Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry

Ranjit Manchanda, MRCOG, PhD; Shreeya Patel, MSc; Antonis C. Antoniou, PhD; Ephrat Levy-Lahad, PhD; Clare Turnbull, PhD; D. Gareth Evans, PhD; John L. Hopper, PhD; Robert J. Macinnis, PhD; Usha Menon, MD; FRCOG; Ian Jacobs, MD, FRCOG; Rosa Legood, PhD

BACKGROUND: Population-based BRCA1/BRCA2 testing has been found to be cost-effective compared with family history—based testing in Ashkenazi-Jewish women were >30 years old with 4 Ashkenazi-Jewish grandparents. However, individuals may have 1, 2, or 3 Ashkenazi-Jewish grandparents, and cost-effectiveness data are lacking at these lower BRCA prevalence estimates. We present an updated cost-effectiveness analysis of population BRCA1/BRCA2 testing for women with 1, 2, and 3 Ashkenazi-Jewish grandparents.

STUDY DESIGN: Decision analysis model.

METHODS: Lifetime costs and effects of population and family history—based testing were compared with the use of a decision analysis model. 56% BRCA carriers are missed by family history criteria alone. Analyses were conducted for United Kingdom and United States populations. Model parameters were obtained from the Genetic Cancer Prediction through Population Screening trial and published literature. Model parameters and BRCA population prevalence for individuals with 3, 2, or 1 Ashkenazi-Jewish grandparent were adjusted for the relative frequency of BRCA mutations in the Ashkenazi-Jewish and general populations. Incremental cost-effectiveness ratios were calculated for all Ashkenazi-Jewish grandparent scenarios. Costs, along with outcomes, were discounted at 3.5%. The time horizon of the analysis is “life-time,” and perspective is “payer.” Probabilistic sensitivity analysis evaluated model uncertainty.

RESULTS: Population testing for BRCA mutations is cost-saving in Ashkenazi-Jewish women with 2, 3, or 4 grandparents (22-33 days life-gained) in the United Kingdom and 1, 2, 3, or 4 grandparents (12-26 days life-gained) in the United States populations, respectively. It is also extremely cost-effective in women in the United Kingdom with just 1 Ashkenazi-Jewish grandparent with an incremental cost-effectiveness ratio of £863 per quality-adjusted life-years and 15 days life gained. Results show that population-testing remains cost-effective at the £20,000—30000 per quality-adjusted life-years and $100,000 per quality-adjusted life-years willingness-to-pay thresholds for all 4 Ashkenazi-Jewish grandparent scenarios, with >95% simulations found to be cost-effective on probabilistic sensitivity analysis. Population-testing remains cost-effective in the absence of reduction in breast cancer risk from oophorectomy and at lower risk-reducing mastectomy (13%) or risk-reducing salpingo-oophorectomy (20%) rates.

CONCLUSION: Population testing for BRCA mutations with varying levels of Ashkenazi-Jewish ancestry is cost-effective in the United Kingdom and the United States. These results support population testing in Ashkenazi-Jewish women with 1-4 Ashkenazi-Jewish grandparent ancestry.

Key words: ancestry, Ashkenazi Jewish, BRCA, cost-effectiveness, population testing

Popu

P


0002-9378/$36.00 © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ajog.2017.06.038

American Journal of Obstetrics & Gynecology

MONTH 2017 1.61

Assessments of the full health economic implications are critical to inform any potential policy change. A health economic assessment allows for the evaluation of the overall costs and benefits for the genetic testing of BRCA1/BRCA2 mutations in women of differing AJ ancestry.

We previously used a decision analytical model to compare the costs and consequences of population-based testing in AJ women who were ≥30 years old with 4 AJ grandparents. The data used in this model was obtained from the Genetic Cancer Prediction through Population Screening randomized trial (ISRCTN73338115) that compared outcomes of population- and FH-based approaches for genetic testing of women with 4 AJ grandparents. The model showed that overall, when the down-stream costs of treatment were taken into account, population-testing
The upper part of the model structure reflects a population-based approach to BRCA testing; the lower part of the model depicts a family history—based approach. Each decision point in the model is called a "node"; each path that extends from a node is called a decision "branch." Each branch represents a
was in fact cost-saving compared with FH-testing. The modelling predicted that this could lead to a significant reduction in breast-and-ovarian cancer incidence and increase life expectancy. However, our original analysis applies only to women with 4 AJ grandparents and is not applicable directly to every woman with AJ ancestry because 25% United Kingdom (UK) and 44% United States (US) Jewish marriages are to non-Jews. These women thus may have just 1, 2, or 3 AJ grandparents; therefore, the prevalence of BRCA1/BRCA2 mutations is lower in these groups. Nevertheless, these women remain at elevated BRCA risk compared with the general (non-Jewish) population. Cost-effectiveness data for these varying lower mutation prevalence levels are unavailable. This important gap in knowledge was highlighted at a recent meeting of experts on population-based AJ BRCA testing in Haifa, Israel, in July 2016. We present an updated cost-effectiveness analysis of population BRCA1/BRCA2 testing for women with 1, 2, and 3 AJ grandparents.

**Methods**  
We previously developed a decision-analytical model (Figure 1) to calculate cost-effectiveness of screening women with 4 AJ grandparents. Model structure, assumptions, analytic features, advantages, and limitations have been described earlier. This model was adapted to model outcomes for women with differing AJ ancestry. Separate analyses were performed for both UK and US populations. Lifetime costs and effects of genetically screening 30-year-old AJ women for BRCA1/BRCA2 AJ founder mutations were compared with current practice of screening with the use of FH-based clinical criteria. Fifty-six percent of BRCA carriers are missed when FH criteria are used alone compared with population screening. Genetic counselling and genetic testing was offered to all women in the population screening arm and only those who fulfilled the FH-based criteria in the FH arm. The criteria for FH-based testing included personal history of ovarian cancer (any age), first-degree relative with ovarian cancer (any age), first-degree relative with or personal history of breast cancer at <50 years old, and/or first-degree relative with or personal history of male breast cancer (any age). Parameter estimates for probabilities, costs, and utilities were obtained and adapted from the earlier decision analytical model.

**Probabilities**  
All parameters in the decision analytical model were kept constant apart from the following 3 parameters: (1) population prevalence of BRCA (P1), (2) probability of having a positive FH (P6), and (3) BRCA prevalence in the FH-negative individuals (P8). These 3 parameters are influenced by change in the number of AJ grandparents. An individual with 3 AJ grandparents would possess 75% AJ genetic makeup and 25% from the general population. Someone with 2 AJ grandparents would have 50% AJ and 50% general population makeup. Therefore, BRCA population prevalence for an individual with 3, 2, or 1 AJ grandparent is adjusted for the relative frequency of BRCA mutations in the AJ and general populations. BRCA prevalence estimates for AJ was obtained from the Genetic Cancer Prediction through Population Screening study (0.0245 [0.0131, 0.0416]) and for the general population (0.0067 [0.00590, 0.0077]) from recent published estimates. BRCA prevalence with 3 AJ grandparents= (0.75*AJ prevalence) + (0.25*General-population prevalence); for 2 AJ grandparents= (0.5*AJ prevalence + 0.5*General-population prevalence); and for 1 AJ grandparent= (0.25*AJ prevalence + 0.75*General-population prevalence). The probability of having a strong FH that fulfilled clinical genetic testing criteria in the non-Jewish population was obtained from unselected control population data from the Australian Breast Cancer Family Registry. Similarly, probability parameters P6 (having a positive FH) and P8 (prevalence in FH-negative individuals) were adjusted for relative BRCA mutation frequency in AJ and general populations. This was done for all 3 parameters and their confidence intervals for all of the different grandparent scenarios. The revised probability table for model parameters is given in Table 1.

**Quality adjusted life-years and costs**  
Utility weights express the preference of an individual in a specific health state. These weights are then combined with survival in life-years to give a measurement known as a quality adjusted life-years (QALY), which is the preferred value of health benefit according to the National Institute of Health & Care excellence (NICE). This decision-analytical model that used revised estimates was run for each of the 4 scenarios: 4, 3, 2, and 1 AJ grandparents. The following utility scores were used for ovarian cancer (OC): 0.81 for early stage OC, 0.55 for advanced disease, 0.61 for recurrent disease, 0.83 for OC remission, and 0.16 for end stage OC. The following utility scores, which were obtained from NICE guidelines, were used for breast cancer (BC): 0.71 for early/local advanced BC, 0.65 for advanced disease, 0.45 for recurrence disease, 0.81 for BC remission, and 0.16 for end stage BC. A breakdown of both UK and US costs at 2014 and 2015 prices are given in Table 2. The analysis covers a health system or payer perspective.

---

**Mutually exclusive course or outcome.** Each decision is given a probability (probabilities “\*p1-14” that were used in the model are explained in Table 1), which is highlighted in a white box along the decision branch. Values for each outcome were calculated. Cancer incidence was estimated by the summing of the probabilities of pathways that ended in ovarian or breast cancer. Final outcomes (blue boxes) of each path include development of breast cancer, ovarian cancer, and no breast/ovarian cancer. BC, breast cancer; NO, no breast cancer developed; NO OC, no ovarian cancer developed; OC, ovarian cancer; RR, risk-reducing mastectomy; RR, risk-reducing salpingo-oophorectomy. From Manchanda R, Legood R, Burrell M, et al. Cost-effectiveness of population screening for BRCA mutations in Ashkenazi Jewish women compared with family history—based testing. J Natl Cancer Inst 2015;107:380. With permission from Oxford University Press. Manchanda R. et al. Cost-effectiveness of population BRCA testing with varying Jewish ancestry. Am J Obstet Gynecol 2017.
TABLE 1
Probabilities that were used in the model

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
<th>95% Confidence interval [range]</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1 (4 AJ GP)</td>
<td>0.0245</td>
<td>0.0131—0.0416</td>
<td>Population prevalence of BRCA FM</td>
<td>Genetic Cancer Prediction through Population Screening study, Manchanda2,8</td>
</tr>
<tr>
<td>P1 (3 AJ GP)</td>
<td>0.0201</td>
<td>0.0113—0.0331</td>
<td>BRCA prevalence with: 3 AJ grandparents: (0.75<em>AJ probability) + (0.25</em>general-population probability); 1 AJ grandparent: (0.25<em>AJ probability) + (0.75</em>general-population probability)</td>
<td>Manchanda,2 Jervis 201512</td>
</tr>
<tr>
<td>P1 (2 AJ GP)</td>
<td>0.0156</td>
<td>0.0095—0.0247</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1 (1 AJ GP)</td>
<td>0.011</td>
<td>0.0077—0.0162</td>
<td>2 AJ grandparents: (0.5<em>AJ probability) + (0.5</em>general-population probability); 1 AJ grandparent: (0.25<em>AJ probability) + (0.75</em>general-population probability)</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>0.52</td>
<td>0.39—0.67</td>
<td>Probability that carrier will undergo RRM</td>
<td>Evans46</td>
</tr>
<tr>
<td>P3</td>
<td>0.96</td>
<td>[0.8—0.96]</td>
<td>Reduction in risk of ovarian cancer from RRSO</td>
<td>Finch,47 Rebbeck33</td>
</tr>
<tr>
<td>P4</td>
<td>0.2987</td>
<td>0.2485—0.3539</td>
<td>Probability that carrier without RRSO will experience ovarian cancer</td>
<td>Chen48</td>
</tr>
<tr>
<td>P5</td>
<td>0.0185</td>
<td>0.0005—0.0989</td>
<td>Probability that a noncarrier will experience ovarian cancer</td>
<td>Cancer Research UK</td>
</tr>
<tr>
<td></td>
<td>0.0128</td>
<td>0.0126—0.0130</td>
<td>Probability that a noncarrier will experience ovarian cancer: US estimate</td>
<td>Surveillance, Epidemiology, and End Results Program21</td>
</tr>
<tr>
<td>P6 (4 AJ GP)</td>
<td>0.1238</td>
<td>0.1043—0.1454</td>
<td>Probability of having a positive FH</td>
<td>Genetic Cancer Prediction through Population Screening study2,8</td>
</tr>
<tr>
<td>P6 (3 AJ GP)</td>
<td>0.095</td>
<td>0.079—0.114</td>
<td>Probability with: 3 AJ grandparents: (0.75<em>AJ probability) + (0.25</em>general-population probability); 2 AJ grandparents: (0.5<em>AJ probability) + (0.5</em>general-population probability); 1 AJ grandparent: (0.25<em>AJ probability) + (0.75</em>general-population probability)</td>
<td></td>
</tr>
<tr>
<td>P6 (2 AJ GP)</td>
<td>0.0668</td>
<td>0.055—0.082</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P6 (1 AJ GP)</td>
<td>0.0383</td>
<td>0.0296—0.0498</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P7</td>
<td>0.0938</td>
<td>0.0637—0.1763</td>
<td>BRCA prevalence in FH-positive individuals</td>
<td>Genetic Cancer Prediction through Population Screening study2,8</td>
</tr>
<tr>
<td>P8 (4 AJ GP)</td>
<td>0.0203</td>
<td>0.0114—0.0332</td>
<td>BRCA prevalence in FH-negative individuals</td>
<td>Genetic Cancer Prediction through Population Screening study2,8</td>
</tr>
<tr>
<td>P8 (3 AJ GP)</td>
<td>0.0166</td>
<td>0.0098—0.0266</td>
<td>Probability with: 3 AJ grandparents: (0.75<em>AJ probability) + (0.25</em>general-population probability); 2 AJ grandparents: (0.5<em>AJ probability) + (0.5</em>general-population probability); 1 AJ grandparent: (0.25<em>AJ probability) + (0.75</em>general-population probability)</td>
<td></td>
</tr>
<tr>
<td>P8 (2 AJ GP)</td>
<td>0.0129</td>
<td>0.0082—0.0199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P8 (1 AJ GP)</td>
<td>0.009</td>
<td>0.006—0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P9</td>
<td>0.91</td>
<td>0.62—0.98</td>
<td>Reduction in breast cancer risk from RRM without RRSO</td>
<td>Rebbeck49</td>
</tr>
<tr>
<td>P10</td>
<td>0.53</td>
<td>0.44—0.62</td>
<td>Probability that carrier without RRM will experience breast cancer</td>
<td>Chen48</td>
</tr>
</tbody>
</table>

TABLE 1
Probabilities that were used in the model (continued)

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
<th>95% Confidence interval [range]</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>P11</td>
<td>0.13</td>
<td>[0.10 – 0.16]</td>
<td>Probability that a noncarrier will experience breast cancer with screening: UK estimate</td>
<td>Cancer Research UK, Office for National Statistics</td>
</tr>
<tr>
<td></td>
<td>0.124</td>
<td>0.1236 – 0.1249</td>
<td>Probability that a noncarrier will experience breast cancer with screening: US estimate</td>
<td>Surveillance, Epidemiology, and End Results Program</td>
</tr>
<tr>
<td>P12</td>
<td>0.55</td>
<td>0.30 – 0.75</td>
<td>Probability that carrier will follow up with RRSO</td>
<td>Manchanda</td>
</tr>
<tr>
<td>P13</td>
<td>0.49</td>
<td>0.37 – 0.65</td>
<td>Reduction in risk of breast cancer from RRSO alone</td>
<td>Rebbeck</td>
</tr>
<tr>
<td>P14</td>
<td>0.95</td>
<td>0.78 – 0.99</td>
<td>Reduction in risk of breast cancer from RRM with RRSO</td>
<td>Rebbeck</td>
</tr>
</tbody>
</table>

AJ, Ashkenazi Jewish; FH, family history; FM, founder mutations; GP, grandparent; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy; UK, United Kingdom; US, United States of America.

Explanation: The probabilities P1, P6, and P8 have been adapted for different levels of AJ ancestry: 4, 3, 2, and 1 grandparents. The other model probabilities remain the same, as previously published.

1. The probability of carrying a BRCA1 FM in the AJ population (p1 = 0.0245) is from the Genetic Cancer Prediction through Population Screening study. This was the probability with 4 AJ grandparents. The probability of having a BRCA mutation in the non-Jewish population (0.0067 (0.0059, 0.0077)) was from up-to-date estimates from Jerivs 2015. BRCA prevalence: 3 AJ grandparents = (0.75*AJ population) + (0.25*general-population); 2 AJ grandparents = (0.5*AJ population) + (0.5*general-population); 1 AJ grandfather = (0.25*AJ population) + (0.75*general-population).

2. The probability that BRCA1/2 carrier will undergo RRM was taken from an analysis of UK BRCA1/2 carriers. A composite uptake rate (p2 = 0.52) for BRCA1 (60% RRM rate) and BRCA2 (43% RRM rate) carriers, weighted for the relative prevalence of BRCA1 and BRCA2 FM that were found in the London AJ population, was computed.

3. The reduction in ovarian cancer risk that was obtained from RRSO (p3 = 0.96) was taken from previous studies that reported a 4% residual risk of primary peritoneal cancer after RRSO.

4. The Genetic Cancer Prediction through Population Screening study model uses ovarian cancer penetrance estimates (40% for BRCA1, 18% for BRCA2) from a metaanalysis that was corrected for ascertainment.

5. To simplify the analysis, the Genetic Cancer Prediction through Population Screening study model used a composite risk for BRCA1 and BRCA2 carriers weighted for the relative prevalence of BRCA1 and BRCA2 FM. The overall risk of ovarian cancer in BRCA carriers was calculated as (0.0132*0.4/2.45 + [0.0113*0.18/2.45]).

6. The probability of having a strong FH of cancer that fulfilled the current clinical criteria (FH-positive) for women with 4 AJ grandparents was obtained from the Genetic Cancer Prediction through Population Screening study. The probability of having a positive FH that fulfilled the non-AJ genetic testing criteria was obtained from previously unpublished unselected control population data from the Australian Breast Cancer Family Registry. The probability for 3, 2, and 1 grandparent was adjusted for the relative prevalence in Jewish and general populations. The probability: 3 AJ grandparents = (0.75*AJ population) + (0.25*general-population); 2 AJ grandparents = (0.5*AJ population) + (0.5*general-population); 1 AJ grandfather = (0.25*AJ population) + (0.75*general-population).

7. The BRCA prevalence in FH-positive individuals was also obtained from the Genetic Cancer Prediction through Population Screening study.

8. The BRCA1 prevalence in FH-negative individuals for women with 4 AJ grandparents was obtained from the Genetic Cancer Prediction through Population Screening study. The probability for 3, 2, and 1 grandparent was adjusted for the relative prevalence in Jewish and general populations. The probability: 3 AJ grandparents = (0.75*AJ population) + (0.25*general-population); 2 AJ grandparents = (0.5*AJ population) + (0.5*general-population); 1 AJ grandfather = (0.25*AJ population) + (0.75*general-population).

9. The breast cancer penetrance for BRCA2 carriers (57% for BRCA1 and 49% for BRCA2) was taken from a metaanalysis that was corrected for ascertainment.

10. To simplify the analysis, the Genetic Cancer Prediction through Population Screening study model used a composite risk for BRCA1 and BRCA2 carriers that was weighted for the relative prevalence of BRCA1 and BRCA2 FM. The overall risk of breast cancer in BRCA carriers was calculated as (0.0132*0.4/2.45 + [0.0113*0.18/2.45]).

11. The risk of breast cancer in a low-risk population was taken from Cancer Research UK and UK Office for National Statistics data and from SEER data for US women.

12. In the Genetic Cancer Prediction through Population Screening study model, we have used the RRSO rates that were reported in high-risk women from London, which reflects the views of carriers from a London population and is within the range reported in the literature.

13. The reduction in breast cancer risk in premenopausal women who underwent RRSO was taken from a metaanalysis by Rebbeck et al.

14. Reduction in breast cancer risk from RRM in BRCA carriers who did not undergo RRSO was taken from the Prevention and Observation of Surgical Endpoints study data.

15. The reduction in breast cancer risk in premenopausal women who underwent RRSO was taken from the Prevention and Observation of Surgical Endpoints study data.


Life-years
A lifetime horizon (extending to the age of 83 years) that captured lifetime risks and consequences was used to model the analysis. Mean ages for BRCA1/BRCA2-related BC and OC in AJ women of 43.5 years and 54.9 years were used in the analysis. The mean ages for sporadic BC and OC in AJ women were 57 and 62 years and 63 and 63 years in the UK/US populations, respectively. Five-year survival rates in the general UK population were used in the absence of AJ survival data. Costs, QALYs, and life-years were discounted at 3.5%.

Analysis
To calculate the probability of being in each branch, the path probabilities of each branch were multiplied together. Total costs, life-years, and QALYs were determined through weighting of the values of each branch by the probability of being in each branch. To establish the
cost-effectiveness of population-based screening against FH-based testing, the incremental cost-effectiveness ratio (ICER) was calculated by dividing differences in cost by the differences in effect. The £20,000—30,000 per QALY cost-effectiveness willingness-to-pay (WTP) threshold that had been used by NICE was used to compare the cost-effectiveness of population-based screening in comparison with FH-based testing in the UK. A WTP threshold of $100,000 per QALY was used for the US analysis.

To account for uncertainty, all model parameters were varied simultaneously across their distributions using 10,000 simulations in a probabilistic sensitivity analysis (PSA) in accordance with the recommendation of NICE methods guidance. Costs were varied by ±30%, confidence intervals were used to vary probabilities and utility scores, if available, or they were varied by +/-10%. Probabilities were assigned a beta distribution, costs a gamma distribution and utilities a log normal distribution in accordance with published literature.

### Results

Baseline ICER results for the 4 different grandparent scenarios are given in Table 3 alongside discounted and undiscounted life-years, QALYs, and lifetime costs for each scenario for women both in the UK and US. Baseline results suggest that population testing in UK women who had ≥2 AJ grandparents and ≥1 grandparent for US women remains cost-saving and highly effective compared with traditional testing that uses FH-based clinical criteria. This corresponds to a life expectancy gain of 15 and 12, 22 and 17, 28 and 22, and 33 and 26 days, respectively, for 1, 2, 3, and 4 AJ grandparents in UK/US women. Population testing in women with just 1 AJ grandparent is also cost-effective, with an ICER that equals £863 per QALY and 15 days life gained. This too is well below the £20,000 per QALY threshold, although not cost-saving. The PSAs for the UK and US (Figures 2 and 3) show that, for populations with 4, 3, 2, or 1 AJ grandparent, ≥95% of simulations are cost-effective for population screening at the £20,000 per QALY NICE WTP and $100,000 per QALY US WTP thresholds. This suggests that, compared with current clinical policy of FH-based clinical testing, population testing in 4, 3, 2, and 1 AJ grandparents is highly cost-effective.

### Comment

Given that a large proportion of marriages in the Jewish population are between Jews and non-Jews, it is important

---

**TABLE 2**

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost UK (£)</th>
<th>Cost US ($)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of BRCA Founder mutation testing</td>
<td>50</td>
<td>300</td>
<td>GCaPPS2</td>
</tr>
<tr>
<td>Cost of genetic counselling</td>
<td>43</td>
<td>41</td>
<td>GCaPPS; PSSRU unit costs of Health and Social Care, Schwartz et al 2014</td>
</tr>
<tr>
<td>Cost of risk-reducing salpingo-oophorectomy (and hormone replacement therapy and osteoporosis prevention)</td>
<td>3,411</td>
<td>8,144</td>
<td>NHS reference costs, BNF</td>
</tr>
<tr>
<td>Cost of ovarian cancer diagnosis and treatment</td>
<td>14,123</td>
<td>127,995</td>
<td>NHS reference costs, NICE guideline</td>
</tr>
<tr>
<td>Yearly cost of ovarian cancer treatment at year 1-2</td>
<td>10,050</td>
<td>14,071</td>
<td>NHS reference costs, NICE guideline, CRUK, Grann et al 2011</td>
</tr>
<tr>
<td>Yearly cost of ovarian cancer treatment at year 3-5</td>
<td>14,387</td>
<td>14,071</td>
<td>NHS reference costs, NICE guideline, CRUK, Grann et al 2011</td>
</tr>
<tr>
<td>Terminal care costs with ovarian cancer</td>
<td>15,450</td>
<td>89,424</td>
<td>National Audit Office, Incisive Health report for CRUK, Grann et al 2011</td>
</tr>
<tr>
<td>Cost of risk-reducing mastectomy</td>
<td>3,901</td>
<td>12,596</td>
<td>NHS reference cost, weighted for 21% complication rate, Grann et al 2011</td>
</tr>
<tr>
<td>Cost of breast screening</td>
<td>347</td>
<td>1,534</td>
<td>Robertson 2011, NHS reference costs, CDC guideline</td>
</tr>
<tr>
<td>Cost of breast screening BRCA carriers</td>
<td>4,582</td>
<td>33,530</td>
<td>NHS reference costs, CDC guideline, NICE guideline, Grann et al 2011</td>
</tr>
<tr>
<td>Cost of breast cancer diagnosis and treatment</td>
<td>15,527</td>
<td>82,030</td>
<td>NHS reference costs, NICE guideline, NICE guideline, Grann et al 2011</td>
</tr>
</tbody>
</table>

TABLE 2
Costs used in the model (2014 prices) (continued)

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost Unité Kingdom (£)</th>
<th>Cost United States ($)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal care costs with breast cancer</td>
<td>15,450</td>
<td>65,403</td>
<td>National Audit office, Grann et al 2011</td>
</tr>
</tbody>
</table>

BNF, British National Formulary; CDC, Centers for Disease Control and Prevention; CRUK, Cancer Research UK; GCaPPS, Genetics Cancer Prediction through Population Screening study; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PSSRU, Personal Social Services Research Unit.

Explanation: Cost of risk-reducing salpingo-oophorectomy: It is assumed that hormone replacement therapy is provided to women from the age that they have risk-reducing salpingo-oophorectomy until the age of menopause (51 years). An 80% compliance rate was assumed with hormone replacement therapy; these costs are added to costs for surgery. For the United Kingdom, risk-reducing salpingo-oophorectomy costs are for an upper genital tract laparoscopic/endoscopic intermediate procedure. To monitor bone health, the cost of 5 DEXA scans and calcium and vitamin-D3 are also included. United States prophylactic salpingo-oophorectomy costs are taken from Grann et al 2011 and inflated with the use of the medical component of the United States consumer price index.

Ovarian cancer costs: Costs were based on ovarian cancer guidelines published by NICE. Diagnosis costs included ultrasound scan, pelvic examination, computed tomography scan, CA125 test, percutaneous biopsy, and peritoneal cytology. Costs of treatment included reference cost for lower and upper genital tract cancer major procedure and 6 cycles of carboplatin and paclitaxel chemotherapy administration. Survivors were assumed to have 3 consultant visits, 4 CA125 tests and a computed tomography scan each for the first 2 years after surgery. In years 3—5 after surgery, survivors were assumed to have 2 consultant visits and 2 CA125 tests. Terminal cancer costs were taken from a report submitted to the National Audit Office, UK. Recurrent ovarian cancer costs were taken from a report that was commissioned by CRUK. For the United States, the cost of ovarian cancer diagnosis, treatment, recurrence, and terminal ovarian cancer costs were taken from Grann et al 2011 and inflated with the use of the medical component of the United States consumer price index.

Breast cancer costs: Costs were based on NICE guidelines on early/locally advanced breast cancer and advanced breast cancer in UK, the BNF, and the Department of Health NHS reference costs.

Cost of breast screening in general population: Women 50—70 years old are offered mammography every 3 years in accordance with the United Kingdom NHS breast cancer screening program. Cost of breast screening based on clinical examination, ultrasound, mammography and biopsy

Cost of breast screening in carriers: Women are offered mammography every 2 years from 50 years old and an annual mammogram at 40—69 years old in accordance with NICE familial breast cancer guidelines.

Cost of breast cancer treatment: In noncarriers, 10% of breast cancer is noninvasive ductal carcinoma in situ and 90% invasive; 95% of invasive breast cancer is early and locally advanced, with 5% being advanced breast cancer. In BRCA1/2 carriers, 20% are noninvasive ductal carcinoma in situ and 80% invasive.

Yearly cost of breast cancer treatment: Costs include sentinel lymph node biopsy and axillary lymph node dissection, as recommended in NICE guideline. Breast-conserving surgery and mastectomy costs with reconstruction are included in treatment costs. Radiotherapy costs that are included are for early invasive/locally advanced cancer; chemotherapy is offered alongside radiotherapy for advanced cancers. Chemotherapy costs are taken from NICE guidelines based on first- and second-line. Polychemotherapy costs take into account the difference in stage at presentation, with 25% of cancers being noninvasive. Costs are also taken into account for the testing of cancers that are estrogen receptor positive and HER2 positive in the general and BRCA-carrier population; 70% general population invasive breast cancers were estrogen receptor positive; 15% of early invasive breast cancers and 25% of advanced breast cancers are HER2 positive. ER-positive cancers receive tamoxifen at 20 mg/day, if the woman is premenopausal, or anastrozole 1 mg/day, if the woman is postmenopausal for 5 years; costs of both are from the BNF. To offset the risk of the development of bone metastases, 65% of individuals are offered bisphosphonates. Per NICE guidelines, it is assumed 50% of those will receive intravenous zoledronic acid or pamidronate, and the other 50% will receive oral clodronate and ibandronate. As per NICE guidelines, HER2-positive patients are given trastuzumab at 3-week intervals for a year or until disease recurrence. Recurrence rates are included for breast cancer as obtained through the United States National-Surgical-Adjuvant Breast and Bowel Project. Follow-up costs for breast cancer include, 6 monthly consultations and annual mammograms with magnetic resonance scans for stage 4 cancers. Costs take into account a 35% progression rate from early and locally advanced to advanced disease and 66% relapse rate in advanced disease. Terminal care cancer costs were obtained from a report published by the National Audit Office, UK.

United States breast cancer costs: The costs of breast cancer diagnosis and treatment was taken from Grann et al 2011 and were inflated with the use of the medical component of the United States consumer price index.

Cost of breast screening in noncarriers: Costs assume that mammograms are conducted every 2 years from 50 years old (CDC guidelines).

Cost of breast screening in carriers: Costs assume that women in the United States are offered a yearly mammography and magnetic resonance image from 30 years old, then from 50 years old onwards women are offered only an annual mammography.

Terminal breast cancer costs: Costs are taken from Grann et al 2011 and inflated with the use of the medical component of the United States consumer price index.

population health and cancer prevention and are of value to healthcare providers and care commissioners.

The number of days of life gained range from 15 and 33 days and 12 and 26 days, respectively, in the UK and US. Although, these figures appear small, it is important to highlight that these numbers are averaged across the population. In health economic terms, these values are significant; for an individual in whom cancer is prevented, this number is many folds higher. Our modelling incorporates the costs of both genetic testing and genetic counselling. The time horizon in our modelling is appropriately long enough to highlight any important variations in costs and outcomes. The sensitivity and scenario analyses that were undertaken add strength to the study. Although risk-reducing salpingo-oophorectomy (RRSO) reduces the risk of BC in premenopausal women, the benefit of

<table>
<thead>
<tr>
<th>Ashkenazi Jewish grandparents</th>
<th>Screening arms</th>
<th>United Kingdom results</th>
<th>United States results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cost (£)</td>
<td>Life-years*</td>
</tr>
<tr>
<td>4</td>
<td>Average population screening</td>
<td>1861</td>
<td>52.26</td>
</tr>
<tr>
<td></td>
<td>Average family history screening</td>
<td>1955</td>
<td>52.17</td>
</tr>
<tr>
<td></td>
<td>Incremental (difference)</td>
<td>−94</td>
<td>0.090</td>
</tr>
<tr>
<td></td>
<td>Incremental cost-effectiveness ratio per quality adjusted life-years</td>
<td>−2960</td>
<td>−19,587</td>
</tr>
<tr>
<td>3</td>
<td>Average population screening</td>
<td>1813</td>
<td>52.27</td>
</tr>
<tr>
<td></td>
<td>Average family history screening</td>
<td>1875</td>
<td>52.19</td>
</tr>
<tr>
<td></td>
<td>Incremental (difference)</td>
<td>−62</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>Incremental cost-effectiveness ratio per quality adjusted life-years</td>
<td>−2327</td>
<td>−16,788</td>
</tr>
<tr>
<td>2</td>
<td>Average population screening</td>
<td>1766</td>
<td>52.28</td>
</tr>
<tr>
<td></td>
<td>Average family history screening</td>
<td>1792</td>
<td>52.22</td>
</tr>
<tr>
<td></td>
<td>Incremental (difference)</td>
<td>−26</td>
<td>0.060</td>
</tr>
<tr>
<td></td>
<td>Incremental cost-effectiveness ratio per quality adjusted life-years</td>
<td>−1254</td>
<td>−12,013</td>
</tr>
<tr>
<td>1</td>
<td>Average population screening</td>
<td>1718</td>
<td>52.29</td>
</tr>
<tr>
<td></td>
<td>Average family history screening</td>
<td>1705</td>
<td>52.25</td>
</tr>
<tr>
<td></td>
<td>Incremental (difference)</td>
<td>13</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>Incremental cost-effectiveness ratio per quality adjusted life-years</td>
<td>863</td>
<td>−2,542</td>
</tr>
</tbody>
</table>

* Undiscounted outcomes shown for life-years; costs and quality adjusted life-years outcomes are discounted.

Cost-effectiveness acceptability curves are generated when the model undergoes probabilistic sensitivity analysis. In the probabilistic sensitivity analysis, all model parameters are varied simultaneously across their distributions. Each of the 4 scenarios (4, 3, 2, 1 grandparent) were simulated 10,000 times; the results shown are the proportion of these simulations that would be cost-effective at different willingness-to-pay thresholds. X-axis: Incremental cost-effectiveness ratio in terms of cost per quality adjusted life-years. Y-axis: Proportion of simulations. The solid red line marks the proportion of simulations that were found to be cost-effective at the £20,000 threshold used by the National Institute for Health and Clinical Excellence. At >95%, simulations are cost-effective for varying levels of Jewish ancestry in this analysis.

£, British pound sterling; AJ, Ashkenazi Jewish; QALY, quality adjusted life-years; UK, United Kingdom.


premenopausal oophorectomy on reduction in BC risk recently has become an issue of ongoing debate. Some Dutch investigators have questioned this benefit. However, the period of follow up in their analysis is short. A number of other investigators have found benefit and disagree with them. Nevertheless, if we assume no benefit of reduction in BC risk from premenopausal oophorectomy, then the ICER per QALY for 1, 2, 3, and 4 grandparents is £1971/$2843 per QALY, £497/$8198 per QALY, £1715/$13595 per QALY, £2420/$16697 per QALY in UK/US women, respectively. This suggests that a population screening approach would be cost-effective, even if there were no benefit on reduction in BC risk from premenopausal oophorectomy. Our model incorporates risk-reducing mastectomy rates that have been seen in the UK. However, these rates may be lower in Israeli BRCA1/BRCA2 carriers. Hence, we explored a scenario analysis at the much lower risk-reducing mastectomy rate of 13% that was reported in Israeli women. The discounted ICERs for a 13% risk-reducing mastectomy rate are £1958/$11059 per QALY, £1177/$7548 per QALY, £196/$1255 per QALY and £3056/$12,103 per QALY for UK/US women with 4, 3, 2, and 1 AJ grandparents, respectively. In addition, a scenario with a much lower RRSO uptake at 20% was explored. The discounted ICERs for this scenario in UK/US women are £2589/$17,786 per QALY, £1759/$14,032 per QALY, £301/$7366 per QALY and £2793/$7110 per QALY for women with 4, 3, 2, and 1 AJ grandparents. Thus, population-based testing in AJ women of differing ancestry remains cost-effective in the UK and US, even with low risk-reducing mastectomy or low RRSO rates too. Given the wide variation in genetic testing costs in the US health system, we also explored thresholds for cost-effectiveness for population testing. We find that population testing remains cost-saving for up to 2 AJ grandparents (cost-effective for 1 AJ grandparent) if the BRCA founder mutation testing costs $526 per test. Additionally the program remains cost-effective (at the $100,000 per QALY WTP threshold) for all 4 AJ grandparents even if the cost of a test rises to $1618, $2417, $3185, and $3934 for 1, 2, 3, and 4 AJ grandparents, respectively.

All surgical interventions have an associated complication rate. The complication rates reported for RRSO are approximately 4%, although that for risk-reducing mastectomy is much higher, with reports that range from 30–64%. Another limitation of the analysis is lack of adjustment for any potential negative impact on quality of life after RRSO. Although worse sexual functioning and vasomotor symptoms have been reported after RRSO, there was no difference in generic quality of life. These issues must be highlighted clearly when women are counselled about these procedures and be incorporated into the informed decision-making process. It is reassuring that most women report high satisfaction rates with surgical prevention, with satisfaction rates that vary from 83% for mastectomy to 97% for oophorectomy.

Our results support the move for changing the paradigm from FH-based to population-based BRCA1/BRCA2 testing across the AJ population. This fulfills the necessary principles for population screening for genetic susceptibility of disease. Population testing offers the ability to maximize the opportunity for prevention in unaffected individuals and to facilitate targeted precision medicine.
approaches in those who may experience the development of cancer. This approach has been advocated by us and others.\textsuperscript{1,8-10} It is also important to highlight that those with fewer grandparents, but a significant FH of cancer (fulfilling non-Jewish general population testing criteria) particularly in non-AJ relatives, should seek genetic advice and not be reassured falsely. It is important to rule out the presence of a non-founder mutation in this situation through a full BRCA1/BRCA2 screen analysis. Additionally, our findings cannot be extrapolated or generalized to BRCA1/BRCA2 testing in the general non-Jewish population, which requires further research. Implementation of a population-testing strategy will require wide-scale propagation and dissemination of information and knowledge, working in close partnership with community stake holders and health professionals. Moreover, implementation issues related to health system delivery, referral and management pathways, logistics, and control, which can vary across different models of care in different countries, remain to be ironed out.

References

27. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn’t it increase at the rate of inflation? Arch Intern Med 2000;160:1637-41.
61. 6174delT mutations: a combined analysis of 22 BRCA1 5382insC and 185delAG and BRCA2 Breast and ovarian cancer risks to carriers of the demiol Biomarkers Prev 2012;21:1458-68

Author and article information
From the Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London (Dr Manchanda and Ms Patel); the Department of Gynaecological Oncology, Barts Health NHS Trust, Royal London Hospital (Dr Manchanda); the Gynaecological Cancer Research Centre, Department of Women’s Cancer, Institute for Women’s Health, University College London (Drs Manchanda and Memori); the Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine (Dr Legood and Ms Patel); and Barts Cancer Institute, Queen Mary University of London (Dr Turnbull), London, UK, the Centre for Cancer Genetic Epidemiology, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, UK (Dr Antoniou), Medical Genetics Institute, Shaare Zedek Hospital, Jerusalem, Israel (Dr Levy-Lahad); Centre for Genomic Medicine, Division of Evolution and Genomic science, University of Manchester, Manchester, UK (Dr Evans); Centre for Epidemiology & Biostatistics, Melbourne School of Population & Global Health, Faculty of Medicine, Dentistry & Health Sciences, University of Melbourne, Victoria, (Dr Hopper); and the Cancer Epidemiology & Intelligence Division, Cancer Council Victoria, (Dr Macinnia), Melbourne, Victoria, Australia; and the University of New South Wales, UNSW Sydney NSW (Dr Jacobs).

Received May 11, 2017; revised June 22, 2017; accepted June 30, 2017.

Supported by “The Eve Appeal” charity, which had no role in the study design, data collection, analysis, interpretation, writing of the report, or decision to submit for publication. The research team was independent of funders.

I.J. and U.M. have a financial interest in Abcodia, Ltd, which is a company formed to develop academic and commercial development of biomarkers for screening and risk prediction; I.J. is a member of the board of Abcodia Ltd and a Director of Women’s Health Specialists Ltd. R.M. declares funding for research from Cancer Research UK and Barts and the London Charity outside this submitted work and an honorarium for grant review from Israel National Institute for Health Policy Research. The other authors declare no conflict of interest.

Ethical approval for cost-effectiveness analysis was received from the Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee (REC Reference number 08/H0713/44), within the GCaPPS trial.


Corresponding author: Ranjit Manchanda, MRCOG, PhD. r.manchanda@qmul.ac.uk