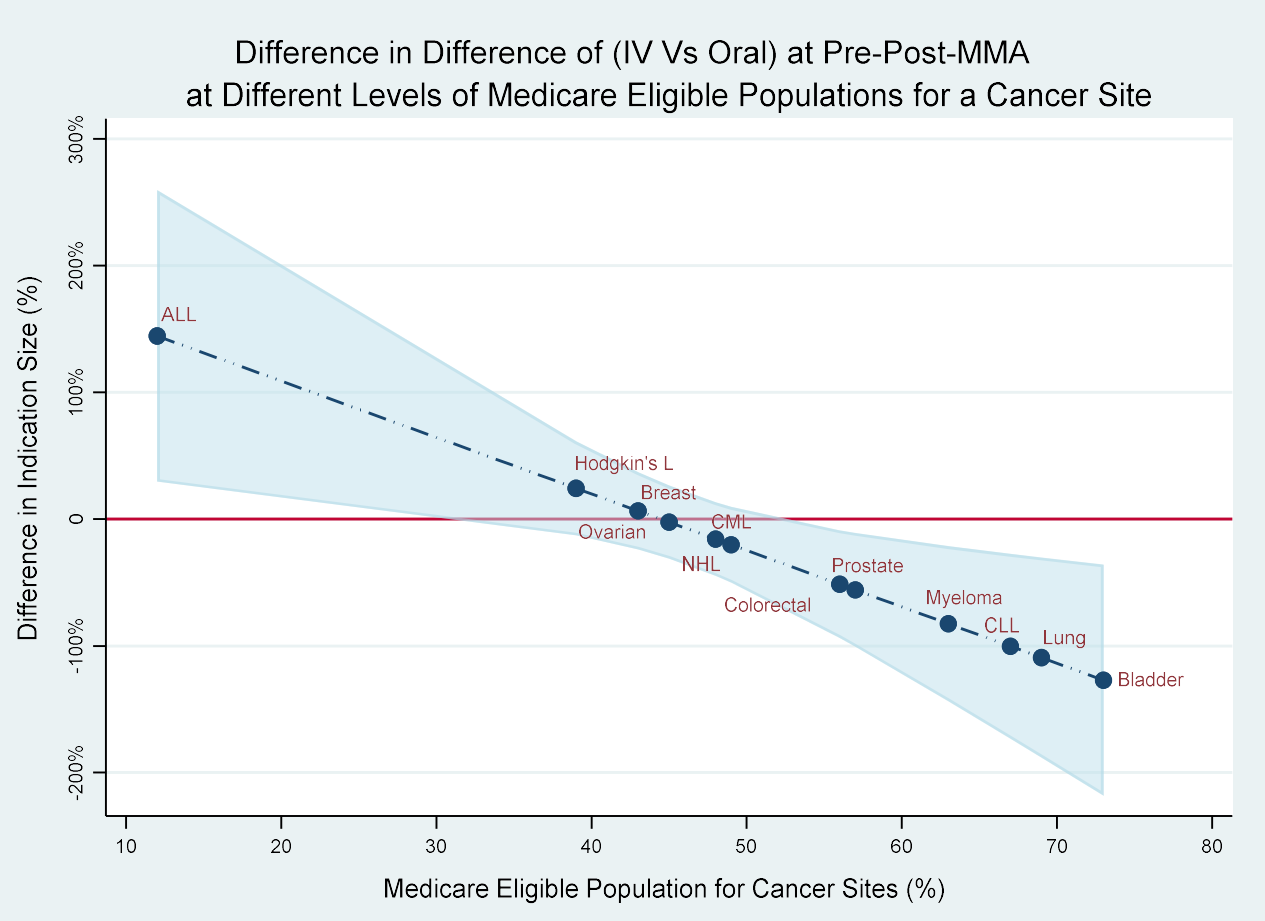

Figure 4: **Difference in the indication size for oral cancer drugs in pre-MMA vs. post-MMA periods at different proportions of Medicare-eligible population for cancer sites.**

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Appendix Tables and Figures

Appendix Table 1. Summary statistics for the indication size by cancer site for the approved labeled indication in our dataset.

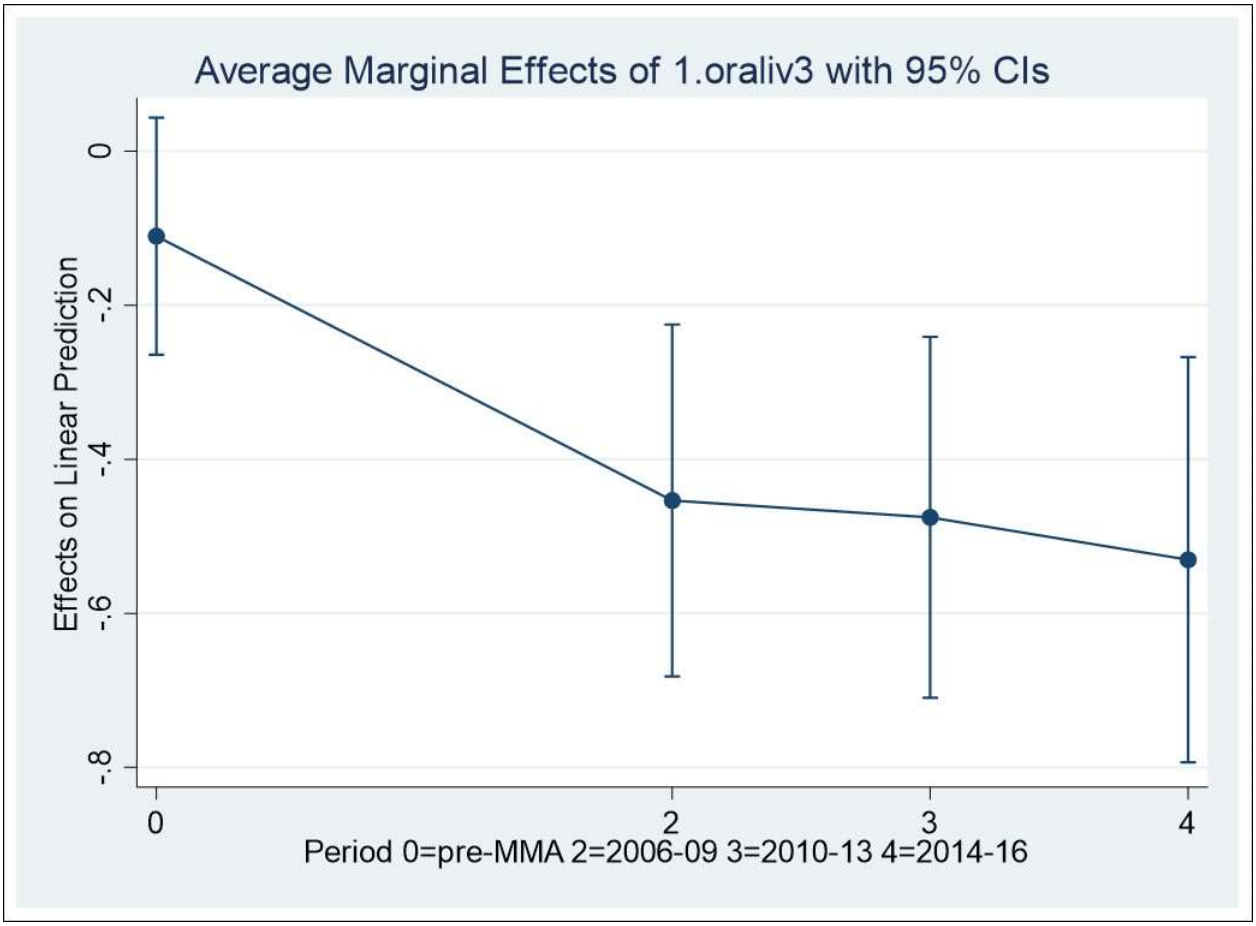
Cancer Site	Number of Drug-indication pairs in our dataset	Mean	Std. Dev.
ALL	11	3780	2073
AML	5	4967	3301
Bladder	3	42911	29774
Breast	30	62914	36832
CLL	14	11940	5928
CML	13	4039	1277
CNS	2	10335	1082
Cervical	2	3704	3398
Colorectal	14	79185	10296
GIST	2	4500	0
Gastric	4	13047	6461
Head & Neck	7	27661	7507
Hodgkin's Lymphoma	2	8665	233
Kidney	9	15647	5510
Liver	1	16382	.
Lung	29	74363	56834
Melanoma	14	30557	26903
Myeloma	17	19636	8752
NHL	29	11877	16043
Neuroblastoma	1	650	.
Ovarian	7	16469	6370
Pancreas	4	35654	6739
Prostate	11	19468	13181
Sarcoma	2	9233	4352
Thyroid	4	10295	8402

Appendix Table 2: Summary statistics of the Dependent and Independent variables included in the analysis						
Variable		Mean	Std. Dev.	Min	Max	Observations
Dependent Variable						
Indication Size	overall	32334.07	37163.05	260	190579	N = 237
	between		21854.49	650	79185	n = 25
	within		25578.61	-40122	148550	T bar = 9.48
Independent Variables						
Year of approval	overall	2008	6.53	1993	2016	N = 237
	between		3.91	1998	2016	n = 25
	within		5.75	1992	2020	T bar = 9.48
Oral-IV	overall	0.43	0.50	0.00	1.00	N = 237
	between		0.32	0.00	1.00	n = 25
	within		0.45	-0.33	1.23	bar = 9.48
Pct≥65 for Cancer Site	overall	52.03	14.52	10.00	73.00	N = 237
	between		18.20	10.00	73.00	n = 25
	within		0.32	48.53	55.53	T bar = 9.48
Median Age of Dx	overall	64.01	12.79	2.00	75.00	N = 237
	between		17.57	2.00	73.00	n = 25
	within		1.23	61.25	69.26	T bar = 9.48
Line of Therapy	overall	1.67	0.78	1.00	4.00	N = 227
	between		0.45	1.00	3.00	n = 25
	within		0.71	0.25	4.07	T bar = 9.08
Companion Dx on label	overall	0.14	0.35	0.00	1.00	N = 236
	between		0.17	0.00	0.57	n = 25
	within		0.32	-0.43	1.08	T bar = 9.44

Cancer Site	overall	12.97	7.49	1.00	28.00	N = 237
	between		8.09	1.00	28.00	n = 25
	within		0.00	12.97	12.97	T bar = 9.48
Cancer Site Incidence rate	overall	35.13	41.94	0.40	141.80	N = 234
	between		30.74	0.40	133.41	n = 24
	within		3.40	26.24	44.99	T bar = 9.75
Post-MMA	overall	0.74	0.44	0.00	1.00	N = 237
	between		0.24	0.00	1.00	n = 25
	within		0.39	-0.20	1.24	T bar = 9.48
postMMA -period	overall	2.26	1.53	0.00	4.00	N = 237
	between		0.92	0.00	4.00	n = 25
	within		1.35	-0.62	4.93	T bar = 9.48

Appendix Table 2: Difference in the predicted probabilities (pre-versus post-Medicare part D) for likely choice of line of therapy at the time of drug approval for oral versus Intravenous (IV) cancer drugs.

Line of Therapy	Difference between pre- vs. post-Medicare part D predicted probabilities for oral cancer drugs vs. IV cancer drugs for line of therapy choice	95% Confidence Interval
First Line	8.16%	-21.5%, 37.8%
Second Line	-11.6%	-40.6%, 17.4%
Third Line	2.6%	-15.2%, 20.4%



Appendix Figure 1: Average marginal effects for indication size of oral cancer drugs in different periods.

Chapter 3

Economic Value and Uncertainty of Expanded Multigene Panels for Hereditary Breast and Ovarian Cancer Screening: All Expanded Panels May Not Yet be Ready for Prime Time

ABSTRACT

Introduction: With the advent of next-generation sequencing and the invalidation of human gene patents, the number of commercially available multigene panels for cancer screening have increased rapidly and ranged from two to hundreds of genes. However, clinical and economic evidence for the impact of adding genes more genes to targeted multigene panels is scarce. There are few studies that estimated the value of adding genes, but the assessment of adding genes on uncertainty is missing available. We hypothesize that adding genes with uncertain clinical utility may add to overall decision uncertainty for multigene panel testing.

Objective: To evaluate the clinical and economic value and associated uncertainty for hereditary breast cancer screening (HCBS) gene panels.

Methods: We developed a decision-analytic model to estimate the long-term outcomes of using HCBS gene panels for breast cancer screening in high-risk women. We created three hypothetical gene panels: Panel 1 included BRCA 1/2 only; Panel 2 included BRCA1/2 plus other high-risk genes with established clinical utility; Panel 3 included all the genes on panel two plus moderate/low-risk genes. Clinical and economic inputs for the model were taken from published epidemiological literature, Surveillance, Epidemiological, and End Results (SEER) program website, and other published cost-effectiveness studies. The outcomes assessed were costs, life years gained (LEs), quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER), the incidence of breast cancer, and ovarian cancer. To characterize uncertainty, we performed one-way and probabilistic sensitivity analyses.

Results: The incremental life years for Panel 1-3 compared to no screening strategy were 0.20, 0.24, and 0.27, respectively. The incremental QALYS for panel 1-3 compared to no screening strategy were 0.17, 0.20, and 0.23. The incremental cost for panel 1-3 compared to no testing strategy were -$345, -$576, and -$697, respectively. All three screening strategies dominated the no screening strategy. Both Panel 2 (BRCA1/2 plus other high-risk genes) and panel 3 (panel 2+ moderate/low-risk genes) dominated (better outcomes, lower cost) panel 1 (BRCA1/2 only) in the deterministic analyses. However, in probabilistic analysis accounting for uncertainty, panel 2 (BRCA1/2 and other high-risk genes) was the optimal strategy at a willingness to pay (WTP) threshold of $100,000 or less.

Conclusions: Our findings indicate that the evidence for adopting the panels with BRCA1/2 plus other high-risk genes may be sufficient, but the evidence is likely insufficient for adopting more expanded panels with moderate/low-risk genes.

INTRODUCTION:

Next-generation sequencing (NGS) has created a paradigm shift in genetic sequencing by enabling sequencing of hundreds to thousands of genes in parallel. NGS has enabled the creation of several commercial hereditary breast cancer-screening gene panels (HBCS), which simultaneously test variants on multiple susceptible genes for breast cancer(1). The results of HBCS panels are reported as a list for presence/absence of variants in the tested genes rather than a single risk score. All commercially available HBCS panels share some key high penetrance genes (e.g., *BRCA1, BRCA2, P53)* and the remainder of the genes added to HBCS panel are of moderate to low penetrance. Each gene provides different information for the individual patient, but the probability of a positive finding ("false positive" if the evidence for cancer risk is missing) increases with more genes on the panel (2). However, the evidence for clinical utility of genes included onto HBCS panels is limited to only a few high penetrance genes, and clinical consensus guidelines are yet to be established for most low- and moderate-risk genes (3). Many US payers consider multigene panel testing that includes genes that do not have sufficient clinical utility evidence or published clinical practice guidelines such as National Comprehensive Cancer Network (NCCN) as experimental(4, 5).

However, the argument for the clinical utility of multi-gene panels with both high and moderate/low penetrance genes has reached a tipping point among the medical community (clinicians and genetic counselors)(6-9). Multi-gene panels offer apparent convenience and economy of testing multiple genes in one test for patients, but research shows that patients maybe ignorant regarding complexities in interpretations of results and clinical management decisions that follow panel testing. Clinicians (medical geneticists and genetic counselors) are faced with complicated decisions regarding interpretation, counseling, and clinical management of patients reported with variants of unknown significance or variants for which there are no clinical guidelines(10). Payers are concerned with the lack of evidentiary requirements, lack of

published clinical guidelines, and (unnecessary) downstream costs due to clinical actions taken because of test findings (4, 5).

At the patient level, the probability of positive findings increases as more genes are included, resulting in a potential increase in the probability of healthcare utilization due to increased medical consultations and risk-reducing interventions (chemoprevention and surgery)(11). Some of these decisions taken based on the positive findings in low to moderate-risk genes may result in unnecessary harm to the patient (12). The breast cancer HBCS panels that include only high-risk genes such as *BRCA1, BRCA2, PTEN, TP53, STK11,* and *CDH1* may provide more clinically actionable results, in line with the evidence-based clinical consensus guideline (3).

Although the literature is abounding with debate regarding the clinical utility of expanded HBCS gene-panel testing for breast cancer, there is a scarcity of well-designed economic evaluations of expanded HBCS multi-gene panels. Moreover, the published economic evaluations failed to estimate uncertainty resulting from the addition of genes with missing evidence of clinical utility.

The objective of this study was to evaluate the clinical and economic value and associated uncertainty for hereditary breast cancer screening (HCBS) gene panels. We hypothesized that the addition of genes with decreasing penetrance and higher uncertainty onto HBCS gene-panels results in diminishing returns on potential clinical & economic value and increasing uncertainty. We used a case study of *hypothetical* HBCS multi-gene panels created by incremental addition of genes ranging from high to moderate risk and used decision-analytical modeling to estimate the clinical and economic value of adding genes onto the BRCA1/2 testing.

METHODS

Overall approach

We used decision analytical modeling approach to compare hypothetical HBCS gene-panels, which were created by adding sets of genes incrementally based on the risks conferred by the genes. We first created hypothetical gene panels by incrementally adding genes with decreasing and more uncertain risks: Panel 1 included only BRCA1/2 genes, panel 2 included BRCA1/2 and other high-risk genes, panel 3 included BRCA1/2, other high-risk genes, and moderate/low-risk genes. Then we created a hybrid decision tree Markov model to estimate the costs and outcomes of a 30-year old woman who had a higher risk of developing breast cancer due to family history. We then estimated the costs and outcomes (life expectancy, quality-adjusted life years gains, breast cancer, and ovarian cancer) for the three screening strategies – Panel 1, panel 2, and panel 3. We then compared each screening strategy to no screening and other screening strategies. We populated the model inputs with different variant probabilities, uptake of risk-reducing probabilities, relative-risks, health outcome probabilities, quality of life estimates, and costs from multiple published sources of current information.

Patient population

The characteristics of the entry cohort were 30-year-old asymptomatic high-risk (either with personal cancer history or ≥ 1 first-degree relative with breast or ovarian cancer) women. Based on the published evidence for eligibility for genetic screening of high-risk genes BRCA1/2 genes, we used the cohort of high-risk women identified by US Preventative Task Force (USPTF). The latest USPTF guidelines recommend genetic screening for asymptomatic women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful variants in breast cancers susceptibility genes BRCA1/2 (13). We used the age for entry cohort as 30 and allowed women to opt for risk-reducing interventions at different ages because most women who choose risk-reducing surgeries wait at least until age

35 due to impact on child-bearing potential, and few breast or ovarian cancers are detected before age 40 and fewer below age 30 (14).

Interventions

We assessed three interventions (screening strategies) of hypothetical HBCS gene-panels and a no-screening strategy. The panel 1(BRCA1/2 only panel) includes BRCA 1/2 screening only, the panel 2 (high-risk panel) included BRCA1/2 genes and other high-risk genes and panel 3 (moderate/low-risk panel) constituted with the highest number of genes and included BRCA1/2 + high-risk genes + moderate/low-risk genes.

Model structure

To estimate the lifetime costs and gains in quality of life adjusted gains in life expectancy, used a Markov model to represent the natural history of high-risk asymptomatic women for breast cancer screening. Our model had two stages as shown in the conceptual model (Fig 1). Firstly, decision tree representing the testing strategies (different HBCS gene-panels) and standard of care followed by the risk-reducing interventions undertaken by the women with and without pathogenic variants. Then we utilized a Markov model for breast cancer to model the mutually exclusive health states that women undergoing genetic testing may take over their lifetimes.

We used the conceptual model in Fig. 1 to structure our decision model. Specifically, as a first step in our model we first identified the variant status of women based on the screening panel used and then categorized the women into different risk categories based on the carrier status: 3 categories of pathogenic variants (BRCA1/2, other high-risk genes, and moderate/low risk genes) 3 categories of VUS status, and no pathogenic no VUS status. All these categories are mutually exclusive because women who have pathogenic variants in high-risk genes and also have pathogenic variants in moderate/low-risk genes act primarily based on the pathogenic variant information of highest risk genes on the panel.

Post identification of carrier status the women could opt for risk-reducing interventions – risk-reducing mastectomy (RRM), risk-reducing salpingo-oophorectomy (RRSO), or both. Once a woman had undergone risk-reducing modality, she could stay in post-risk-reducing intervention state or could transition to breast cancer, ovarian cancer, or death. The women in breast and ovarian cancer state stayed in that health state for one cycle following which they could enter the post-cancer health state or death. The women from post-cancer health states stayed in that health state till they died. Our Markov model consisted of following health states: 1) pre-cancer diagnosis; 2) Risk-reducing interventions (RRM, RRSO); 3) Post-risk reducing intervention; 4) Cancer (breast and ovarian), and 5) Death. The risk-reducing intervention and cancer health states were transition states, i.e. women could only stay in those health states for one year.

We used age-specific transition probabilities for women transitioning from one health state to another. The women after being identified with their variant results could undertake the risk-reducing interventions right away or could wait before opting for the procedures.
Women from all the health states transitioned to the death state based on age-specific probabilities of dying from either the breast or ovarian cancers or age-specific probabilities of dying from other causes. We used 1-year cycle length, i.e., the allowed transition from one health state to other health states was allowed at 1-year intervals only. The probabilities of choosing risk-reducing interventions by women undergoing HBCS gene-panels testing may differ based on their classification under the presence of gene-specific variants.

The women in the cohort were followed until either they reach 100 years of age, or they die. The lifetime costs and outcomes were estimated for all women in the cohort.

Model inputs

Clinical inputs

Clinical inputs are listed in Appendix Table 1. Clinical parameters are based on the peer-reviewed literature, Medicare fee schedules, and previously published cost-effectiveness studies. The frequencies of BRCA1 and BRCA 2 pathogenic carriers were taken from the published cross-sectional study, which analyzed 46,276 high-risk women in the US (15). The frequencies for other high-risk genes were taken from a published study that analyzed more than 2,000 US patients (16). The frequencies for other moderate/low-risk genes included in the study were based on another published study analyzing the pathogenic carrier frequencies of various genes in BRCA1/2 negative women. The frequencies of the VUS carriers in the genes included was estimated based on the included genes and were taken from the study comparing the traditional and multi-gene panel testing in more than 1,000 US patients ((2).

The mortality benefits from HBCS gene-panels testing are because the women with pathogenic variant opt for prophylactic risk-reducing surgeries. As per US Preventative Task Force (USPTF) review, mastectomy reduced the breast cancer risk by 85% to 100%, and oophorectomy or salpingo-oophorectomy reduced the breast cancer risk by 37% to 100% (13). Risk-reduction with oophorectomy was more pronounced if undertaken in women at pre-menopausal age. We used the uptake rates for different risk-reducing interventions (RRM and RRSO) for BRCA1 and BRCA2 carriers from a study in which the researchers estimated the uptake of risk-reducing surgeries in a prospective cohort of 1,499 BRCA1 and BRCA2 mutation carriers (17). There were no published studies for the uptake of risk-reducing surgeries in non-BRCA1/2 gene variants. Therefore, we assumed the uptake of risk-reducing surgeries in other high-risk variants to be same as that in BRCA1/2 carriers and for the moderate/low-risk pathogenic variants we assumed the uptake risk to be half as that of BRCA1/2 variants. The age-specific risk of developing breast and/or ovarian cancer among BRCA1 and BRCA2 carriers were taken from the prospective study, which estimated the risk of developing breast and ovarian cancer among 9,856 BRCA1 and BRCA2 mutation carriers (18). We assumed that the

age-specific risk of developing breast and ovarian cancer to be same as that of BRCA1/2 for the other high-risk carriers and half that of BRCA1/2 for the moderate/low-risk genes.

The age-specific yearly probabilities of dying from breast and ovarian cancer were estimated from the 5-year survival rates of patients with breast and ovarian cancer in Surveillance, Epidemiology, and End Results program (SEER) and age-specific female mortality tables from the US life tables of 2012.

Utility estimates

The utility estimates and utility multipliers used in our model are presented in Appendix Table 1. We used the general population utility in women estimates for the women without variants (19). We applied a disutility of -0.005 for one year for knowing the pathogenic variant result. We also applied the disutility -0.03 for RRM and RRSO (20) for the year of the surgery and then a small disutility of -0.001 until the women turned 55 years. For breast cancer. The disutility applied to breast cancer and ovarian cancer for the year one were 0.20 and 0.40, respectively. We applied a small disutility of 0.001 and 0.005 for post-year one breast and ovarian cancer health states, respectively. The utility estimates used for last year of breast and ovarian cancer states, before the patient transitions to death state was 0.60.

Costs

The cost estimates used for our study are presented in Appendix Table 1 and were estimated from the US payer perspective. The cost of cancer treatments was categorized based on women's age-group – separate treatment costs were applied for women < 65years and women ≥ 65 years based on previously published estimates (21). The cost estimates were for 2016 costs. The cost of hereditary panel testing can range from $199 to > $4000 – but we chose the test cost to be $750 for all the panels included. In our model the cohort of women entering the

model was high-risk due to family history, therefore, for most a full gene sequencing was not required.

Key Assumptions

We assumed that all women in target population would have the lifetime breast cancer risk of ≥ 20% and thus will undergo enhanced screening (annual MRI + mammography) as recommended by NCCN guidelines until either detection of breast cancer, death, or bilateral mastectomy. We assumed that all women who were eligible for enhanced screening and adhered to it. We assumed the penetrance estimates for all the high risk-genes to be same as that of BRCA1/2 and penetrance estimates for moderate/low-risk genes to be half as that of BRCA1/2. We assumed that the uptake of risk-reducing interventions for other high-risk genes was the same as that for BRCA1/2 and the uptake for moderate/low-risk genes was half as that of BRCA1/2. We assumed that some younger women wait before they opt for risk-reducing interventions. We assumed the test costs to be similar for the three screening panels included in our analyses.

Uncertainty Analysis

We conducted one-way sensitivity analyses by varying one parameter over the plausible range at a time to assess the influence of parameter uncertainty on the incremental outcomes and costs. In these analyses, low and high values were specified for each model input and cost, and health outcomes were calculated for each value. Tornado diagrams were generated to rank the impact for each parameter from descending order of impact on QALYs, costs, and ICERs.

We varied all the input parameters at the same time by drawing a value for each parameter from its assigned distribution. In this probabilistic sensitivity analysis, we used normal and log-normal distributions for costs and relative risk, respectively (Table 1). Monte Carlo simulation was

performed for 5,000 iterations to generate mean and 95% credible ranges. We created a cost-effectiveness acceptability curve (CEAC) to denote the probabilities that each option was most likely to be cost-effective across a range of willingness-to-pay thresholds.

Net Monetary Benefits

We calculated the expected net monetary benefit (NMB) for each testing strategy using the results generated in the Monte Carlo simulations. The NMB combines the cost and the QALYs in a single metric for each strategy using the formula: ENMB=[λ*QALYs] – Cost, where λ is the WTP per QALY gained. The ENMB of different strategies over 5000 Monte Carlo simulations were compared, and the testing strategy with higher average ENMB over a WTP was defined as the optimal testing strategy. We estimated the ENMB over a range of WTP from 0 to $150,000.

Scenario Analysis

The cost of the individual panel was assumed to be the same in our base case analysis. We conducted a scenario analysis to explore the impact of different test costs on our results by adopting the different test costs than the base case analysis. We used test cost for BRCA 1/2 panel to $2180 (CMS rate for reimbursement of full sequence analysis and common duplication/deletion variants) and used $250 as incremental test cost for the high-risk panel and $500 as the incremental testing cost for the moderate/low-risk panel. The test costs for genetic testing in this analysis were higher than the base case testing cost. Most of the published studies for economic evaluations of BRCA1/2 testing were conducted with higher test cost than what we used. Therefore, to compare our results with the previously published studies, we tested the higher test cost scenario.

RESULTS

Life expectancy and quality-adjusted life years (QALYs)

In the base case analysis, BRCA1/2 screening resulted in incremental LYs (discounted) of 0.20 and incremental QALYs (discounted) 0.17 compared to no screening. The high-risk panel, which included other high-risk genes in addition to the BRCA1/2, resulted in incremental LYs and QALYs of 0.24 and 0.20, respectively compared to no screening strategy. The moderate/low-risk panel, which included moderate/ low-risk genes in addition to BRCA1/2 and other high-risk genes resulted in incremental LYs and QALYs of 0.27 and 0.23, respectively.

When BRCA1/2 panel was used as a comparator, the high-risk panel screening strategy resulted in incremental LYs and QALYs of 0.04 and 0.03, respectively. Moderate/low-risk panel when compared to BRCA1/2 only screening, resulted in the incremental LYs and QALYs of 0.07 a 0.06, respectively. Both high-risk and moderate/low-risk panel dominated the BRCA1/2 only screening strategy.

All the three testing strategies have a higher discounted LYs, and QALYs compared to the no testing strategy. The incremental LYs and QALYs for BRCA screening compared to no screening were 0.199 and 0.169, for high-risk panel vs. BRCA only screening was 0.038 and 0.032, and for moderate/low-risk genes panel screening vs. the high-risk panel was 0.034 and 0.028.

Costs

The undiscounted total cost for no screening strategy was $57,154, for BRCA1/2 only screening was $54,591, for the high-risk panel was $53,925, and for the moderate/low-risk panel was $53,354. The cost for pre-diagnosis/pre-risk reducing surgeries health state, which included the cost of pre- and post-test counseling, cost of testing, and cost of annual mammogram and MRI, were $30,205, $29,186, $28,827, and $28,195 for no screening, BRCA only screening, high-risk

genes screening, and moderate/low-risk genes screening, respectively. The cost of risk-reducing surgeries was $0, $1,115, $1,339, and $1,605, for no screening and three screening panels, respectively. The cost of cancer health state for the no screening and three screening panels were $12,380, $10,145, $9,716, and $9,275, respectively.

The total discounted costs for no screening and the three screening strategies were $26,058, $25,712, $25,482, and $25,361, respectively. The incremental costs

ll the three testing strategies have a higher discounted total cost compared to the no testing strategy. The incremental discounted cost for BRCA screening compared to no screening was -$345, for high-risk panel vs. BRCA only screening was -$359, and for moderate/low-risk genes panel screening vs. the high-risk panel was -$632.

Incremental cost-effectiveness

All three panels dominated the no screening strategy in the base case, i.e. the QALYs for all the panels were higher than QALYs for no screening strategy, and the cost for all the three panels were lower than the cost for no screening strategy. The

One-way sensitivity analysis

The results of one-way sensitivity analysis are shown in figs XX-YY in the appendix. The key drivers for the model were 1) the probability of pathogenic variants, 2) penetrance of the genes included on the respective panels, 3) breast and ovarian cancer risk reduction due to risk-reducing surgeries (RRM and RRSO), 4) uptake of risk-reducing surgeries and 5) test costs.

Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis are presented in tables XX-YY. Compared to no screening, 95% credible range for incremental LYs for BRCA only screening, was 0.14 to 0.28. Compared to BRCA only, the 95% credible range for incremental LYs for the high-risk panel

was 0.02 to 0.04 and for incremental QALYs was 0.02 to 0.03. Compared to panel 2, the 95% credible range for incremental LYs for panel three was 0.01 to 0.07 and for incremental QALYs was 0.01 to 0.06.

Cost-effectiveness acceptability curves (CEAC)

The cost-effectiveness acceptability of all the panels and no testing are shown in figs XX. The high-risk panel was an optimal strategy up to a willingness to pay (WTP) threshold of $100,000. High-risk panel is the optimal strategy in ~70%, 67%, and 51% of simulations at WTP of $25,000, $50,000, and $100,000. The moderate/low-risk panel was not optimal strategy up to WTP threshold of $100,000.

Test cost scenarios

The results of the cost-effectiveness acceptability did not change even when we used the higher test cost for high-risk panel and moderate-risk panel compared to BRCA 1/2 only panel. The high-risk panel was the optimal screening strategy up to WTP of $100,000, and the moderate-risk panel was not the optimal strategy.

We used the higher test cost scenario with BRCA 1/2 test cost of $2,180 and the high-risk panel, and the moderate/low-risk panel had an incremental test cost of $250 and $500, respectively. The no screening strategy was the optimal strategy up to the WTP threshold of $12,000 and above $12,000 WTP up to $100,000, the high-risk panel screening strategy was the optimal strategy. Moderate/low-risk panel screening strategy was not the optimal strategy.

DISCUSSION

We estimated the economic value and resulting uncertainty of adding genes to a BRCA 1/2 panel for hereditary breast cancer screening. When uncertainty is not considered, the economic value was highest for the most expanded HCBS gene panel, which included BRCA1/2, other

high risk, and moderate-risk genes. However, when uncertainty was considered, we found that the gene panel with BRCA1/2 and high-risk genes (panel 2) was the optimal strategy. The main sources for uncertainty were the risk conferred by the moderate-risk genes, risk-reduction due to the preventive RRSO and RRM surgeries, and the uptake rates of the risk-reducing surgeries.

Our study findings have important implications for the clinical and economic guidelines. First, the BRCA1/2 and other high-risk genes when added to BRCA1/2 are cost saving compared to the no screening strategies for younger women (30- year old). Second, compared to BRCA1/2 the expanded panel with other high-risk genes included has sufficient evidence of being cost-saving. Therefore, the clinical and reimbursement guidelines should include an expanded panel with BRCA1/2 plus other high-risk genes as the standard of care. Third, The evidence is not sufficient for including expanded panels with moderate/low-risk genes to the HBCS multigene panels. Fourth, the deterministic point estimates for cost-effectiveness, if not used without uncertainty analysis, can be misleading as was seen in case of moderate/low-risk panels. In the deterministic analysis we found it to be dominant strategy compared to BRCA1/2 and high-risk panel, but, in uncertainty analysis, we found that high-risk panel was the optimal strategy up to WTP of $100,000.

The deterministic point estimates for cost-effectiveness analysis provides an easy to understand metric, ICER. However, deterministic results (ICER) do not consider uncertainty analyses. We should interpret the deterministic ICERs with caution and more so when the health technology being evaluated is not yet in the mature stages of its lifecycle. In case of the HBCS multi-gene expanded panels, there is significant uncertainty regarding the penetrance, pathogenicity, and prevalence estimates of the moderate to low risk genes. Moreover, an additional source of uncertainty for the multigene testing panels is lack of real-world evidence of uptake of risk-reducing interventions among the moderate/ low-risk gene variant carriers.

The BRCA1/2 (panel 1) testing strategy dominated the no screening strategy in our study. These results are different from results from other studies which compared BRCA1/2 testing to no testing with a high pre-test variant probability (22-25). We used lower costs for BRCA 1/2 testing compared to other studies. Several recent studies evaluated the cost-effectiveness of multigene panels. Li et al. (2017) found that in 40-year-old high-risk women a seven-gene (BRCA1/2 plus five other high-risk genes) panel was cost-effective compared to the to BRCA1/2 testing, with and incremental QALY gain of 0.006 and the incremental cost of $277, resulting in an ICER of $48,328 (26). Manchanda et al. (2018) in a similar study also added five other genes onto BRCA1/2 and compared to the BRCA1/2 testing scenario (27). The population in Manchanda et al. study was different from ours. In our study, the cohort of women entering the model was younger (30-year old), and we assumed the test costs to be lower ($750) and same for all the screening strategies than that was in Li et al.

Our study has several important limitations. First, the gene panels that we tested were created hypothetically by categorizing the genes according to their penetrance estimate for breast cancer. The commercially marketed multi-gene screening panels may not have a similar combination of breast cancer susceptibility genes. Second, due to lack of evidence on the uptake of risk-reducing surgeries other than for BRCA 1/2, we assumed the uptake rate for surgeries for other high-risk genes to be same as for BRCA1/2 variant carriers and 50% for the moderate/low-risk gene variants carriers. Third, due to lack of the penetrance estimates for moderate risk genes, we assumed the penetrance estimates for moderate risk genes to be 25% of the penetrance estimates of BRCA1/2. We also assumed that the uncertainty surrounding the penetrance estimates to be highest for the moderate risk estimates. We made these assumptions due to lack of credible estimates of penetrance and risk-reducing surgeries uptake rates for moderate risk genes. We kept our assumptions conservative so that if there is any bias in our assumptions, it may make our results conservative rather than liberal. For example, it is

very likely that penetrance estimate for moderate/low-risk genes may be lower than 25%. Therefore the results of our study will likely be conservative.

We assessed the economic value and uncertainty of hypothetical HBCS gene-panels for genetic screening of breast cancer in high-risk women. Our results support the economic value of the HBCS gene-panels was higher with the addition of other high-risk genes to BRCA1/2. The addition of moderate/low-risk genes resulted in further economic value in the deterministic analysis, but the resultant uncertainty, when propagated in the probabilistic analysis, resulted in the panel with high-risk genes only being optimal. Our results indicate that the evidence for adopting HBCS panels with BRCA1/2 plus other high-risk genes is likely sufficient but is insufficient for adopting more expanded panels with moderate/low-risk genes. Clinical guidelines and reimbursement policies should explicitly consider uncertainty, and decision makers should be wary of the fragility of relying solely on deterministic results from cost-effectiveness analysis in areas of precision medicine where there is a paucity of data.

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Tables and figures

Table 1: Model Outcomes for different genetic testing strategies for hereditary breast cancer screening (HCBS) A) Test cost are same for the three panels ($750); B) Test costs are different panels and are based on Medicare reimbursement rates for BRCA1/2 testing Panel 1: $2,180; Panel 2: $2,430; Panel 3: $2,680.

Strategy	Total Costs	Total Disc. cost	LEs (Undisc)	LEs (Disc.)	QALYs (Undisc.)	QALYs (Disc.)	ICER
No Testing	$57,154	$26,058	48.600	25.317	41.728	22.062	
BRCA1/2 (Panel 1)	$54,591	$25,712	49.218	25.516	42.247	22.231	
BRCA1/2 + High Risk (Panel 2)	$53,935	$25,712	49.336	25.554	42.347	22.263	
BRCA + High + Moderate Risk (Panel 3)	$53,354	$25,361	49.448	25.587	42.441	22.291	
Incremental Costs and Outcomes Vs No Genetic Testing							
Incremental Panel 1 vs NT	-$2,563	-$345	0.617	0.199	0.519	0.169	Dominant (-$2,047)
Incremental Panel 2 vs 1	-$656	-$230	0.118	0.038	0.100	0.032	Dominant (-$10,595)
Incremental Panel 3 vs 2	-$1,237	-$351	0.230	0.072	0.194	0.061	Dominant (-$7,650)

Strategy	Total Costs	Total Disc. cost	LEs (Undisc)	LEs (Disc.)	QALYs (Undisc.)	QALYs (Disc.)	ICER
No Testing	$57,154	$26,058	48.600	25.317	41.728	22.062	
BRCA1/2 (Panel 1)	$56,021	$27,142	49.218	25.516	42.247	22.231	
BRCA1/2 + High Risk (Panel 2)	$55,615	$27,162	49.336	25.554	42.347	22.263	
BRCA + High + Moderate Risk (Panel 3)	$55,284	$27,291	49.448	25.587	42.441	22.291	
Incremental Costs and Outcomes Vs No Genetic Testing							
Incremental Panel 1 vs NT	-$1,133	$1,085	0.617	0.199	0.519	0.169	$6,428
Incremental Panel 2 vs 1	-$406	$20	0.118	0.038	0.100	0.032	$607
Incremental Panel 3 vs 2	-$331	$129	0.230	0.072	0.194	0.061	$4,568

Table 2: Results of probabilistic sensitivity analysis (PSA) for model outcomes

Incremental Results						
	BRCA1/2 Vs No Screening (Panel 1 vs No screening)		High-risk Panel vs BRCA1/2 (Panel 2 vs Panel 1)		Moderate-risk vs High-risk Panel 3 vs Panel 2)	
	Deterministic	95% Credible Range	Deterministic	95% Credible Range	Deterministic	95% Credible Range
Total Costs	-$2,577	(-$4,074 - -$1,180)	-$656	(-$2,182 - $705)	-$581	(-$1,875 - $998)
Total Disc cost	-$360	(-$1,545 - $760)	-$230	(-$1,674 - $1,184)	-$121	(-$1,457 - $1,374)
Life-years	0.62	(0.48 - 0.78)	0.118	(0.069 - 0.115)	0.112	(0.046 - 0.199)
Disc LE s	0.20	(0.14 - 0.28)	0.038	(0.019 - 0.04)	0.034	(0.013 - 0.07)
QALYs	0.52	(0.4 - 0.66)	0.100	(0.058 - 0.097)	0.094	(0.038 - 0.168)
Disc. QALYs	0.17	(0.12 - 0.24)	0.032	(0.016 - 0.034)	0.028	(0.01 - 0.059)
Breast Cancer	-0.040	(-0.05 - -0.031)	-0.008	(-0.007 - -0.004)	-0.007	(-0.013 - -0.003)
Ovarian Cancer	0.001	(0.001 - 0.001)	0.000	(-0.001 - 0.)	-0.001	(-0.001 - 0.)

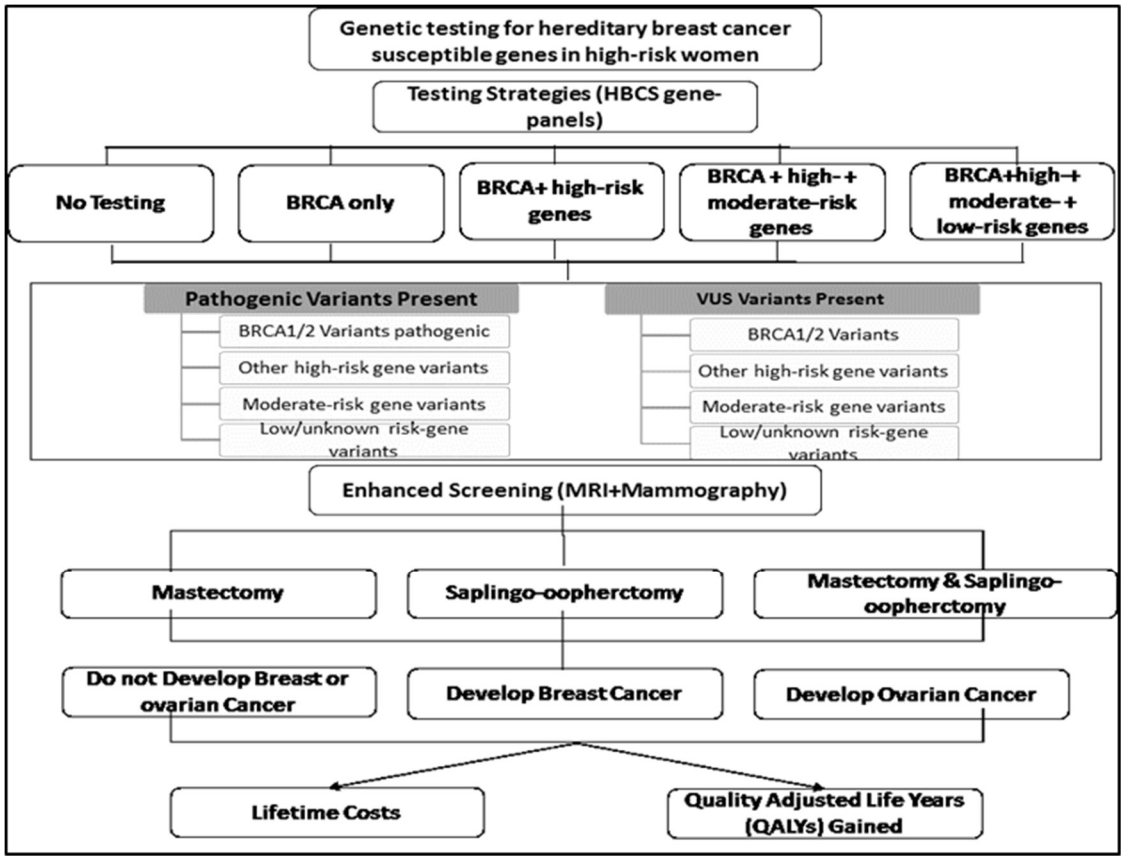


Figure 1: Conceptual Model

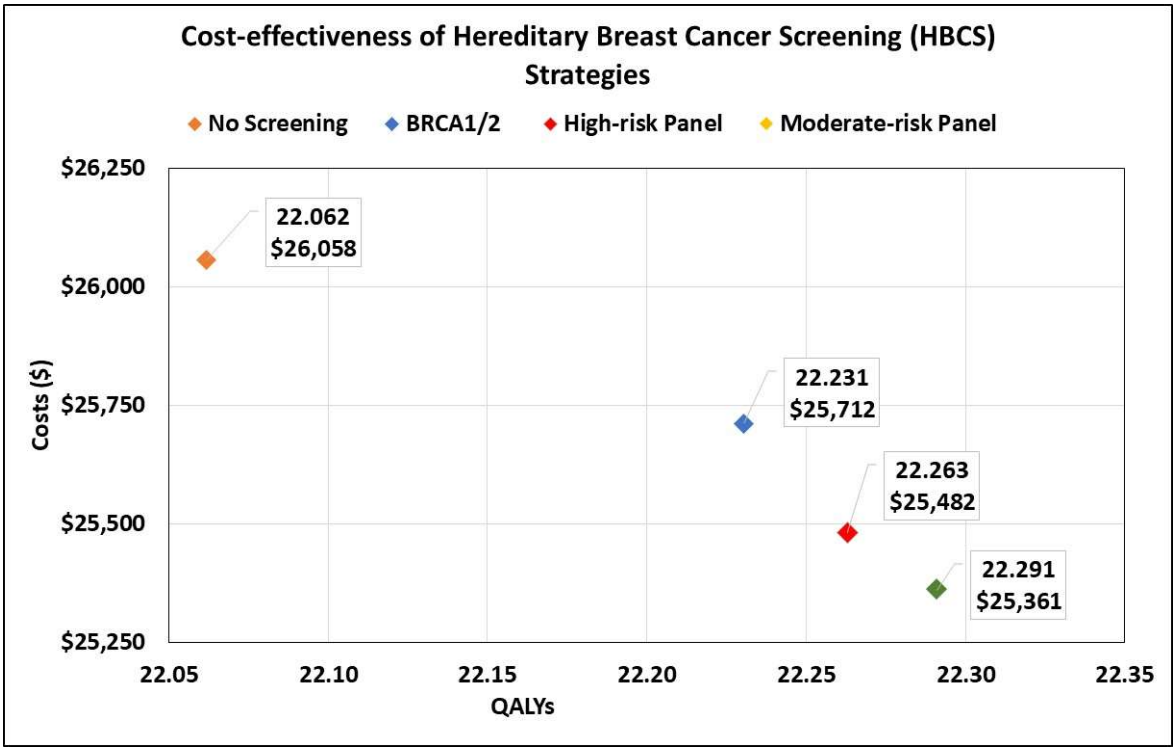


Figure 2: Cost-effectiveness of different genetic testing strategies in hereditary breast cancer screening using panel testing

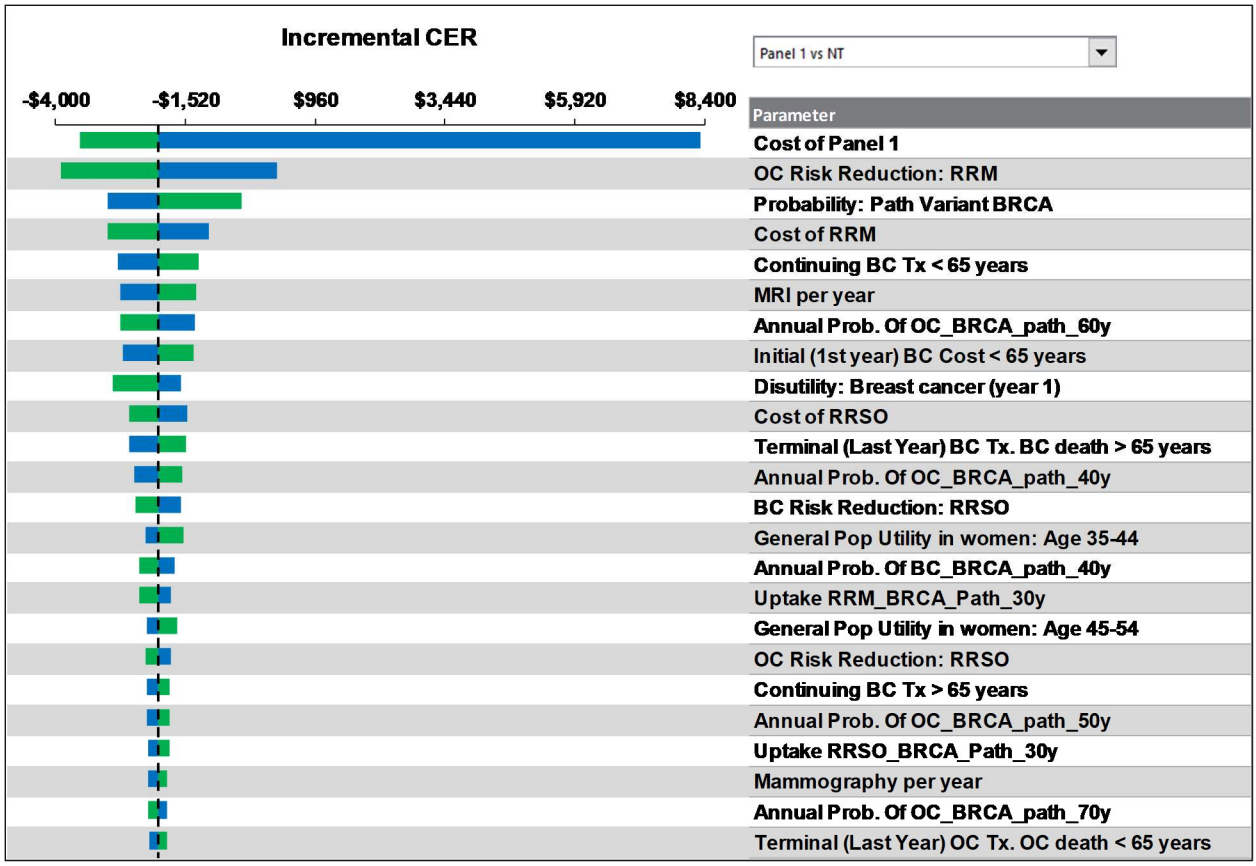


Figure 3A): Tornado chart for incremental cost-effectiveness ratio (ICER) when comparing BRCA1/2 screening (panel 1) to no screening.

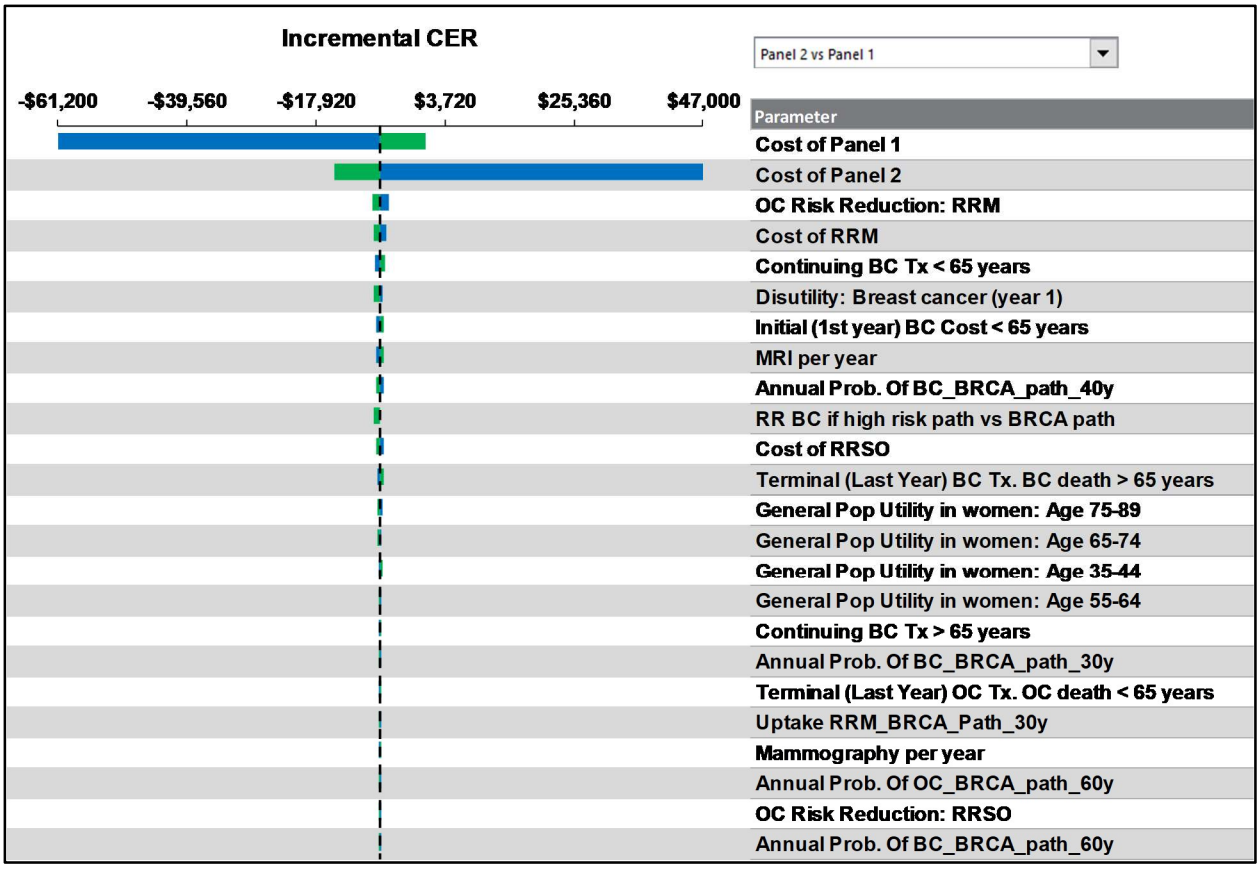


Figure 3B): Tornado chart for incremental cost-effectiveness ratio (ICER) when comparing High-risk panel (panel 2) to BRCA1/2 screening (panel 1).

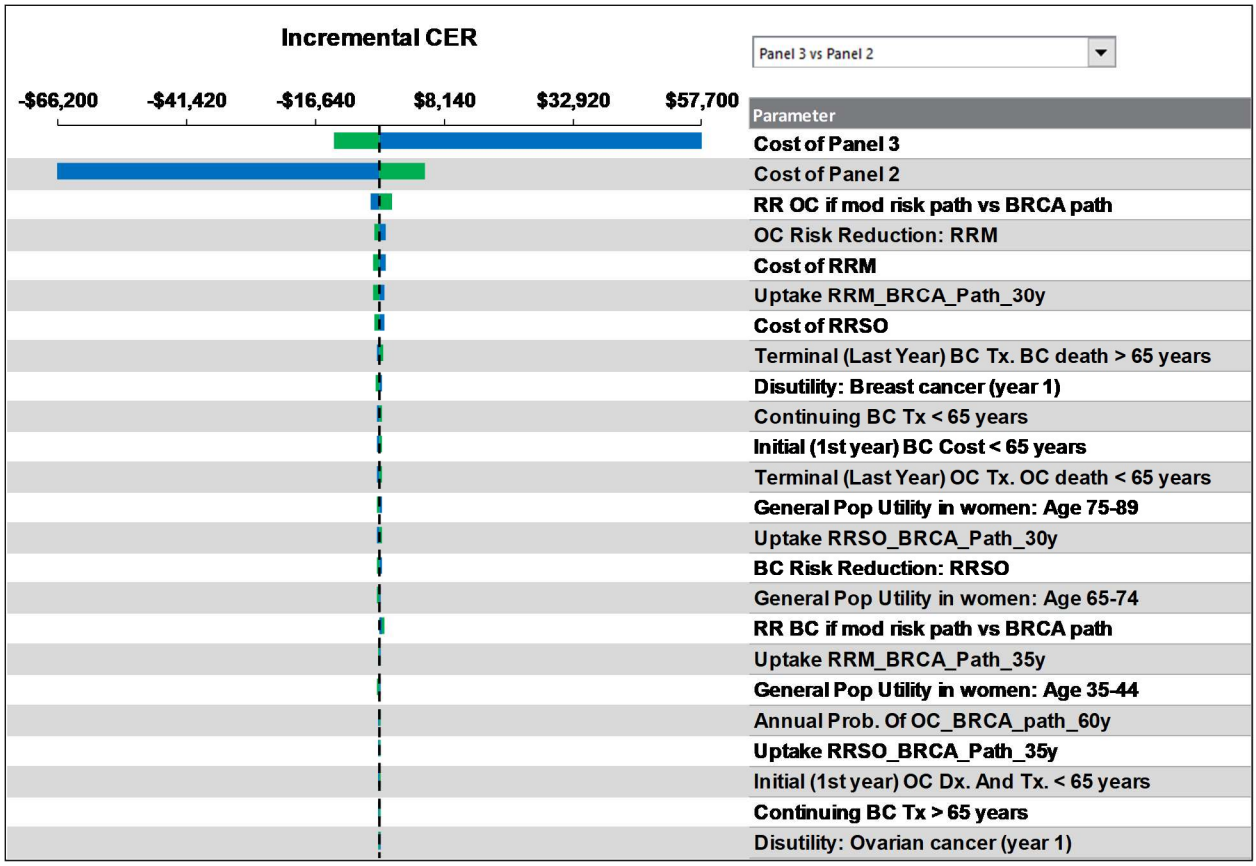


Figure 3C): Tornado chart for incremental cost-effectiveness ratio (ICER) when comparing Moderate-risk panel (Panel 3) to High-risk panel (panel 2). .

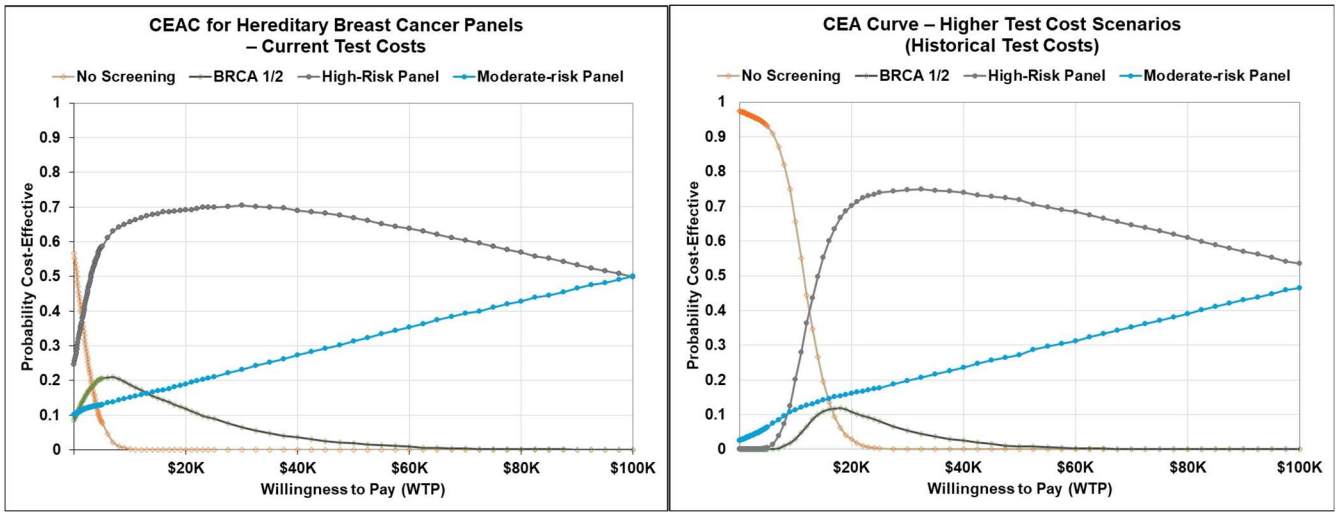


Figure 3: Cost-effectiveness acceptability curves for hereditary breast cancer screening (HBCS) panels at the current testing cost. A) The test cost for all three panels was same $750. B) The test cost for BRCA 1/2 testing for this analysis was $2,180, for high-risk panel (panel 2) was $2,430, and for moderate-risk panel (Panel 3) was $2,680.

APPENDIX TABLES AND FIGURES

Appendix Table 1: **Model Input Parameters**

Prevalence (Based on Panels)	**Current Value**	**Base Case**	**Low**	**High**	**Distribution**
Probability: Path Variant BRCA	0.125	0.125	0.094	0.156	Beta
Probability: Path Variant (High Risk genes)	0.024	0.024	0.018	0.030	Beta
Probability: Path. Variant(Mod. Risk genes)	0.033	0.033	0.025	0.041	Beta
Probability: None Pathogenic	0.818	0.818	0.614	1.000	Beta
Penetrance of Genes on Panels	**Current Value**	**Base Case**	**Low**	**High**	**Distribution**
Annual Prob. Of BC_BRCA_path_30y	0.018	0.018	0.013	0.020	Beta
Annual Prob. Of BC_BRCA_path_40y	0.028	0.028	0.021	0.030	Beta
Annual Prob. Of BC_BRCA_path_50y	0.028	0.028	0.021	0.030	Beta
Annual Prob. Of BC_BRCA_path_60y	0.024	0.024	0.018	0.030	Beta
Annual Prob. Of BC_BRCA_path_70y	0.019	0.019	0.014	0.020	Beta
Annual Prob. Of BC_BRCA_path_80y	0.019	0.019	0.014	0.020	Beta
Annual Prob. Of OC_BRCA_path_30y	0.001	0.001	0.001	0.000	Beta
Annual Prob. Of OC_BRCA_path_40y	0.004	0.004	0.003	0.000	Beta
Annual Prob. Of OC_BRCA_path_50y	0.010	0.010	0.008	0.010	Beta
Annual Prob. Of OC_BRCA_path_60y	0.021	0.021	0.015	0.030	Beta
Annual Prob. Of OC_BRCA_path_70y	0.004	0.004	0.003	0.010	Beta
Annual Prob. Of OC_BRCA_path_80y	0.004	0.004	0.003	0.010	Beta
Annual Prob. Of BC_genpop_30y	0.000	0.000	0.000	0.000	Beta
Annual Prob. Of BC_genpop_40y	0.001	0.001	0.001	0.000	Beta

Annual Prob. Of BC_genpop_50y	0.002	0.002	0.002	0.000	Beta
Annual Prob. Of BC_genpop_60y	0.003	0.003	0.003	0.000	Beta
Annual Prob. Of BC_genpop_70y	0.004	0.004	0.003	0.000	Beta
Annual Prob. Of BC_genpop_80y	0.003	0.003	0.002	0.000	Beta
Annual Prob. Of OC_genpop_30y	0.000	0.000	0.000	0.000	Beta
Annual Prob. Of OC_genpop_40y	0.000	0.000	0.000	0.000	Beta
Annual Prob. Of OC_genpop_50y	0.000	0.000	0.000	0.000	Beta
Annual Prob. Of OC_genpop_60y	0.000	0.000	0.000	0.000	Beta
Annual Prob. Of OC_genpop_70y	0.000	0.000	0.000	0.000	Beta
Annual Prob. Of OC_genpop_80y	0.000	0.000	0.000	0.000	Beta
RR BC if high risk path vs BRCA path	1.000	1.000	0.750	1.000	Log-Normal
RR OC if high risk path vs BRCA path	1.000	1.000	0.750	1.000	Log-Normal
RR BC if high risk VUS vs BRCA VUS	0.500	1.000	0.500	1.000	Log-Normal
RR OC if high risk VUS vs BRCA VUS	0.500	1.000	0.500	1.000	Log-Normal
RR BC if mod risk path vs BRCA path	0.500	0.500	0.050	1.000	Log-Normal
RR OC if mod risk path vs BRCA path	0.500	0.500	0.050	1.000	Log-Normal
RR BC if mod risk VUS vs BRCA VUS	0.250	0.500	0.250	1.000	Log-Normal
RR OC if mod risk VUS vs BRCA VUS	0.250	0.500	0.250	1.000	Log-Normal
Risk Reducing Interventions and Risk Reduction	**Current Value**	**Base Case**	**Low**	**High**	**Distribution**
Probability: Pathogenic & RRM only	0.464	0.460	0.350	0.580	Beta
Probability: Pathogenic & RRSO only	0.962	0.960	0.720	1.200	Beta
Probability: Pathogenic & RRM+RRSO	0.160	0.160	0.120	0.200	Beta
Probability: Pathogenic & No Intervention (Screen only)	0.000	0.000	0.000	0.000	Beta
BC Risk Reduction: RRM	0.110	0.110	0.080	0.140	Beta
BC Risk Reduction: RRSO	0.550	0.550	0.410	0.690	Beta

BC Risk Reduction: RRM + RRSO	0.110	0.110	0.080	0.140	Beta
OC Risk Reduction: RRM	1.000	1.000	0.750	1.250	Beta
OC Risk Reduction: RRSO	0.166	0.170	0.120	0.210	Beta
OC Risk Reduction: RRM + RRSO	0.166	0.170	0.120	0.210	Beta
Prob: Pathogenic and RRM at 35 yrs	0.315	0.310	0.240	0.390	Beta
Max likelihood of RRM	0.464	0.460	0.350	0.580	Beta
Prob: Pathogenic and RRSO at 35 yrs	0.392	0.390	0.290	0.490	Beta
Max likelihood of RRSO	0.962	0.960	0.720	1.000	Beta
RR Intervention uptake Mod Risk genes vs BRCA	0.500	0.500	0.050	1.000	Log-Normal
RR Intervention uptake High Risk genes vs BRCA	1.000	1.000	0.750	1.000	Log-Normal
UTILITY MEASURES	**Current Value**	**Base Case**	**Low**	**High**	**Distribution**
General Pop Utility in women: Age 30-35	0.910	0.910	0.680	1.000	Beta
General Pop Utility in women: Age 35-44	0.890	0.890	0.670	1.000	Beta
General Pop Utility in women: Age 45-54	0.870	0.870	0.650	1.000	Beta
General Pop Utility in women: Age 55-64	0.840	0.840	0.630	1.000	Beta
General Pop Utility in women: Age 65-74	0.840	0.840	0.630	1.000	Beta
General Pop Utility in women: Age 75-89	0.820	0.820	0.620	1.000	Beta
Disutility: Breast cancer (year 1)	0.200	0.200	0.010	0.300	Beta
Utility: Breast cancer (last year)	0.600	0.600	0.450	0.750	Beta
Disutility: Ovarian cancer (year 1)	0.400	0.400	0.300	0.500	Beta
Utility: Ovarian cancer (last year)	0.600	0.600	0.450	0.750	Beta
Disutility : RRM (Year 1)	0.030	0.030	0.020	0.040	Beta
Disutility: RRM (year 2 until 55 yrs)	0.001	0.001	0.000	0.000	Beta
Disutility: RRSO (Year 1)	0.030	0.030	0.020	0.040	Beta

Disutility: RRM +RRSO(Year 1)	0.110	0.110	0.080	0.140	Beta
Disutility: RRM+RRSO (year 2 until 55 yrs)	0.001	0.001	0.000	0.000	Beta
Disutility: BRCA Path. Variant result(year-1 only)	0.005	0.005	0.000	0.010	Beta
Utility multiplier: High risk Path. Variant result	0.005	0.005	0.000	0.010	Beta
Disutility BC continuing	0.001	0.001	0.000	0.000	Beta
Disutility OC continuing	0.005	0.005	0.000	0.010	Beta
MARKOV PARAMETERS (Annual Prob.)	**Current Value**	**Base Case**	**Low**	**High**	**Distribution**
Uptake RRM_BRCA_Path_30y	0.199	0.199	0.100	0.300	Normal
Uptake RRM_BRCA_Path_35y	0.115	0.115	0.060	0.170	Normal
Uptake RRM_BRCA_Path_40y	0.073	0.073	0.040	0.110	Normal
Uptake RRM_BRCA_Path_45y	0.039	0.039	0.020	0.060	Normal
Uptake RRM_BRCA_Path_50y	0.034	0.034	0.020	0.050	Normal
Uptake RRM_BRCA_Path_55y	0.005	0.005	0.000	0.010	Normal
Uptake RRSO_BRCA_Path_30y	0.115	0.115	0.060	0.170	Normal
Uptake RRSO_BRCA_Path_35y	0.278	0.278	0.140	0.420	Normal
Uptake RRSO_BRCA_Path_40y	0.228	0.228	0.110	0.340	Normal
Uptake RRSO_BRCA_Path_45y	0.171	0.171	0.090	0.260	Normal
Uptake RRSO_BRCA_Path_50y	0.089	0.089	0.040	0.130	Normal
Uptake RRSO_BRCA_Path_55y	0.043	0.043	0.020	0.060	Normal
Uptake RRSO_BRCA_Path_60y	0.028	0.028	0.010	0.040	Normal
Uptake RRSO_BRCA_Path_65y	0.011	0.011	0.010	0.020	Normal
Mortality_BC_30	0.001	0.001	0.000	0.000	Normal
Mortality_BC_40	0.004	0.004	0.000	0.000	Normal
Mortality_BC_50	0.010	0.010	0.010	0.010	Normal

Mortality_BC_60	0.021	0.021	0.020	0.030	Normal
Mortality_BC_70	0.004	0.004	0.000	0.010	Normal
Mortality_BC_80	0.004	0.004	0.000	0.010	Normal
Mortality_OC_30	0.009	0.009	0.010	0.010	Normal
Mortality_OC_40	0.009	0.009	0.010	0.010	Normal
Mortality_OC_50	0.009	0.009	0.010	0.010	Normal
Mortality_OC_60	0.009	0.009	0.010	0.010	Normal
Mortality_OC_70	0.007	0.007	0.010	0.010	Normal
Mortality_OC_80	0.005	0.005	0.000	0.010	Normal
Genetic Test/Counselling Costs	**Current Value**	**Base Case**	**Low**	**High**	**Distribution**
Cost of Panel 1	$750	$750	$500	$2,500	Normal
Cost of Panel 2	$750	$750	$500	$2,500	Normal
Cost of Panel 3	$750	$750	$500	$2,500	Normal
Cost of genetic counselling (Pre-test)	$43	$43	$32	$54	Normal
Cost of genetic counselling (Post +ve Results)	$5,000	$331	$248	$414	Normal
Annual Cost of Cancer Screening/Treatment	**Current Value**	**Base Case**	**Low**	**High**	**Distribution**
Costs for age < 65 years					
Initial (1st year) BC Cost < 65 years	$27,693	$27,693	$20,770	$34,616	Normal
Continuing BC Tx < 65 years	$2,207	$2,207	$1,655	$2,759	Normal
Terminal (Last Year) BC Tx. BC death < 65 years	$94,284	$94,284	$70,713	$117,855	Normal
Terminal (Last Year) BC Tx. Other death < 65 years	$748	$748	$561	$935	Normal

Initial (1st year) OC Dx. And Tx. < 65 years	$98,788	$98,788	$74,091	$123,485	Normal
Continuing OC Tx. < 65 years	$8,296	$8,296	$6,222	$10,370	Normal
Terminal (Last Year) OC Tx. OC death < 65 years	$149,573	$149,573	$112,180	$186,966	Normal
Terminal (Last Year) OC Tx. Other cause death < 65 years	$12,257	$12,257	$9,193	$15,321	Normal
Costs for age > 65 years					
Initial (1st year) BC Dx. And Tx > 65 years	$23,078	$23,078	$17,309	$28,848	Normal
Continuing BC Tx > 65 years	$2,207	$2,207	$1,655	$2,759	Normal
Terminal (Last Year) BC Tx. BC death > 65 years	$62,856	$62,856	$47,142	$78,570	Normal
Initial (1st year) OC Dx. And Tx. > 65 years	$82,324	$82,324	$61,743	$102,905	Normal
Continuing OC Tx. > 65 years	$8,296	$8,296	$6,222	$10,370	Normal
Terminal (Last Year) OC Tx. OC death > 65 years	$99,715	$99,715	$74,786	$124,644	Normal
Terminal (Last Year) OC Tx. Other cause death > 65 years	$99,716	$99,716	$74,787	$124,645	Normal
Cost of Cancer Screening and preventative surgery	**Current Value**	**Base Case**	**Low**	**High**	**Distribution**
Mammography per year	$135	$135	$101	$169	Normal
MRI per year	$535	$535	$401	$669	Normal
Cost of RRM	$10,618	$10,618	$7,964	$13,273	Normal
Cost of RRSO	$8,144	$8,144	$6,108	$10,180	Normal
ADDITIONAL PARAMETERS	**Current Value**	**Base Case**	**Low**	**High**	**Distribution**

Discount Rate	0.03	0.03	0.02	0.04	Normal

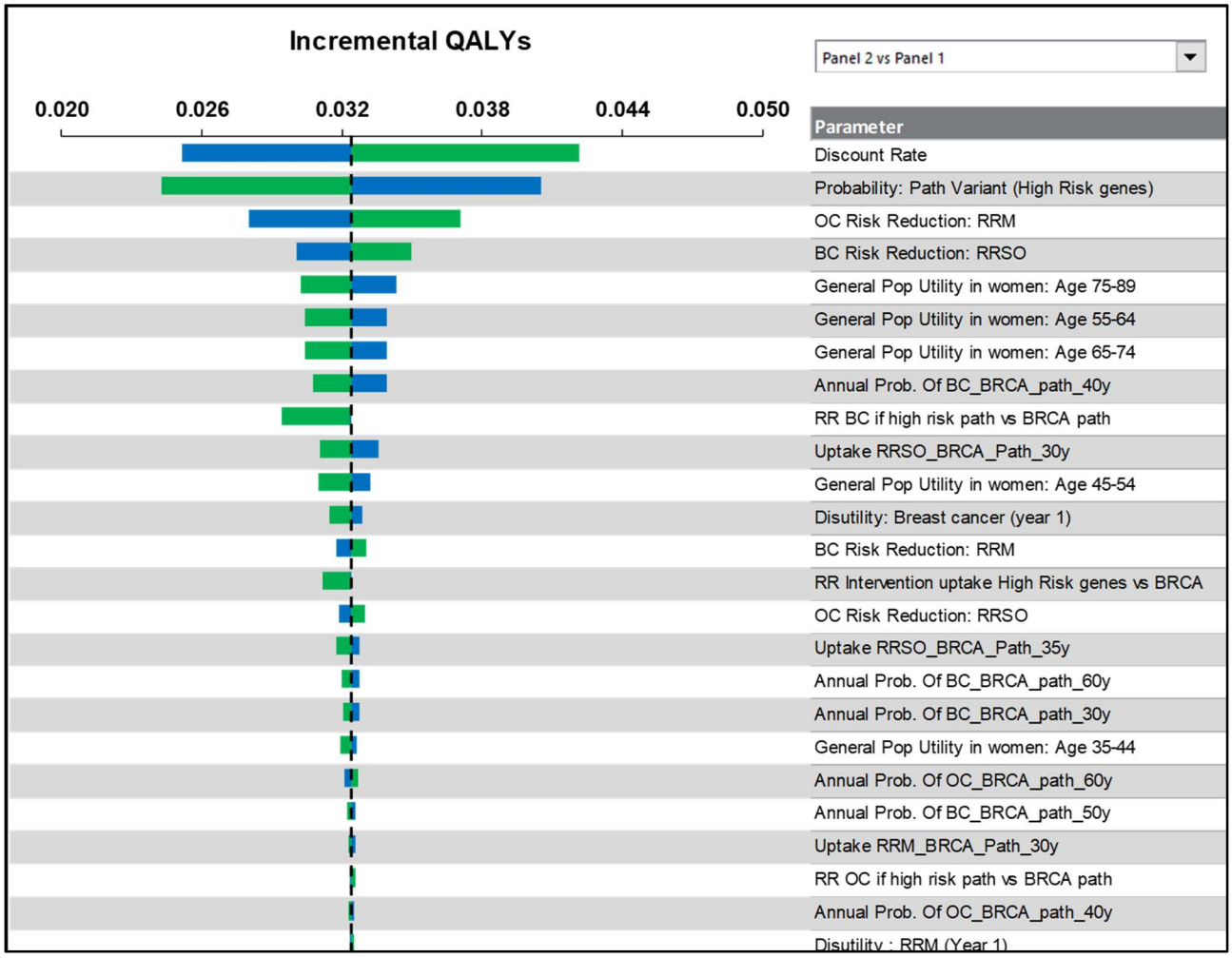


Figure 4: Tornado chart for incremental quality adjusted life years (QALYs) when comparing panel 2 to panel 1 (BRCA1/2)

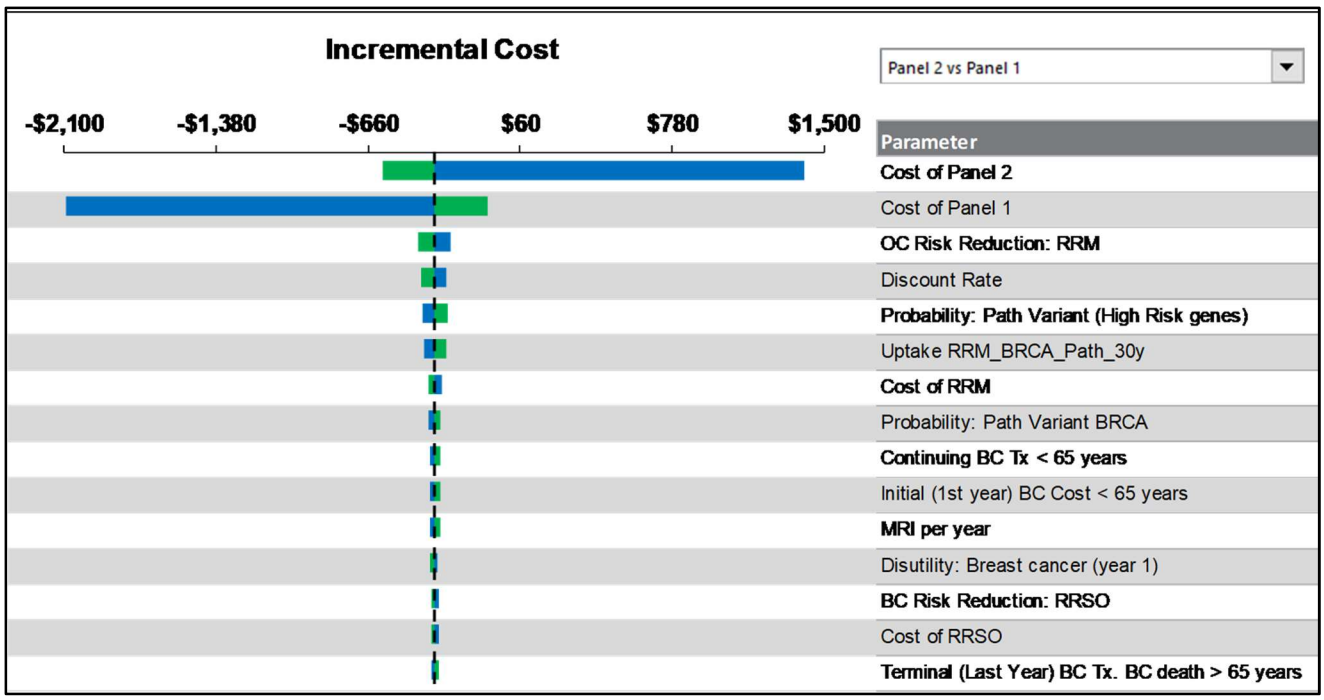


Figure 5:Tornado chart for incremental cost when comparing panel 2 to panel 1 (BRCA1/2)

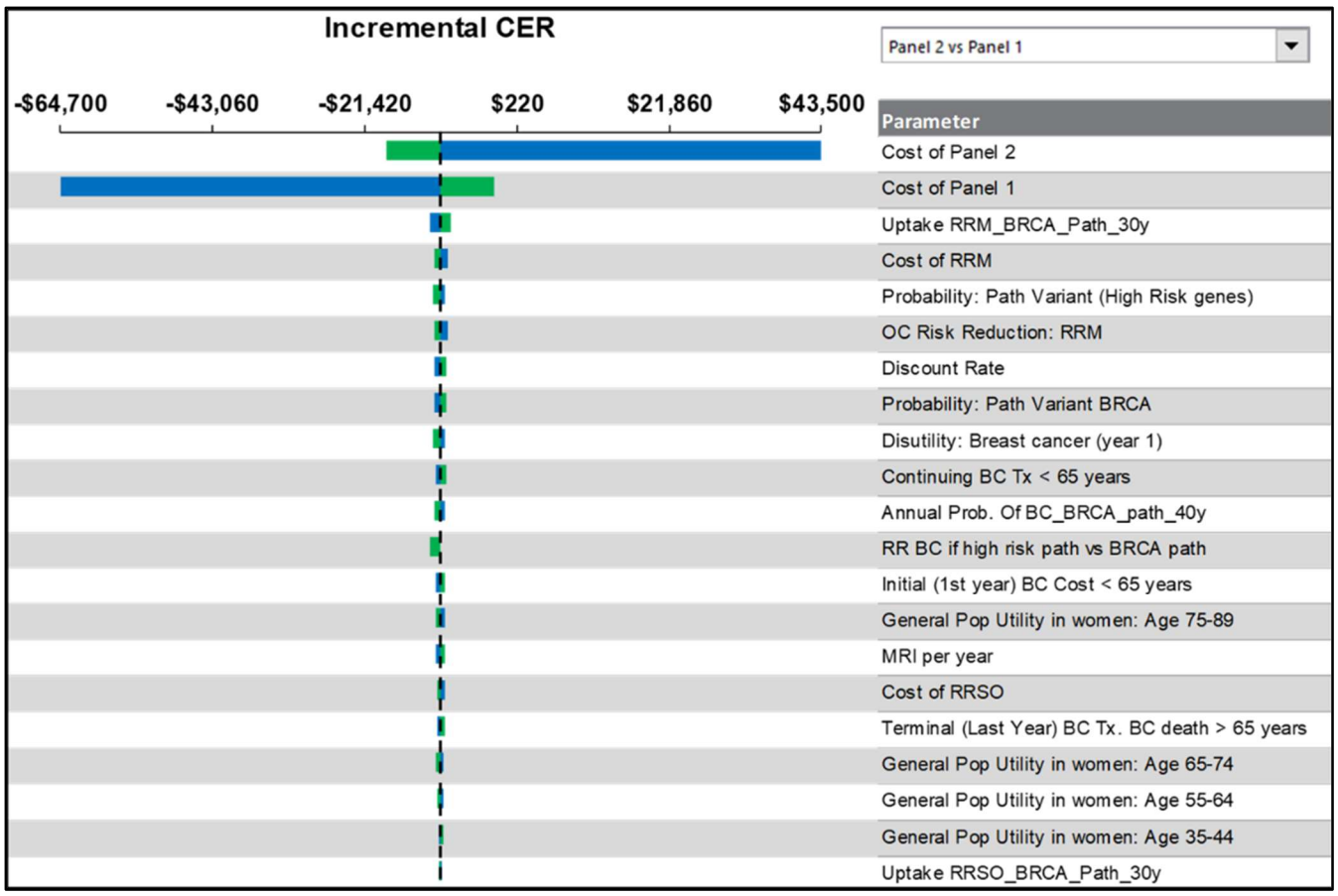


Figure 6: Tornado chart for incremental cost-effectiveness ratio (ICER) when comparing panel 2 to panel 1 (BRCA1/2)

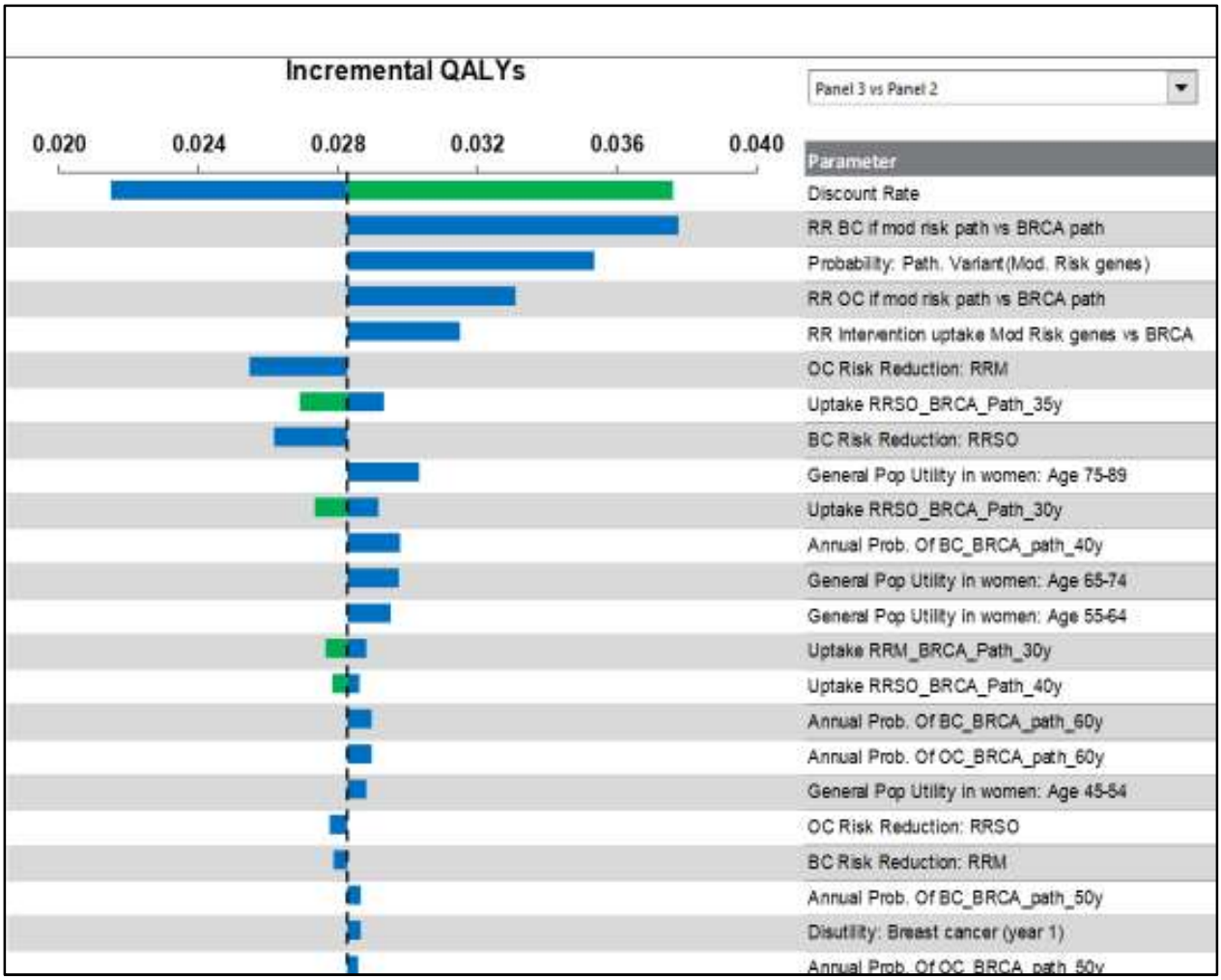


Figure 7:Tornado chart for incremental quality adjusted life years (QALYs) when comparing panel 3 to panel 2

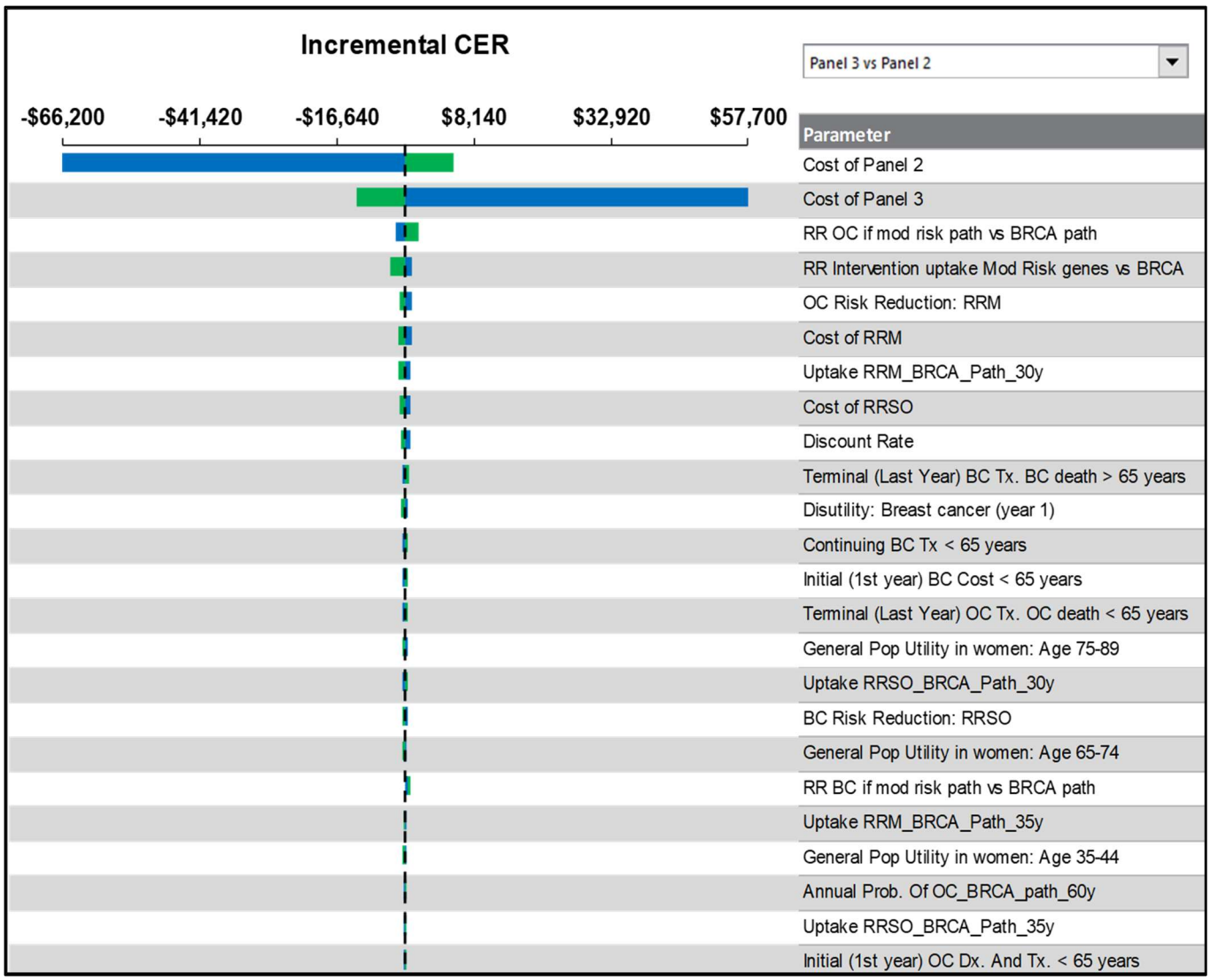


Figure 8: Tornado chart for incremental cost-effectiveness ratio (ICER) when comparing panel 3 to panel 2

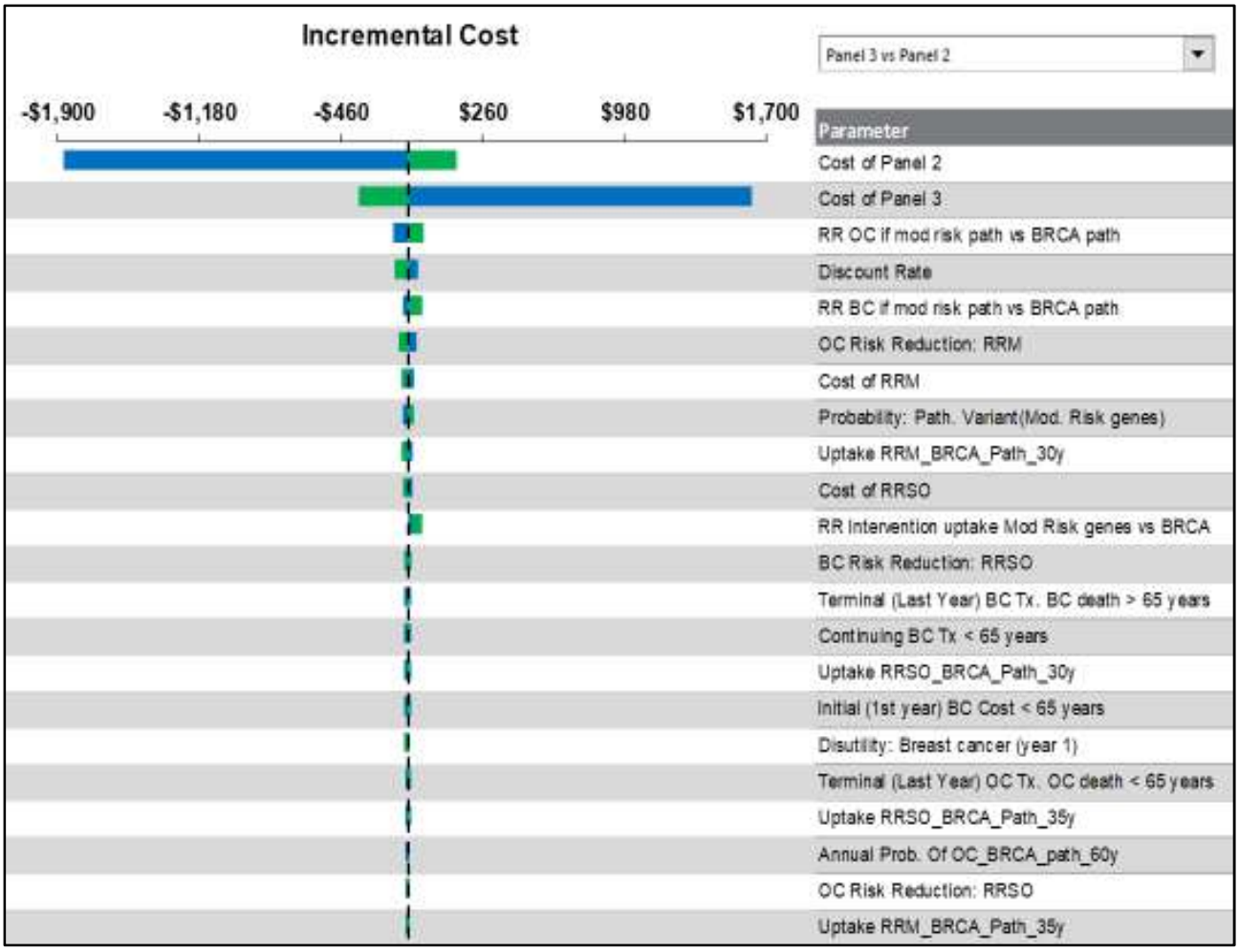


Figure 9: Tornado chart for incremental cost when comparing panel 3 to panel 2.

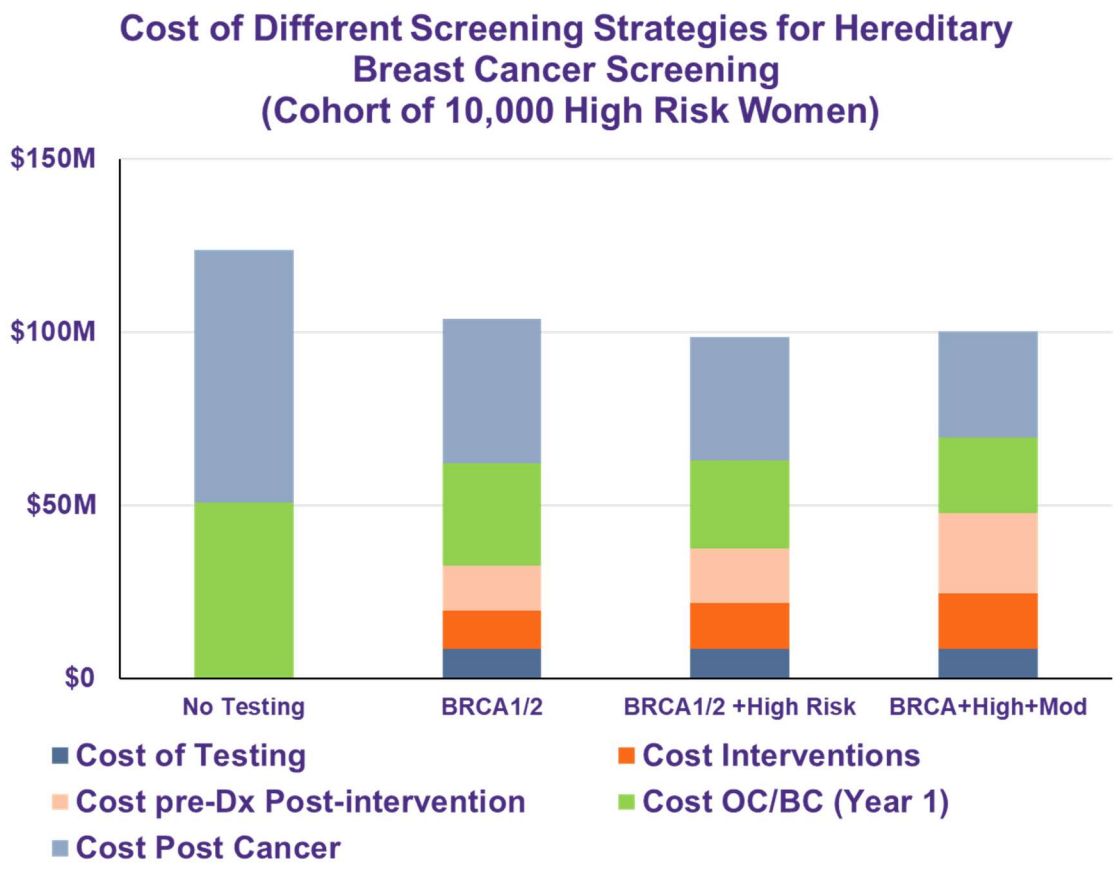
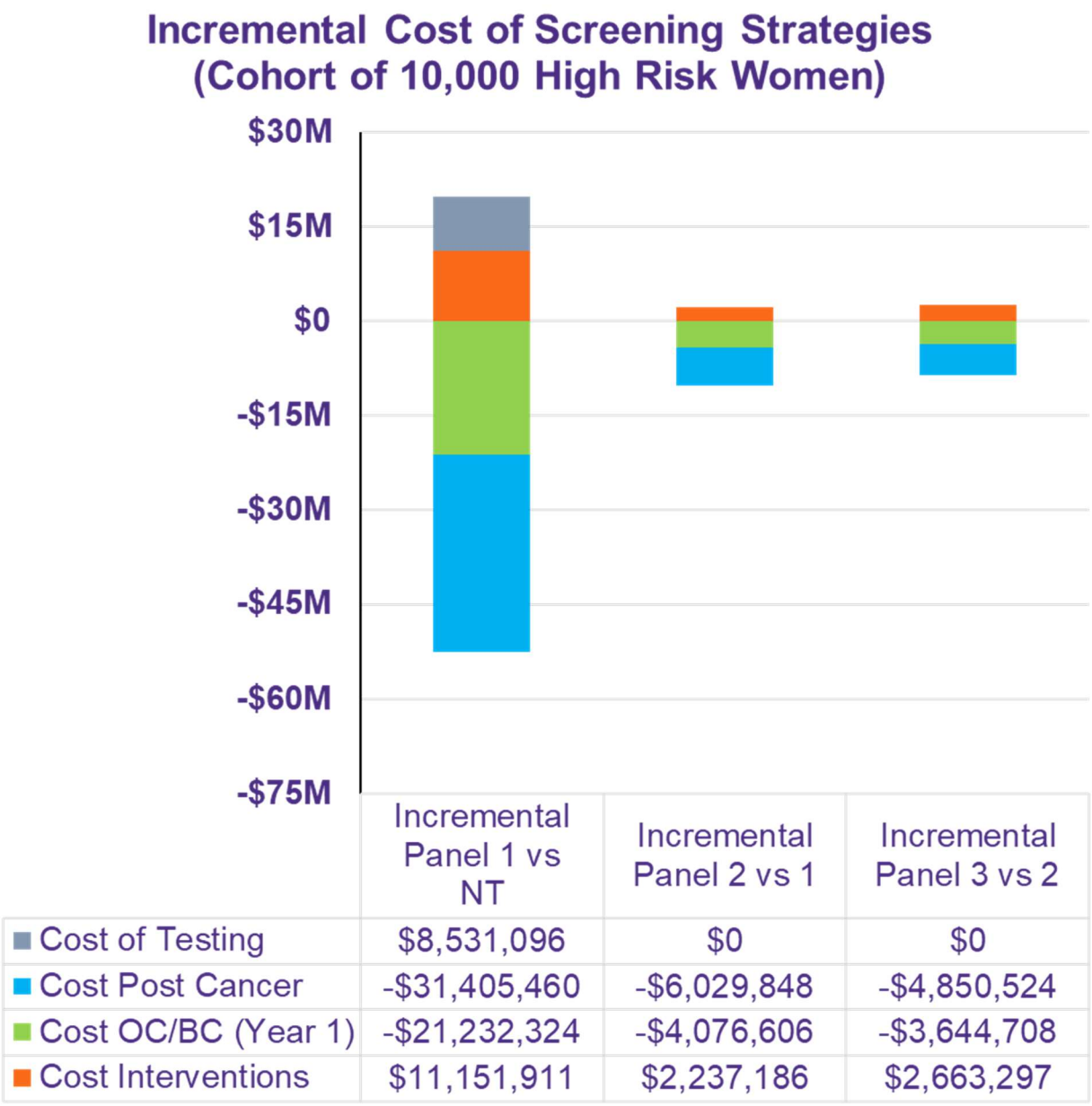


Figure 10: Cost of different screening strategies for hereditary breast cancer screening in a cohort of 10,000 women with high-risk of breast cancer.



	Incremental Panel 1 vs NT	Incremental Panel 2 vs 1	Incremental Panel 3 vs 2
Cost of Testing	$8,531,096	$0	$0
Cost Post Cancer	-$31,405,460	-$6,029,848	-$4,850,524
Cost OC/BC (Year 1)	-$21,232,324	-$4,076,606	-$3,644,708
Cost Interventions	$11,151,911	$2,237,186	$2,663,297

Figure 11: Incremental cost of screening strategies using gene panels among a cohort of 10,000 high-risk women.

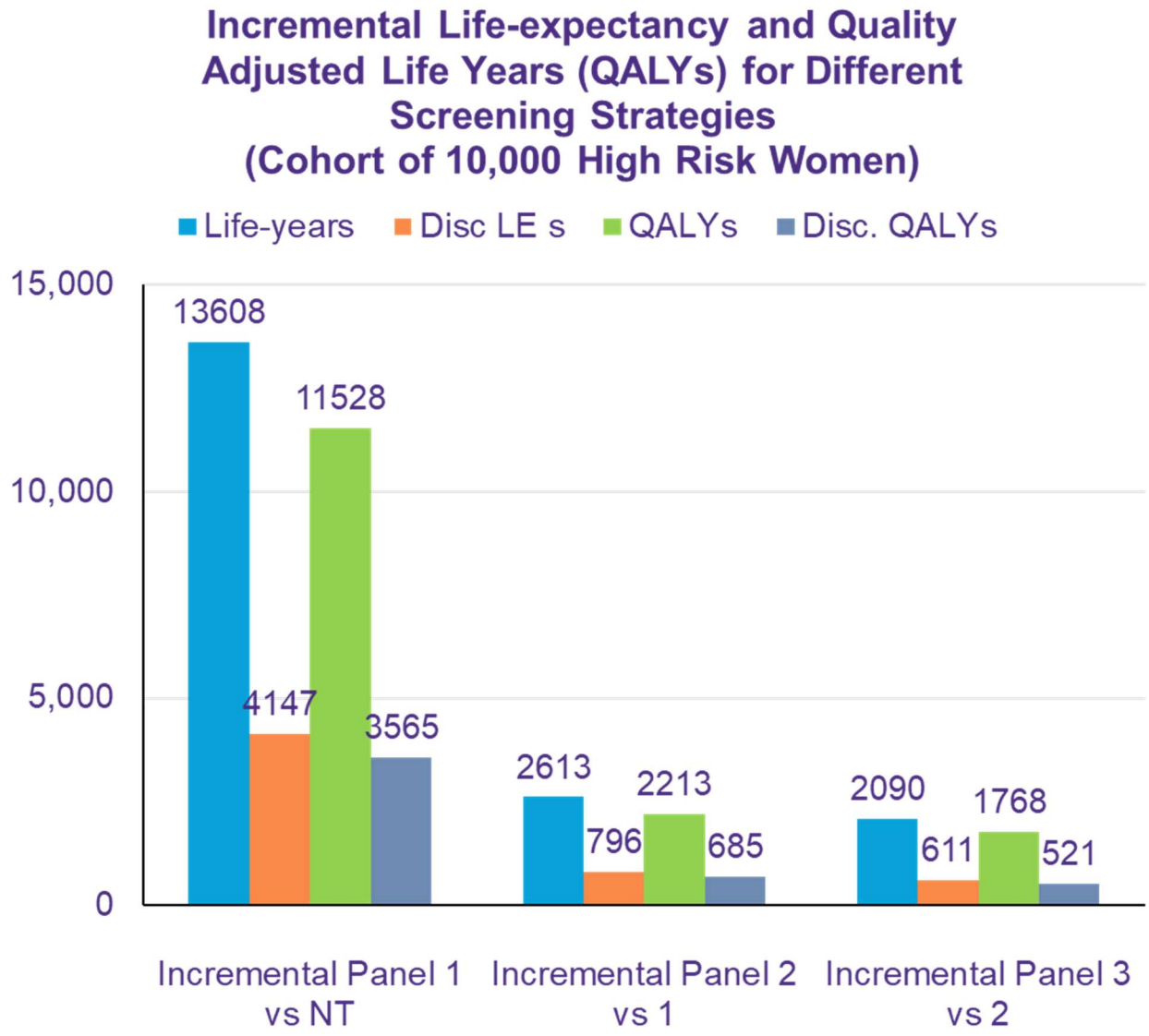


Figure 12: Incremental life-expectancy and quality-adjusted life years (QALYs) for different screening strategies for a cohort of 10,000 women with high-risk of breast cancer.

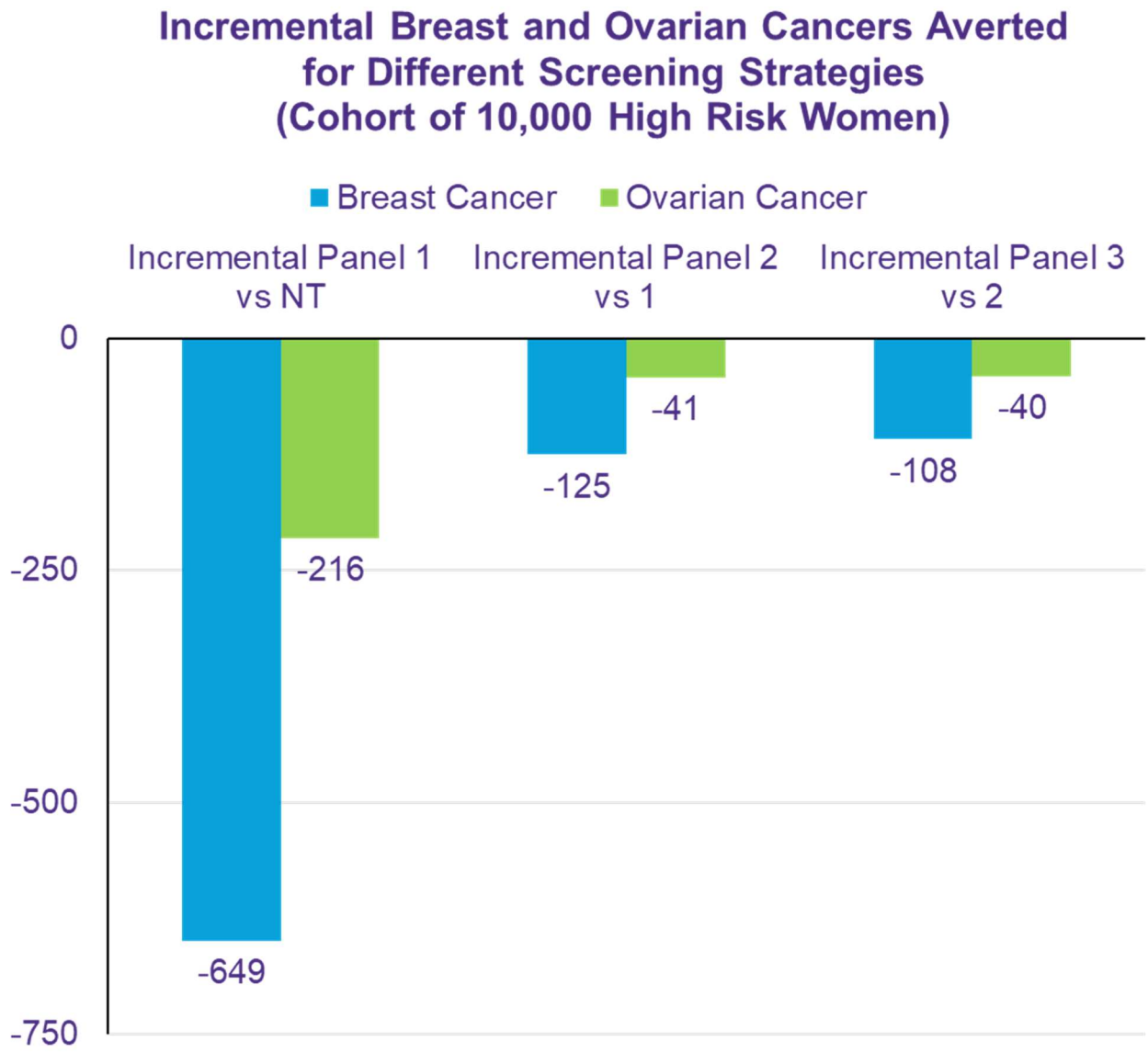


Figure 13: Incremental breast and ovarian cancers averted for different screening strategies among a cohort of 10,000 women with high-risk of breast cancer.