

# Cost-effectiveness of population-based *BRCA1/2* testing and ovarian cancer prevention for Ashkenazi Jews: A call for dialogue

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**Purpose:** About half of unaffected *BRCA1/2* carriers have a negative family history, confounding efforts toward presymptomatic carrier identification. Ovarian cancer is preventable for known carriers but is otherwise highly lethal. Cost-effectiveness and gains in life expectancy are important factors in evaluating the desirability of population-based genetic screening, currently the only viable strategy to identify carriers with unrevealing family histories. **Methods:** Cost-utility analysis for a population-based genetic screening program offered to American Ashkenazi Jewish women aged 35–55 years measuring cancer incidence, life expectancy, and cost. **Results:** Our model predicts that a genetic screening program would result in 2811 fewer cases of ovarian cancer, with a life expectancy gain of 1.83 quality-adjusted life years among carriers. At a cost of \$460 for founder mutation testing, the cost of the program is \$8300 (discounted) per year of quality-adjusted life gained. **Conclusion:** In populations with a high prevalence of *BRCA1/2* founder mutations, genetic screening may be cost-effective when compared with recommended public health interventions such as mammographic screening. We advocate the initiation of a dialogue among Jewish stakeholders, genetics professionals, and public health leaders to determine whether a population-based *BRCA1/2* genetic screening program should be pursued. *Genet Med* 2009;11(9):629–639.

**Key Words:** *BRCA1*, *BRCA2*, decision analysis, ovarian carcinoma, population-based genetic screening

An inherited predisposition to hereditary breast and ovarian cancer should be heralded by a strong cancer family history, but surprisingly often, it is not. Incomplete penetrance, sex-limited expression, limited family structure, and incomplete family history information all contribute to the frequent observation of hereditary cancer cases, which lack premonitory clues. Female *BRCA1/2* carriers who are unaware of their genetic status cannot undertake recommended measures such as early mammography and breast magnetic resonance imaging (MRI)

or avail themselves of risk-reducing salpingo-oophorectomy after completion of childbearing. Women with nonscreen detected, early-onset breast cancer and those who develop ovarian cancer can be expected to face much higher morbidity and mortality than if they were undergoing high-risk management.

An underlying assumption in clinical cancer genetics is that by maximizing the efficiency of the referral pipeline through such means as physician and patient education and computerized family history tools, most unaffected *BRCA1/2* carriers could be identified before developing cancer. High-risk management could then be instituted in a family-centered manner to reduce the cancer burden. Although this holds true for families with recognizable features of hereditary cancer, several studies suggest that about half of all *BRCA1/2* families cannot be identified using this approach.<sup>1–8</sup>

*BRCA1/2* mutation prevalence rates have been measured in several population-based series of incident breast or ovarian cancer cases, which were unselected for family history. Cases with germline *BRCA1/2* mutations were then analyzed regarding family history of breast and ovarian cancer. In a New-York-based study of 1008 Ashkenazi Jewish women with breast cancer unselected for age or family history, 104 had *BRCA1/2* founder mutations; of these carriers, only 52 (50%) had any family history of breast or ovarian cancer among the first or the second degree relatives.<sup>1</sup> Studies of early-onset breast cancer, unselected for family history, in British,<sup>2</sup> Spanish,<sup>3</sup> Dutch,<sup>4</sup> Australian,<sup>5</sup> Norwegian,<sup>6</sup> Swedish,<sup>7</sup> and Polish<sup>8</sup> populations have found that 43%–72%<sup>5</sup> of cases have no family history of breast or ovarian cancer within one, two, or three degrees of relationship. In a population-based study of 232 incident ovarian cancer cases in Florida, a family history of breast or ovarian cancer was absent in 31% of *BRCA1/2* carriers.<sup>9</sup>

Population-based genetic screening is currently the only feasible way to gain prior knowledge of *BRCA1/2* mutation status in asymptomatic carriers with unrevealing family histories. Here, we examine the effect of a population-based genetic screening program on cancer incidence, life expectancy, and costs in the Ashkenazi Jewish population where the mutation prevalence rate is high, founder mutations account for a large proportion of mutations, relatively low-cost genetic testing is available, and historical acceptance of genetic testing is high. We restrict our analysis to the effect of a genetic screening program on ovarian cancer surgical prevention and treatment because no effective surveillance methods exist; most cases present at an advanced stage; there is a high burden of suffering because of low survival and high morbidity<sup>10</sup>; treatment costs are high; surgical prevention is very effective with moderate patient acceptance; and prevention costs are low. Additional benefits and costs will result from breast MRI once it is routinely implemented. Decision analyses incorporating breast cancer outcomes must await the attainment of more experience with screening uptake, effect on uptake of risk-reducing surgeries, and costs.

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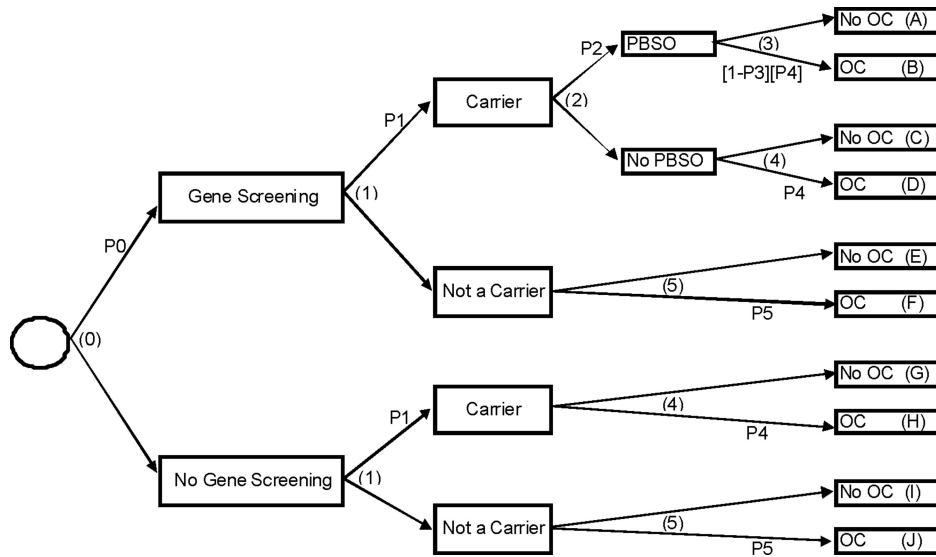
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**Fig. 1.** Decision tree. Numbers in parentheses at branch points refer to nodes in Table 1. Probabilities for specific nodes are marked as P0, P1, etc. Letters A–J in boxes at right-hand margin correspond to the branches in Table 3. OC, ovarian cancer and PBSO, prophylactic bilateral salpingo-oophorectomy.

This cost-utility analysis fits within a larger framework for public health policy on genetic screening for adult-onset conditions<sup>11,12</sup> in that we assess the balance between the costs of case finding in relation to possible expenditure on medical care. Although a favorable cost-benefit analysis would suggest that population-based genetic screening might be beneficial, there are many additional elements of evidence that would also require evaluation. An important part of public dialogue would be to determine the mode of program delivery, which will influence program uptake, costs and ultimate outcomes, the ability to measure outcomes, and whether a clinical trial should first be initiated. Consensus building with stakeholders, policy development and a framework for program delivery, and evaluation spanning the T1 to T4 translational continuum<sup>12</sup> would all be obligatory before embarking on a genetic screening program.

**MATERIALS AND METHODS**

We performed a decision analysis in the context of a population-based genetic screening program offered to Ashkenazi Jewish women aged 35–55 years in the United States. The overall goal of this analysis was to estimate three outcome measures: (a) the proportion of ovarian cancer diagnoses prevented by the program (cancer incidence), (b) the number of quality-adjusted life-years (QALY) gained by the program (life expectancy), and (c) the discounted cost of the program per QALY (cost). Averages of these measures were calculated on a per-person (in the total population) basis and then applied to the entire population of Ashkenazi Jewish women in the United States.

Effects of the screening program on the entire population of Ashkenazi Jewish women in the United States are calculated based on the estimated US total population of Ashkenazi Jews and the US Census data from the year 2000<sup>13</sup> on the number of women aged 35–55 years. The total population of Ashkenazi Jews in the United States is approximately 6.4 million.<sup>14</sup> There may be a wide margin of error in this figure. Approximately 90–95% American Jews are of Ashkenazi (eastern European)

origin.<sup>15</sup> The estimated percentage of all US females in the age range of 35–55 years is 30.12%. Thus, we estimate the number of American Ashkenazi Jewish females aged 35–55 years to be about 963,840.

**The model**

Women aged 35–55 years were selected for consideration because childbearing is completed within this age range, age-related competing mortality rates are not high, and women commonly present in this age range for clinical cancer risk counseling and genetic testing. Women who will have genetic testing in the absence of a screening program based on high familial risk, reflecting the current situation, are excluded in the analysis. Figure 1 shows the decision tree and describes the general choices that would be available to women if a genetic screening program existed. Table 1 defines the probabilities in the decision tree. For the purposes of explaining and interpreting the model, our best estimates of the probabilities, supported by references, are given in Table 1 and are inserted into the model. Other values for these probabilities are also evaluated after the model has been described. In Figure 1, an individual decision point is called a “node,” and any pathway through the decision tree is called a “branch.” Statistical calculations were done using R programming software.

**Cancer incidence**

The upper pathways in Figure 1 in the “gene screening” section reflect the choice of having genetic testing (irrespective of family history) through a mass screening program when such a program exists, as determined by the screening program participation rate P0. The lower pathways in the “no gene screening” section reflect the choice of not having genetic testing when a mass screening program exists, which is 1 – P0. The population mutation carrier rate (P1) is 0.025.<sup>16–19</sup> We do not differentiate between the value of P1 for gene screening and no gene screening but recognize that to the extent that family history is a motivating factor; the observed carrier rate may be higher than 0.025 in the gene screening pathway and lower in

**Table 1** Parameters used in the decision analysis

Node	Parameter	Value <sup>a</sup>	Source
0	Screening program participation rate: (P0)	0.90	Richards et al. <sup>29</sup>
1	Mutation carrier rate: (P1)	0.025	Roa et al. <sup>16</sup> Struewing et al. <sup>19</sup> Struewing et al. <sup>17</sup> Hartge et al. <sup>18</sup>
2	Probability that a carrier will follow-up with PBSO: (P2)	0.50	Rebbeck et al. <sup>20</sup> Finch et al. <sup>21</sup> Kauff et al. <sup>22</sup>
3	Amount of reduction due to PBSO in the probability that a carrier will get ovarian cancer: (P3)	0.96	Kauff et al. <sup>22</sup> Rebbeck et al. <sup>25</sup>
4	Probability that a carrier without PBSO will get ovarian cancer: (P4)	0.27	Chen et al. <sup>27</sup>
5	Probability that a noncarrier will get ovarian cancer: (P5)	0.0144	2001–2003 SEER <sup>28</sup>

<sup>a</sup>Best estimates of model probabilities. See text for alternate values evaluated.

the no gene screening pathway. We treat each subsequent node identically in these two pathways, except for the addition of a node for prophylactic bilateral salpingo-oophorectomy (PBSO; also called risk-reducing salpingo-oophorectomy) for women who found to be carriers after testing.

The probability that a 40-year-old woman *BRCA1/2* mutation carrier will undergo PBSO (P2) ranges from 0.34 to 0.57 among studies,<sup>20–22</sup> and a probability of 0.50 is used. The observed rate may be closer to 0.68 in *BRCA1/2* carriers aged 40 years and older<sup>23</sup> but could be lower in a genetic screening program. Similarly, a single-site high-risk clinic-based study with a long period of follow-up also found a 70% PBSO uptake rate with a median age of surgery of 44 years.<sup>24</sup> We vary P2 from 0.35 to 0.68 in evaluating the model's outcome measures. The effect of PBSO on reducing ovarian cancer risk (P3) is taken as 0.96, a rate reflected by most studies.<sup>22,25</sup> A lower risk reduction of 0.80<sup>21</sup> is also examined.

The probability that a mutation carrier who does not undergo PBSO will develop ovarian cancer, P4 (more commonly known as the lifetime penetrance), is a key determinant of the outcome of this decision analysis. Although reduced penetrance might be expected in families ascertained through population-based studies, the New York<sup>1</sup> and Norwegian<sup>6</sup> studies found this not to be the case. However, others have shown that population penetrance estimates can be inflated by the use of single incident cases of breast or ovarian cancer.<sup>26</sup> P4 is taken as 0.27 based on a meta-analysis involving Jewish and non-Jewish families, which reported a lifetime ovarian cancer penetrance of 40% for *BRCA1* carriers and 18% for *BRCA2* carriers.<sup>27</sup> In the Ashkenazi Jewish population, 1% are *BRCA1* carriers and 1.5% are *BRCA2* carriers<sup>16–18</sup>; therefore, the weighted ovarian cancer penetrance is  $0.40 \times 1/2.5 + 0.18 \times 1.5/2.5 = 0.27$ . We vary P4 among 0.16, 0.27, and 0.35 to reflect the wide range of

penetrance figures that have been reported. The lower value of 0.16 for P4 is taken from a large population-based genetic screening program of Ashkenazi Jewish individuals.<sup>17</sup> The higher value of 0.35 for P4 is derived from a population-based study of Ashkenazi Jewish women with breast cancer,<sup>1</sup> which genotyped relatives to estimate penetrance, leading to smaller standard errors than seen in most population-based studies (weighted ovarian cancer penetrance =  $0.54 \times 1/2.5 + 0.23 \times 1.5/2.5 = 0.35$ ).

The probability that a noncarrier will develop ovarian cancer (P5) is taken as 0.0144 as per Surveillance, Epidemiology and End Results (SEER) program data.<sup>28</sup> Once all the parameters have been set, the probability of developing ovarian cancer is obtained by summing the probabilities of all the "OC" branches.

To evaluate the model for a range of probabilities in the model, the following set of model probabilities were used:

Node (0): Screening program participation rate: P0 = 0.1, 0.2, 0.3, 0.4, 0.5, 0.7, 0.7, 0.8, 0.9,<sup>29</sup> and 1.0.

Node (1): Carrier rate of mutation: P1 =  $1/40 = 0.025$ .<sup>16–19</sup>  
Node (2): The probability that a 35–55-year-old mutation carrier will follow-up with PBSO treatment: P2 = 0.35, 0.50,<sup>20–22</sup> and 0.68.

Node (3): The probability that a mutation carrier after PBSO treatment will develop ovarian cancer: P4(1 – P3), where P3 = 0.80, 0.96 is the risk reduction parameter with PBSO treatment, and P4 is defined below.

Node (4): The probability that a mutation carrier without PBSO treatment will develop ovarian cancer: P4 = 0.16,<sup>17</sup> 0.27,<sup>27</sup> and 0.35.<sup>1</sup>

Node (5): The probability that a noncarrier will develop ovarian cancer: P5 = 0.0144.

## Life expectancy

Among available data to estimate the mean age at diagnosis of ovarian cancer,<sup>1,17,30</sup> we chose the study of Boyd et al.<sup>30</sup> where the average age at diagnosis of ovarian cancer is 54 years for *BRCA1* carriers, 62 years for *BRCA2* carriers, and 63 years for sporadic ovarian cancer. In the Ashkenazi Jewish population, 1% are *BRCA1* carriers, and 1.5% are *BRCA2* carriers<sup>16–18</sup>; therefore, the average age at ovarian cancer diagnosis is  $54 \times 1/2.5 + 62 \times 1.5/2.5 = 58.8$  years.

Life expectancy is derived from the National Vital Statistics Reports 2003 United States Life Tables,<sup>31</sup> wherein a 40-year-old woman has a life expectancy of 81.5 years. For mortality rate calculations, we assume (as did Anderson et al.<sup>32</sup>) that *BRCA1* and *BRCA2* carriers who develop ovarian cancer have the same conditional probability of death as women with ovarian cancer in the general population. Several reports indicate that *BRCA1/2*-related ovarian cancers have improved survival, but others do not find this effect.<sup>33</sup> Potential differences in ovarian cancer survival between *BRCA1* and *BRCA2* carriers<sup>34</sup> are not considered in our model. We use the SEER 2004 data, in particular the ovarian cancer survival rates for the year 1994 of diagnosis, which is 38.4%.<sup>35</sup> We assume that the survival rate is uniformly distributed within each year, and that the ovarian cancer patients who survive 10 years beyond the initial diagnosis will have the same survival rate as the general population. For example, if a 40-year-old woman is diagnosed with ovarian cancer at the age of 63 years, then the life expectancy (using 1994 data) is  $(63-40) + (0.5 \times [100-72.3]) + 1.5 \times [72.3-61.5] + 2.5 \times [61.5-54.4] + 3.5 \times [54.4-48.6] + 4.5 \times [48.6-46.1] + 5.5 \times [46.1-42.8] + 6.5 \times [42.8-41.2] + 7.5 \times [41.2-40.6] + 8.5 \times [40.6-39.1] + 9.5 \times [39.1-38.4] + [81.5-63] \times 38.4/100 = 31.422$  years.

**Table 2** Costs

Procedure	Cost	Source
Gene test	\$460	Myriad genetics, on file
PBSO treatment	\$4,622	Anderson et al. <sup>32</sup>
Ovarian cancer treatment	\$55,323	Anderson et al.
Yearly cost <sup>a</sup>	\$10,055	Anderson et al.
Terminal care costs, last year of life		
With ovarian cancer	\$38,743	Anderson et al.
Without ovarian cancer	\$28,787	Anderson et al.

<sup>a</sup>After the initial ovarian cancer treatment—follow-up examinations and tests

**Cost**

Costs are summarized in Table 2 and are derived as follows. The commercial cost of genetic testing for the three Ashkenazi Jewish founder mutations is \$460 (data on file, Myriad Genetic Laboratories, Inc.), and we use this value. Genetic testing can be accomplished at a lower cost of about \$50–200 in private laboratories (Karen Kaul, personal communication). Thus, if licensing at a lower cost or a discounted commercial cost were negotiated, the cost-effectiveness of a mass screening program would be dramatically higher than we report. The costs of PBSO (\$4,622), initial ovarian cancer treatment (\$55,323), yearly cost after initial treatment, follow-up examination and

tests (\$10,055), and terminal care costs in the last year of life with ovarian cancer (\$38,743) and without ovarian cancer (\$28,787) are taken from the study of Anderson et al.<sup>32</sup> (Medicare payments in 1995 reflecting costs). Note that if a person is diagnosed with ovarian cancer at the age of 60 years and dies at the age of 72 years, then the cost of cancer treatment is computed as  $\$55,323 + (72 - 60 - 1) \times \$10,055 + \$38,743 = \$204,671$ . Costs are discounted at a rate of 3% per year.

**RESULTS**

**Model outcomes**

Table 3 gives a summary of the model’s outcome measures for the model probabilities assumed in Table 1. These outcomes include the probability of the outcome, life expectancy, quality-adjusted life expectancy, cost, and discounted cost. The outcomes are given per woman in the US Ashkenazi Jewish female population aged 40 years and for that entire population of 963,840 Ashkenazi Jewish women aged 35–55 years.

**Cancer incidence**

Table 3 indicates that there is a 0.292% lowering of ovarian cancer incidence because of the gene screening program, resulting in 2811 fewer cases of ovarian cancer. These numbers assume a fixed cohort is followed through life, when in fact, numerous staggered cohorts will actually exist in the population at any point in time. These numbers apply to any parts or combinations of cohorts of total size about 1 million who proceed through the life cycle from 35 years to death.

**Table 3** Model outcomes for best estimates of model probabilities, P0 = 0.9, P1 = 0.025, P2 = 0.50, P3 = 0.96, P4 = 0.27, P5 = 0.0144, for a 40-year-old woman

Branch	Probability	LE	QALE	DCOST	
				Test cost = \$460	Test cost = \$50
A. GS, carrier, PBSO, no OC	0.01113	41.5000	41.5000	\$13,650	\$13,240
B. GS, carrier, PBSO, OC	0.00012	28.8348	25.7697	\$104,593	\$104,183
C. GS, carrier, no PBSO, no OC	0.00821	41.5000	41.5000	\$9,028	\$8,618
D. GS, carrier, no PBSO, OC	0.00304	28.8348	25.7697	\$99,971	\$99,561
E. GS, noncarrier, no PBSO, no OC	0.86486	41.5000	41.5000	\$9,028	\$8,618
F. GS, noncarrier, no PBSO, OC	0.01264	31.4220	28.8246	\$82,552	\$82,142
G. No GS, carrier, no OC	0.00183	41.5000	41.5000	\$8,568	\$8,568
H. No GS, carrier, OC	0.00068	28.8348	25.7697	\$67,774	\$67,774
I. No GS, noncarrier, no OC	0.09610	41.5000	41.5000	\$8,568	\$8,568
J. No GS, noncarrier, OC	0.00140	31.4220	28.8246	\$82,092	\$82,092
Outcome under screening program	0.01787	41.3099	41.2617	\$10,393	\$10,024
Outcome under no screening program	0.02079	41.2730	41.2159	\$10,000	\$10,000
Effect of screening program in one woman	-0.00292	0.0369	0.0459	\$394	\$25
Effect of screening program in population	-2,811	35,596	44,211	\$366,960,558	\$11,303,598

Also included is the effect of the screening program on these outcomes for one woman in the population and for the total population of 963,840 women. Branches A–J can be visualized in Figure 1.

Probability, probability of ovarian cancer occurrence (negative numbers mean lower with screening); LE, life expectancy in years; QALE, quality-adjusted life expectancy in years (positive numbers mean higher with screening); DCOST, discounted cost at a rate of 3% per year (positive numbers mean higher with screening); GS, gene screening; PBSO, prophylactic bilateral salpingo-oophorectomy; OC, ovarian cancer.

**Table 4** The percentage of women who will be saved from having ovarian cancer when the population wide gene screening program is available

P2	P3	P4	P0 = 0.1	P0 = 0.2	P0 = 0.3	P0 = 0.4	P0 = 0.5	P0 = 0.6	P0 = 0.7	P0 = 0.8	P0 = 0.9	P0 = 1.0
0.35	0.80	0.16	0.011	0.022	0.034	0.045	0.056	0.067	0.078	0.090	0.101	0.112
		0.27	0.019	0.038	0.057	0.076	0.095	0.113	0.132	0.151	0.170	0.189
		0.35	0.024	0.049	0.074	0.098	0.123	0.147	0.172	0.196	0.220	0.245
	0.96	0.16	0.013	0.027	0.040	0.054	0.067	0.081	0.094	0.108	0.121	0.134
		0.27	0.023	0.045	0.068	0.091	0.113	0.136	0.159	0.181	0.204	0.227
		0.35	0.029	0.059	0.088	0.118	0.147	0.176	0.206	0.235	0.265	0.294
0.50	0.80	0.16	0.016	0.032	0.048	0.064	0.080	0.096	0.112	0.128	0.144	0.160
		0.27	0.027	0.054	0.081	0.108	0.135	0.162	0.189	0.216	0.243	0.270
		0.35	0.035	0.070	0.105	0.140	0.175	0.210	0.245	0.280	0.315	0.350
	0.96	0.16	0.019	0.038	0.058	0.077	0.096	0.115	0.134	0.154	0.173	0.192
		0.27	0.032	0.065	0.097	0.130	0.162	0.194	0.227	0.259	0.292	0.324
		0.35	0.042	0.084	0.126	0.168	0.210	0.252	0.294	0.336	0.378	0.420
0.68	0.80	0.16	0.022	0.044	0.065	0.087	0.109	0.131	0.152	0.174	0.196	0.218
		0.27	0.037	0.073	0.110	0.147	0.184	0.220	0.257	0.294	0.330	0.367
		0.35	0.048	0.095	0.143	0.190	0.238	0.286	0.333	0.381	0.428	0.476
	0.96	0.16	0.026	0.052	0.078	0.104	0.131	0.157	0.183	0.209	0.235	0.261
		0.27	0.044	0.088	0.132	0.176	0.220	0.264	0.308	0.353	0.397	0.441
		0.35	0.057	0.114	0.171	0.228	0.286	0.343	0.400	0.457	0.514	0.571

Percentages are given as a function of P0 (screening program participation rate), P2 (rate of carrier having PBSO), P4 (rate of ovarian cancer in carrier without PBSO) and P3 (reduction in rate of ovarian cancer in carrier with PBSO). Note that the rate of ovarian cancer in a carrier with PBSO is  $P4 \times (1 - P3)$ .

Next, we examined the effects of a range of probability settings for the model on the chance of developing ovarian cancer. Table 4 describes the effects of screening program participation rate (P0) on the percent of women saved from having ovarian cancer and reports sensitivity to estimates of probabilities P2, P3, and P4. The numbers in this table are the difference in percent of women who would be expected to get ovarian cancer, where the difference is calculated as percent without program—percent with program, i.e., “0.292” means 0.292% of women are saved from having ovarian cancer. The table indicates that the effectiveness of the program (size of the difference in Table 4) increases as: (a) participation in the program (P0) increases; (b) PBSO rate after a positive screen (P2) increases; (c) chance of ovarian cancer in a carrier after PBSO ( $1 - P3$ ) decreases; and (d) chance of ovarian cancer in a carrier with no PBSO (P4) increases.

Taking the values of P0 through P5 that are specified in Table 1, the estimated percentage of women saved from ovarian cancer is about 0.292%. As noted, if the whole population of Ashkenazi Jewish women aged 35–55 years is 963,840, then 2,811 women will be saved from having ovarian cancer.

All ovarian cancer incidence prevented by the screening program occurs in the carriers. If the above percentage of ovarian cancer prevented were reported only for carriers, then there would be an incidence of 15.34% with a screening program and 27% without the screening program for a savings of 11.66%, which would translate into the same number of 2811 women because these savings are applied to the smaller population of carriers.

The effects of modifying parameters P0 through P5 are considerable. For example, if the participation rate P0 is increased from 90 to 100% and the chance that a carrier will have PBSO is increased from 50 to 68% and the chance that a carrier without PBSO will have ovarian cancer is increased from 27 to 35%, then the percentage of ovarian cancers prevented from Table 4 is 0.571%, which represents 5504 women.

**Life expectancy**

We examined the prolongation in average survival taking into account gene screening versus no gene screening. Assume the average life expectancy for the general population of American Ashkenazi Jews is 81.5 years.<sup>31</sup> For any 35–55-year-old woman in the American Ashkenazi Jewish population, the prolongation in average survival because of the gene screening program is a gain of 0.0369 years or 13 days (0.0459 QALY or 17 days, Table 3). This calculation includes all Ashkenazi Jewish women in the gene screening program, most of whom would not benefit from the screening program.

Consideration of only carriers results in greater effects of the program. For a 40-year-old woman, carrier life expectancy under a screening program is 39.56 years and 38.08 years with no screening program, so that the screening program increases life expectancy in carriers by 1.48 years (1.83 QALY). This calculation continues to assume that PBSO reduces the risk of ovarian cancer by a factor of  $P3 = 0.96$  and the lifetime penetrance of ovarian cancer for mutation carriers without PBSO treatment by a factor of  $P4 = 0.27$ . The prolongation increases to 1.91 years (2.38 QALY) for  $P4 = 0.35$ . When risk

reduction due to PBSO is as low as  $P3 = 0.80$ , the prolongation in average survival is 1.23 years (1.53 quality adjusted) and 1.60 years (1.98 quality adjusted) for  $P4 = 0.27$  and 0.35, respectively.

### Cost

For the 40-year-old women in the American Ashkenazi Jewish population, Table 3 indicates that there is a discounted cost of \$394 per woman if the screening program is implemented. If all women in the population are considered, then this translates into a 367 million dollar discounted cost of the program. The cost of the program is 10,309 discounted dollars per year of life expectancy gained and 8,300 discounted dollars per year of quality-adjusted life gained. These costs assume a cost of \$460 for gene screening.

When the cost of gene screening is \$50, then Table 3 indicates that there is a discounted cost of \$25 per woman if the screening program is implemented. If all women in the population are considered, then this translates into an 11 million dollar discounted cost of the program. Then the discounted cost of the program is 318 discounted dollars per year of life expectancy gained and 256 discounted dollars per year of quality-adjusted life gained.

The average cost for a carrier when the gene screening program is available is \$28,006 (discounted). Because noncarriers do not benefit from this gene screening program, gene screening cost for the noncarriers should be distributed into the group of carriers. On average, there are 39 noncarriers and 1 carrier in a randomly chosen sample of 40 when the carrier rate is 1/40. Therefore, the average cost for a carrier is adjusted to be  $\$28,006 + 39 \times P0 \times \$460 = \$44,152$  (discounted), when the carrier rate is  $P1 = 1/40$ , PBSO uptake rate  $P2 = 0.5$ , gene screening cost is \$460, and  $P4 = 0.27$ . This adjusted average cost becomes \$29,392 (discounted) per person if the gene screening cost is reduced to \$50 per person.

When the gene screening program is not available, the average cost for a carrier is \$28,923 (discounted) when  $P4 = 0.27$ . This average cost could increase to \$34,502 (discounted) when  $P4 = 0.35$ .

## DISCUSSION

The results of this analysis indicate that if a population-wide screening program were implemented at a cost of \$460 per gene test in the current cohort of American Ashkenazi Jewish females aged 35–55 years, which numbers about 0.96 million women, then 2,811 ovarian cancers would be prevented, about 13 days of life per woman would be gained (spread over the whole population), and the total discounted cost would be about \$367 million or \$8,300 per year of quality-adjusted life gained. Considering only the 24,096 carriers in the population, all 2,811 prevented cancers would be in the carriers (11.66% of carriers would have ovarian cancers prevented), and the average discounted cost per carrier would be \$44,152. If the cost of gene testing were \$50, then the cost of the program would be 256 discounted dollars per QALY gained.

### Acceptable costs and lifesavings

What constitutes an acceptable cost to society for lifesaving strategies and what number of lives saved is sufficient to merit public health intervention? Seat belt use provides an interesting perspective. During the 20-year period from 1982 to 2001, there was a 49% reduction in mortality from traffic crashes attributable to not wearing a seat belt, resulting in 129,297 fewer deaths or 6,465 fewer deaths per year.<sup>36</sup> Public health initiatives come

at a price, which, in the case of seat belts, includes public education, enactment and enforcement of laws, establishment of car manufacturing standards, and a mechanism for monitoring outcomes.

Mammographic screening is a pertinent benchmark with which to compare a genetic screening program intended to prevent cancer-related deaths. The cost-effectiveness of mammographic screening is \$10,000 to \$25,000 per QALY gained and has an implementation rate of 50–70%.<sup>37</sup> It has been estimated that about 1,500 mammographic examinations are needed to save one life.<sup>38</sup> Predictive genetic testing is done once and then prophylactic surgery is either performed once or not at all, whereas cancer screening is ongoing. Taking into account the cost of genetic testing and the costs associated with ovarian cancer prevention and treatment, our model indicates that 386 genetic tests need to be done to prevent one case of ovarian cancer, and that a conservative cost estimate is just over 8,000 discounted dollars per quality-adjusted year of life gained. These are favorable economic costs, and when compared with mammographic screening and other accepted interventions such as implantable cardioverter defibrillators (\$30,000–85,000/QALY) and dialysis in end-stage renal disease (\$50,000–100,000/QALY),<sup>37</sup> the economic acceptability seems even clearer.

### Effect of uncertain variants on cost-effectiveness

One study found that the cost-effectiveness of testing for breast cancer susceptibility genes was sensitive to the frequency of inconclusive test results.<sup>39</sup> The identification of a pseudo-deficiency mutation in the Tay-Sachs disease screening program foretold the occurrence of benign polymorphisms in other screening settings.<sup>40</sup> One advantage to ethnicity-based genetic screening is the comparatively low frequency of variants of uncertain significance (rare for Ashkenazi founder mutation testing versus 7% for comprehensive DNA sequencing<sup>41</sup>). The rate of variant identification would be low in the Ashkenazi Jewish population, and with enough testing, common variants would likely be definitively classified.

### Comparison with previous decision analyses

Our model differs from previous decision analyses in certain ways. The starting point has generally been a known *BRCA1/2* carrier or a woman having less expensive single-site testing as would apply in the setting of a known familial mutation.<sup>32,42,43</sup> Such analyses do not address the cost of case identification through high-risk clinics or in populations. We have also taken a conservative approach in the selection of penetrance estimates, as higher figures (e.g., Refs. 32 and 44) will tend to overestimate benefits of genetic screening; instead we use lower penetrance estimates based on a meta-analysis.<sup>27</sup>

Using more updated literature we could ascribe a higher effectiveness (96%) to PBSO than earlier studies, which used a rate of 45%.<sup>43,45</sup>; this parameter has a marked effect on ovarian cancer-related health outcomes and costs. However, we also considered a lower estimate of 80% of PBSO effectiveness based on a large prospective cohort study.<sup>21</sup> Our use of higher effectiveness rates for PBSO likely contributes to the finding that not all women need undergo prophylactic surgery to realize benefits of a genetic screening program in Ashkenazi Jews, in contrast to the conclusion of Grann et al.<sup>45</sup> that prophylactic surgery would need to be accepted by all participants to realize an overall benefit.

Our model is the first to consider the effect of screening program participation rates, which influences the total number of lives saved by such a program. For example, for a screening

program participation rate (P0) of 90%, PBSO uptake (P2) of 50%, effectiveness (P3) of 96%, and a carrier cancer rate (P4) of 0.35,  $0.378\% \times 963,840 = 3,643$  lives would be saved. The corresponding number of lives saved for a program participation rate of P0 = 30% is smaller, i.e.,  $0.126\% \times 963,840 = 1,214$  lives saved.

A genetic screening program will generally be more cost-efficient if participation rates are high. To the extent that reduced fees can be negotiated for high-volume genetic testing, a higher participation rate will result in a lower cost per QALY. *BRCA1/2* testing at a reduced research rate has previously been offered, and obtaining a lower cost for population-based testing seems feasible.<sup>46</sup> Putting aside licensing fees, the availability of next-generation sequencing has already driven down the cost of genetic testing beyond the lower levels considered in our model.<sup>47</sup>

Historically, carrier screening program participation rates of Ashkenazi Jews has been high for Tay-Sachs disease and other autosomal recessive disorders, leading to more than a 90% reduction in the incidence of Tay-Sachs disease in the Jewish population in the United States and Canada.<sup>40</sup> A high screening program participation rate is also suggested by the 79% self-reported testing rate in an early study<sup>48</sup> and widespread participation by Ashkenazi Jews in a variety of *BRCA1/2* research studies.<sup>49</sup> Nonetheless, screening program participation rates may be lower in actual practice and will likely be quite sensitive to the mode of delivery. The participation rate would be an important parameter to measure during implementation and diffusion phases.

The costs of administering a genetic screening program are beyond the scope of our study but would clearly need to be factored in depending on the delivery framework decided upon. The carrier screening program at the Chicago Center for Jewish Genetic Disorders provides a 4-hour educational session and genetic testing for Ashkenazi Jewish disorders at a cost of about \$400 per participant, not including the cost of genetic testing, follow-up genetic counseling, development of educational materials, advertising, or food (personal communication, Karen Litwack).

### Quality of life adjustment

We considered whether to calculate QALY for women undergoing PBSO but ultimately did not incorporate these factors into our model. We did take into consideration the reduction in QALY for women diagnosed with ovarian cancer.<sup>50</sup> Although time-tradeoff preference ratings<sup>51</sup> have been used for *BRCA1/2* decision analyses,<sup>43</sup> these were performed before a time when short-term hormone replacement therapy (HRT) was considered to be an acceptable approach toward symptom management for premenopausal *BRCA1/2* carriers undergoing PBSO.<sup>20</sup> In a Dutch study evaluating quality of life in high-risk women, no differences were observed in generic quality of life when comparing women who underwent PBSO with those undergoing gynecologic screening or women in the general population.<sup>52</sup> Although the group undergoing PBSO experienced worse sexual functioning and endocrine symptoms than women undergoing gynecologic screening<sup>52</sup> and these effects were not completely ameliorated by HRT,<sup>53</sup> the reduction in cancer worries and more favorable cancer risk perception effectively balanced out these effects in the PBSO study group. Therefore, we felt it was reasonable not to make QALY adjustments for women having prophylactic surgery.

Nonetheless, it is important to consider the uptake rate of HRT for premenopausal women because those experiencing severe climacteric symptoms from surgical menopause may

have a reduced quality of life. The rate of HRT use for *BRCA1/2* carriers undergoing PBSO was 60% in a study that first reported safety information in *BRCA1/2* carriers<sup>20</sup> and in a Dutch study,<sup>53</sup> 47% of women who had PBSO were current HRT users. A decision analysis assessing HRT use and life expectancy in *BRCA1/2* carriers undergoing PBSO concluded that short-term HRT decision making should be focused on quality of life and not life expectancy.<sup>54</sup> A more recent study examining HRT in postmenopausal *BRCA1* carriers found that estrogen-only HRT was associated with a 42% reduction in the risk of breast cancer, further lending support to HRT after PBSO.<sup>55</sup>

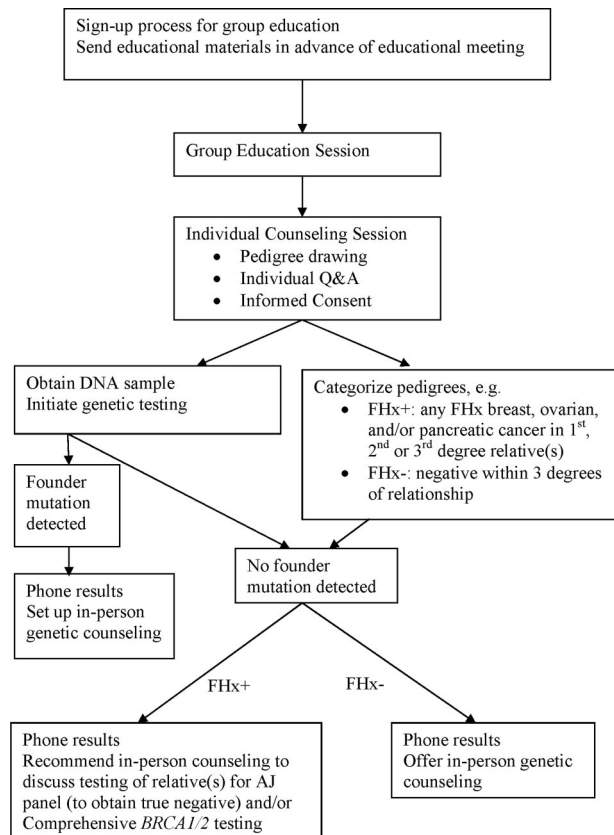
HRT usage could increase over time as recognition of the medical literature takes place. Conversely, given the media attention toward HRT and the risk of breast cancer in postmenopausal women, physicians may well be reluctant to base their therapeutic decision to prescribe HRT for surgically menopausal *BRCA1/2* carriers on a limited number of studies.<sup>20,54–56</sup> Therefore, QALY adjustment should perhaps be taken into consideration for those women not electing to use HRT.

### Limitations

Our study focused on the effects of genetic testing with respect to ovarian cancer risk management but did not address the high rate of breast cancer faced by *BRCA1/2* carriers. In contrast to ovarian cancer, where no effective early detection methods exist, there are several acceptable management strategies for breast cancer including prophylactic mastectomy (PM), high-risk screening, and chemoprevention, in addition to the marked reduction in breast cancer risk afforded by PBSO. The multiple avenues open to carriers for breast cancer risk management make decision analysis far more difficult to accurately model than ovarian risk management. Neither have we incorporated the costs of genetic counseling because that is dependent on the mode of program delivery, but we have attempted to outline a possible framework for genetic counseling (see discussion later and Fig. 2) and to begin to provide reasonable cost estimates.

The addition of PM was found to have an incremental cost-effectiveness over PBSO<sup>32</sup> in an analysis that applied the cost of single-site testing (pertinent in the setting of a known familial mutation) and higher penetrance estimates.<sup>1</sup> Improvement in life expectancy and cost-effectiveness of PM has been demonstrated in numerous studies,<sup>42,54,57–60</sup> but the uptake of this procedure in unaffected women is low, only about 20% in American women.<sup>23</sup> To the extent that *BRCA1/2* carriers identified through a population-based screening study would choose to undergo PM, the effect of a screening program should be more effective in terms of life expectancy and costs.

However, following the publication of more comprehensive decision analyses, the American Cancer Society issued recommendations that *BRCA1/2* carriers not choosing PM undergo annual breast MRI as an adjunct to mammography<sup>61</sup> and high-risk breast MRI screening has shifted from the research realm to clinical practice. Thus, breast MRI has become a crucially important component of breast cancer decision trees, but at present, limited data are available on the cost, insurance coverage, uptake, and patient utilities of breast MRI screening. We found only one publication citing an uptake rate for breast MRI.<sup>62</sup> The 37% uptake rate was observed in the context of a breast cancer surveillance program prospective database at an academic institution, was limited to women with a family history of breast and/or ovarian cancer (but not limited to *BRCA1/2* carriers), and took into consideration cost and insurance reimbursement issues. The generalizability of this uptake rate to a



**Fig. 2.** Proposed algorithm for a population-based *BRCA1/2* carrier screening program. FHx+, positive family history and FHx-, negative family history.

population-based screening program is uncertain given these important differences with our analysis.

Because screening is recommended to begin very early for *BRCA1/2* carriers and to continue annually, screening costs may be considerable over the course of time. Clinical utility of breast MRI in down-staging cancer has been reported<sup>61</sup> and unless lead-time bias is the cause, should result in improved life expectancy. No trials have addressed this issue directly, but a decision analysis predicted that the addition of breast MRI in *BRCA1/2* carriers from age 25 to 69 years would reduce breast cancer mortality by 23% when compared with mammography alone.<sup>63</sup> Costs were highly dependent on the screening strategy; the lowest cost per QALY gained was achieved for MRI screening from age 40 to 49 for *BRCA1* (\$43,484) and *BRCA2* (\$111,600) carriers. Furthermore, the relatively high-recall rates for breast MRI have posed concerns about quality of life. In general, psychological disturbance seems not to be a crucial factor for the high-risk screening population,<sup>61</sup> even for those undergoing screening recall events,<sup>64</sup> but vulnerable subgroups may exist. Overall, the lack of clear parameters needed to model life expectancy and costs impedes the development of a more comprehensive decision analysis. It seems conceivable that the effects of a screening program would entail more significant gains in life expectancy but be somewhat less cost-effective than we have portrayed.

Pre-menopausal *BRCA1/2* carriers who undergo PBSO also benefit from a reduction in breast cancer risk on the order of 40–50%<sup>65</sup>; therefore, the effect of PBSO on reducing breast

cancer mortality may be considerable. Taking this into account along with patient preferences, breast screening and PBSO may be the optimal management strategy.<sup>60</sup> Therefore, we think that our model underestimates the gains in life expectancy because of a genetic screening program. However, women may choose PBSO but forgo PM in favor of breast MRI, knowing that they achieve a significant reduction in the risk of breast cancer, and this could lead to increased costs. Although the literature speaks to surgery uptake rates (e.g., PM, PBSO, both, and neither) for *BRCA1* and *BRCA2* carriers,<sup>23</sup> we know of no published literature on how the availability of breast MRI influences uptake of surgery. Furthermore, the choice of breast cancer screening versus surgery may well be different among women learning about their mutation status by virtue of presenting to high-risk clinics because of personal and family history when compared with those identified through a population-based genetic screening program. Thus, we are circumspect in claiming that the overall cost-effectiveness of a genetic screening program would be more beneficial than our model indicates because of decreased breast cancer incidence and concede that the costs could be higher because of breast cancer screening.

**A translational research framework**

The process of determining whether to proceed with population-based screening and (if so) how to proceed are best considered within the context of an existing generalized framework for a continuum of translational research in genomic medicine.<sup>12</sup> Our study falls within T2 research (e.g., clinical utility and economic benefits) that is to be ultimately used for evidence-based reviews and recommendations, such as through an Evaluation of Genomic Applications in Practice and Prevention Working Group review. An evidence-based review might conclude that Ashkenazi Jewish population-based screening of *BRCA1/2* is not recommended or that there may be insufficient evidence at present to recommend in favor of proceeding, but we think it is worthwhile to anticipate and discuss certain aspects of later translational phases.

Moving evidence-based guidelines into health practice (Phase T3) through delivery, dissemination, and diffusion research requires a careful appraisal. Equally important is outcomes research (Phase T4), including social outcomes. Before embarking on later translational phases, it is useful to contemplate potential approaches and their pros and cons. One approach would be to perform genetic screening in the context of traditional medical care with usual clinical fees, along with a framework for genetic counseling. Another approach would be to coordinate program activities in a regional or national genetic screening framework encompassing overall delivery and assessment. We think that if evidence-based guidelines were to emerge in the absence of a structured programmatic framework, then genetic screening would likely diffuse into practice in a passive manner, with more loosely coordinated delivery in physician offices and limited opportunity to evaluate and potentially to influence T3 and T4 phases or to achieve economies of scale.

Despite its linear nomenclature, the overall framework of the T1–T4 translational continuum is envisioned as an iterative process. The effectiveness of an iterative process applied to a genetic screening program is well illustrated by the Tay-Sachs screening program set up in the 1970s.<sup>40</sup> A programmatic delivery structure for the Tay-Sachs disease testing proved to be useful for measuring T2-related parameters such as mutation prevalence, penetrance, and test performance and was a crucial component of overall implementation. This program evolved into the Jewish Genetic Disease Consortium, a network of

organizations which aims to increase awareness and facilitate testing for genetic diseases that affect the Ashkenazi Jewish population.<sup>66</sup> This consortium seems well-positioned to help examine ethical, legal, and social issues to evaluate the desirability of pursuing a screening program, and if such a program were to proceed, how to structure it.

Consequently, we believe that several aspects of genetic screening are best addressed in a programmatic manner. For example, nonfounder mutations account for 4–22% of identifiable *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish individuals.<sup>67,68</sup> Algorithms and processes would need to be developed to avoid missing these mutations and to provide accurate counseling to families. Figure 2 proposes one possible approach where cancer family histories are elicited and categorized, and for those with significant family histories (to be defined), either founder mutation testing in relatives (for unaffected individuals with negative founder mutation results) or comprehensive genetic analysis is offered. The acquisition of family history information with uniform standards could present a logistical challenge in a large screening program, perhaps addressed in part by computerized family history tools. Furthermore, individuals may be of mixed ancestry (e.g., Ashkenazi, Sephardic, and non-Jewish), and in addition, self-reported ancestry may not be wholly accurate,<sup>69</sup> all raising questions about criteria for offering screening and measurement of test performance. Clearly, a framework to address these issues would need to be developed, evaluated, and likely adjusted in an iterative manner, best accomplished under the aegis of a coordinated program. Such a framework would determine the costs of genetic counseling, which would need to be incorporated into a decision analysis such as ours.

It seems likely that if pre- and posttest genetic counseling were to be conducted in physician offices, a very wide range of standards would be applied, without a clear way to evaluate outcomes, even basic T3 parameters such as screening program participation rates. There would be limited ability to measure false reassurance engendered by a negative genetic test in the setting of a positive family history of cancer. Furthermore, physicians generally do not follow a family-centered approach where communication of positive results from a mutation-positive proband is encouraged and facilitated (e.g., through family letters). This seems especially pertinent in the context of population-based screening where individuals may have little if any family history of cancer. Therefore, a systematic role for genetic counselors should be predetermined to address the needs of these newly identified at-risk family members for cancer risk counseling and cancer screening and prevention strategies. The major trend in *BRCA1/2* testing through health care providers outside of the context of genetic counseling<sup>70</sup> magnifies the importance of structuring a genetic screening program in a responsible manner.

Importantly, population-based screening for autosomal dominant disorders is largely uncharted territory and differs in many fundamental ways from carrier screening for autosomal recessive conditions.<sup>11</sup> Although population-based carrier screening for autosomal recessive disorders seems to not have caused social stigma in the Ashkenazim, this would require careful attention in a *BRCA1/2* screening program where a positive screen directly identifies an at-risk individual. Genetic screening for a dominant disorder based on ethnicity could well have unanticipated adverse consequences both for individuals and communities. Although unaffected carriers are provided protection against genetic discrimination based on the Genetic Information Nondiscrimination Act of 2008 and applicable state laws, it has been pointed out that Genetic Information Non-

Discrimination Act provides a floor for protection and may not be comprehensive, nor easily actionable.<sup>71</sup> Even if legal protections were comprehensive and airtight, we should appreciate that perception alone is enough to create social stigma.

Conversely, it is also important to consider the effects on the nonscreened population: an argument has been made that targeted screening for Tay-Sachs disease in the Ashkenazim has detracted attention from non-Ashkenazi Jewish populations.<sup>69</sup> It seems quite plausible that emphasis on Ashkenazi ancestry as a risk factor for *BRCA1/2* mutations could lead to misperceptions and complacency in non-Jewish individuals. The ethics and societal impact of not conducting genetic screening in non-Jewish populations, based mainly on cost-effectiveness, should also be considered. One study suggested that genetic testing (i.e., comprehensive analysis at higher costs) was cost-effective even when the mutation detection probability was low, as long as a modest level of utility was gained from a negative result.<sup>39</sup> Of note, non-Jewish individuals volunteering for the Tay-Sachs screening program were offered testing.<sup>40</sup>

## CONCLUSIONS

Our model predicts a significant lifesaving potential for a population-based genetic screening program to prevent the occurrence of ovarian cancer by screening for founder mutations in the Ashkenazi Jewish population, at a cost which compares very favorably with recommended public health interventions such as mammographic screening. The costs of breast cancer surveillance, prevention, and treatment and effect on life expectancy must also be taken into consideration. Although the costs of implementation, administration, and program evaluation would need to be factored in, the cost of genetic testing seems to be well balanced by the benefits of avoiding a diagnosis of ovarian cancer and its attendant treatment. We advocate the initiation of a dialogue among Jewish stakeholders, genetics professionals, and public health leaders to determine whether a population-based *BRCA1/2* genetic screening program should be pursued.

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