Research Article

Cancer Prevention Research

Cost-effectiveness of a Genetic Test for Breast Cancer Risk

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Abstract

Genetic testing of seven single-nucleotide polymorphisms (7SNP) can improve estimates of risk of breast cancer relative to the Gail risk test alone, for the purpose of recommending MRI screening for women at high risk. A simulation of breast cancer and health care processes was used to conduct a virtual trial comparing the use of the 7SNP test with the Gail risk test to categorize patients by risk. Average-risk patients received annual mammogram, whereas high-risk patients received annual MRI. Cancer incidence was based on Surveillance, Epidemiology, and End Results data and validated to Cancer Prevention Study II Nutrition Cohort data. Risk factor values were drawn from National Health and Nutrition Examination Survey (NHANES-4) and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial data. Mammogram characteristics were derived from Breast Cancer Surveillance Consortium data. The test was most cost-effective when given to patients at an intermediate lifetime risk of breast cancer. For patients with a risk of 16% to 28%, it resulted in a 1.91% reduction in cancer deaths, saving 0.005 quality-adjusted life years per person at a cost of $163,264 per QALY. These results were sensitive to the age at which the test is given, the discount rate, and the costs of the genetic test and MRI. The cost effectiveness of using the 7SNP test for patients with intermediate Gail risk is similar to that of other recommended strategies, including annual MRI for patients with a lifetime risk greater than 20% or *BRCA1/2* mutations. *Cancer Prev Res; 6(12); 1328–36. ©2013 AACR.*

Introduction

Since 2007, a number of single-nucleotide polymorphisms (SNP) have been identified that are associated with an increased risk of breast cancer (1–5). These SNPs are different from the *BRCA1/2* mutations. Although the latter confer a large increase in risk, they are found at very low frequencies. In contrast, although the new SNPs confer only moderate risk, they are found at much higher frequencies. Although no single SNP is very informative, the hope is that a polygenic approach to genetic screening will improve estimates of individual risk, allowing screening strategies individually tailored to each patient (4). This would improve the efficiency of screening, increasing benefits while reducing costs, false positives, and other harms.

In 2007, the American Cancer Society (ACS) recommended MRI as an adjunct to mammography for the screening of breast cancer in women who have a lifetime risk of breast cancer of approximately 20% to 25% or greater (6), as determined by models based on family history such as the Gail (7), Claus (8), or Tyrer–Cuzick models (9). Although the ACS guidelines emphasize family history, other genetic and nongenetic factors can contribute to estimating risk, and we take the guidelines to indicate interest in alternative imaging when risk exceeds 20% for any reason. For example, the Gail model estimates risk using information on age, race, family history, age of menarche and first live birth, and number of previous biopsies. We focus on the Gail model due to its widespread use, for example, by the National Cancer Institute (Bethesda, MD; ref. 10).

Several studies have shown that supplementing the Gail model with genetic information from SNPs can improve the predictive accuracy of the test, although the demonstrated gains have been modest (11–14). This suggests that the efficiency of MRI screening could be improved by supplementing the Gail test with genetic data. However, would such gains outweigh the costs of genetic screening? The purpose of this study is to evaluate the cost-effectiveness of a genetic test using seven SNPs in combination with the Gail model to recommend annual MRI screening for women at high risk of breast cancer. We use a detailed simulation model of breast cancer risk factors, disease progression, and health care processes to estimate the costs and benefits of genetic testing.

Materials and Methods

Model of breast cancer

Overview. The Archimedes model is a large-scale, individually based, continuous-time discrete-event simulation (15–17). This model includes diabetes, congestive heart failure, coronary artery disease, stroke, hypertension, obesity, and cancers of the breast, lung, colon, and bladder. For

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purposes of this study, we focus on the breast cancer model, which includes the growth, detection and spread of tumors as well as screening and treatment (17). Each patient receives a random age of breast cancer diagnosis by symptoms, calculated by integrating over the hazard function specific to her risk. The baseline hazard function is computed from the Surveillance, Epidemiology, and End Results (SEER) dataset, 1995–2004 (18), adjusted for the use of mammograms and hormone replacement therapy (HRT) during those years. The Archimedes breast cancer model was validated against the American Cancer Society's Cancer Prevention Study-II (CPS-II) Nutrition Cohort data set (19). Table 1 provides a summary of data sources.

Nongenetic risk factors. The model of nongenetic risk factors is based on a parameterization of the Gail model based on the Nurses Health Study (20), which includes age of menarche, age of first live birth, and family history. The ages of menarche and first live birth of each patient are drawn from the fourth National Health and Nutrition Examination Survey (NHANES-4) dataset (21), and we modify the Gail model to treat these as continuous variables. Because family history is not available in NHANES, we independently assign family history with a probability of exactly one first-degree relative with breast cancer of 10.7% and of at least two of 1.1%, as estimated from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) dataset (22).

Genetic risk factors. The model of genetic risk factors includes seven genetic loci (SNPs; Table 2; ref. 14). We assume that genotype frequencies are in Hardy–Weinberg equilibrium, so that each patient receives an independent, random genotype at each locus following the binomial distribution. Of the seven loci, six are on different chromosomes, and the two that share a chromosome fall on opposite ends of the centromere. Therefore, it is unlikely that there is significant linkage between loci. We assume that the effect of each allele is independent of the other allele at that locus, the six other genetic loci, and the components of the Gail risk. This assumption is supported by the results of a case–control study, which found no significant pairwise interactions between SNPs and only a weak correlation between Gail and 7SNP risk (14). Each high-risk allele that a patient has multiplies their risk by the relative risk listed in Table 2. Each individual's risk is divided by the population average relative risk, so that the average risk is not altered by the addition of the genetic risk factors to the model.

Model of health care processes

Risk tests. The model includes two tests of lifetime risk, the Gail risk test and the 7SNP test. The Gail risk test is based only on the age of menarche, age of first live birth, and family history, and uses the standard parameterization of this test as used by the National Cancer Institute Breast Cancer Risk Assessment Tool (10). The breast cancer model does not include information on previous biopsies, so these are coded as unknown in the Gail risk test. The 7SNP test computes a relative risk based on the genotype of the patient as described above. We assume that this test always provides the correct genotype and associated relative risk. The result of the Gail risk test is multiplied by this relative risk to get the 7SNP risk.

Screening test characteristics. The sensitivity of mammogram increases with tumor size and patient age, and is computed for a patient of age i as

$$p = 1 - exp\left(-a_i * y^2\right)$$

where y is the diameter of the tumor. The a_i parameters were fit to data from the Breast Cancer Surveillance Consortium (BCSC; ref. 23) for ages 45 and 65 years and interpolated for all other ages. The false-positive rate for mammograms has a constant value of 0.10, based on BCSC data.

The sensitivity of MRI increases with size, but is independent of age. It follows the same functional form, but with the a_{MRI} parameter fit to data from a meta-analysis (24). The false-positive rate is 0.13 for the first MRI and 0.11 for subsequent MRIs, based on the data from four

Table 1. Data sources

Data source	Used to parameterize
SEER	Baseline breast cancer hazard function
CPS-II	Breast cancer incidence validation targets
Nurses Health Study	Risk function for nongenetic risk factors
NHANES	Age of menarche, age of first live birth, and other biomarkers
PLCO	Rates of family history of breast cancer
BCSC	Sensitivity of mammography
Medicare Physician Fee Schedule	Costs of mammogram, MRI, clinical breast exam, and diagnostic tests
British Columbia Screening Program	Weights of diagnostic procedures use to compute average cost of diagnosis
SEER-Medicare	Costs of cancer treatment
MEPS	Disutility weights of breast cancer
National Health Interview Survey	Validation of breast cancer risk distribution

NOTE: This table shows the various data sources used to parameterize the model.

Table 2. Source data for the 7SNPs

Reference	SNP	Gene	Chromosomal location	Frequency	Relative risk
Easton and colleagues (1)	rs2981582	*FGFR2*	10q26	0.38	1.26
Easton and colleagues (1)	rs3803662	*TOX3*	16q12	0.25	1.20
Easton and colleagues (1)	rs889312	*MAP3K1*	5q11	0.28	1.13
Stacey and colleagues (2)	rs13387042	—	2q35	0.50	1.20
Easton and colleagues (1)	rs13281615	—	8q24	0.40	1.08
Stacey and colleagues (2)	rs4415084	*FGF10*	5p12	0.40	1.16
Easton and colleagues (1)	rs3817198	*LSP1-H19*	11p15	0.30	1.07

NOTE: This table is reproduced with permission from Mealiffe and colleagues (14).

studies (25–28). All mammogram and MRI tests are independent.

Screening follow-up. If a patient's screening test result is negative, she simply returns the following year for her next screening test. If her result is positive, she returns in 4 days for a diagnostic test, which we assume has perfect sensitivity and specificity. This overestimates the effectiveness of diagnosis because in reality, many different tests are used for diagnosis, with varying sensitivity and specificity. If the patient does not have cancer, she returns to regular screening. If she does have cancer, she receives a diagnosis of her stage of cancer based on the diameter of the tumor, number of lymph nodes involved, and the presence of distant metastases. Patients may also have their cancer diagnosed via symptoms during the interval between screening events. After diagnosis, the patient is referred to treatment.

Costs and health utilities. The costs of mammogram, MRI, clinical breast exam, and the diagnostic test come from the Medicare Physician Fee Schedule for 2012 (ref. 29; Table 3). The cost of the diagnostic test is a weighted average of different diagnostic procedures, including diagnostic mammogram, ultrasound, fine needle aspiration, core biopsy, and surgical biopsy. The weights of these procedures are based on data from the British Columbia Screening Program (30). We assume that the cost of the Gail Risk Test is negligible. The costs for cancer treatment are based on SEER-Medicare data (31) updated to 2012 dollars using the U.S. Medical Cost Inflation Data Set, which is part of the Consumer Price Index for all Urban Consumers (CPI-U, annual average; Table 3). Costs depend on the stage of cancer and the time since diagnosis. The values for cancer health utilities are based on the EQ-5D scores collected by the Medical Expenditure Panel Survey (MEPS; ref. 32) and are consistent with those used by the Cancer Intervention and Surveillance Modelling Network (CISNET) (ref. 33; Table 3). All costs and utilities are discounted at a rate of 3% per year.

Table 3. Model parameters

Costs of tests ($)	
Gail risk test	0.00
SNP genetic test	945.00
Mammogram	81.35
MRI	716.83
Clinical breast exam	169.12
Diagnostic test	259.32
Costs of cancer treatment ($)	
Stage 0, initial	7,975.27
Stage 0, continuing	917.87
Stage 0, final	43,493.23
Stage I, initial	14,322.92
Stage I, continuing	1,302.08
Stage I, final	41,485.85
Stage II, initial	23,907.71
Stage II, continuing	2,441.41
Stage II, final	47,110.13
Stage III, initial	1,9024.89
Stage III, continuing	3,074.37
Stage III, final	53,349.28
Stage IV, initial	42,679.43
Stage IV, continuing	12,098.53
Stage IV, final	68,504.10
Cancer health state utilities	
Stage 0	1.00
Stage I	0.90
Stage II	0.75
Stage III	0.75
Stave IV	0.60

NOTE: These include the costs of all tests and cancer treatments and the utilities associated with cancer. For cancer costs, "initial" refers to the first 12 months after diagnosis, "final" to the last 12 months of life before death from cancer, and "continuing" to all intervening years.

Study population

The simulated study population consists of 100,000 non-Hispanic White women starting at the age of 40 with no

prior history of cancer and a lifetime Gail risk of breast cancer of at least 10%. Each patient is first simulated from birth to the age of 40. If she is diagnosed with cancer of any type before the age of 40 or if her Gail risk is below 10%, she is removed from the simulation. Otherwise, she then enters the trial.

Study protocol

At the start of the trial, she is given a test of her lifetime risk of breast cancer, either the Gail risk test or the 7SNP test. A patient is assigned to the average-risk category if her risk is below 20% and to the high-risk category if her risk is greater than 20%. In this population, average estimated risk was 11.3%, and only 2% of the population had a Gail risk greater than 20%. Patients in the average-risk category receive annual screening by mammogram, and patients in the high-risk category receive annual screening by MRI. This varies slightly from the ACS guidelines, which recommend MRI screening in conjunction with mammography for high-risk patients, whereas our protocol uses MRI in place of mammogram.

Trial arms

The arms of the trial differ only by who receives which risk test. In the Gail arm, which represents standard care, all patients receive the Gail test. The five intervention arms are defined by a series of concentric bands of risk centered on 20%. Patients within the risk band for a given arm receive the 7SNP test, and patients outside the risk band receive the Gail test. We determined the cut points for the risk bands based on the conditional probability that the 7SNP test changes a patient's risk category by moving them across the 20% threshold, given their lifetime risk on the Gail test. We chose cutoff values of 1%, 3%, 10%, 25%, and 30% for this probability, defining five concentric risk bands (Table 4). The reason for this design is that patients only benefit from the 7SNP test if it changes their risk category, which is more likely if they are closer to the cutoff point of 20%. Thus trial arms with narrower bands restrict the 7SNP test to those patients who are most likely to benefit from the test. Those with wider bands benefit more patients, but are less efficient in terms of the number of people who need to be tested in order for one person to be recategorized. As an additional control, we also include a mammogram arm, in which all patients receive annual mammogram regardless of their risk.

Table 4. Risk bands

Risk range (%)	Probability of change (%)	Fraction of population (%)
10–38	1	50.3
12–36	3	36.9
14–32	10	15.4
16–28	25	10.8
18–26	30	6.7

NOTE: These are based on a patient's lifetime Gail risk. Each band defines a strategy where only patients within the band receive the 7SNP test. The bands are chosen based on the probability that a patient within the band has their risk category changed by the 7SNP test. The table also lists the percentage of the total population (before truncating those below 10% lifetime Gail risk) within each band.

In all trial arms, screening stops at the age of 75, but the simulation continues until death. Each patient is run through all the trial arms, eliminating differences that are solely due to random sampling error in the assignment of participants to trial arms. We assume that adherence to the screening regime is perfect across all trial arms.

Model outputs and analysis

The primary outputs of the model are total deaths from breast cancer, total (discounted) costs, and total (discounted) quality-adjusted life years (QALY). From these outputs, we calculate the incremental reduction in mortality and the incremental cost-effectiveness ratio (ICER) of the Gail and 7SNP strategies. Each strategy is compared with the previous most effective strategy, so incremental values for Gail are computed relative to mammogram, incremental values for the narrowest risk band are computed relative to Gail, and incremental values for subsequent risk bands are computed relative to the previous band.

Sensitivity Analysis

We performed a one-way sensitivity analysis on a number of key parameters. We varied the costs of the 7SNP test, mammogram, MRI, diagnostic test, and cancer treatment, and the disutilities of cancer each by ±40%. We reduced the discounting rate to 0% and doubled it to 6%. Finally, we changed the starting age from 40 to 50 years.

Results

Risk distribution

Before truncating those below 10%, the average lifetime risk of invasive cancer for 40-year-old patients was 11.3% according to both the Gail risk test and the 7SNP test. The SD was 0.041 for the former and 0.054 for the latter. Although the 7SNP test has the same mean, the higher SD leads to a greater number of people above the 20% threshold (Fig. 1). The percentage of people with a lifetime risk of invasive cancer greater than 20% was 1.95% for the Gail test and 6.31% for the 7SNP test. We validated this distribution against an estimated distribution based on the 2000 and 2005 National Health Interview Survey (34). In this dataset, the percentage of people ages 40 to 49 years with a risk of more than 20% was 1.57%, with a 95% confidence interval of (1.21%–2.03%). Thus, the estimate from the model falls within this confidence interval. We also computed the conditional probability that the 7SNP test changes a patient's risk category given their initial risk on the Gail test (Fig. 2),

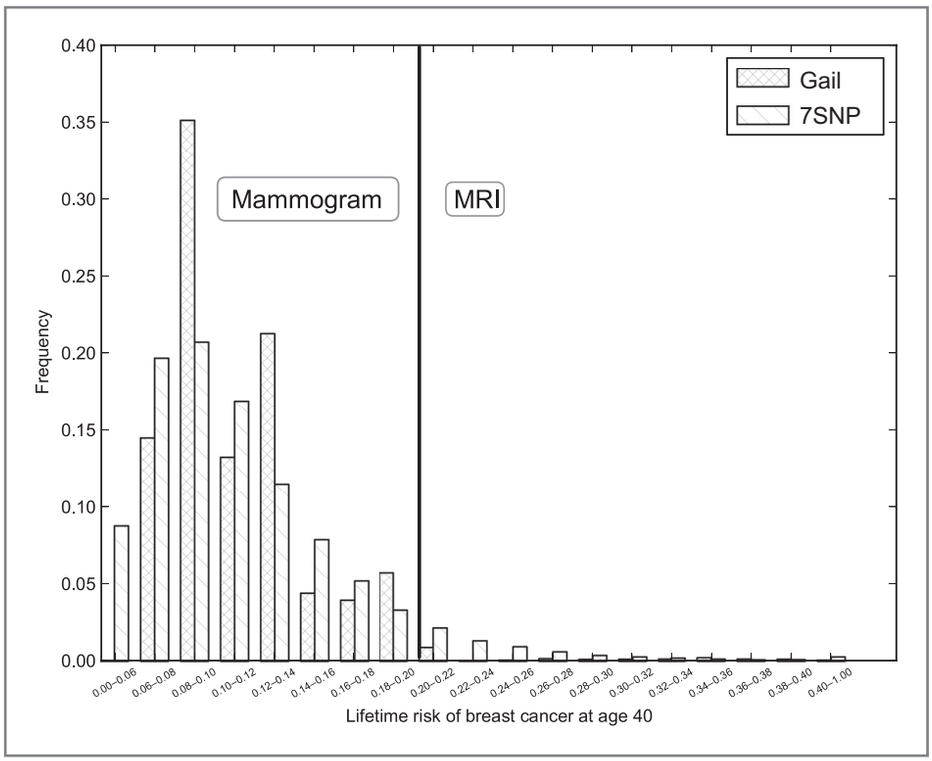

Figure 1. The distribution of lifetime risk of breast cancer as reported by the Gail test (double-hatched) and 7SNP combination test (single-hatched). The vertical bar at 0.2 shows the risk cutoff value. Patients to the left of this bar receive annual mammogram and patients to the right receive annual MRI.

and used this probability to determine the ranges of the five risk bands (Table 4).

Base case analysis

The total number of breast cancer deaths per 100,000 was 2,945 for mammogram, 2,928 for Gail, and ranged from 2,889 for the narrowest band to 2,850 for the widest band in the intervention arms (Table 5). The narrowest band, 18–26, had the highest incremental reduction in cancer deaths, 1.33%. The 14–32 band was weakly dominated. The incremental costs per QALY of the remaining bands were $141,415 for Gail, $162,840 for 18–26, $163,988 for 16–28, $454,186 for 12–36, and $634,133 for 10–38 (Table 5; Fig. 3). The 18–26 band was nearly weakly dominated, because its cost per QALY is only very slightly less than that of 16–28. The costs per QALY of the 12–36 and 10–38 bands are very high. This leaves 16–28 as the most efficient band to receive the 7SNP test. The cost per QALY of this band relative to Gail is $163,264.

Sensitivity analysis

The ICERs were most sensitive to the starting age, followed by the discount rate, the costs of the 7SNP test and MRI, and the cancer disutility (Fig. 4). They were not sensitive to the cost of mammogram, cancer treatment, or diagnostic tests. The 18–26 band was dominated in three alternative scenarios. When the start age was increased to 50 years, the 18–26 and 16–28 risk bands were both dominated, and the 14–32 band was not. Thus, if screening is done at the age of 50 instead of 40, a wider risk band should be used.

Discussion

We have used an individual-based simulation model to evaluate the cost-effectiveness of the 7SNP genetic test for breast cancer risk in conjunction with MRI screening for patients with a lifetime risk of greater than 20%, as recommended by the guidelines of the ACS (6). This genetic test gives a relative risk, which multiplies the patient's risk on the Gail risk test (7), to refine the estimate of her risk. The 7SNP test does not affect the mean of the risk distribution, but increases its variance. Depending on how many high-risk alleles they have, some patients will have their risk reduced, and others will have it increased. This is clinically desirable because it gives us a better estimate of which patients are most likely to benefit from screening with MRI. The net effect is that about 6% of the population falls in the high-risk category of greater than 20% risk, compared with only 2% for the Gail test alone.

However, for most patients, it is unlikely that the 7SNP test changes their risk category. Therefore, we limit its application to only those patients who are most likely to have their risk category changed. We defined a series of five concentric risk bands around 20%, based on the minimum probability that the 7SNP test changes a patient's screening category from the Gail test alone. Narrower bands with a higher minimum probability apply the test to fewer people, but have a lower cost per QALY. The 16–28 band is particularly cost-effective. This band is based on a minimum probability of 25% of switching risk categories and includes approximately 11% of the population. With a cost per QALY of $163,264 relative to Gail, it is only slightly less cost-

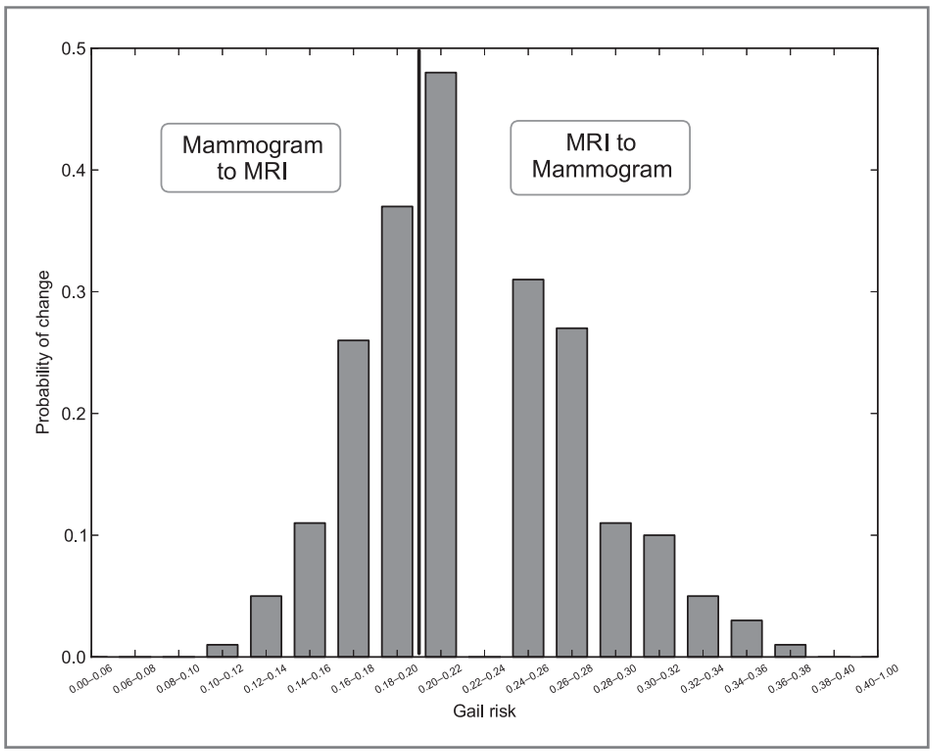

Figure 2. The probability that the 7SNP test changes a patient's risk category, given their initial risk on the Gail test. The vertical bar at 0.2 shows the risk cutoff. Patients to the left may have their screening test changed from mammogram to MRI, and patients to the right may have their test changed from MRI to mammogram. No patients were found with a Gail risk between 22% and 24%, so this space is left blank.

effective than the Gail alone strategy, which had a cost per QALY of $141,415. However, the exact cut points of this band are sensitive to the age at which lifetime risk is calculated. These results suggest that although universal genetic screening may not be cost effective, screening those patients with an intermediate risk near 20% is relatively efficient. This conclusion is similar to that of Mealiffe and colleagues (14) that the efficiency of the 7SNP test is improved by limiting the test to those at intermediate risk near the cut points of categories.

Several other modeling studies have estimated the cost effectiveness of MRI screening (35–37). Plevritis and colleagues (35) found a cost of $154,654 per QALY to screen *BRCA1* carriers with MRI from the age of 30 to 64 and a cost of $209,585 to screen *BRCA2* carriers with MRI from the age of 35 to 69, with a discount rate of 3%. Moore and colleagues (36) found a cost of MRI screening of $179,599 per QALY for women over the age of 25 with a risk of greater than 15% on the Claus tables, with a discount rate of 5%. Lee and colleagues (37) found a cost of MRI screening of $69,125 per QALY to screen 25-year-old *BRCA1* mutation carriers, with a discount rate of 3%. When comparing our results with the two studies that focused on *BRCA* mutation carriers (35, 37), two important considerations must be kept in mind. First, the lifetime risk for carriers of mutations in *BRCA1* and *BRCA2* are 65% and 45%, respectively, whereas this analysis used a threshold of 20%. Screening on a more high-risk population will result in a lower cost per QALY, but with results that are applicable to a smaller

Table 5. Base case results

Trial arm	Cancer deaths	Reduction	QALYs	Costs ($)	ICER ($/QALY)
Mammogram	2,945	N/A	2,313,731	629,297,039	N/A
Gail	2,928	0.58%	2,314,046	673,868,793	141,415
7SNP, 18–26	2,889	1.33%	2,314,360	724,967,343	162,840
7SNP, 16–28	2,872	0.59%	2,314,543	755,078,514	163,988
7SNP, 14–32	2,871	Dominated	2,314,548	775,618,753	Dominated
7SNP, 12–36	2,855	0.59%	2,314,736	842,856,745	454,186
7SNP, 10–38	2,850	0.18%	2,314,780	870,639,365	634,133

NOTE: These include the absolute number of cancer deaths, incremental percent reduction, absolute number of QALYs, absolute costs ($US), and the ICER.

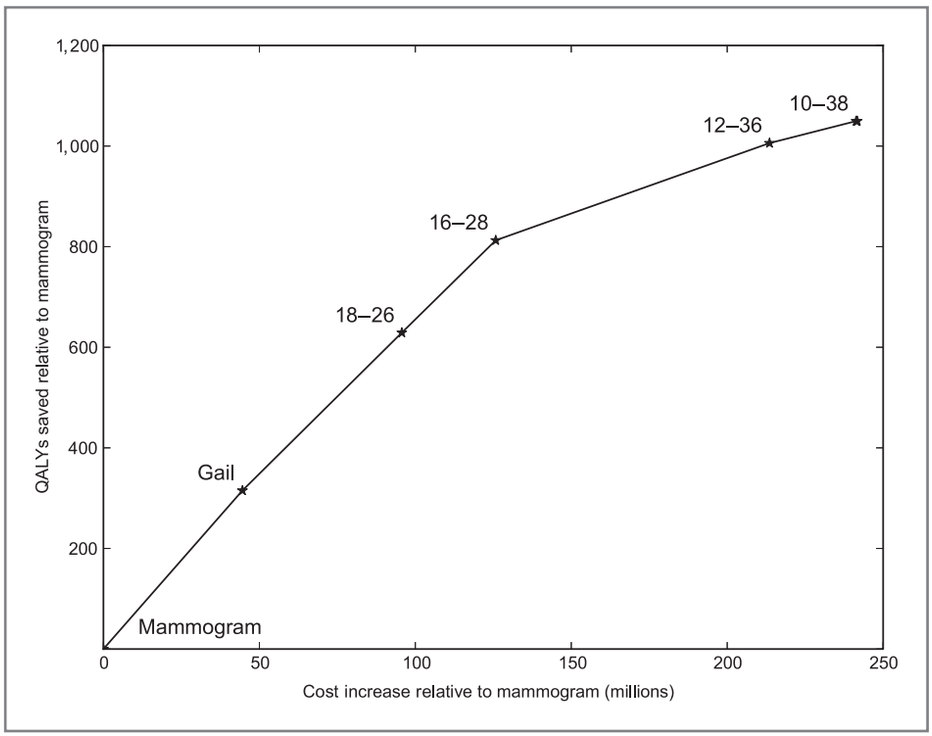

Figure 3. Efficient frontier for application of the 7SNP test. QALYs saved are plotted versus the cost increase of each strategy relative to mammogram. The top four strategies represent applying the 7SNP test to different risk bands in the population. The 14–32 band is dominated.

population. Second, the costs considered in these two models do not include the cost of the *BRCA* genetic test itself. We found that nearly half of the incremental cost was due to the cost of the genetic test, with the other half due to the greater number of MRIs. This is for a test with a cost of only $945, which is much lower than the cost of the *BRCA* test, which ranges from $3000 to $4000 (38, 39). If the costs of genetic testing were included in the evaluation of MRI screening for *BRCA* mutation carriers, the costs would no doubt be considerably higher. In

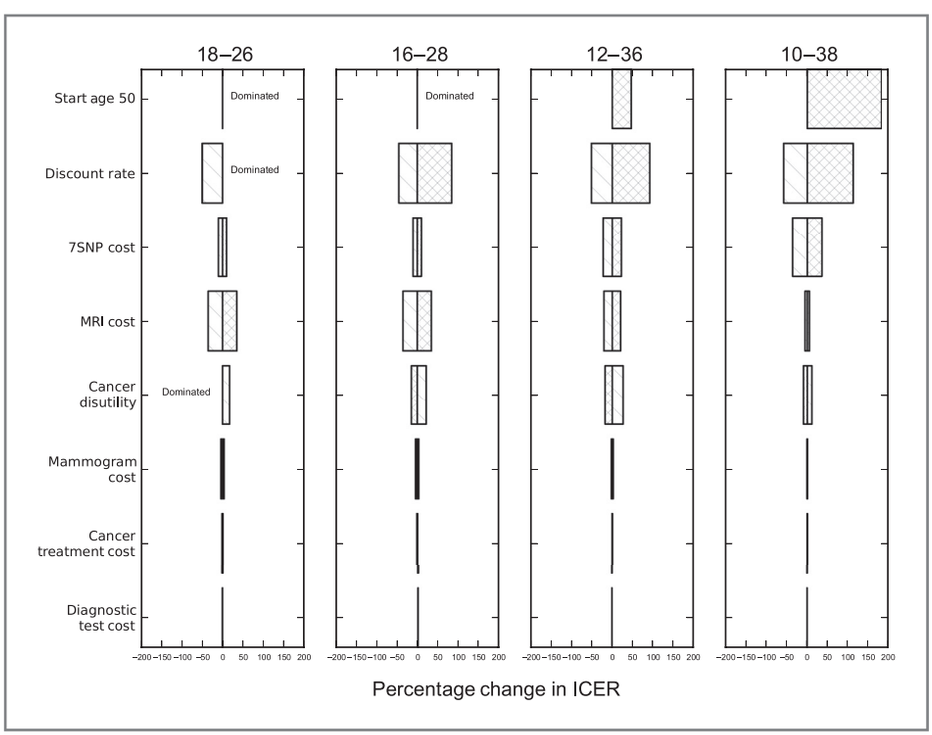

Figure 4. Results of the sensitivity analysis. This shows the percentage change in cost per QALY relative to base case for the four risk bands not dominated in the base case. Base case values for the four risk bands are $162,840 for 18–26, $163,988 for 16–28, $454,186 for 12–36, and $634,133 for 10–38 (see Table 5). These ICERs are computed relative to the previous most effective strategy. The start age was varied only to the age of 50 (double hatched). The discount rate was varied to 6% (double hatched) and 0% (single hatched). All other parameters were varied by +40% (double hatched) and −40% (single hatched). The parameters are ranked according to the absolute magnitude of their effect.

short, although the cost per QALY for the 7SNP test in conjunction with MRI does not fall below thresholds for what is normally considered cost-effective, it is comparable with other strategies recommended by the ACS guidelines.

Our model is subject to several limitations. First, it only applies to White women in the United States, because the data used to calculate the genetic risks and frequencies as well as the data used to parameterize the risk model are both based on predominantly White populations. However, as more genetic studies are performed on other racial and ethnic groups, that data can be incorporated into the model. Second, costs for screening procedures are parameterized using Medicare payments, but these may not accurately represent the true costs. Costs of cancer treatment are based on costs in 2007, and although they have been updated to 2012 dollars to account for inflation, they may still underestimate the current costs of cancer treatment. Third, the mammogram model is based on film mammography, but many centers have switched to digital mammography. Fourth, the model assumes that adherence to screening is perfect, whereas in reality, most women are not adherent to annual screening (40). One potential value of the genetic test is to promote adherence among high-risk women, but the model has not been parameterized to account for these benefits. Fifth, the model assumes that diagnostic tests have perfect sensitivity and specificity, whereas in reality, diagnostic tests may miss some cancers and incur additional costs due to false positives. This slightly exaggerates the effectiveness of screening overall, although the effect is the same across trial arms in this study. Sixth, the model accounts for only economic costs, and does not include the time cost or harm of mental anxiety to the patient due to false positives.

More generally, the effectiveness of treatment has increased over the past two decades, and is likely to continue to do so. As treatment becomes more effective, the relative importance of early detection is reduced. These facts raise broad questions for the relevance of screening for breast cancer, and guidelines will no doubt continue to evolve as technologies change. However, even if the guidelines were to no longer recommend screening for low- or intermediate-risk patients, it is unlikely that they would stop recommending screening for the high-risk patients that are the focus of this study. In fact, if new guidelines further emphasize the importance of risk stratification for screening policy, the relevance of the present study would be enhanced rather than diminished.

More generally still, this study illustrates that risk modeling may provide information that allows stratification of patients by disease risk, with alternate strategies of genetic testing, screening, and/or preventative treatment for different risk categories. In the present case, an initial round of inexpensive risk estimation was used to stratify patients roughly, and then a second round of more precise genetic testing was used for patients falling near the threshold of different treatment groups to refine risk estimates for these patients, with additional screening for patients still found to be at high risk. This iterative method of nested risk estimation and stratification helps to focus resources where they are most beneficial.

Disclosure of Potential Conflicts of Interest

H.J. Folse is employed as a consultant in Genetic Technologies. L.E. Green is a consultant/advisory board member of Archimedes, Inc. Genetic Technologies holds a patent on the Brevagen test, the genetic test for breast cancer risk modeled in this paper (although the branded name is not used). Archimedes, Inc. was contracted by Genetic Technologies to perform this research. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Development of methodology: H.J. Folse, L.E. Green, A. Kress, T.A. Dinh
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Kress, T.A. Dinh
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.J. Folse, A. Kress, T.A. Dinh
Writing, review, and/or revision of the manuscript: H.J. Folse, L.E. Green, A. Kress, R. Allman, T.A. Dinh
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.J. Folse, R. Allman, T.A. Dinh
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References

1. Easton DF, Pooley KA, Dunning AM, Pharoah PDP, Thompson D, Ballinger DG, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447:1087–93.
2. Stacey SN, Manolescu A, Sulem P, Rafnar T, Gudmundsson J, Gudjonsson SA, et al. Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor–positive breast cancer. Nat Genet 2007;39:865–9.
3. Stacey SN, Manolescu A, Sulem P, Thorlacius S, Gudjonsson SA, Jonsson GF, et al. Common variants on chromosome 5p12 confer susceptibility to estrogen receptor–positive breast cancer. Nat Genet 2008;40:703–6.
4. Pharoah PDP, Antoniou AC, Easton DF, Ponder BAJ. Polygenes, risk prediction, and targeted prevention of breast cancer. N Engl J Med 2008;358:2796–803.
5. Garcia-Closas M, Chanock S. Genetic susceptibility loci for breast cancer by estrogen receptor status. Clin Cancer Res 2008;14:8000–9.
6. Saslow D, Boetes C, Burke W, Harms S, Leach M, Lehman CD, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75–89.
7. Gail MH, Brinton LA, Byar DP, Corle DL, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81:1879–86.
8. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 1994;73:643–51.
9. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23:1111–30.

10. National Cancer Institute. Breast Cancer Risk Assessment Tool. National Cancer Institute; 2011. Available from: http://www.cancer.gov/bcrisktool/.
11. Gail MH. Discriminatory accuracy from single-nucleotide polymorphisms in models to predict breast cancer risk. J Natl Cancer Inst 2008;100:1037–41.
12. Gail MH. Value of adding single-nucleotide polymorphism genotypes to a breast cancer risk model. J Natl Cancer Inst 2009;101:959–63.
13. Wacholder S, Hartge P, Prentice R, Garcia-Closas M, Feigelson HS, Diver WR, et al. Performance of common genetic variants in breast-cancer risk models. N Engl J Med 2010;362:986–93.
14. Mealiffe ME, Stokowski RP, Rhees BK, Prentice RL, Pettinger M, Hinds DA. Assessment of clinical validity of a breast cancer risk model combining genetic and clinical information. J Natl Cancer Inst 2010; 102:1618–27.
15. Schlessinger L, Eddy DM. Archimedes: a new model for simulating health care systems—the mathematical formulation. J Biomed Inform 2002;35:37–50.
16. Kahn R, Alperin P, Eddy D, Borch-Johnsen K, Buse J, Feigelman J, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. Lancet 2010;375: 1365–74.
17. Noah-Vanhoucke J, Green LE, Dinh TA, Alperin P, Smith RA. Cost-effectiveness of chemoprevention of breast cancer using tamoxifen in a postmenopausal US population. Cancer 2011;117:3322–31.
18. Surveillance, Epidemiology, and End Results (SEER) Data, 1973–2007 [database on the Internet]. National Cancer Institute 2007.
19. Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, et al. The American cancer society cancer prevention study II nutrition cohort. Cancer 2002;94:2490–501.
20. Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail et al. model for predicting individual breast cancer risk. J Natl Cancer Inst 1994;86:600–7.
21. Centers for Disease Control and Prevention and National Center for Health Statistics. National Health and Nutrition Examination Survey Data 1999–2006. 2006 [cited 2008 September].
22. Pinsky PF, Kramer BS, Reding D, Buys S. Reported family history of cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Am J Epidemiol 2003;157:792–9.
23. NCI-funded Breast Cancer Surveillance Consortium (U01CA63740 UC, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, U01CA70040, HHSN261201100031C). 2009 [cited 2009 01/08]; Available from: http://breastscreening.cancer.gov/data/mammography_data.html.
24. Warner E, Messersmith H, Causer PA, Eisen A, Shumak R, Plewes DB. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med 2008;148:671–9.
25. Warner E, Plewes DB, Hill K, Causer PA, Zubovits JT, Jong RA, et al. Surveillance of *BRCA1* and *BRCA2* mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004;292:1317–25.
26. Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365:1769–78.
27. Kriege M, Brekelmans CTM, Obdeijn IM, Boetes C, Zonderland HM, Muller SH, et al. Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer. Breast Cancer Res Treat 2006;100:109–19.
28. Abramovici G, Mainiero MB. Screening breast MR imaging: comparison of interpretation of baseline and annual follow-up studies. Radiology 2011;259:85–91.
29. Services CfMaM. Physicians Fee Schedule. 2012 [cited 2012 Apr 12]; Available from: http://www.cms.gov/apps/physician-fee-schedule/.
30. Warren Burhenne LJ, Coldman AJ, Kan L, editors. Organized Breast Cancer Screening in British Columbia: The Screening Mammography Program of British Columbia. Seminars in Breast Disease; Elsevier; 2007.
31. Yabroff KR, Warren JL, Brown ML. Costs of cancer care in the USA: a descriptive review. Nat Clin Pract Oncol 2007;4:643–56.
32. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Med Decis Making 2006;26:410–20.
33. Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective cost-effectiveness analysis of screening mammography. J Natl Cancer Inst 2006;98:774–82.
34. Graubard BI, Freedman AN, Gail MH. Five-year and lifetime risk of breast cancer among U.S. subpopulations: implications for magnetic resonance imaging screening. Cancer Epidemiol Biomarkers Prev 2010;19:2430–6.
35. Plevritis SK, Kurian AW, Sigal BM, Daniel BL, Ikeda DM, Stockdale FE, et al. Cost-effectiveness of screening *BRCA1/2* mutation carriers with breast magnetic resonance imaging. JAMA 2006;295:2374–84.
36. Moore SG, Shenoy PJ, Fanucchi L, Tumeh JW, Flowers CR. Cost-effectiveness of MRI compared to mammography for breast cancer screening in a high risk population. BMC Health Serv Res 2009;9;9.
37. Lee JM, McMahon PM, Kong CY, Kopans DB, Ryan PD, Ozanne EM, et al. Cost-effectiveness of breast MR imaging and screen-film mammography for screening *BRCA1* gene mutation carriers. Radiology 2010;254:793–800.
38. Classe JS. Genes and the supremes: will the supreme court uphold patents for isolated gene sequences? Tex Tech L Rev 2013;45: 533–65.
39. Viswanathan KS, Lemaire J, Withers K, Armstrong K, Baumritter A, Hershey JC, et al. Adverse selection in term life insurance purchasing due to the *BRCA1/2* genetic test and elastic demand. J Risk Insur 2007;74:65–86.
40. Gierisch JM, Earp JA, Brewer NT, Rimer BK. Longitudinal predictors of nonadherence to maintenance of mammography. Cancer Epidemiol Biomarkers Prev 2010;19:1103–11.