The Cost-Effectiveness of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer in Norway

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Abstract

Background. Expansion of routine genetic testing for hereditary breast and ovarian cancer from conventional *BRCA* testing to a multigene test could improve diagnostic yield and increase the opportunity for cancer prevention in both identified carriers and their relatives. We use an economic decision model to assess whether the current knowledge on non-*BRCA* mutation prevalence, cancer risk, and patient preferences justifies switching to a multigene panel for testing of early-onset breast cancer patients. **Methods.** We evaluated routine testing by *BRCA* testing, a 7-gene panel, and a 14-gene panel using individual-level simulations of annual health state transitions over a lifetime perspective. Breast and ovarian cancer incidence is reduced and posttreatment survival is improved when high-risk mutations are detected and risk-reducing treatment offered. Most model inputs were synthesized from published literature. Intermediate health outcomes included breast and ovarian cancer incidence rates, along with organ-specific cancer mortality. Cost-effectiveness outcomes were health sector costs and quality-adjusted life years. **Results.** Intermediate health outcomes improved by testing with multigene panels. At a cost-effectiveness threshold of $77,000, a 7-gene panel test with five non-*BRCA* genes was the optimal strategy with an incremental cost-effectiveness ratio of $53,310 per quality-adjusted life year compared to *BRCA*-only testing. **Limitations.** Unable to stratify carriers to specific mutations within genes, we can only make predictions on the gene level, with combined risk estimates for known variants. As mutation prevalence is the absolute upper bound of returns to more expansive testing, the rarity of modelled mutations makes analysis outcomes sensitive to model implementation. **Conclusions.** A 7-gene panel to diagnose hereditary breast and ovarian cancer in early-onset breast cancer patients can be a cost-effective alternative to current *BRCA*-only testing in Norway.

Keywords

cost-effectiveness, diagosis, genetic testing, individual-level simulation

In 1990, a University of California laboratory discovered an association between mutations in a gene on chromosome 17 and families with early-onset breast cancer, marking the beginning of genetic testing for inherited breast cancer susceptibility.[1] Four years later, two genes were isolated—*BRCA1* and *BRCA2*—both of which codes for proteins that protect against tumors in several organs, notably in the breasts and ovaries.[2,3] Importantly, mutations in these genes were found to be inherited dominantly, such that a child or sibling of a

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carrier has a 50% probability of also being at increased risk for cancer in these organs.[4] The foremost benefit of identifying carriers is that clinical actions can be taken to reduce risk of recurrence, or primary cancer in affected relatives. For carriers of high-risk mutations, that is, those very likely to cause cancer, prophylactic surgery to reduce this risk is the most effective option.[5]

Over the recent 25 years, harmful mutations in other genes have been discovered, new technology to sequence DNA has reduced testing costs, and a valuable market with multigene direct-to-consumer tests emerged.

The Norwegian health care service has for many years offered *BRCA* testing to patients with early-onset breast cancer. If a hereditary etiology cannot be ruled out, relatives would also be offered a test. Oslo University Hospital (OUH), the country's largest provider of specialist health care services, offers full sequencing of all exons on *BRCA1* and *BRCA2* to breast cancer patients age 60 or younger. While many cases of hereditary breast and ovarian cancer (HBOC) are found in these genes, it is estimated that as much as 70% of HBOC cases could be caused by mutations in other genes.[6] To explore this, this hospital recently began using a multigene panel (a set of genes sequenced simultaneously) to diagnose rare cancer syndromes and hereditary cancer. Five of these are non-*BRCA* genes associated with HBOC. There are good indications that current routine *BRCA* testing is a cost-effective practice in Norway,[7] and the prevalence and pathogenicity of their variants are well understood. Whether expanding testing beyond these two genes also could be cost-effective, however, has not yet been assessed.

A direct-to-consumer panel with the same five HBOC genes as used by OUH and the *BRCA*s is on the market. The manufacturer published an analysis that predicted acceptable cost-effectiveness compared to *BRCA*-only testing in an American setting.[8] They did not include cascade testing of relatives of identified family index carriers however, which lowers the policy transferability to a Norwegian setting. In fact, to our knowledge, only one previous study has included cascade testing for HBOC,[9] but only the *BRCA*s were examined.

With this analysis, we aim to complete the picture by using a health economic decision model to provide insight into the scope of genetic testing for early-onset breast cancer patients and their relatives in Norway. We compare the cost-effectiveness of expanding routine testing from current *BRCA*-only testing with cascade testing for relatives to either a 7-gene panel test with five non-*BRCA* genes or a 14-gene panel with seven additional genes that are included in the largest direct-to-consumer

tests for HBOC on the market.[10] We include targeted cascade testing of relatives of identified carriers for all strategies.

Methods

Testing Strategies

We compared three strategies: 1) current practice involving full sequencing of the genes *BRCA1* and *BRCA2*; 2) the 7-gene panel involving full sequencing of *BRCA1* and *BRCA2*, and five additional genes (*CDH1, PALB2, PTEN, STK11,* and *TP53*); and 3) the 14-gene panel that includes the 7-gene panel and seven additional genes (*ATM, BARD1, BRIP1, CHEK2, NBN, RAD51C,* and *RAD51D*).

We assumed the laboratory work and subsequent interpretations provide 100% technical sensitivity and specificity; however, due to the prevalence of mutations of each gene among women, the tests will have varying predictive values. For example, an individual with a mutation in a gene not included in the applied test will be considered a "false negative." In this respect, the largest panel will be considered "gold standard" because it tests for all possible mutations. The degree to which the tests examining fewer genes will have a lower negative predictive value is a function of the prevalence of the mutations. Although examining more genes can improve diagnostic yield, genes with a more recent association to hereditary cancer in the breasts or ovaries also yields a higher rate of variants of unknown significance (VUS), giving an inconclusive test result. Since establishing pathogenicity of variants is ongoing, tests that examine genes with more established use have more available information to classify the variants found.

Evaluating the value of a genetic test beyond predictive value requires establishing a link to clinical action, or rather how likely it is that a test will significantly improve patient outcomes.[11] We assumed the identified mutation greater than a high-risk threshold would be offered prophylactic surgery. The recommended breast cancer risk-reducing intervention for patients older than 25 with a positive genetic test in Norway is bilateral mastectomy with reconstructive surgery. In addition, to reduce the risk of ovarian cancer, bilateral salpingo-oophorectomy (BSO) is an option for high-risk carriers who are at least 35 years old.[12] We applied the relative risk threshold value proposed by Easton and colleagues that suggested a cutoff value for the relative risk of at least 4 to consider a mutation imposing a high cancer risk upon a carrier with an unknown family history of HBOC.[10]

Model Description

Our decision model is an individual-level simulation model programmed with Python 3.6. This structure permits directly specifying attributes to the hypothetical individuals, which would otherwise require several separate cohorts to be reflected in traditional cohort models. Another advantage of an individual-level model is that one can easily keep track of past events and update elements such as transition probabilities and costs during simulation.

Conceptually, our model has two parts. The first part relates to generating the hypothetical individuals with different risk profiles and the interfamily inheritance of possible genetic mutations. The second part reflects transitions between possible health-related events during the lifetime of each simulated individual.

Generating Individuals

We created index patients age 55 years (with 1 year standard deviation) to reflect an age distribution of breast cancer patients under 60 years old in Norway.[13] Each index patient was given a (true) mutation carrier status governed by the estimated prevalence of pathogenic mutations and VUS, and specific characteristics of their breast cancer follow-up (e.g., HER2-tumour status and treatment preferences). Carrier status was unobservable to the patients and their physician until after testing, and we assumed testing to take place parallel with initial radical surgery, as per clinical practice in Norway. Patients not receiving a positive test result for a high-risk mutation would be treated as per the normal breast cancer follow-up care pathway (adjuvant systemic-, hormonal-, and radiotherapy). Undetected carriers (false negatives) would also follow this pathway, albeit with an increased risk of recurrence, or ovarian cancer, by the relative risk from a mutation in that gene. Individuals carrying what would currently be classified as a VUS would receive follow-up as test-negative due to the invasiveness of the treatment for test-positives.

As germline HBOC mutations are passed on with autosomal dominant inheritance, a first-degree relative of an affected carrier has a 50% probability of carrying the same allele.[4] Therefore, in clinical practice testing both female and male relatives of an identified carrier, that is, cascade testing, provides opportunities to identify those individuals at greatest risk.[14] Whereas male breast cancer is very rare, daughters of male relatives could be at increased risk for cancer in the breasts or ovaries if inheriting a high-risk mutation. While more realistic, modelling cascade testing of male relatives and their possible sons and daughters would greatly increase model complexity and computational burden. Therefore, for the current analysis, cascade testing opportunities included testing of daughters and sisters only. The index patients were assigned binomial sets of daughters and sisters (both ranging between 0 and 3) such that the average would equal that of the age-matched Norwegian population, 0.84 and 0.41, respectively.[15,16] Relatives of high-risk mutation carrying index patients were offered testing for the same variant as found for the index patient if they opted in (Figure 1, upper panel). If also carrying this genetic variant, the relative would be offered prophylactic surgery. If the index test result was negative, VUS, or positive for a mutation with low-to-moderate risk, relatives did not receive an offer of genetic testing. Declining genetic testing, a relative would be untreated and assumed healthy, but cancer would develop with a probability governed by the relative cancer risk of the mutation.

Lifetime Simulation

We simulated the index patients and their relatives simultaneously to update the test eligibility of relatives as a function of the index patients' result. We tracked each individual over their lifetime, or until 100 years of age. Each year, individuals could transition between eight discrete health states ("at risk," "prophylactic surgery," "at risk, but risk reduced," "breast cancer [recurrence or primary]," "breast cancer survivor," "ovarian cancer," "ovarian cancer survivor," and "dead"), and face different risks of events, depending on their characteristics and history of past events (Figure 1, lower panel). Upon start, both index patients and relatives were initiated in the same health state, "at risk," wherein index patients faced risk of breast cancer recurrence, ovarian cancer, and all-cause mortality. In case of a positive test result for a high-risk mutation they could opt for prophylactic surgery (mastectomy, BSO, or both).

Non-carriers, index patients with an inconclusive test result (i.e., VUS), and carriers declining further surgery remained in this state with subsequent follow-up for their primary breast cancer (see Supplementary Appendix 5 for a detailed description of breast cancer follow-up). For index patients opting for risk-reducing prophylactic surgery, cancer risk decreased depending on type of surgery chosen.[17,18]

We assumed relatives were disease-free in the "at risk" state, but subject to risk of cancer in the breasts or ovaries. Non-carrier relatives faced organ-specific risks equal to annual incidences in the age-matched Norwegian
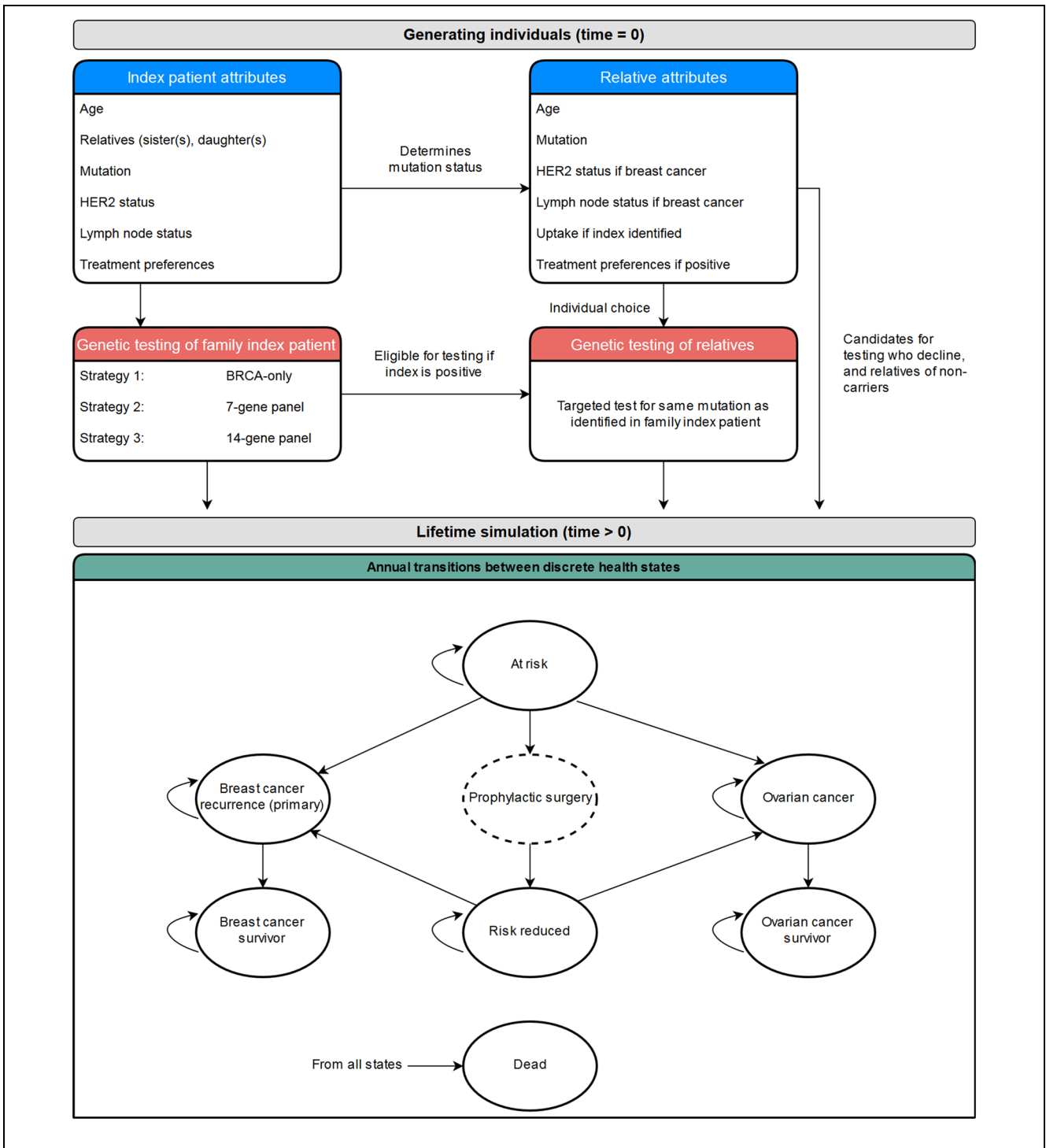
Figure 1 Model overview. *Upper panel*: Patient-generating process. Whether an index patent is a carrier of a high-risk mutation or not determines the risk profiles of their relatives. Furthermore, a genetic test to detect the mutation determines if any cancer prevention is offered, thereby influencing the health-related events in the individual simulations of each index and relative. *Lower panel*: Simplified illustration of the model's health states with key transitions. Solid ovals are recurrent health states in which individuals can reside in for multiple consecutive years; dashed oval is the "tunnel" health state of risk-reducing prophylactic surgery. The single arrow entering the "dead" state illustrates the possibility of transitioning there from all health states.

population, with a multiplicative relative risk for mutation-carrying relatives.[14]

Relatives of index patients identified as carriers of a high-risk mutation opting for testing could be offered prophylactic mastectomy, BSO (conditional on being older than 35 years, and mutation having high associated ovarian cancer risk), or both (same conditions as BSO only).

If recurrent (primary for relatives) breast cancer, or ovarian cancer developed, a stage at diagnosis was assigned according to the distribution of these for Norwegian patients.[19,20] In the absence of good evidence on recurrence for mutation carriers, we made the simplifying assumption that the risk of recurrence would be approximately proportional to the risk of a primary tumor. The recurrence risk for *BRCA* carriers has been reported as quite similar to the relative risks for a primary tumor used in this model[21,22]; however, there is very little evidence on recurrence risk for carriers of other mutations.

The length of survival for each individual was tracked; conditional on surviving breast cancer for 5 years, and ovarian cancer for 10 years, the relative survival rate was 100% and 80%, respectively, of that of the background Norwegian population.[14] As a 2016 meta-analysis of over 10,000 patients found no statistical difference in mortality between *BRCA* carriers and sporadic cases,[23] we assumed mutation status would not influence mortality risk directly. Therefore, carriers and non-carriers alike faced mortality risks only governed by their breast cancer stage.

Model Parametrization

The model input parameters were primarily estimated from published literature. Detailed search strategies and source selection are available in Supplementary Appendices 2 and 3. Summary data on mutation prevalence among Norwegian breast cancer patients as well as resource use consumed in testing were provided by the medical genetics laboratory at OUH (personal communication Sarah L. Ariansen, laboratory manager). The latter was included in the costing analysis to estimate the costs of the different testing strategies. Key parameters are presented in Tables 1, 2, and 3, and all parameters in Supplementary Appendix 1.

Mutation Parameters

We undertook evidence syntheses to assess the organ-specific cancer risks for carriers of pathogenic variants in the included genes, and for the prevalence among breast cancer patients (Figure 2). When necessary, we employed Bayesian meta-analysis methods (Appendix 2). For these parameters, we were unable to differentiate between specific pathogenic variants within the genes; therefore, prevalence and risk estimates for mutation carriers were aggregated for several variants.

We obtained Norwegian-specific data for mutations in the genes in current practice, and those included in the 7-gene panel. For prevalence of *BRCA* mutations, we used the results of diagnostic testing at OUH during 2016. Of 1,587 breast cancer patients, 78 ($\sim$ 5%) had a pathogenic mutation in either of the two genes. We assumed 60% had a *BRCA1* mutation and 40% a *BRCA2* mutation because this distribution has previously been found for the same population.[24] For the five non-*BRCA* genes in the 7-gene panel the laboratory had only sequenced 72 patients at the time of our study, and discovered no pathogenic variants. Since study results from larger samples of breast cancer patients were available in published literature we used these as priors for the hospital's observations. The resulting posterior distributions were included as estimates of the prevalence for mutations in the "7-gene panel genes." For genes lacking domestic observations, that is, those exclusively on the 14-gene panel, the mutation prevalence estimates were completely based on extracted literature data (Appendix 3).

For the probability of a mutated variant being of uncertain clinical significance, we used the findings from HBOC testing of 488 patients in the 2015 study by Tung and colleagues.[25] To control for their uncertain variants having been reclassified as either pathogenic or non-pathogenic since 2015, we reviewed each reported variant in the US National Library of Medicine's "ClinVar" database.[26] Where there was conflicting clinical significance, we adopted the most recent evaluation, not accounting for size or status of the laboratories.

Costs

We used a bottom-up approach to estimate the costs arising within the health care sector from the various clinical events in the model. The direct costs of genetic testing were derived from the resource utilization involved at the medical genetics laboratory at OUH during 2016. Consumed resources were categorized to materials and equipment, direct labor, indirect labor, overhead, capital, and maintenance costs. Common to all testing strategies were costs related to genetic counselling, DNA extraction, and multiplex ligation-dependent probe amplification.

Table 1 Epidemiological Model Parameters[a]

Description[b]	Mean	95% CI[c]	Distribution (Parameters)		
Age at initiation					
Index patient	55 (1 year SD)				
Daughter (index age—25 years)					
Sister (index age ±2 years)					
Breast cancer risk, relatives by age[14]	Age-dependent incidence of breast cancer in Norway		Assumed fixed		
Ovarian cancer risk, relatives by age[14]	Age-dependent incidence of breast cancer in Norway		Assumed fixed		
All-cause mortality Norwegian population[38]			Assumed fixed		
Relative survival breast cancer patients[14]			Assumed fixed		
Stage I	0.990				
Stage II	0.920				
Stage III	0.760				
Stage IV	0.255				
Relative survival ovarian cancer patients[14]			Assumed fixed		
Local	0.932				
Regional	0.616				
Distant	0.342				
Recurrence of breast cancer index patient by age[39]			Beta		
50–59	0.016	(0.010, 0.024)		$\alpha = 17.76$	$\beta = 1075.24$
60–69	0.015	(0.008, 0.023)		$\alpha = 17.43$	$\beta = 1120.57$
≥70	0.009	(0.003, 0.017)		$\alpha = 6.23$	$\beta = 672.75$
Relative risk of breast cancer			Log-normal		
ATM mutation	2.8	(2.04, 3.85)		$\mu = 1.03$	$\sigma = 0.16$
BARD1 mutation[d]	1.4	(0.63, 3.04)		$\mu = 0.31$	$\sigma = 0.35$
BRCA1 mutation[d]	11–36			Appendix 1	Appendix 1
BRCA2 mutation[d]	9.2–19			Appendix 1	Appendix 1
BRIP1 mutation	1.6	(0.89, 3.00)		$\mu = 0.48$	$\sigma = 0.39$
CDH1 mutation	6.6	(2.20, 19.9)		$\mu = 1.88$	$\sigma = 0.67$
CHEK2 mutation	3.0	(2.60, 3.50)		$\mu = 1.10$	$\sigma = 0.09$
NBN mutation	2.7	(1.90, 3.70)		$\mu = 0.99$	$\sigma = 0.20$
PALB2 mutation	5.3	(3.00, 9.40)		$\mu = 1.67$	$\sigma = 0.29$
PTEN mutation	41.4	(13.5, 118)		$\mu = 3.72$	$\sigma = 0.55$
RAD51C mutation	0.9	(0.34, 2.61)		$\mu = -0.06$	$\sigma = 0.52$
RAD51D mutation	1.1	(0.55, 1.88)		$\mu = 0.06$	$\sigma = 0.31$
STK11 mutation	15.2	(7.60, 68.0)		$\mu = 2.73$	$\sigma = 0.32$
TP53 mutation	19.9	(9.15, 40.5)		$\mu = 2.98$	$\sigma = 0.43$
Relative risk of ovarian cancer			Log-normal		
ATM mutation	2.78	(1.41, 5.51)		$\mu = 1.02$	$\sigma = 0.35$
BARD1 mutation	2.12	(0.30, 23.3)		$\mu = 0.75$	$\sigma = 1.10$
BRCA1 mutation[d]	1–61			Appendix 1	Appendix 1
BRCA2 mutation[d]	1–19			Appendix 1	Appendix 1
BRIP1 mutation	7.14	(4.52, 10.5)		$\mu = 1.97$	$\sigma = 0.21$

(*continued*)

Table 1 (continued)

Description[b]	Mean	95% CI[c]	Distribution (Parameters)	
CDH1 mutation	1.98	(0.46, 6.90)	μ = 0.68	σ = 0.69
CHEK2 mutation	0.69	(0.34, 1.27)	μ = −0.36	σ = 0.33
NBN mutation	1.19	(0.45, 3.09)	μ = 0.17	σ = 0.48
PALB2 mutation	3.18	(0.68, 18.3)	μ = 1.16	σ = 0.84
PTEN mutation	1.00		μ = 0.00	σ = 0.00
RAD51C mutation	5.37	(2.47, 10.7)	μ = 1.68	σ = 0.37
RAD51D mutation	14.55	(6.60, 28.2)	μ = 2.67	σ = 0.37
STK11 mutation	27.00	(7.30, 68.0)	μ = 3.30	σ = 0.57
TP53 mutation	2.92	(1.01, 6.96)	μ = 1.07	σ = 0.49

CI, confidence interval.
[a] All probabilities denote annual events.
[b] Numbered references, where reference is "Appendix parameter" values are based on own calculations.
[c] Confidence intervals bootstrapped from distributions of size 10,000 and derived using the percentile method (values at indexes 250 and 9,750) for missing original ranges.
[d] Risk as function of age, see Appendix 2.

We estimated the cancer and prophylactic treatment costs using the official guidelines for treatment, with additional input from a clinical expert (Appendices 4–6).[27,28] We assumed conservative 95% confidence intervals around cost parameters' point estimates of ±20%. We valued costs in 2016 Norwegian kroner (NOK) and adjusted to US dollars (USD) with the NOK/USD yearly average exchange rate for 2016 of 8.39 NOK/USD.[29]

Health State Utilities

We used age-specific utility weights for all individuals using EQ-5D values for the Swedish general population, adjusted with British tariffs to account for health-related quality of life.[30,31] Utility weights pertaining to specific events such as the cancer states, surgical interventions, and disutility of a positive test result were multiplicatively adjusted. We adjusted time spent in the health states by the utility weights which aggregated give the quality-adjusted life years (QALYs) for each individual.

Intermediate Clinical Outcomes

We report the lifetime risk of disaggregated intermediate health outcomes breast cancer, ovarian cancer, breast cancer–specific mortality, and ovarian cancer–specific mortality for both index patients and relatives. From a cost-effectiveness perspective, lifetime risk may not give the most relevant picture seeing as prevention of earlier cases would result in better lifetime outcomes for aggregated life-years and QALYs. Therefore, we also report age-specific incidence rates to account for the timing of prevention.

Cost-Effectiveness Analysis

Outcomes of the cost-effectiveness analysis (CEA) included costs and QALYs from a health care sector perspective (Appendix 7), discounted at an annual rate of 4%, in accordance with Norwegian guidelines for economic evaluation.[32] We summarize main model outcomes with incremental cost-effectiveness ratios (ICERs). The ICER is the cost difference between one strategy and the next least costly strategy, divided by the difference in QALYs, interpreted as the additional cost per QALY gained. The net monetary benefit is the difference in monetized QALYs and costs for each strategy, where the QALYs are monetized at a cost-effectiveness threshold (CE-threshold) per unit increase. The cost-effective strategy is the one with the highest ICER below the CE-threshold value.[33]

As Norway does not have a single CE threshold for which a strategy is considered "good value for money"

Table 2 Individual Choice Parameters

Description	Mean	95% CI	Distribution (Parameters)		
Uptake of genetic testing for female relatives of high risk mutation carriers by age[40]					
18–29	0.30	(0.15, 0.47)	Beta	$\alpha = 9$	$\beta = 21$
30–49	0.82	(0.68, 0.93)		$\alpha = 28$	$\beta = 6$
≥50	0.80	(0.60, 0.94)		$\alpha = 16$	$\beta = 4$
Uptake of prophylactic BMx, positive carriers					
Index patients[41]	0.39	(0.34, 0.45)	Beta	$\alpha = 137$	$\beta = 209$
Relatives by age[42]					
25–34	0.12	(0.08, 0.16)	Beta	$\alpha = 46$	$\beta = 333$
35–60	0.11	(0.10, 0.14)		$\alpha = 108$	$\beta = 803$
Uptake of prophylactic BSO positive carriers					
Index patients[42]	0.36	(0.34, 0.40)	Beta	$\alpha = 321$	$\beta = 554$
Relatives by age[42]					
25–34	0.10	(0.07, 0.14)	Beta	$\alpha = 39$	$\beta = 340$
35–39	0.28	(0.23, 0.33)		$\alpha = 76$	$\beta = 199$
40–60	0.35	(0.31, 0.38)		$\alpha = 221$	$\beta = 416$
Both prophylactic procedures—Pr(BMx) $\times$ Pr(BSO)[a]					

CI, confidence interval.
[a]Decisions assumed independent.

(cost-effectiveness is only partly a factor in implementation decisions), we use a commonly cited threshold of 588,000 NOK per QALY gained (2012).[32] Inflated to 2016 NOK and converted to USD, approximately 648,000 NOK per QALY gained, or $77,000 per QALY gained.[34]

Uncertainty and Value of Information Analysis

In health economic decision models, most input parameter values have the moments expected value and variance, giving estimates of the unknown true value of that parameter. We accounted for variation in parameter values by probabilistic sensitivity analysis (PSA) wherein the model was run with input parameters varying over their probability distributions. This resulted in joint distributions for the model output that incorporates the parameter uncertainty. The variance around model output of individual-level simulations can be separated into the between-patient variation within each model run due to patient heterogeneity and stochasticity of events, and the between-run variation due to parameter uncertainty. Reducing the bias in output estimates' variation due to between-patient stochasticity is possible by sampling sufficiently large numbers of individuals.[35] As our model produced fairly stable estimates at 100,000 individuals using the expected values for the input parameters, we ran the model for each strategy with 100,000 individuals and 500 unique parameter sets to get joint distributions of model outcomes capturing parameter uncertainty.

From the sample of PSA outcomes, we calculated the net monetary benefit (NMB), that is, effectiveness monetized by a CE threshold less the costs, and the proportion of model runs each strategy would have the largest NMB over a range of CE threshold values from zero to $150,000. We show this graphically with cost-effectiveness acceptability curves (CEACs) for each strategy, where the height of a curve for a strategy on the *y*-axis show the proportion of the 500 model runs that strategy has the highest NMB, over the CE thresholds. While CEACs are very useful to illustrate the uncertainty in choosing between the strategies, they do not reveal the magnitude of the underlying NMBs. Therefore, to derive the optimal strategy at each CE threshold, we calculated the expected NMBs, and show the strategy maximizing expected NMB as the frontier. The NMBs for the strategies may also be skewed differently over the CE thresholds, resulting in an optimal strategy that does not also have the highest proportion of highest NMBs, but is still considered optimal because it has the highest expected NMB.

Because early analyses revealed considerable decision uncertainty we sought to quantify the value of eliminating parameter uncertainty by partial expected value of perfect information (EVPPI) for the model's parameters, clustered in appropriate groups. The EVPPIs indicate the effect parameters have on the net-benefit difference between the testing strategies, that is, which parameters produce more decision uncertainty.[36] Because the standard approach to calculating of EVPPIs (i.e., through two-level nested Monte Carlo simulation) is

Table 3 Costs (2016 USD) and Health State Utility Weights

Description[a]	Mean	95% CI[b]	Distribution (Parameters)		
Cost of genetic testing (Appendix 4)			Gamma		
BRCA-only, index patient	$2,195	(1,446, 3,127)		α = 25	β = 87.80
7-gene panel, index patient	$3,711	(2,408, 5,262)		α = 25	β = 148.44
14-gene panel, index patient	$4,796	(3,084, 6,847)		α = 25	β = 191.84
Targeted testing of relative	$138	(90, 196)		α = 25	β = 5.52
Cost of breast cancer treatment (Appendix 5)			Gamma		
Examination and diagnosing	$1,414	(911, 2,018)		α = 25	β = 56.56
Breast conserving surgery, benign	$5,396	(3,500, 7,670)		α = 25	β = 215.84
Breast conserving surgery, malign	$4,500	(2,919, 6,455)		α = 25	β = 180.00
Total mastectomy with reconstructive surgery	$15,607	(10,112, 22,240)		α = 25	β = 624.28
Axillary lymph node excision	$2,774	(1,791, 3,966)		α = 25	β = 110.96
Axillary lymph node excision with metastasis	$7,737	(5,000, 11,025)		α = 25	β = 309.48
Systemic adjuvant therapy, HER2 negative	$2,763	(1,790, 3,980)		α = 25	β = 110.52
Systemic adjuvant therapy, HER2 positive	$30,156	(19,586, 43,250)		α = 25	β = 1206.24
Hormonal therapy premenopausal	$151	(97, 214)		α = 25	β = 6.04
Hormonal therapy postmenopausal	$2,466	(1,596, 3,517)		α = 25	β = 98.64
Adjuvant radiotherapy	$3,131	(2,040, 4,470)		α = 25	β = 125.24
Follow-up mammogram	$26	(17, 37)		α = 25	β = 1.04
Follow-up GP consultation	$36	(23, 51)		α = 25	β = 1.44
Follow-up breast surgeon consultation	$33	(21, 47)		α = 25	β = 1.32
Cost of ovarian cancer treatment (Appendix 6)					
Examination and diagnosing	$66	(43, 98)	Gamma	α = 25	β = 2.64
Bilateral salpingo-oophorectomy	$3,869	(2,505, 5,550)		α = 25	β = 154.76
Adjuvant systemic therapy	$1,904	(1,225, 2,724)		α = 25	β = 76.16
Follow-up year 1–2	$327	(210, 468)		α = 25	β = 13.08
Follow-up year 3–5	$218	(140, 310)		α = 25	β = 8.72
Follow-up year 6–10	$36	(23–51)		α = 25	β = 1.44
Cost of prophylactic treatment (Appendix 5)					
Prophylactic bilateral mastectomy with reconstructive surgery	$15,607	(10,102, 22,117)	Gamma	α = 25	β = 624.28
Prophylactic bilateral salpingo-oophorectomy	$3,869	(2,505, 5,550)		α = 25	β = 154.76
Baseline utility weight			Fixed		
Age 20–34[43,44]	0.87				
Age 35–44[43,44]	0.85				
Age 45–54[30,43]	0.82				
Age 55–74[30,43]	0.80				
Age 75–88[30,43]	0.76				
Age ≥89[43]	0.72				
Utility weights testing					
Negative result/at risk relative	1.00				
Positive/uncertain result[45]	0.995	(0.994, 0.996)	Beta	α = 4574	β = 24
Utility weights breast cancer					
Stages I and II[46]	0.73	(0.67, 0.78)	Beta	α = 171	β = 64
Stages III and IV[46]	0.55	(0.46, 0.64)	Beta	α = 64	β = 52
Utility weights ovarian cancer					
Local disease[47]	0.81	(0.57, 0.95)	Beta	α = 12	β = 3
Regional metastasis[47]	0.55	(0.28, 0.79)	Beta	α = 7	β = 6
Distant metastasis[47]	0.16	(0.02, 0.36)	Beta	α = 2	β = 12
Utility weights prophylactic surgery					
Bilateral mastectomy[45,46]	0.97	(0.94, 0.98)	Beta	α = 225	β = 7
Bilateral salpingo-oophorectomy[45]	0.92	(0.81, 0.97)	Beta	α = 41	β = 4
Both surgeries within cycle[45]	0.89	(0.78, 0.98)	Beta	α = 28	β = 3

CI, confidence interval.

[a]Numbered references, where reference is "Appendix parameter" values are based on own calculations.

[b]Assumed ±20% variation around expected value of costs and parameterized with the method of moments approach.
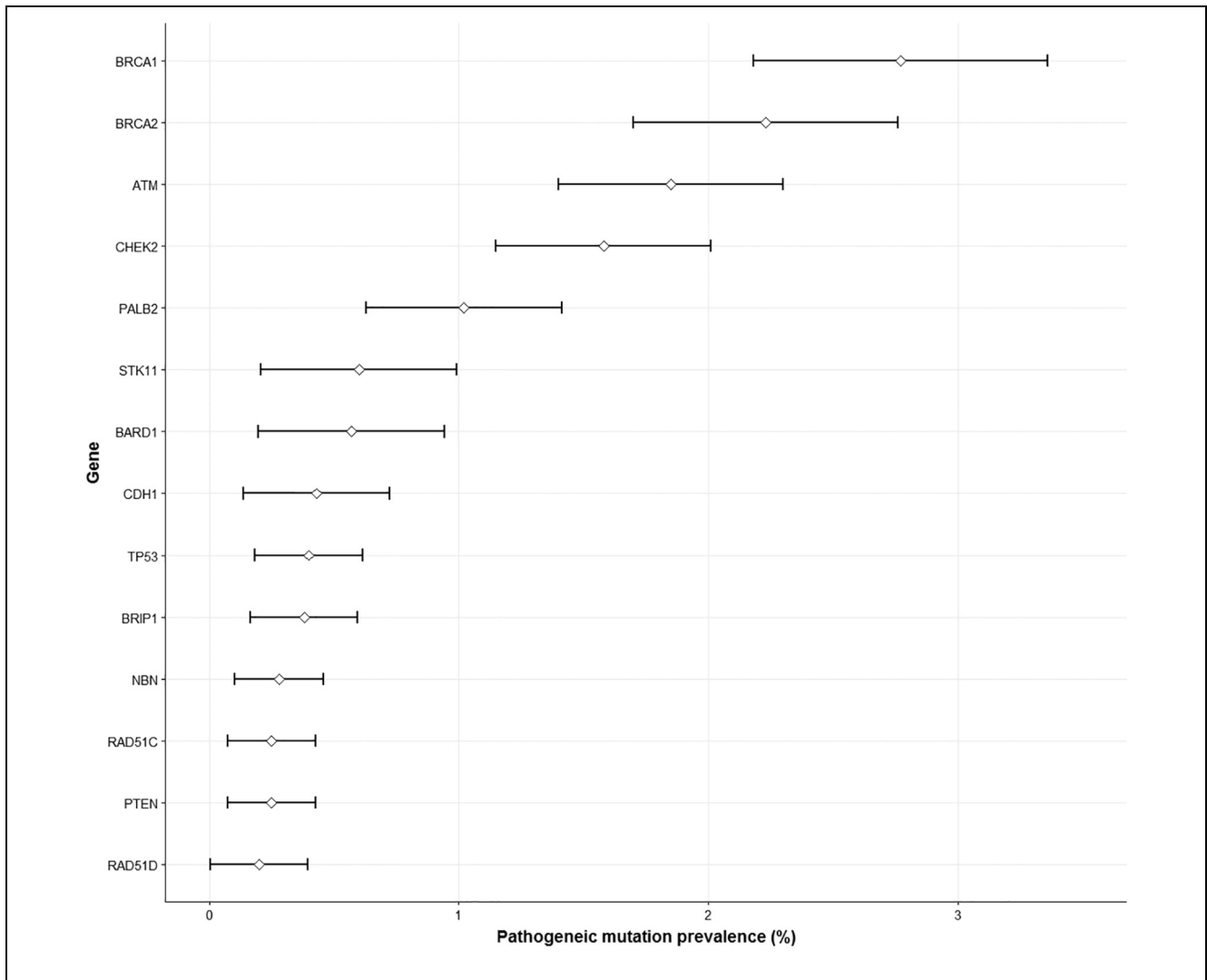
Figure 2 Posterior estimates of mutation prevalence in modelled genes in breast cancer patients: means and 95% confidence intervals.

computationally challenging for our modelling approach, we employed the Sheffield Accelerated Value of Information framework,[35] which uses nonparametric regression to estimate the EVPPIs. We grouped the parameters such that research efforts to reduce the model decision uncertainty of them could be simultaneously considered.

The funding source had no role in the study.

Results

Model Validation

External validation, which included Norwegian breast and ovarian cancer and survival rates[37,38] not used to

inform model transitions, generally showed good correspondence between predicted and observed outcomes (Appendix 8). In addition, model outcomes were reviewed by a group of clinical experts in medical genetics and breast cancer surgery to attain face validity.

Projected Intermediate Clinical Outcomes

On an aggregated level both multigene panels resulted in lower lifetime risk of intermediate clinical outcomes than *BRCA*-only testing (Table 4); however, reductions are arguably modest suggesting that timing of prevention could be important. For breast cancer recurrence among index patients (Figure 3, panel "a") there was a lower

Table 4 Lifetime Risk of Breast or Ovarian Cancer, Breast or Ovarian Cancer Mortality by Test Strategy

Lifetime Risk of Event[a]	*BRCA* Only	7-Gene Panel	14-Gene Panel
Breast cancer, index	29.17%	29%	29%
Breast cancer, relatives	10.81%	10.80%	10.74%
Ovarian cancer, index	1.46%	1.44%	1.44%
Ovarian cancer, relatives	1.78%	1.73%	1.73%
Breast cancer mortality, index	12.13%	11.89%	11.89%
Breast cancer mortality, relatives	4.68%	4.59%	4.53%
Ovarian cancer mortality, index	1.55%	1.46%	1.44%
Ovarian cancer mortality, relatives	1.61%	1.56%	1.59%

[a]Outcomes calculated from base-case analysis using expected values for all model parameters.

incidence in the 55 to 59 age group on both multigene panels, which indicates that some of the mutation carriers who would have had early recurrence due to mutations in non-*BRCA* genes would avoid recurrence. Prophylactic treatment for these patients also reduced breast cancer mortality incidence in the age group 60 to 64 (Figure 4, panel "a"). For breast cancer in relatives the effect of sequencing more genes were largest for relatives in the age group 60 to 64, which has high uptake of testing and likelihood of undergoing prophylactic treatment. The best proportional effect of multigene panels was in ovarian cancer incidence among index patients between the ages 55 and 69 (Figure 3, panel "c"), almost halving ovarian cancer deaths in that age group 60 to 64 (Figure 4, panel "c"). As for the difference between the multigene panels, there was only negligible differences in intermediate outcomes for index patients. There was, however, a trend toward more prevention of middle-age cancer-specific mortality for relatives by testing their family index patient with the 14-gene panel (Figure 4, panels "b" and "d").

Cost-Effectiveness Analysis Results

Based on 15 million individual lifetime simulations, the cost-effective testing strategy considered was the 7-gene panel at an incremental cost-effectiveness ratio of $53,310 per QALY gained compared to *BRCA*-only testing (Table 5). This is below the normally cited Norwegian CE threshold of $77,000 per QALY.

Uncertainty Analysis Results

The CEAC of the *BRCA*-only strategy is decreasing with higher CE thresholds, while the multigene panels become more likely to be cost-effective at higher levels (Figure 5). Beyond a threshold of approximately $50,000 per QALY, the probabilities that one of the multigene panels is cost-effective are very similar, as seen by the closeness

of the cost-effectiveness acceptability curves. However, for most CE thresholds, the expected payoff, that is, expected NMB, would be higher by implementing the 7-gene panel, which is why this strategy is the frontier strategy at from approximately $53,000 per QALY up to $127,000 per QALY, where the 14-gene panel becomes optimal. These switch points correspond to the ICERs of the strategies. As the frontier curve shows, the 7-gene panel would be the optimal strategy to implement both well below and above the Norwegian CE threshold.

Value of Information

As illustrated by the CEACs in Figure 5, there is considerable decision uncertainty around the CE threshold. Our partial expected value of perfect information analysis revealed that the relative cancer risk parameters were associated with the highest decision uncertainty (Figure 6). The wide variation around the risk estimates for *BRCA* mutation carriers were associated with the largest decision uncertainty, followed by the risk estimates for genes examined only on the 14-gene panel. These parameters have a direct influence on the clinical value of the testing as defined by reaching the level where prophylactic surgery is warranted.

Discussion

Our cost-effectiveness analysis suggests that compared to *BRCA*-only testing, the 7-gene panel can be a cost-effective alternative for testing early-onset breast cancer patients and their relatives in Norway.

While cost-effective, on average for all patients tested and their relatives the effectiveness was 0.0096 QALYs gained, which is arguably low in absolute terms. The path to realizing a clinical benefit from a multigene test that is also cost-effective has some noticeable barriers.
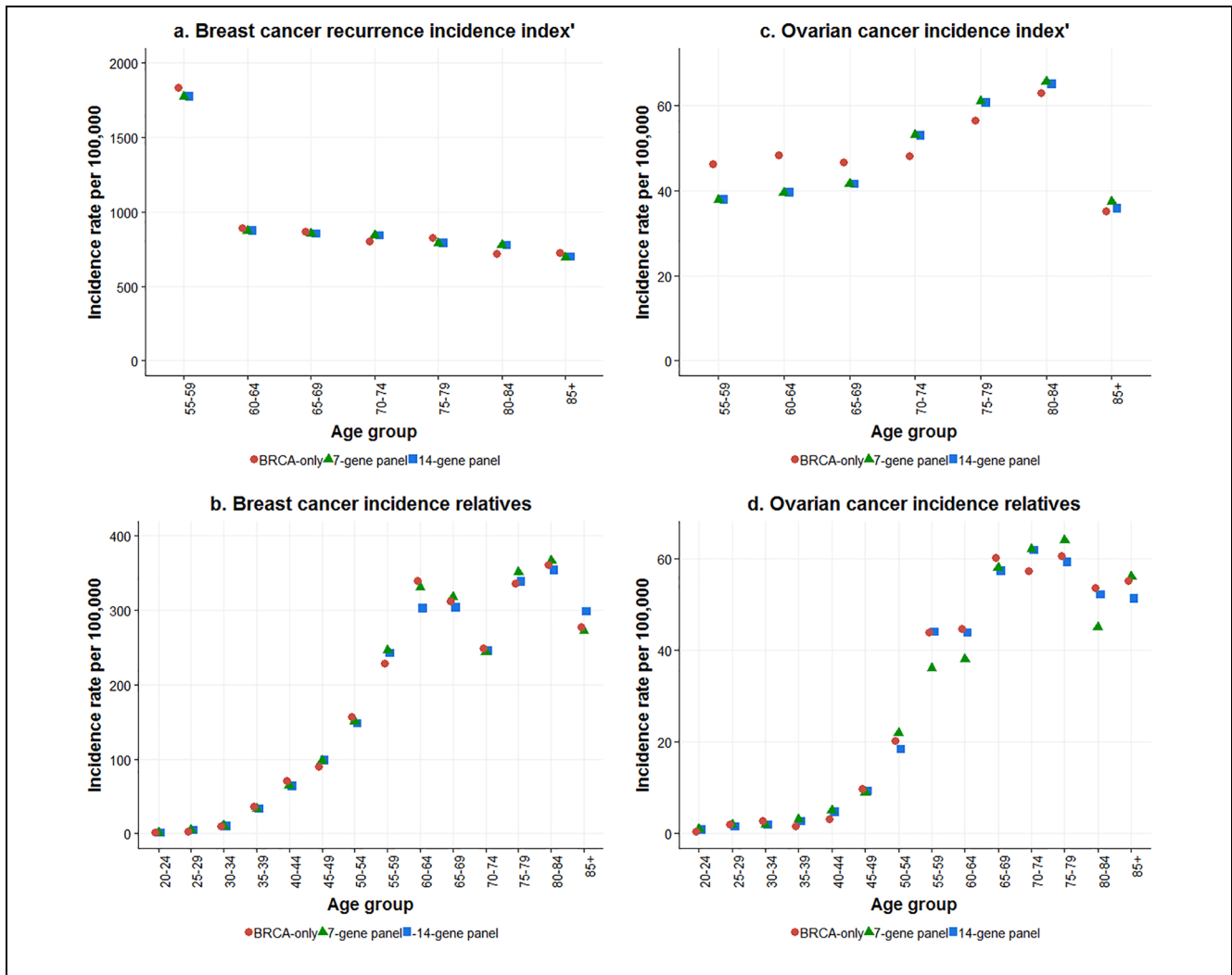
Figure 3 Incidence rates per 100,000 women by age groups in model outcomes breast cancer—and ovarian cancer rates under the alternative testing strategies. Calculated from base-case analysis using expected values for all model parameters.

First, mutations in non-*BRCA* genes in breast cancer patients eligible for testing because of early onset are very rare. Only three of the non-*BRCA* genes have mutations in more than 1% of breast cancer patients. This puts the absolute upper bound to the possible returns of testing for mutations in these genes. Second, not all genes have mutations that would categorize a carrier with an unknown family history of breast cancer as high risk. Only five of the modelled non-*BRCA* genes have mutations where the relative breast cancer risks have confidence intervals including at least a relative risk of four. As we assumed that this was a necessary condition to be offered risk reducing treatment and testing of relatives, the clinical usefulness is reduced compared to assuming treating all regardless of risk of developing breast cancer. While all of the genes on the 7-gene panel had expected values for associated breast cancer risks that would place a carrier in the high-risk category and becoming a candidate for prophylactic treatment, the 14-gene panel did not test for any additional such high-risk mutations. It did, however, have nine non-*BRCA* genes wherein mutations are associated with a high ovarian cancer risk. Third, an inconclusive test result due to finding variants of unknown significance are much more likely with the larger panels where most of the genes do not have well-characterized pathogenicity. Finally, even if a high-risk mutation is detected in an index patient there is still the question of whether that patient wishes
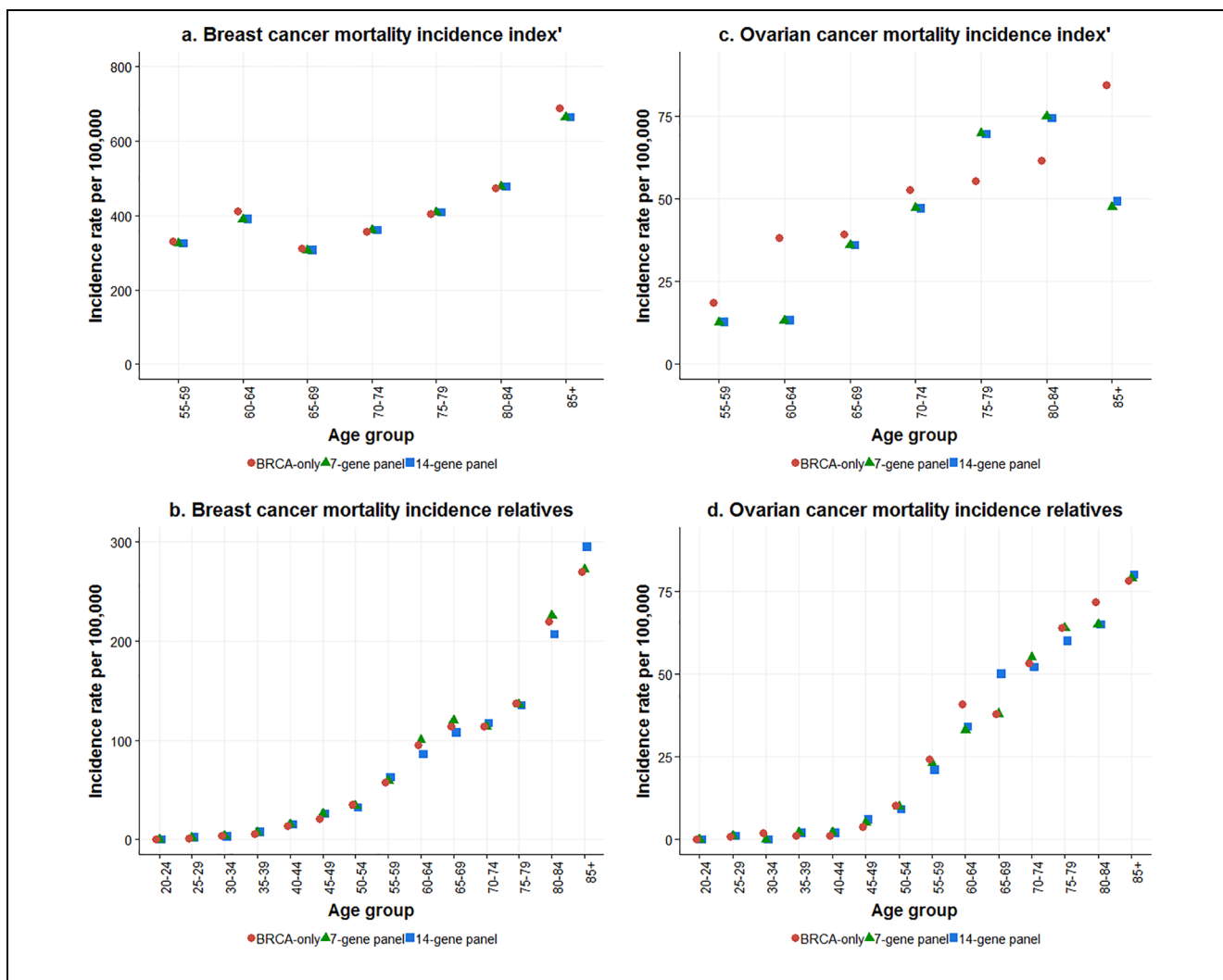
Figure 4 Incidence rates per 100,000 women by age groups in model outcomes breast cancer mortality—and ovarian cancer mortality rates under the alternative testing strategies. Calculated from base-case analysis using expected values for all model parameters.

Table 5 Lifetime Cost-effectiveness Results (Per Individual), Costs and QALYs Discounted at 4% Per Annum

Strategy[a]	Cost, $, Mean (SE)	Life Years, Mean (SE)	QALYs, Mean (SE)	Incremental Cost	Incremental QALYs	ICER
BRCA only	$14,532 (94.5)	19.506 (0.001)	14.208 (0.007)			
7- gene panel	$15,043 (96.2)	19.514 (0.002)	14.217 (0.007)	$510.7	0.0096	$53 310
14-gene panel	$15,114 (96.2)	19.515 (0.002)	14.218 (0.007)	$71.2	0.0006	$127 071

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
[a]The incremental cost, incremental QALYs, incremental net-monetary benefits, and ICERs of the strategies estimated in relation to the next best alternative.
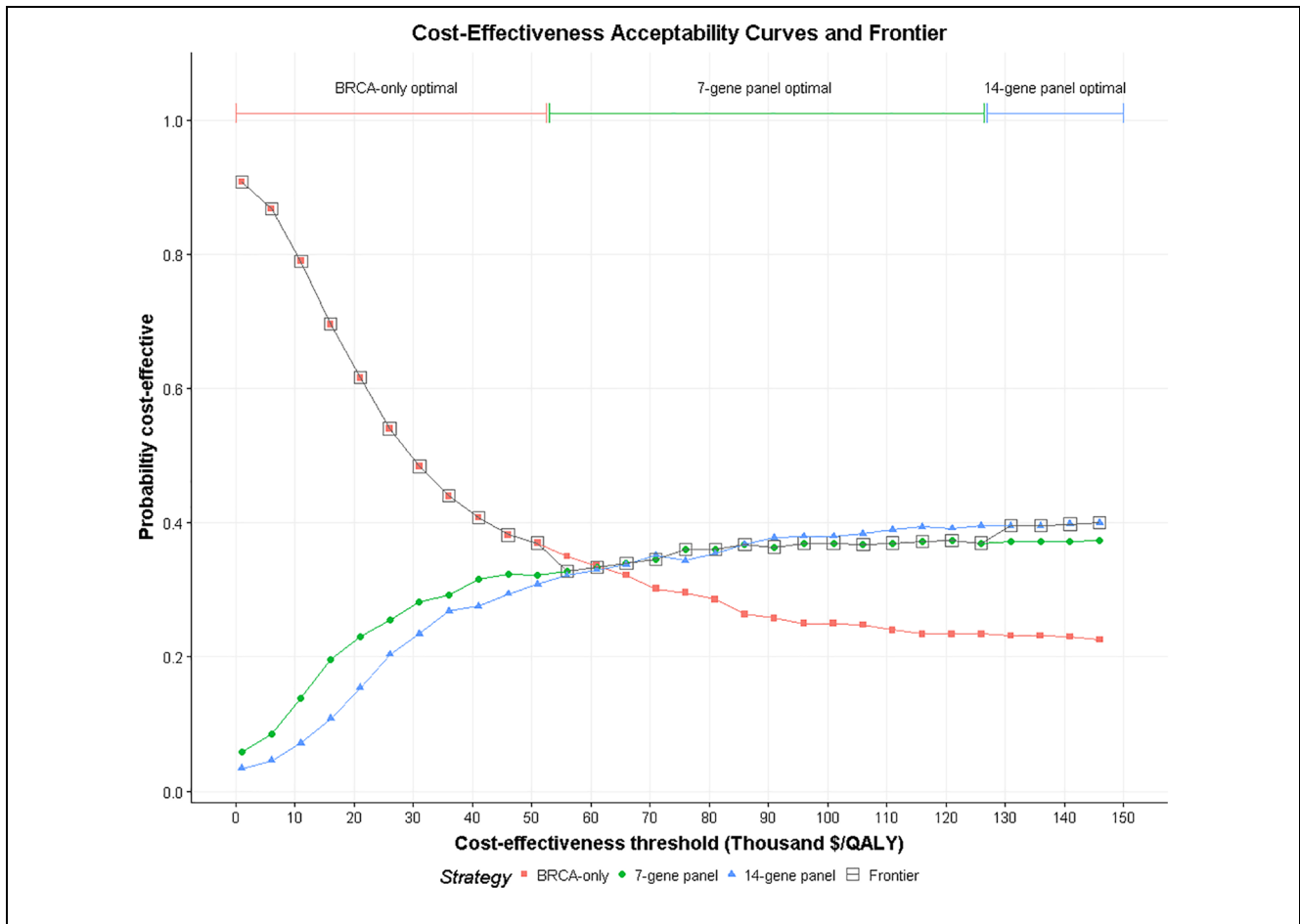
Cost-Effectiveness Acceptability Curves and Frontier

Figure 5 Cost-effectiveness acceptability curves and frontier for the choice of which genetic test strategy to apply for routine testing for HBOC. Optimal strategy at each CE threshold level is indicated by cost-effectiveness acceptability frontier: the strategy with the highest expected net monetary benefit.

to undergo more surgery, and whether or not their relatives would want to be tested at all.

Li et al. evaluated the cost-effectiveness of a 7-gene panel identical to OUH's panel against *BRCA*-only testing for index patients only.[8] They assumed equal prevalence and risk for all non-*BRCA* genes and did not consider finding VUS. For a cohort of 50 year olds, the gain in QALYs was 0.004, at an incremental cost of $282, resulting in an ICER of approximately $70,000. Considering the differences in study design, these are quite similar results as ours.

Our analysis has limitations. As our value of information analysis revealed, the parameters responsible for most of the decision uncertainty at the CE threshold were the relative risk parameters. The *BRCA*-risk estimates varies greatly in the literature due to the different

pathogenicity of variants. If we could have obtained variant-specific prevalence data, within-gene stratification would have been possible. This would have further enabled including variant-specific risk estimates, resulting in less variation and possibly less decision uncertainty. Risk estimates in non-*BRCA* genes have wide confidence intervals as well, and it is reasonable to assume that with variant-specific information the decision uncertainty could be reduced also from those parameters.

As for all models, our study has constrained scope. We did not expand the analysis to include increased cancer surveillance options, which could be offered to low-to-moderate risk mutation carriers, for example, more frequent mammography or magnetic resonance imaging examinations. There could also be spillover effects in clinical practice not captured by the model due to risk of
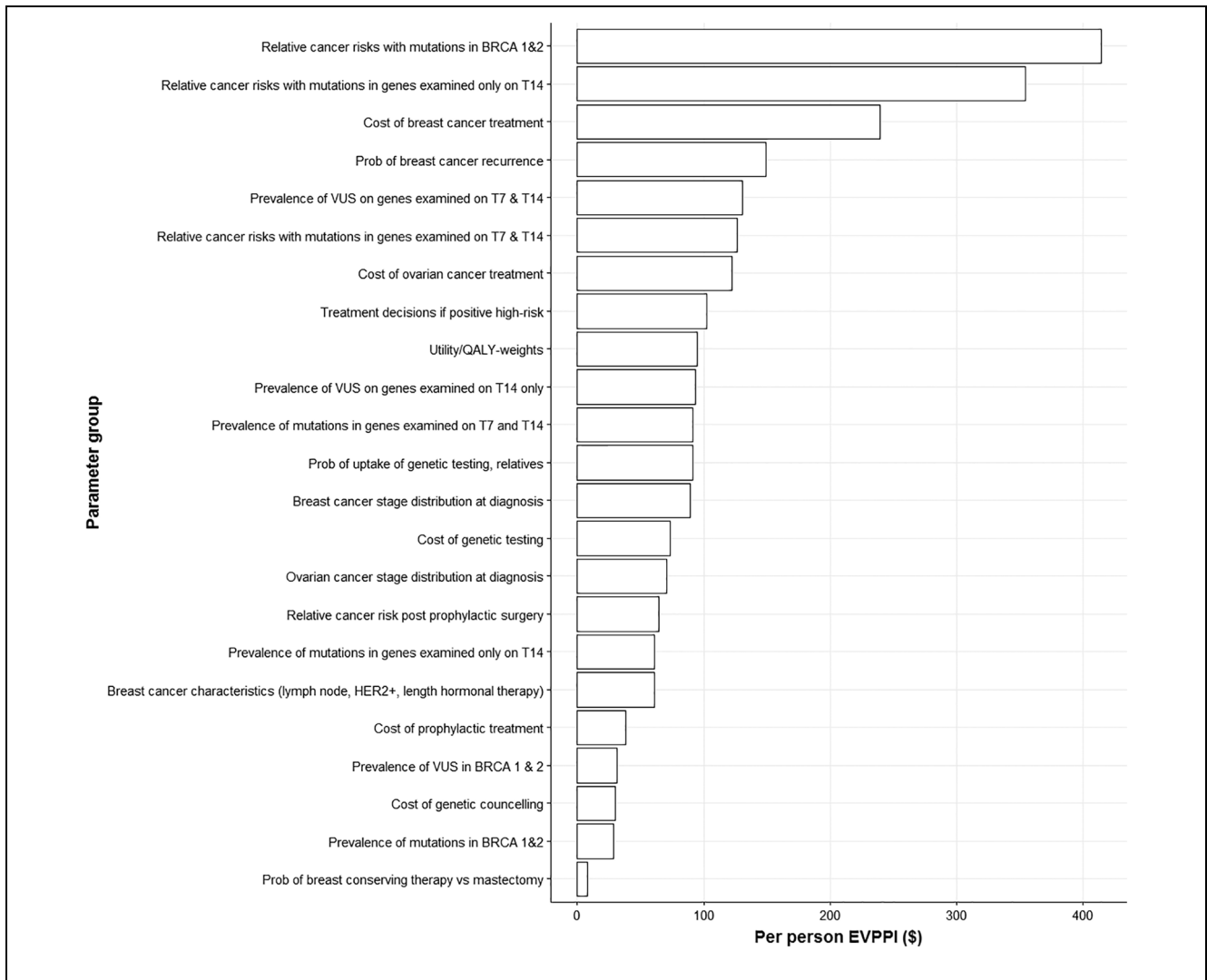
Figure 6 Partial expected value of perfect information (EVPPI) for parameter groups: the maximum return in terms of net monetary benefit from removal of uncertainty around parameter values. High EVPPI for a parameter group is indicative of these parameters causing high decision uncertainty.

cancer in other organs by overlapping mutations. For example, *BRCA2* has an association to prostate and pancreatic cancer, *CDH1* to gastric cancer, and *CHEK2* could both increase and reduce lung cancer risk depending on the variant.[10]

As mentioned, a challenge in characterizing parameter uncertainty in individual-level simulations is to reduce the influence of between-patient variation (first-order uncertainty), as this creates stochastic noise in the variance of model output. Sampling a sufficiently large number of individuals achieves this. However, this is computationally expensive, and with capacity constraints

forces a reduction in the number of parameter sets. To be sure we actually captured parameter uncertainty we had to tradeoff some of the parameters' probability spaces for reducing noise in the output. While sampling more from the parameters' probability distributions would usually be an improvement, in the current analysis, the rarity of mutations spoke in favor of emphasizing reduction of the first-order uncertainty. This was a particularly pressing issue in our model where, as discussed above, the potential in incremental effectiveness is bounded by the prevalence of very rare mutations. Therefore, our analysis outcomes are sensitive to model

implementation in that a large number of individuals is required to both ensure that each possible mutation is represented by a large enough group of carriers and that the influence of first-order uncertainty is reduced in the sensitivity analysis.

Despite the limitations, this study has a number of contributions to the health economic literature. To our knowledge, this is the only study of multigene panel tests evaluated with both index patients and cascade testing of relatives for HBOC. This arguably provides a fuller picture in a policy context seeing, as in clinical practice, the test used for the index patient could have large implications for undetected family members. It is also the only cost-effectiveness analysis that includes the element of finding variants of unknown significance, a relatively likely test result when testing for mutations in newly discovered non-*BRCA* genes. As the knowledge of new associations between mutations and HBOC progresses, our framework could be a useful tool for decision makers in evaluating the potential cost-effectiveness of other panel combinations.

In conclusion, routine testing for HBOC in early-onset breast cancer patients and their relatives with a multigene panel tests for mutations in *BRCA1, BRCA2, CDH1, PALB2, STK11*, and *TP53* can be a cost-effective alternative to *BRCA*-only testing.

Supplemental Material

The online supplementary appendix for this article is available on the *Medical Decision Making Policy & Practice* website at http://journals.sagepub.com/home/mpp.

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