Cost effectiveness of population based BRCA1 founder mutation testing in Sephardi Jewish women

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Disclosures

IJ and UM have a financial interest in Abcodia, Ltd., a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. IJ is a member of the board of Abcodia Ltd and a Director of Women's Health Specialists Ltd. RM declares funding for research from Cancer Research UK and Barts and the London Charity outside this submitted work as well as honorarium for grant review from Israel National institute for Health Policy Research. The other authors declare no conflict of interest.

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ABSTRACT:

Background

Population-based *BRCA1/BRCA2* founder-mutation testing has been demonstrated as cost-effective compared to family-history(FH) based testing in Ashkenazi Jewish(AJ) women. However, only one of the three AJ *BRCA1/BRCA2* founder-mutations *(185delAG(c.68_69delAG), 5382insC(c.5266dupC) and 6174delT(c.5946delT))* is found in the Sephardi Jewish(SJ) population *(185delAG(c.68_69delAG))* and the overall prevalence of *BRCA* mutations in the SJ population is accordingly lower (0.7% compared to 2.5% in the AJ population). Cost-effectiveness analyses of BRCA testing have not previously been performed at these lower *BRCA* prevalence levels seen in SJ. Here we present a cost-effectiveness analysis for UK and US populations comparing population-testing with Clinical-criteria/FH-based testing in SJ women.

Methods

A Markov model was built comparing the lifetime costs-&-effects of population-based *BRCA1*-testing with testing using FH-based clinical criteria in SJ women ≥30years. *BRCA1*-carriers identified were offered MRI/mammograms and risk-reducing surgery. Costs are reported at 2015 prices. Outcomes include breast cancer(BC), ovarian cancer(OC) and excess deaths from heart disease. All costs-&-outcomes are discounted at 3.5%. The time horizon is life-time, and perspective is payer. The incremental-cost-effectiveness-ratio (ICER) per quality-adjusted life-year (QALY) was calculated. Parameter uncertainty was evaluated through one-way and probabilistic-sensitivity-analysis (PSA).

Results

Population-testing resulted in gain in life-expectancy of 12months (QALY=1.00). The baseline discounted ICER for UK population-based testing =£67.04/QALY and for US population=$308.42/QALY. Results were robust in the one-way sensitivity analysis. The PSA showed 100% of simulations were cost-effective at £20,000/QALY UK and the $100,000/QALY US WTP thresholds. Scenario analysis showed, population-testing remains cost-effective in UK and US populations even if pre-menopausal oophorectomy does not reduce BC-risk or if hormone-replacement-therapy compliance is nil.

Conclusion

Population-based *BRCA1*- testing is highly cost-effective compared to clinical-criteria driven approach in SJ women. This supports changing the paradigm to population-based *BRCA*-testing in the Jewish population regardless of Ashkenazi/Sephardi ancestry.

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INTRODUCTION

Genetic testing for *BRCA1/BRCA2* mutations has conventionally been offered to affected individuals or those fulfilling strict clinical or family-history (FH) based criteria. However, using this FH-based approach results in over 50% of *BRCA1/BRCA2* carriers being missed, as they do not meet the threshold for these clinical criteria.[1, 2] The Genetic Cancer Prediction through Population Screening (GCaPPS) randomized trial (ISRCTN73338115), demonstrated population-based *BRCA1/BRCA2* founder mutation testing (performed regardless of personal or family history of cancer) in women of Ashkenazi Jewish (AJ) descent, to be both cost-saving and more effective compared to FH-based testing[3] providing strong supporting evidence for its adoption. UK and Israeli studies have shown that population-based *BRCA1/BRCA2* testing in Ashkenazi Jews is feasible, acceptable, identifies more people at risk and does not cause detrimental psychological and quality-of-life consequences.[1, 2, 4] The increasing availability and access to Next Generation Sequencing platforms and concomitant decreasing cost of genetic-testing[5] has rendered large scale high throughput testing of populations both more affordable and technically feasible. Given the findings of the GCaPPS randomized control trial, and corroborating cohort studies, many have advocated for *BRCA1/BRCA2* testing to be offered to the whole Jewish population, regardless of family history.

AJ are descendants of Jews who emigrated from France, Germany, and Eastern Europe in 1800s-1900s. Sephardi Jews (SJ) are descendants of Jews from Spain and Portugal (Sephardim) as well as, North Africa, Iraq and Morocco (Mizrachim). Around 25% of the Jewish population is not of Ashkenazi descent.[6] Importantly, while three *BRCA1/BRCA2*

founder mutations (185delAG(c.68_69delAG), 5382insC(c.5266dupC) and 6174delT(c.5946delT)) have been described in AJ, only one of these (185delAG(c.68_69delAG)) is found in SJ.[7-9] Hence, the mutation prevalence in much lower in SJ (0.5%-1%) [8, 9] compared to AJ (2.5%).[2] Population-testing studies have been undertaken in the AJ population in the UK, Israel and Canada and show acceptability of this approach as well as the feasibility of providing this outside a hospital setting.[2, 4, 10] While, evidence exists to support a shift towards population-based testing in the AJ community, this evidence cannot be used to reach the same conclusion for the whole Jewish community as corresponding data on cost-effectiveness are lacking for the Sephardi population with the lower prevalence of mutations. This highlights the need for a greater evidence base in the SJ population.

A cost-effectiveness assessment is a vital tool used to evaluate the costs and benefits of different health interventions. This helps with the allocation of scarce resources within healthcare and assists with policy decision making.[11] In this study we for the first time evaluate and report on the cost-effectiveness of population-based *BRCA*-testing in the SJ population.

METHODS

The lifetime costs and effects of *BRCA1* testing were analyzed through a Markov model (Figure-1) comparing the current practice of Clinical criteria/FH testing to population testing of all SJ women ≥30 years for the *BRCA1* SJ mutation. Separate analyses were performed for UK and US populations. Other analytical models assume all events occur simultaneously in the same time sequence. However, with a disease such as cancer events are likely to occur over a period of time. A Markov model allows for this temporal element and permits

patients to move through mutually exclusive health states through a series of transition probabilities over a period of time. The Markov model assumes genetic counselling and genetic testing was undertaken in women fulfilling clinical testing criteria in the FH arm and in all women in the population-testing arm. Clinical criteria for testing includes: personal history of ovarian cancer (OC) at any age; first degree relative with OC (any age); first-degree-relative with or personal history of breast cancer (BC) <50 years; first-degree-relative with or personal history of male breast cancer at any age.[2] Testing positive for the *BRCA1* mutation resulted in women being offered a risk-reducing salpingo-oophorectomy (RRSO) which would lead to a reduction in their OC risk.[12] To reduce their BC risk, women testing positive were offered MRI and mammography screening or a risk-reducing mastectomy (RRM).[13] Pre-menopausal bilateral oophorectomy is associated with an increased risk in cardiovascular mortality, especially in women who do not take hormone-replacement-therapy (HRT).[14, 15] The increased cardiovascular risk (number needed to harm (NNH)=1:33) is integrated in the model and HRT is given to women till the age of 51 (menopause) if they have an RRSO, with HRT compliance assumed to be 80% (CI:76%,83%).[16] Additionally, costs of bone health monitoring and HRT supplementation are included in the model. All costs and outcomes were discounted at a rate of 3.5% in line with the reference case guidelines published by the National Institute of Health and Care Excellence (NICE).[17] BC risk is not affected by taking short-term HRT after RRSO.[18] As a mortality benefit has not been shown with OC screening, it has been excluded from the model.[18]

Probabilities

The various probabilities used in the model are described in Table-1.

Costs

Costs are reported at 2015 prices and where required have been converted using the Hospital and Community Health Service Index.[19, 20] They are derived from the health system/payer perspectives. These are described in detail in Table-2. In line with NICE recommendations, future healthcare costs outside of those associated with OC/BC were not considered.[17]

Life years

Lifetime horizons extending to 83/82 years for the female UK/US populations were used to model the lifetime risks and consequences of *BRCA*-testing. General population life tables were obtained from the Office of National Statistics for the UK population and from Surveillance, Epidemiology, and End Results Program for the USA population. Specific SJ data are unavailable for these estimates. Hence, life time SJ risks and survival estimates are assumed to be the same as the rest of the general population. The mean age for BC/OC onset was 41/54 years for *BRCA1* mutations in SJ women respectively.[21, 22] The mean ages for sporadic BC and OC were 57/62 years and 63/63 years in the UK/US populations respectively.[22-24] Probability of dying from background mortality was taken from the general UK and US populations in the absence of SJ distinct data.[25] Statistically significant differences in survival have not been observed between *BRCA1* genetic and sporadic BC cases.[26, 27 28] No statistically significant difference in 10year survival rates have been found between *BRCA1*-OC and sporadic-OC either. [29] The average 10-year survival for BC is 78.4%/84.6% and OC is 34.5%/34.2% in UK/US populations.[29, 30] After ten years survival, the probability of death was assumed to be the same as the general population.

Quality adjusted life years (QALY)

QALYs are a measure of health outcomes recommended by NICE for use in economic evaluations. It uses utility-weights which reflects the preference of an individual for a particular health state between 1, indicating perfect health, and 0, indicating death. Utility weights are multiplied by survival in life-years to produce the QALY measure.[31] The following utility-scores were used for early, advanced, recurrent and end stages of BC: 0.71, 0.65, 0.45 and 0.16 respectively and were obtained from NICE guidance.[32] The following utility-scores were used for early, advanced, recurrent and end stages of OC: 0.81, 0.55, 0.61 and 0.16 respectively.[33] In addition, women may experience negative health effects from undertaking a RRM and RRSO. [34, 35] To account for this, utility-scores of 0.88(SD=0.22) for RRM and 0.95(SD=0.10) for RRSO were incorporated in the model.[36]

Analysis

The Markov model used to evaluate the costs and outcomes is illustrated in Figure-1. All analyses were conducted in TreeAge Pro 2016 (Williamson, Massachusetts). The costs of the population-testing arm were compared to the costs of the FH-based testing arm. The effects evaluated in both arms were evaluated in terms of total life-years and QALYs. The discount rate of 3.5% was used for both costs-&-effects, in line with the NICE reference case which acknowledges values for future costs and benefits are considered lower in value than in the present.[37] The incremental cost-effectiveness ratio (ICER) was estimated by dividing the difference in cost between the two strategies (Population testing and Criteria/FH testing) by the difference in effect. $\mathrm{ICER} = (\mathrm{Cost}^{\text{Population testing}} - \mathrm{Cost}^{\text{Criteria/FH testing}})/(\mathrm{QALYs}^{\text{Population testing}} - \mathrm{QALYs}^{\text{Criteria/FH testing}})$. The ICER calculated was compared to the NICE cost-effectiveness willingness-to-pay (WTP) threshold (£20,000-£30,000/QALY) for UK analysis,[38] and

$100,000/QALY WTP for US analysis[39, 40] to assess the cost-effectiveness of population-based *BRCA1* founder-mutation testing in SJ women.

The baseline ICER calculated includes the benefit in BC-risk reduction from undergoing a RRSO. However, this benefit has recently been questioned by a Dutch group.[41] Therefore, scenario analyses were performed for comparing population-testing with FH-testing where no reduction in BC-risk occurred following RRSO. A further scenario explored the impact on the results where no HRT was offered. Additionally, as RRM and RRSO rates in Israeli Jews are reported to be lower than *BRCA*-carriers living in Europe/North America, a scenario analysis of lower RRM rate (13%) and lower RRSO rate (49%) was also evaluated.[42]

The parameters used in the model have a certain degree of uncertainty associated with them. To explore the uncertainty of the model results, extensive sensitivity analysis was undertaken. One-way sensitivity analysis varies the estimate of one parameter at a time, keeping all other parameters at their baseline to assess the impact of that parameter on the ICER. Probabilities and utility-scores were varied by their 95% confidence-intervals, whilst costs were altered by +/-30%. One-way analysis provides information on which parameter has the largest impact on the ICER and therefore, highlights parameters of major significance which could be the focus of further research. However, parameters are most likely to vary together and not independently of each other and so probabilistic sensitivity analysis (PSA) was also conducted. In the PSA parameters were varied simultaneously according to their distributions for a total of 10,000 iterations to investigate joint uncertainty. Distributions were assigned according to the literature: probabilities and utilities were fitted with a beta distribution and costs with gamma distributions.[43, 44] The results of the 10,000 iterations were plotted on a cost-effectiveness acceptability curve

which portrays the proportion of simulations that are cost-effective at differing WTP thresholds for each arm of the Markov model.

RESULTS

The discounted values for total cost, QALYs and life-years for both the population-based testing and the Clinical Criteria/FH-based testing approaches are given in Table-3. The results show population-testing in SJ is cost-effective compared to current practice of *BRCA*-testing using FH-based clinical criteria in both UK and US populations. Baseline results show population-testing extends average life expectancy by 12.19/12.17 months and has an ICER of £67.04/QALY and $308.42/QALY in UK and US populations respectively. This is significantly below the NICE threshold of £20,000/QALY and $100,000/QALY US WTP threshold indicating population-testing is highly cost-effective.

One way sensitivity analysis was undertaken for all the probabilities, costs and utilities. Figure-2 and Figure-3 show the parameters that had the largest impact on the ICER in the UK and US one-way analysis respectively. The model was most sensitive overall to *BRCA1* mutation prevalence estimates in the Sephardi population and in FH-positive individuals. However, these results still remain cost-effective at much well below the £20,000-£30,000/QALY and $100,000/QALY WTP thresholds. The PSA (Figure-4 and Figure-5) shows that 100% of the iterations are cost-effective for population-based testing at the £20,000/QALY and $100,000/QALY WTP thresholds, again reconfirming that this strategy is highly cost-effective.

The model remains cost-effective for the various scenario analyses undertaken. If it is assumed there is no risk reduction in BC-risk following RRSO then the ICER becomes £67.69/QALY with 12.18 months gain in life expectancy in the UK and an ICER of

$311.25/QALY with 12.17 months gain in life expectancy in the US. If women decline or are unable to take HRT, then the ICER for population testing increases to £67.05/QALY and $308.48/QALY, with a gain in life expectancy of 12.18/12.17 months in the UK/US respectively. The model is not very sensitive to the parameter of HRT use and the PSA shows that at >99% simulations remain cost-effective at lower rates of use. A lower uptake of RRM at 13% and RRSO at 49% has been reported in the Jewish population.[42] Assuming a lower uptake of both surgeries, the ICER increases to £67.81/QALY and $312.84/QALY in UK/US populations with 12.17 months gain in life expectancy in both populations. All three scenarios represent a slight increase from the baseline ICERs of £67.04 and $308.42 in the UK and US populations. However, all scenarios remain cost-effective and markedly below the NICE £20,000/QALY and US $100,000/QALY WTP thresholds. In addition, even if the cost of testing rises to $2000/test population testing remains cost-effective, with an ICER= $1798/QALY.

DISCUSSION

Population-based *BRCA*-testing in the SJ population is highly cost-effective compared with a clinical criteria /FH-based strategy with an ICER of £67.04/QALY and $308.42/QALY, well below the NICE £20,000-£30,000/QALY and US $100,000/QALY WTP thresholds respectively. That 100% of simulations are cost-effective (£20,000/QALY and $100,000/QALY WTP thresholds), despite uncertainty in model parameters, is highly reassuring. Whilst evidence exists on the cost-effectiveness of population-testing in other Jewish populations, notably the AJ population,[3] the literature has been lacking for the SJ population. This report addresses this knowledge gap and finds population-testing for *BRCA1* founder mutations in SJ women to also be highly cost-effective, resulting in 12 months estimated life expectancy

gained, over clinical criteria driven testing. Around 20% of the Jewish population is Sephardi.[6] These findings coupled with our earlier analysis showing cost-effectiveness in the AJ population,[3, 45] support population-based *BRCA*-testing in the entire Jewish population.

This study has a number of advantages. The comparator used in this analysis is based on current practice and NICE/ published clinical guidelines for *BRCA* management. In addition, the analysis meets NICE guidelines on economic evaluations. QALYs have been used as the measure of health effects, and costs and outcomes are discounted at the recommended 3.5% rate. The lifetime time-horizon used is advantageous in mapping the full costs and outcomes over the lifetime of female SJ and not just the costs and outcomes occurred at the point of intervention. Furthermore, the possible adverse effects of undertaking prophylactic RRM and/or RRSO are reflected in the utility-values assigned to the prophylactic surgeries. We also include a detriment for cardiovascular mortality associated with HRT non-compliance. Incorporating these effects limits overestimating the number of QALYs acquired through surgical prevention, which in turn minimizes underestimating the final baseline ICER/QALY. The one-way sensitivity and PSA show that the model is robust to the various parameter estimates. The confidence-intervals or range of these estimates are reasonably wide. Costs of surgical prevention or treatment costs for OC, BC, or cardiovascular events do not significantly impact model results.

There are also limitations of this model. As far as possible, population-based data have been used to obtain the parameters in the analysis. However, primary data for the *BRCA* mutation prevalence in FH-negative SJ women are unavailable and this has been calculated by using a combination of other parameters, such as the overall *BRCA* mutation prevalence in SJ women, *BRCA* mutation prevalence in FH-positive individuals and the probability of having a

positive FH fulfilling the genetic testing criteria (Table-1). But the three probabilities used to calculate this value have been determined from population-based data and the value used in the analysis (0.000493) is realistic and similar to estimates expected from a low-risk general population.[46] Additionally, sensitivity analysis has found population-testing to still be cost-effective despite the significant uncertainty around this parameter. We have not included the benefit of Tamoxifen based chemoprevention reported in high-risk women. Tamoxifen prevents mainly estrogen receptor positive BC and ~70% off *BRCA1*-associated BC are ER negative.[47, 48] Besides overall uptake rates reported in the literature are low (~16%)[49] and unknown for the SJ population. Including Tamoxifen would make the model more cost-effective and we chose not to overestimate its benefit given that tamoxifen has not been shown to reduce incidence of ER negative BC. Our analysis covers testing for the *BRCA1* founder mutation which is common in SJ. Women with very strong FH of cancer (similar to that found in the non-Jewish general population) who test negative for the SJ founder mutation should be referred to clinical genetics for a full/extended *BRCA1/BRCA2* screen analysis for non-founder mutations.

The different scenarios tested by the model add to the strength of the analyses. The risk of CHD from undertaking a RRSO has been incorporated in the model assuming an 80% HRT compliance, yet the true compliance rate in a SJ population has not been fully determined. This is important as HRT alleviates cardiovascular risk and the cardiovascular mortality impact is seen predominantly in those who are non-compliant.[14] However, HRT compliance does not seem to have a major impact on the overall results, as population-testing remains highly cost-effective even at 0% compliance rate in our scenario analysis. Our analysis does not include the excess mortality due to lung/colorectal cancer reported in the Nurses Health Study, as it may be confounded by cigarette smoking or other risk related behaviours and

this finding has not been corroborated in some other larger studies. Smoking itself is associated with early menopause.[50, 51] Additionally, results of the NIH-AARP (American Association of Retired Persons) Diet-&-Health Study in 185,017 women, found stratification by smoking status, demonstrated that increased lung cancer risk associated with bilateral oophorectomy was absent in non-smokers and restricted only to smokers.[50] Additionally, the European Prospective Investigation into Cancer and Nutrition (EPIC) study (337,802 women) results found no significant association between colorectal cancer risk and age at menarche/menopause or type of menopause (surgical/natural).[52] Nevertheless, we modelled a scenario of increased all-cause mortality (NNH of 1 in 8) reported by Parker et al,[14] and found that population testing in SJ remains cost-effective (ICER=£67/QALY or $308/QALY). Whether pre-menopausal oophorectomy leads to a reduction in BC-risk has recently been the subject of recent debate. Although a recent Dutch paper found no such benefit,[41]other investigators have reported BC-risk reduction with pre-menopausal oophorectomy.[53-55] Given the recent uncertainty around this parameter, if we assume no benefit from pre-menopausal oophorectomy then the ICER increases, but the value is still well below the NICE and USA WTP thresholds indicating that population based testing is still cost effective. Specific uptake rates of RRM and RRSO in SJ women are lacking. In the absence of these data, we use RRM and RRSO rate data from UK *BRCA1* carriers. It is reassuring that population testing remains cost-effective even at lower uptake rates of 13% for RRM and 49% for RRSO (ICER= £67.81/QALY and $312.84/QALY) reported in Israeli women compared to women from western populations.[42]

The Jewish population is the first population in whom unselected population-based *BRCA*-testing has been extensively evaluated and can become a reality. Overall this does not harm psychological well-being or quality of life.[2] Our study shows population testing for *BRCA1*

mutations in SJ is extremely cost-effective compared to traditional FH-based testing and supports a paradigm change to population-based testing in the SJ population. This corroborates initial results from the AJ population,[3, 45] providing the rationale for offering *BRCA* founder-mutation testing in the entire Jewish population. This could have implications for *BRCA*-testing in other founder populations too. The number of cases of BC and OC are expected to increase by 24% and 27% in the UK, by 34% and 39% in the USA, by 51% and 55% in Israel and by 55% and 55% worldwide by 2035.[56] Identification of high-risk individuals who can benefit from effective preventive interventions provides an excellent opportunity to reduce the burden of BC and OC. It is extremely important that we utilize this opportunity offered by a population testing strategy for maximizing cancer prevention. Delivering such a strategy will warrant broadening of existing, and development of new referral and management pathways. These will differ from one country to another. There is also the need to increase public and health professional awareness and knowledge; as well as develop closer coordination and better communication between general practitioners, hospital health professionals, stakeholder and professional organizations, community charities and public at large.

Ethics approval

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

Contribution to authorship

RM conceived the analysis. RM, RL, SP and AA developed the adapted model parameters. SP, RM, RL undertook the revised analysis. RM, SP, RL prepared an initial draft. SP, RM, RL, GR, CT, AA, UM, IJ critically contributed to writing the manuscript and approved the final version.

Disclaimers/ Conflict of interest statement

IJ and UM have a financial interest in Abcodia, Ltd., a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. IJ is a member of the board of Abcodia Ltd and a Director of Women's Health Specialists Ltd. RM declares funding for research from Cancer Research UK and Barts and the London Charity outside this submitted work as well as honorarium for grant review from Israel National institute for Health Policy Research. The other authors declare no conflict of interest.

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Table-1: Probabilities used in the Markov Model

Probability	Value	(95% confidence interval) [Range]	Description	Source
P1	0.007049	(0.0028 – 0.0145)	BRCA1 mutation prevalence in Sephardi population	Barsade[8]
P2	0.60	(0.47 – 0.74)	Probability that *BRCA1* carrier will undergo RRM	Evans[57]
P3	0.85	(0.44 – 0.96)	Reduction in risk of ovarian cancer from RRSO	Kauff[54]
P4	0.40	(0.35 – 0.46)	Probability that *BRCA1* carrier without RRSO will get ovarian cancer	Chen[12]
P5	0.0185	(0.0005 – 0.09898)	Probability that a non-carrier will get ovarian cancer	CRUK[58]
	0.0128	(0.0126 – 0.013)	Probability that a non-carrier will get ovarian cancer – US estimate	SEER[59]
P6	0.1238	(0.1043 – 0.1454)	Probability of having a positive family history fulfilling genetic testing clinical criteria	Manchanda[3]
P7	0.053	(0.0199 – 0.113)	*BRCA1* mutation prevalence in FH positive individuals	Barsade[8]
P8	0.000493	[0.000345 – 0.000641]	*BRCA1* prevalence in family history negative individuals	
P9	0.91	(0.62 – 0.98)	Reduction in breast cancer risk from RRM without RRSO in *BRCA1* carriers	Rebbeck[13]
P10	0.57	(0.47 – 0.66)	Probability that *BRCA1* carrier without RRM will get breast cancer	Chen[12]
P11	0.129	(0.11 – 0.14)	Probability that a non-carrier will get breast cancer	CRUK[58]
	0.1243	(0.1236 – 0.1249)	Probability that a non-carrier will get breast cancer – US estimate	SEER[23]
P12	0.66	(0.53 – 0.80)	Probability that a *BRCA1* carrier will follow-up with RRSO	Evans[57]
P13	0.47	(0.35 – 0.64)	Reduction in risk of breast cancer from RRSO alone in *BRCA1* carrier	Rebbeck[60]
P14	0.95	(0.78 – 0.99)	Reduction in risk of breast cancer from RRM with RRSO in *BRCA1* carrier	Rebbeck[13]
P15	0.0303	(0.011 – 0.043)	Risk of mortality from CHD after	Parker[14]

			RRSO	
P16	0.8008	(0.25 – 0.83)	Compliance with HRT	Read[16] Garcia[61]

CRUK – Cancer Research United Kingdom, CHD – coronary heart disease, FH – family history, HRT – Hormone replacement therapy, RRM – risk reducing mastectomy, RRSO – risk reducing salpingo-oophorectomy, SEER – Surveillance, Epidemiology, and End Results Program, SJ – Sephardi Jewish

P1: The probability of carrying a *BRCA* founder mutation in an unselected SJ population is calculated from analysis carried out by Bar-sade.[8]. The estimate was calculated by dividing the number of 185delAG *BRCA1* mutations detected in the Iraqi and Moroccan Jews by the total number of samples taken from those two countries=7/993.

P2: The probability of RRM uptake for a *BRCA1* carrier is taken from Evans et al, 2009.[57]

P3: The reduction in ovarian cancer risk in *BRCA1* carriers is obtained from Kauff et al 2008, whose findings are consistent with other studies reporting that following an RRSO, a 4% risk of peritoneal cancer remains.[54]

P4: The probability that a *BRCA1* carrier without RRSO will get ovarian cancer is taken from Chen et al, 2007.[12]

P5: Estimates for of risk of ovarian cancer in non-*BRCA* UK carriers is obtained from Cancer Research UK[58] and from SEER data[59] for US carriers.

P6: GCaPPS study provides the estimates for probability of having a positive family history fulfilling current clinical criteria for genetic testing in a Jewish population.[3]

P7: *BRCA1* mutation prevalence in FH positive individuals is obtained from Bar-sade et al, 1998[8] : 6 carriers detected in 112 Sephardi individuals with of breast or ovarian cases, giving a probability of (6/112) 0.053.

P8: *BRCA1* prevalence in family history negative individuals is obtained by multiplying the probability of having a strong FH fulfilling current clinical criteria for genetic testing (P6) by the *BRCA1* mutation prevalence in FH positive individuals (P7). This value was then taken away from the BRCA1 mutation prevalence in general population controls (P1) to get the BRCA1 Mutation prevalence in FH negative individuals (P8): 0.007049 – (0.123 * 0.053).

P9: Reduction in breast cancer risk from RRM in *BRCA1* carriers is obtained from PROSE study data reported by Rebbeck et al, 2004.[13]

P10: The probability that *BRCA1* carrier without RRM will get breast cancer is obtained from a meta-analysis conducted by Chen et al, 2007 [12]

P11: Estimates for risk of breast cancer in UK non-*BRCA* carriers is taken from the UK Office for National Statistics and from Cancer Research UK[58] and from SEER data[59] for US women.

P12: Probability of a *BRCA1* carrier undergoing an RRSO are taken from Evans et al, 2009.[57]

P13: Reduction in risk of breast cancer from RRSO alone in a *BRCA1* carrier is obtained from a meta-analysis by Rebbeck et al, 2009.[60]

P14: Reduction in risk of breast cancer in *BRCA1* carriers undergoing RRM and RRSO is obtained from data from the PROSE study by Rebbeck et al, 2004.[13]

P15: Risk of mortality from CHD after RRSO is taken from the Nurses Health Study. [14] This is reported as 0.0303 pre-menopausal women not taking HRT but undergoing a RRSO.

P16: Compliance rate for HRT is taken from Read et al, 2010[16] and the lower limit of the range modelled is from Garcia 2015.[61]

Table 2: UK and US costs used in the Markov Model

Item	UK cost (£)	US cost ($)	Source
Cost of genetic testing for *BRCA1* founder mutation	50	300	GCaPPS[2]
Cost of counselling with DVD	26	41	GCaPPS,[2] PSSRU Unit costs of Health and Social Care,[20] Schwartz[62]
Cost of RRSO (and HRT and osteoporosis prevention)	2772	8144	NHS Reference costs,[19] BNF,[63] Grann,[36], Williams-Frame[64]
Cost of ovarian cancer diagnosis and treatment	14,201	127,995	NHS Reference costs,[19] NICE guideline,[65] Grann[36]
Yearly cost of ovarian cancer treatment year 1-2	5169	14,071	NHS Reference costs,[19] NICE guideline,[65] CRUK,[66] Grann[36]
Yearly cost of ovarian cancer treatment year 3-5	4798	14,071	NHS Reference costs,[19] NICE guideline[65] CRUK,[66] Grann[36]
Terminal care cost with ovarian cancer	15588	89,424	National Audit Office,[67] [36]
Cost of risk reducing mastectomy	4058	12,596	NHS reference cost,[19] weighted for 21% complication rate,[68] Grann[36]
Cost of breast screening	50	153	Robertson 2011,[69] NHS Reference costs,[19] Grann[36]
Cost of breast screening genetic	50 - 214	153 – 1603	NHS Reference costs[19], NICE guideline,[70] Grann[36]
Cost of breast cancer diagnosis and treatment in non-*BRCA* carriers	15,993	82,030	NHS Reference costs[19], NICE guideline[71], NICE guideline,[32] Grann[36]
Cost of breast cancer diagnosis and treatment in *BRCA1* carriers	14,476	75,873	NHS Reference costs[19], NICE guideline[71], NICE guideline,[32] Grann[36]
Yearly cost of breast cancer treatment for 5 years	1852	7738	NHS Reference costs[19], Robertson 2011[69], BNF[63], NICE guideline[71], NICE guideline,[32] Grann[36]
Yearly cost of genetic breast cancer for 5 years	1746	7738	NHS Reference costs[19], Robertson 2011[69], BNF[63], NICE guideline[71], NICE guideline,[32] Grann[36]
Terminal care cost with breast cancer	15,588	65,403	National Audit Office,[67] Grann[36]
Cost of coronary heart disease	3343	23,012	NHS Reference costs,[19] Afana[72]
BNF – British National Formulary, GCaPPS – Genetics Cancer Prediction through Population Screening study, HRT – hormone replacement therapy, NHS – National Health Service, NICE – National Institute for Health and Clinical Excellence, PSSRU – Personal Social Services Research Unit, RRSO – risk reducing salpingo-oophorectomy, RRM – risk reducing mastectomy. Model costs are estimated at 2015 prices			
RRSO costs: Calculated using national reference costs for upper genital tract laparoscopic/endoscopic intermediate procedure. RRSO costs include HRT costs taken from			

the BNF[63], until the average age of menopause at 51 years with an 80% compliance rate assumed. Bone health monitoring and osteo-protection costs are comprised of three follow up dual energy X-ray absorptiometry (DEXA) scans and daily calcium and vitamin-D3 supplementation for osteo-protection.[19] Prophylactic salpingo-oophorectomy costs in the US population are taken from Grann et al, 2011[36] and inflated to 2015 prices using the medical component of the US consumer price index.

Ovarian cancer costs: Diagnosis costs include pelvic exam, ultrasound, percutaneous biopsy and cytology, CT scan and CA125 test. Treatment costs include surgical costs for a lower and upper genital tract procedure with 6 chemotherapy cycles of carboplatin and paclitaxel and chemotherapy administration costs. Follow-up costs include consultant visits, CT scan and CA125 tests and recurrent ovarian cancer treatment costs.[19, 65] UK costs are taken from NICE guideline and NHS reference costs.[19, 65] Ovarian cancer costs for the US population are taken from Grann et al, 2011[36] and inflated to 2015 prices using the medical component of the US consumer price index.

Breast cancer screening for non-*BRCA* carriers: follows the UK NHS breast cancer screening program where mammography is offered every 3 years from the age of 50 until 70.[73] For the US, recommendations in a CDC report were followed where mammography is offered every 2 years from the age of 50 until 70.[74]

Breast cancer screening for *BRCA1* carriers: follows NICE guideline on familial breast cancer where annual MRI is offered from the age of 30 to 49. Annual mammogram is offered from the age of 40 to 69.[70] For the US, recommendations in a CDC report were followed where MRI and mammography are offered annually from the age of 30 until 50. Mammography is then offered annually from the age of 50 until 70.[74] UK costs are obtained from NHS reference costs.[19] US costs of mammography and MRI are taken from Grann et al, 2011[36] and inflated to 2015 prices using the medical component of the US consumer price index.

RRM costs are weighted for a 21% complication rate [68, 75]and obtained from NHS reference costs[19]. Cost of RRM is taken from Grann et al, 2011[36] and inflated to 2015 prices using the medical component of the US consumer price index.

Breast cancer treatment: costs include mammogram, ultrasound, clinical examination biopsy[71] and sentinel lymph node biopsy and axillary lymph node dissection. [76] Differences in non-*BRCA* and *BRCA* cancer treatment costs arise from the proportion of cancers that are non-invasive DCIS and invasive. In non-*BRCA* populations, 10% breast cancer is non-invasive DCIS and 90% breast cancer is invasive.[76-79] In *BRCA* populations 20% of cancers are DCIS and 80% invasive.[68, 80] Costs include costs of breast conserving surgery, radiotherapy,[71] chemotherapy, endocrine therapy,[32, 71] and bisphosphonate costs[63] and trastuzumab costs for HER2 positive breast cancer.[76] Follow-up costs and treatment of relapse/ recurrence are included.[81-83] Cost of breast cancer treatment is taken from Grann et al, 2011 and inflated to 2015 prices using the medical component of the US consumer price index.[36]

Terminal cancer costs: End of life care costs for breast and ovarian cancer are obtained form end of life care report submitted to the National Audit Office, UK[67] and from Grann et al, 2011 for the US population and inflated to 2015 prices using the medical component of the

US consumer price index.[36]

Table-3: Model outcomes for Population testing and Family-history based strategies

Strategy	Cost (£)	Life years*	QALYs	Cost ($)	Life years*	QALYs
Clinical criteria/ Family history based testing	1647.53	47.0416	22.4220	5972.93	45.7200	22.1224
Population based testing	1714.61	48.0432	23.4226	6281.38	46.7205	23.1224
ICER/QALY	67.04			308.42		

QALY – Quality Adjusted Life Years, ICER – Incremental Cost-effectiveness Ratio

*Undiscounted values shown for life years. Costs and QALYs are discounted.

Figure-1: Markov model structure

Schematic diagram showing the Markov model structure for population and clinical criteria/family history (FH) based testing for *BRCA* mutations. In the population testing arm, all Sephardi Jewish (SJ) women ≥ 30 years old are offered *BRCA1* founder mutation testing. If SJ women test *BRCA1* positive they are then offered a risk reducing mastectomy (RRM) and risk reducing salpingo-oophorectomy (RRSO). Depending on the probability of women undertaking a RRM and/or RRSO they are placed into different health states and then progress to either *BRCA1* associated breast cancer (BC) or ovarian cancer (OC). In the FH arm, only women who have positive FH criteria matching the current guidelines on genetic testing are offered a genetic test. They then follow the same pathway as women in the population testing. Women with a negative FH are either *BRCA1* negative or have an undetected *BRCA1* mutation. *BRCA1* negative women progress to sporadic non-*BRCA* OC or non-*BRCA* BC. Undetected *BRCA1* SJ women progress to *BRCA1* associated BC or *BRCA1* associated OC. All women undergoing an RRSO have an increased risk of fatal coronary heart disease (CHD). Although not shown in the figure, background mortality has been modelled for all health states. Progression through the model is dependent on the probabilities presented in Table 1.

BC- Breast Cancer; CHD- Coronary heart disease; FH – Family history OC-Ovarian Cancer; RRM – Risk reducing mastectomy; RRSO –Risk reducing salpingo-oophorectomy

Figure-2: One-way sensitivity analysis for top 6 parameters affecting UK incremental cost-effectiveness ratio (ICER)

One-way sensitivity analysis in the form of a tornado diagram for the top 6 parameters that have the largest impact on the incremental cost-effectiveness ratio (ICER) of population based testing for *BRCA1* founder mutations, compared to a family history (FH) based approach in the UK.

Y-axis: top 6 parameters with greatest impact on ICER. X-axis: ICER per quality adjusted life year (QALY) (discounted) calculated through varying probabilities and utilities by its upper and lower 95% confidence interval or range as described in Table-1. Costs were varied by +/- 30%. The 'minimum value' represents the lower and the 'maximum value' represents the upper limit of the parameter.

Figure-3: One-way sensitivity analysis for top 6 parameters affecting US incremental cost-effectiveness ratio (ICER)

One-way sensitivity analysis in the form of a tornado diagram for the top 6 parameters that have the largest impact on the incremental cost-effectiveness ratio (ICER) of population based testing for *BRCA1* founder mutations, compared to a family history (FH) based approach in the US.

Y-axis: top 6 parameters with greatest impact on ICER. X-axis: ICER per quality adjusted life year (QALY) (discounted) calculated through varying probabilities and utilities by its upper and lower 95% confidence interval or range as described in Table-1. Costs were varied by +/- 30%. The 'minimum value' represents the lower and the 'maximum value' represents the upper limit of the parameter.

Figure-4: UK Probabilistic Sensitivity Analysis for Sephardi Jewish population

Probabilistic sensitivity analysis showing the percentage of iterations that are cost-effective in the UK at different willingness to pay (WTP) thresholds per quality adjusted life year (QALY) when model parameters are varied simultaneously based on their distributions.

The Y axis represents 10,000 iterations plotted on a cost-effectiveness acceptability curve (CEAC) presenting the proportion of simulations that are cost-effective. The X axis shows the willingness to pay thresholds/QALY. The square marked line shows the CEAC for the family history arm whilst the triangle marked line shows the CEAC for the population testing arm.

Figure-5: US Probabilistic Sensitivity Analysis for Sephardi Jewish population

Probabilistic sensitivity analysis showing the percentage of iterations that are cost-effective in the USA at different willingness to pay (WTP) thresholds per quality adjusted life year (QALY) when model parameters are varied simultaneously based on their distributions.

The Y axis represents 10,000 iterations plotted on a cost-effectiveness acceptability curve (CEAC) presenting the proportion of simulations that are cost-effective. The X axis shows the willingness to pay thresholds/QALY. The square marked line shows the CEAC for the family history arm whilst the triangle marked line shows the CEAC for the population testing arm.