

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

*Ranjit MANCHANDA^{1,2,3} MRCOG, PhD, Shreeya PATEL^{1,4} MSc, Antonis C ANTONIOU⁵ PhD, Ephrat LEVY-LAHAD⁶ PhD, Clare TURNBULL⁷ PhD, Gareth EVANS⁸ PhD, John HOPPER⁹ PhD, Robert J. MACINNIS¹⁰ PhD, Usha MENON³ MD, FRCOG, Ian JACOBS¹¹ MD, FRCOG, Rosa LEGOOD⁴ PhD

¹Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London EC1M 6BQ, UK

²Department of Gynaecological Oncology, Barts health NHS Trust, Royal London Hospital, London E1 1BB, UK

³Gynaecological Cancer Research Centre, Department of Women's Cancer, Institute for Women's Health, University College London, London, UK, W1T 7DN

⁴Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, WC1H 9SH, UK

⁵Centre for Cancer Genetic Epidemiology, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, CB1 8RN, UK

⁶Medical Genetics Institute, Shaare Zedek Hospital, Jerusalem, Israel

⁷Barts Cancer Institute, Queen Mary University of London, London EC1M 6BQ, UK

⁸Centre for Genomic Medicine, Division of Evolution and Genomic science, University of Manchester, Manchester, UK

⁹Centre for Epidemiology & Biostatistics, Melbourne School of Population & Global Health, Faculty of Medicine, Dentistry & Health Sciences, University of Melbourne, Victoria 3010 Australia

¹⁰Cancer Epidemiology & Intelligence Division, Cancer Council Victoria, Melbourne, VIC 3004, Australia

¹¹University of New South Wales, Australia, Level 1, Chancellery Building, UNSW Sydney NSW 2052

***Corresponding Author**

Dr Ranjit Manchanda

Clinical Senior Lecturer & Consultant Gynaecological Oncologist

Barts Cancer Institute, Queen Mary University of London

Room 4, Basement, Old Anatomy Building

Charterhouse Square, London EC1M 6BQ

Email: r.manchanda@qmul.ac.uk

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.

Funding

This study was funded by 'The Eve Appeal' charity. The funding body (The Eve Appeal charity) 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.

Meeting:

This work has been accepted for presentation at the upcoming meeting of the 2017 Annual Scientific Meeting of the British Gynaecological Cancer Society in Newcastle, 15-16th June 2017.

Key Words

BRCA, Ashkenazi Jewish, ancestry, population testing, cost effectiveness

Word Count abstract: 310

Word count article: 2499

Table for print version: Table-3

1-sentence condensation of the paper:

Population testing for *BRCA* mutations is cost-effective in UK & US Ashkenazi Jewish women >30 years with varying levels of Jewish ancestry: one, two, three, four AJ grandparents.

Shortened Title:

Cost-effectiveness of population *BRCA* testing with varying Jewish ancestry

Abstract:

Background

Population based *BRCA1/BRCA2* testing has been found to be cost-effective compared to family-history based testing in Ashkenazi-Jewish (AJ) women >30years with four AJ-grandparents. However, individuals may have one, two or three AJ 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 one, two and three AJ grandparents.

Methods

Life time costs and effects of population and family-history based testing were compared using a decision analysis model. 56% *BRCA* carriers are missed by family-history criteria alone. Analyses are conducted for UK and USA populations. Model parameters are obtained from the GCaPPS trial and published literature. Model parameters and *BRCA* population prevalence for individuals with three, two or one AJ grandparents are adjusted for the relative frequency of *BRCA* mutations in the AJ and general populations. Incremental cost-effectiveness ratios were calculated for all AJ-grandparent scenarios. Costs along with outcomes discounted at 3.5%. The time horizon of the analysis is 'life-time' and perspective is 'payer'. Probabilistic sensitivity-analysis (PSA) evaluated model uncertainty.

Results

Population testing for *BRCA* mutations is cost saving in AJ women with two, three or four grandparents (22-33 days life-gained) in UK and one, two, three or four grandparents (12-26 days life-gained) in USA populations respectively. It is also extremely cost-effective in UK women with just one AJ-grandparent with an incremental-cost-effectiveness-ratio (ICER)= £863/QALY and 15days life-gained. Results show that population-testing remains cost-effective at the £20,000-30000/QALY and \$100,000/QALY willingness-to-pay thresholds for all four AJ-grandparent scenarios with ≥95% simulations found to be cost-effective on PSA. Population-testing remains cost-effective in the

absence of reduction in breast cancer risk from oophorectomy and at lower RRM (13%)/RRSO (20%) rates.

Conclusions

Population-testing for *BRCA* mutations is cost-effective in the UK and USA with varying levels of AJ ancestry. These results support population testing in AJ women with 1-4 AJ-grandparent ancestry.

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

INTRODUCTION

Population-based *BRCA1/BRCA2* testing has been extensively investigated in the Ashkenazi-Jewish (AJ) population and shown to have several advantages compared to family-history (FH) based testing. FH based testing requires individuals to fulfil stringent clinical criteria but many *BRCA1/BRCA2* carriers do not meet this clinical threshold for genetic testing based on cancer history in the family. This approach results in over 50% of additional at-risk carriers being missed by FH driven clinical criteria based testing.^{1,2} Randomised trial data show that population-testing does not detrimentally impact psychological well-being or quality-of-life.² There is an overall reduction in anxiety, distress, and uncertainty,²⁻⁴ though higher levels of cancer related distress in those testing positive are reported.^{3,5} Additionally delivery of testing through a population-based model is acceptable and testing can be delivered in the community outside of hospital-based genetic clinics with high satisfaction rates.^{1,5,6} Also, the feasibility of population based genetic testing has been accelerated by the availability of next generation sequencing and the decreasing costs of genetic-testing⁷.

There are significant resource implications to consider around population-based *BRCA1/BRCA2* testing. 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 ≥ 30 years with four AJ grandparents. The data used in this model was obtained from the Genetic Cancer Prediction through Population Screening (GCaPPS) randomised trial (ISRCTN73338115) which compared outcomes of population and FH-based approaches for genetic testing women with four AJ grandparents. The model showed overall when

the down-stream costs of treatment were taken into account population-testing was in fact cost saving compared with FH-testing.⁸ The modelling predicted that this could lead to a significant reduction in breast-&-ovarian cancer incidence, and increase life-expectancy. However, our original analysis only applies to women with 'four' AJ grandparents and is not directly applicable to every woman with AJ ancestry as 25% UK⁹ and 44% USA¹⁰ Jewish marriages are to non-Jews. These women thus may have just one, two or three AJ grandparents and 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, July-2016.¹¹ We present an updated cost-effectiveness analysis of population *BRCA1/BRCA2* testing for women with one, two and three AJ grandparents.

METHODS

We previously developed a decision-analytical model (Figure-1) to calculate cost-effectiveness of screening women with four AJ grandparents. Model structure, assumptions, analytic features, advantages and limitations have been described earlier.⁸ This model was adapted to model outcomes for women with differing AJ ancestry.⁸ Separate analyses were performed for both UK and USA populations. Lifetime costs and effects of genetically screening AJ women ≥ 30 years for *BRCA1/BRCA2* AJ founder mutations were compared with current practice of screening using FH-based clinical criteria. 56% of BRCA carriers are missed by using family history criteria alone compared to 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 <50 years; first degree relative with or personal history of male breast cancer (any age).² 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 three: Population prevalence of *BRCA* (P1); Probability of having a positive FH (P6); and *BRCA* prevalence in the FH-negative individuals (P8). These three 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 three, two or one AJ grandparents is adjusted for the relative frequency of *BRCA* mutations in the AJ and general populations. *BRCA* prevalence estimates for AJ is obtained from the GCaPPS study (0.0245 (0.0131, 0.0416))² and for the general population (0.0067 (0.00590, 0.0077)) from recent published estimates.¹² *BRCA* prevalence with 3AJ 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, fulfilling clinical genetic testing criteria in the non-Jewish population is 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 three parameters and their confidence intervals for all different grandparent scenarios. The revised probability table for model parameters is given in Table-1.

Quality adjusted life year (QALY) 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 year (QALY) which is the preferred value of health benefit according to the National Institute of Health &

Care excellence (NICE).¹³ This decision-analytical model using revised estimates was run for each of the four scenarios: four, three, two and one AJ grandparent. The following utility scores were used for 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.¹⁴ The following utility scores, obtained from NICE guidelines¹⁵⁻¹⁸ were used for BC: 0.71 for early/locally 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 USA costs at 2014/15 prices are given in Table 2. The analysis covers a health system or payer perspective.

Life years

A lifetime horizon (extending till the age of 83 years) capturing lifetime risks and consequences was used to model the analysis. Mean ages for *BRCA1/BRCA2* related breast and ovarian cancer in AJ women was 43.5 years and 54.9 years were used in the analysis. Whilst the mean ages for sporadic breast and ovarian cancer in AJ women were 57/62 years and 63/63 years in the UK/USA populations respectively.¹⁹⁻²² Five year survival rates, in the general UK population were used in the absence of AJ survival data.²³ Costs, QALYs and life years were discounted at 3.5%.²⁴

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 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 differences in effect. The £20,000 - £30,000/QALY cost-effectiveness willingness to pay (WTP) threshold used by NICE²⁵ was used to compare the cost-effectiveness of population-based screening in comparison to FH-based testing in the UK. A WTP threshold of \$100,000/QALY was used for the USA analysis.^{26, 27}

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.²⁸ 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.²⁹

RESULTS

Baseline ICER results for the four different grandparent scenarios are given in Table-3 alongside discounted and undiscounted life years, QALYs and lifetime costs for each scenario for both UK and USA women. Baseline results suggest that population testing in UK women having ≥ 2 AJ grandparents and ≥ 1 grandparent for USA women remains cost saving and highly effective compared with traditional testing using FH-based clinical criteria. This corresponds to a life expectancy gain of 15/12, 22/17, 28/22 and 33/26 days for one, two, three and four AJ grandparents in UK/USA women respectively. Population testing in women with just one AJ grandparent is also cost-effective, with an ICER= £863/QALY, and 15 days life gained. This too is well below the £20,000/QALY threshold, though not cost saving.

The PSAs for the UK and USA (Figure-2 and Figure-3) show that for populations with four, three, two or one AJ grandparent(s) $\geq 95\%$ of simulations are cost-effective for population screening at the £20,000/QALY NICE WTP and \$100,000/QALY USA WTP thresholds. This suggests, compared to current clinical policy of FH based clinical testing, population testing in four, three, two and one AJ grandparent(s) is highly cost-effective.

DISCUSSION

Given that a large proportion of marriages in the Jewish population are between Jews and non-Jews, it is important to explore the cost-effectiveness of population testing in women with differing AJ ancestry and *BRCA* prevalence rates as a consequence. Our findings confirm the cost-effectiveness of population based *BRCA1/BRCA2* testing (compared to testing based on clinical FH criteria) in unselected UK & USA AJ women aged 30 and older, who have one, two or three AJ grandparents in addition to those with four AJ grandparents. That $\geq 95\%$ PSA simulations remain cost-effective despite significant variability in model parameters is significant and reassuring for all UK/USA women with differing AJ ancestry. This approach has the potential to reduce the number of ovarian and breast cancers in the AJ population. Such a programme would be cost-saving for those with four, three and two/ four, three, two and one AJ grandparents in the UK/USA populations respectively. There are not many interventions that can save both lives and money.³⁰ AJ screening might be the most cost-effective and maybe the only cost-saving program among those programs that use *BRCA* testing.³¹ These data have important implications for population health and cancer prevention and are of value to healthcare providers and care commissioners.

The number of days of life gained range from 15-33/12-26 days in the UK/USA. 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, and 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 undertaken add strength to the study. Although RRSO reduces the risk of breast cancer in premenopausal women, the benefit of premenopausal oophorectomy on reduction in breast cancer risk has recently become an issue of ongoing debate. Some Dutch investigators³² have recently 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.³³⁻³⁶ Nevertheless, if we assume no benefit of reduction in breast cancer risk from premenopausal oophorectomy, then the ICER/QALY for one, two, three and four grandparents is: £1971/\$2843/QALY, £-497/\$-8198/QALY, £-1715/\$-13595/QALY, £-2420/\$-16697/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 breast cancer risk from premenopausal oophorectomy. Our model incorporates risk reducing mastectomy rates seen in the UK. However, these rates may be lower in Israeli *BRCA1/BRCA2* carriers.³⁷ Hence, we explored a scenario analysis at much lower risk reducing mastectomy rate of 13% reported in Israeli women. The discounted ICERs for a 13% risk reducing mastectomy rate are £-1958/\$-11059/QALY, £-1177/\$-7548/QALY, £196/\$-1255/QALY and £3056/\$12103/QALY, for UK/US women with four, three, two and one 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/\$-17786/QALY, £-1759/\$-14032/QALY, £-301/\$-7366/QALY and £2793/\$7110/QALY for women with four, three, two and one AJ grandparents. Thus population based testing in AJ women of differing ancestry remains cost-effective in the UK and USA even with low risk reducing mastectomy or low risk reducing salpingo-oophorectomy 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/test. Additionally the program remains cost-effective (at the \$100,000/QALY WTP threshold) for all 4 AJ grandparents even if the cost of a test rises till \$1618, \$2417, \$3185 and \$3934 for one, two, three and four AJ grandparents respectively.

All surgical interventions have an associated complication rate. The complication rates reported for RRSO are around 4%,³⁸ while that for risk reducing mastectomy is much higher with reports ranging from 30-64%³⁹. Another limitation of the analysis is lack of adjustment for any potential negative

impact on quality of life after RRSO. While worse sexual functioning and vasomotor symptoms have been reported following RRSO, there was no difference in generic quality of life.⁴⁰⁻⁴² These issues need to be clearly highlighted when counselling women about these procedures and incorporated into the informed decision making process. It is reassuring that most women report high satisfaction rates with surgical prevention, with satisfaction rates varying from 83% for mastectomy³⁹ to 97% for oophorectomy⁴⁰.

Our results support the move for changing the paradigm from FH to population based *BRCA1/BRCA2* testing across the AJ population. This fulfils the necessary principles for population screening for genetic susceptibility of disease.⁴³ Population testing offers the ability to maximise the opportunity for prevention in unaffected individuals as well as facilitate targeted precision medicine approaches in those who may develop cancer. This approach has been advocated by us and others.^{1, 8, 44, 45} 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 falsely reassured. 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 generalised 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.

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, AA, ELL, CT, GE, JH, RJM, 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.

Role of Funding Source

This study was funded by 'The Eve Appeal' charity. The funding body (The Eve Appeal charity) 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.

References

1. GABAI-KAPARA E, LAHAD A, KAUFMAN B, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. *Proc Natl Acad Sci U S A* 2014;111:14205-10.
2. MANCHANDA R, LOGGENBERG K, SANDERSON S, et al. Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: a randomized controlled trial. *J Natl Cancer Inst* 2015;107:379.
3. METCALFE KA, POLL A, ROYER R, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. *J Clin Oncol* 2010;28:387-91.
4. NELSON HD, FU R, GODDARD K, et al. *Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the US Preventive Services Task Force Recommendation*. Rockville (MD), 2013.
5. LIEBERMAN S, TOMER A, BEN-CHETRIT A, et al. Population screening for BRCA1/BRCA2 founder mutations in Ashkenazi Jews: proactive recruitment compared with self-referral. *Genet Med* 2016.
6. MANCHANDA R, BURNELL M, LOGGENBERG K, et al. Cluster-randomised non-inferiority trial comparing DVD-assisted and traditional genetic counselling in systematic population testing for BRCA1/2 mutations. *J Med Genet* 2016;53:472-80.
7. SHENDURE J, Ji H. Next-generation DNA sequencing. *Nat Biotechnol* 2008;26:1135-45.
8. MANCHANDA R, LEGOOD R, BURNELL 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.
9. GRAHAM D, SCHMOOL M, WATERMAN S. *Jews in Britain: a snapshot from the 2001 Census*. London: Institute for Jewish Policy Research, 2007 (vol No. 1).
10. PEW RESEARCH CENTER. *A Portrait of Jewish Americans Findings from a Pew Research Center Survey of US Jews*. Washington DC, USA: Pew Research Center, 2013.
11. Founder Populations and their Contribution to our Understanding of Biology and History – Lessons from the Jewish Genome *Think Tank on BRCA Screening*. Haifa, Israel 10/7/2016: <https://www.founder-genomics.com/>, 2016.
12. JERVIS S, SONG H, LEE A, et al. A risk prediction algorithm for ovarian cancer incorporating BRCA1, BRCA2, common alleles and other familial effects. *J Med Genet* 2015.
13. NICE. *Guide to the methods of technology appraisal*. London: National Institute for Health and Clinical Excellence (NICE), 2008.

14. HAVRILESKY LJ, BROADWATER G, DAVIS DM, et al. Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. *Gynecologic oncology* 2009;113:216-20.
15. NICE. Clinical Guideline (CG81) – Advanced breast cancer: diagnosis and treatment. Cardiff, Wales, UK: National Collaborating Centre for Cancer, National Institute for Health and Clinical Excellence, 2009.
16. NICE. Early and locally advanced breast cancer: diagnosis and treatment *NICE Clinical Guideline, CG80*. Cardiff, Wales, UK: National Collaborating Centre for Cancer, National Institute for Health and Clinical Excellence, 2009.
17. NICE. National costing report: Early and locally advanced breast cancer/Advanced breast cancer. London, UK: National Institute for Health and Clinical Excellence, 2009.
18. PEASGOOD T, WARD SE, BRAZIER J. Health-state utility values in breast cancer. *Expert Rev Pharmacoecon Outcomes Res* 2010;10:553-66.
19. BOYD J, SONODA Y, FEDERICI MG, et al. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. *Jama* 2000;283:2260-5.
20. CRUK. Cancer Incidence in the UK in 2011. London, UK: Cancer Research UK, 2014.
21. SEER. Cancer Stat Facts: Ovary Cancer. Bethesda, MD, USA: National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program, 2014.
22. SEER. Cancer Stat Facts: Female Breast Cancer. Bethesda, USA: National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program, 2014.
23. ABDEL-RAHMAN M, STOCKTON D, RACHET B, HAKULINEN T, COLEMAN MP. What if cancer survival in Britain were the same as in Europe: how many deaths are avoidable? *British journal of cancer* 2009;101 Suppl 2:S115-24.
24. NICE. Guide to the methods of technology appraisal *N1618*. London, UK: National Institute for Health and Clinical Excellence (NICE), 2008.
25. NICE. Social value judgements: principles for the development of NICE guidance. (*NICE NifHaCE*). London, UK: National Institute for Health and Clinical Excellence (NICE), 2008.
26. NEUMANN PJ, COHEN JT, WEINSTEIN MC. Updating cost-effectiveness--the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med* 2014;371:796-7.
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* 2003;163:1637-41.
28. ANDRONIS L, BARTON P, BRYAN S. Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making. *Health technology assessment* 2009;13:iii, ix-xi, 1-61.

29. BRIGGS A. Probabilistic Analysis of Cost-Effectiveness Models: Statistical Representation of Parameter Uncertainty. *Value in Health* 2005;8:1-2.
30. COHEN JT, NEUMANN PJ, WEINSTEIN MC. Does preventive care save money? *Health economics and the presidential candidates*. *N Engl J Med* 2008;358:661-3.
31. D'ANDREA E, MARZUILLO C, DE VITO C, et al. Which BRCA genetic testing programs are ready for implementation in health care? A systematic review of economic evaluations. *Genet Med* 2016;18:1171-80.
32. HEEMSKERK-GERRITSEN BA, SEYNAEVE C, VAN ASPEREN CJ, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. *J Natl Cancer Inst* 2015;107.
33. REBBECK TR, KAUFF ND, DOMCHEK SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *Journal of the National Cancer Institute* 2009;101:80-7.
34. DOMCHEK SM, FRIEBEL TM, SINGER CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 2010;304:967-75.
35. KAUFF ND, DOMCHEK SM, FRIEBEL TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol* 2008;26:1331-7.
36. CHAI X, DOMCHEK S, KAUFF N, REBBECK T, CHEN J. RE: Breast Cancer Risk After Salpingo-Oophorectomy in Healthy BRCA1/2 Mutation Carriers: Revisiting the Evidence for Risk Reduction. *J Natl Cancer Inst* 2015;107.
37. LAITMAN Y, VAISMAN Y, FELDMAN D, et al. Rates of risk-reducing surgery in Israeli BRCA1 and BRCA2 mutation carriers. *Clin Genet* 2014;85:68-71.
38. MANCHANDA R, ABDELRAHEIM A, JOHNSON M, et al. Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. *Bjog* 2011;118:814-24.
39. LOSTUMBO L, CARBINE NE, WALLACE J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev* 2010:CD002748.
40. MADALINSKA JB, HOLLENSTEIN J, BLEIKER E, et al. Quality-of-life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer. *J Clin Oncol* 2005;23:6890-8.
41. FINCH A, METCALFE KA, CHIANG JK, et al. The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. *Gynecologic Oncology* 2011;121:163-8.

42. ROBSON M, HENSLEY M, BARAKAT R, et al. Quality of life in women at risk for ovarian cancer who have undergone risk-reducing oophorectomy. *Gynecologic Oncology* 2003;89:281-7.
43. MANCHANDA R, JACOBS I. Genetic screening for gynecological cancer: where are we heading? *Future Oncol* 2015.
44. GALLAGHER J. 'Screen more' for cancer risk genes. British Broadcasting Corporation, London, UK: BBC News, 2014.
45. LEVY-LAHAD E, LAHAD A, KING MC. Precision medicine meets public health: population screening for BRCA1 and BRCA2. *J Natl Cancer Inst* 2015;107:420.
46. EVANS DG, LALLOO F, ASHCROFT L, et al. Uptake of risk-reducing surgery in unaffected women at high risk of breast and ovarian cancer is risk, age, and time dependent. *Cancer Epidemiol Biomarkers Prev* 2009;18:2318-24.
47. FINCH A, BEINER M, LUBINSKI J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. *Jama* 2006;296:185-92.
48. CHEN S, PARMIGIANI G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol* 2007;25:1329-33.
49. REBBECK TR, FRIEBEL T, LYNCH HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2004;22:1055-62.
50. CRUK. Breast Cancer Incidence Statistics UK 2009-2011 *Breast Cancer (C50), Average Number of New Cases per Year and Age-Specific Incidence Rates, Females, UK, 2009-2011*: Cancer Research UK, 2012.
51. ONS. Cancer Registration Statistics, England, 2011 *Office for National Statistics*. London, UK: Office for National Statistics, 2013.
52. MANCHANDA R, BURNELL M, ABDELRAHEIM A, et al. Factors influencing uptake and timing of risk reducing salpingo-oophorectomy in women at risk of familial ovarian cancer: a competing risk time to event analysis. *Bjog* 2012.
53. CRUK. Ovarian Cancer Incidence Statistics: 2011. London, UK: Cancer Research UK, 2014.
54. CURTIS L. Unit Costs of Health and Social Care 2011. Canterbury, Kent: Personal Social Services Research Unit (PSSRU), 2011.
55. SCHWARTZ MD, VALDIMARSDOTTIR HB, PESHKIN BN, et al. Randomized noninferiority trial of telephone versus in-person genetic counseling for hereditary breast and ovarian cancer. *J Clin Oncol* 2014;32:618-26.

56. DEPARTMENT OF HEALTH. NHS Reference Costs 2012-2013. London: Department of Health, 2013.
57. BNF. *British National Formulary 67*. London, UK: BMJ Group, and the Pharmaceutical Press (Royal Pharmaceutical Society of Great Britain); Number of pages.
58. NICE. Ovarian cancer: the recognition and initial management of ovarian cancer. London: National Institute for Health and Clinical Excellence (NICE), 2011 (vol CG122).
59. INCISIVE HEALTH. London, UK: Cancer Research UK.
60. GRANN VR, PATEL PR, JACOBSON JS, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. *Breast Cancer Res Treat* 2011;125:837-47.
61. NAO. End of life care. In: Burr TCaAG, ed. London: National Audit Office (NAO), House of Commons, 2008.
62. INCISIVE HEALTH AND CANCER RESEARCH UK. Saving lives, averting costs. An analysis of the financial implications of achieving earlier diagnosis of colorectal, lung and ovarian cancer London UK: Cancer Research UK, 2014.
63. ROBERTSON C, ARCOT RAGUPATHY SK, BOACHIE C, et al. The clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer: systematic reviews registry database analyses and economic evaluation. *Health Technol Assess* 2011;15:v-vi, 1-322.
64. CDC. Breast Cancer Screening Guidelines for Women. Atlanta, USA: Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, 2016.
65. NICE. Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. London, UK: National Institute for Health and Care Excellence, 2013.
66. WALDRON J. Breast Screening Programme, England 2008-09. UK: The NHS Information Centre, for Health and Social Care, Government Statistical Service, 2010.
67. HEIJNSDIJK EA, WARNER E, GILBERT FJ, et al. Differences in natural history between breast cancers in BRCA1 and BRCA2 mutation carriers and effects of MRI screening-MRISC, MARIBS, and Canadian studies combined. *Cancer Epidemiol Biomarkers Prev* 2012;21:1458-68.
68. ANTONIOU AC, PHAROAH PD, NAROD S, et al. Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies. *J Med Genet* 2005;42:602-3.

69. WAPNIR IL, ANDERSON SJ, MAMOUNAS EP, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. *J Clin Oncol* 2006;24:2028-37.
70. ANDERSON SJ, WAPNIR I, DIGNAM JJ, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. *J Clin Oncol* 2009;27:2466-73.
71. GENNARI A, CONTE P, ROSSO R, ORLANDINI C, BRUZZI P. Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. *Cancer* 2005;104:1742-50.

Table -1: Probabilities used in the model

Probability	Value	(95%CI) [Range]	Description	Source
P1 (4 AJ GP)	0.0245	(0.0131-0.0416)	Population prevalence of BRCA FM	GCaPPS, Manchanda ^{2, 8}
P1 (3 AJ GP)	0.0201	(0.0113-0.0331)	BRCA prevalence with: 3AJ grandparents= $(0.75 * AJ^{prevalence})$ + $(0.25 * \text{General-population}^{prevalence})$; 2 AJ grandparents= $(0.5 * AJ^{prevalence})$ + $(0.5 * \text{General-population}^{prevalence})$; 1 AJ grandparent= $(0.25 * AJ^{prevalence})$ + $(0.75 * \text{General-population}^{prevalence})$	Manchanda ^{2, 8} , Jervis 2015 ¹²
P1 (2 AJ GP)	0.0156	(0.0095-0.0247)		
P1 (1 AJ GP)	0.011	(0.0077-0.0162)		
P2	0.52	(0.39-0.67)	Probability that carrier will undergo RRM	Evans ⁴⁶
P3	0.96	[0.8-0.96]	Reduction in risk of ovarian cancer from RRSO	Finch ⁴⁷ , Rebbeck ³³
P4	0.2987	(0.2485-0.3539)	Probability that carrier without RRSO will get ovarian cancer	Chen ⁴⁸
P5	0.0185	(0.0005-0.0989)	Probability that a non-carrier will get ovarian cancer	CRUK
	0.0128	(0.0126-0.0130)	Probability that a non-carrier will get ovarian cancer – USA estimate	SEER ²¹
P6 (4 AJ GP)	0.1238	(0.1043-0.1454)	Probability of having a positive FH	GCaPPS ^{2, 8}
P6 (3 AJ GP)	0.095	(0.079-0.114)	Probability with: 3AJ grandparents= $(0.75 * AJ^{probability})$ + $(0.25 * \text{General-population}^{probability})$; 2 AJ grandparents= $(0.5 * AJ^{probability})$ + $(0.5 * \text{General-population}^{probability})$; 1 AJ grandparent= $(0.25 * AJ^{probability})$ + $(0.75 * \text{General-population}^{probability})$	
P6 (2 AJ GP)	0.0668	(0.055-0.082)		
P6 (1 AJ GP)	0.0383	(0.0296-0.0498)		
P7	0.0938	(0.0637-0.1763)	BRCA prevalence in FH positive individuals	GCaPPS ^{2, 8}
P8 (4 AJ GP)	0.0203	(0.0114-0.0332)	BRCA prevalence in FH negative individuals	GCaPPS ^{2, 8}
P8 (3 AJ GP)	0.0166	(0.0098-0.0266)	Probability with: 3AJ grandparents= $(0.75 * AJ^{probability})$ + $(0.25 * \text{General-population}^{probability})$; 2 AJ grandparents= $(0.5 * AJ^{probability})$ + $(0.5 * \text{General-population}^{probability})$; 1 AJ grandparent= $(0.25 * AJ^{probability})$ + $(0.75 * \text{General-population}^{probability})$	
P8 (2 AJ GP)	0.0129	(0.0082-0.0199)		
P8 (1 AJ GP)	0.009	(0.006-0.013)		

			population ^{probability})	
P9	0.91	(0.62-0.98)	Reduction in breast cancer risk from RRM without RRSO	Rebbeck ⁴⁹
P10	0.53	(0.44-0.62)	Probability that carrier without RRM will get breast cancer	Chen ⁴⁸
P11	0.13	[0.11-0.14]	Probability that a non-carrier will get breast cancer with screening – UK estimate	CRUK ⁵⁰ , ONS ⁵¹
	0.124	(0.1236-0.1249)	Probability that a non-carrier will get breast cancer with screening – USA estimate	SEER ²²
P12	0.55	(0.30-0.75)	Probability that carrier will follow-up with RRSO	Manchanda ⁵²
P13	0.49	(0.37-0.65)	Reduction in risk of breast cancer from RRSO alone	Rebbeck ³³
P14	0.95	(0.78-0.99)	Reduction in risk of breast cancer from RRM with RRSO	Rebbeck ⁴⁹

95%CI- 95% confidence interval, AJ- Ashkenazi Jewish, FH- family history, FM- founder mutations, GCaPPS- Genetic Cancer Prediction through Population Screening study; GP- grandparent, RRSO- risk reducing salpingo-oophorectomy, RRM: Risk reducing Mastectomy

Explanation:

The probabilities P1, P6 and P8 have been adapted for different levels of AJ ancestry: four, three, two and one grandparent. The other model probabilities remain the same as previously published.⁸

P1: The probability of carrying a BRCA FM in the AJ population ($p_1 = 0.0245$) is taken from the GCaPPS study. This is the probability with 4 AJ grandparents. The probability of having a BRCA mutation in the non-Jewish population (0.0067 (0.00590. 0.0077) is taken from up to date estimates from Jerivs 2015. BRCA prevalence with: 3AJ grandparents= $(0.75 * AJ^{prevalence}) + (0.25 * General-population^{prevalence})$; 2 AJ grandparents= $(0.5 * AJ^{prevalence}) + (0.5 * General-population^{prevalence})$; 1 AJ grandparent= $(0.25 * AJ^{prevalence}) + (0.75 * General-population^{prevalence})$

P2: The probability that BRCA1/2 carrier will undergo RRM is taken is taken from an analysis of UK BRCA1/2 carriers by Evans et al 2009. A composite uptake rate ($p_2 = 0.52$) for BRCA1 (60% RRM rate) and BRCA2 (43% RRM rate) carriers weighted for the relative prevalence of BRCA1 and BRCA2 FM found in the London AJ population was computed.⁴⁶

P3: The reduction in ovarian cancer risk obtained from RRSO ($p_3 = 0.96$) is taken from previous studies which report a 4% residual-risk of primary peritoneal cancer following RRSO.⁴⁷

P4: The GCaPPS model⁸ uses ovarian cancer penetrance estimates (40% for BRCA1, 18% for BRCA2) from a meta-analysis, corrected for ascertainment.⁴⁸ To simplify the analysis the GCaPPS 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 is calculated as $((0.0132 * 0.4) / 2.45 + (0.0113 * 0.18) / 2.45)$.⁸

P5: The risk of ovarian cancer in a low-risk population ($p_5 = 0.0185$) is obtained from Cancer Research UK⁵³ for UK women and SEER data²¹ was used for USA women.

P6: The probability of having a strong FH of cancer fulfilling the current clinical criteria (FH-positive) for women with four AJ grandparents is obtained from the GCaPPS study.^{2,8} The

probability of having a positive FH fulfilling non-AJ genetic-testing criteria is obtained from previously unpublished unselected control population data from the Australian Breast Cancer Family Registry (ABCFR). The probability for three, two and one grandparent is adjusted for the relative prevalence in Jewish and general populations. The Probability with: 3AJ grandparents= $(0.75 * AJ^{probability}) + (0.25 * General-population^{probability})$; 2 AJ grandparents= $(0.5 * AJ^{probability}) + (0.5 * General-population^{probability})$; 1 AJ grandparent= $(0.25 * AJ^{probability}) + (0.75 * General-population^{probability})$

P7: The BRCA prevalence in FH-positive individuals is also obtained from GCaPPS^{2, 8}

P8: The BRCA prevalence in FH-negative individuals for women with four AJ grandparents is obtained from the GCaPPS study^{2, 8} The probability for three, two and one grandparents is adjusted for the relative prevalence in Jewish and general populations. The Probability with: 3AJ grandparents= $(0.75 * AJ^{probability}) + (0.25 * General-population^{probability})$; 2 AJ grandparents= $(0.5 * AJ^{probability}) + (0.5 * General-population^{probability})$; 1 AJ grandparent= $(0.25 * AJ^{probability}) + (0.75 * General-population^{probability})$

P9: Reduction in breast cancer risk from RRM in BRCA carriers not undergoing RRSO is taken from the PROSE study data by Rebbeck et al, JCO 2004.⁴⁹

P10: The breast cancer penetrance for BRCA carriers (57% for BRCA1 and 49% for BRCA2) is taken from a meta-analysis, corrected for ascertainment.⁴⁸ To simplify the analysis the GCaPPS model used a composite risk for BRCA1 and BRCA2 carriers weighted for the relative prevalence of BRCA1 and BRCA2 FM (GCaPPS study). The overall risk of breast cancer in BRCA carriers is calculated as $((0.0132 * 0.57) / 2.45 + (0.0113 * 0.49) / 2.45)$.^{2, 8}

P11: The risk of breast cancer in a low risk population is taken from Cancer Research UK and UK Office for National Statistics data,^{50, 51} and from SEER data²² for USA women

P12: In the GCaPPS model⁸ we have used the RRSO rates 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.⁵²

P13: The reduction in breast cancer risk in pre-menopausal women undergoing RRSO is taken from a meta-analysis by Rebbeck et al.³³

P14: Reduction in breast cancer risk from RRM in BRCA carriers undergoing RRSO is taken from the PROSE study data by Rebbeck et al, JCO 2004.⁴⁹

Table 2: Costs used in the model (2014 prices)

Item	Cost UK (£)	Cost USA (\$)	Source
Cost of BRCA Founder mutation testing	50	300	GCaPPS ²
Cost of genetic counselling	43	41	GCaPPS, ² PSSRU Unit costs of Health and Social Care ⁵⁴ , Schwartz, 2014 ⁵⁵
Cost of RRSO (and HRT and osteoporosis prevention)	3411	8144	NHS Reference costs, ⁵⁶ BNF ⁵⁷
Cost of ovarian cancer diagnosis and treatment	14123	127,995	NHS Reference costs, ⁵⁶ NICE guideline ⁵⁸
Yearly cost of ovarian cancer treatment year 1-2	10050	14,071	NHS Reference costs, ⁵⁶ NICE guideline ⁵⁸ CRUK ⁵⁹ Grann 2011 ⁶⁰
Yearly cost of ovarian cancer treatment year 3-5	14387	14,071	NHS Reference costs, ⁵⁶ NICE guideline ⁵⁸ CRUK ⁵⁹ Grann 2011 ⁶⁰
Terminal care costs with ovarian cancer	15450	89,424	National Audit office ⁶¹ Incisive Health report for CRUK ⁶² Grann 2011 ⁶⁰
Cost of risk reducing mastectomy	3901	12,596	NHS reference cost, ⁵⁶ weighted for 21% complication rate ⁴ Grann 2011 ⁶⁰
Cost of breast screening	347	1534	Robertson 2011, ⁶³ NHS Reference costs ⁵⁶ CDC guideline ⁶⁴
Cost of breast screening BRCA carriers	4582	33,530	NHS Reference costs ⁵⁶ , NICE guideline ⁶⁵ CDC guideline, ⁶⁴ Grann 2011 ⁶⁰
Cost of breast cancer diagnosis and treatment	15527	82,030	NHS Reference costs ⁵⁶ , NICE guideline ¹⁶ , NICE guideline ¹⁵ , Grann 2011 ⁶⁰
Yearly cost of breast cancer treatment	2008	7738	NHS Reference costs ⁵⁶ , Robertson 2011 ⁶³ , BNF ⁵⁷ , NICE guideline ¹⁶ , NICE guideline ¹⁵ , Implementing NICE guidance ¹⁶ Grann 2011 ⁶⁰
Yearly cost of BRCA associated breast cancer	1917	7738	NHS Reference costs ⁵⁶ , Robertson 2011 ⁶³ , BNF ⁵⁷ , NICE guideline ¹⁶ , NICE guideline ¹⁵ , Implementing NICE guidance ¹⁶ Grann 2011 ⁶⁰
Terminal care costs with breast cancer	15,450	65,403	National Audit office, ⁶¹ Grann 2011 ⁶⁰

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

Explanation

Cost of RRSO: It is assumed HRT is provided to women from the age they have RRSO until the age of menopause (51 years).⁵⁷ An 80% compliance rate is assumed with HRT, and these costs are added to costs for surgery. For the UK RRSO costs are for an upper genital tract laparoscopic/endoscopic intermediate procedure.⁵⁶ To monitor bone health, the cost of three DEXA scans and calcium and vitamin-D3 are also included. USA prophylactic salpingo-oophorectomy costs are taken from Grann 2011⁶⁰ and inflated using the medical component of the USA consumer price index.

Ovarian Cancer Costs:

Based on ovarian cancer guideline published by NICE.⁵⁸ Diagnosis costs include ultrasound scan, pelvic examination, CT scan, CA125 test, percutaneous biopsy and peritoneal cytology.

Costs of treatment include reference cost for lower and upper genital tract complex major procedure and 6 cycles of carboplatin and paclitaxel chemotherapy administration. Survivors were assumed to have three consultant visits, 4 CA125 tests and a CT scan each year for the first two years post-surgery. In years 3 to 5 post surgery, survivors were assumed to have 2 consultant visits and 2 CA125 tests. Terminal cancer costs are taken from a report submitted to the National Audit Office, UK.⁶¹ Recurrent ovarian cancer costs are taken from a report commissioned by CRUK.⁶² For the USA, the cost of ovarian cancer diagnosis, treatment, recurrence and terminal ovarian cancer costs is taken from Grann 2011⁶⁰ and inflated using the medical component of the USA consumer price index.

Breast Cancer Costs:

Based on NICE guidelines on early/locally advanced breast cancer¹⁶ and advanced breast cancer in UK¹⁵; the BNF⁵⁷ and Department of Health NHS reference costs⁵⁶.

Cost of breast screening in general population: women between 50-70years are offered mammography every three years in accordance with the UK NHS breast cancer screening program.⁶⁶

Cost of diagnosis based on clinical examination, ultrasound, mammography and biopsy.

Cost of breast screening in carriers: women are offered an annual MRI from 30-49 years and an annual mammogram from 40-69 years in accordance with NICE familial breast cancer guidelines.⁶⁵

Cost of breast cancer treatment: in non-carriers, 10% of breast cancer is non-invasive DCIS and 90% invasive. 95% of invasive breast cancer is early and locally advanced with 5% being advanced breast cancer.¹⁶ In BRCA1/2 carriers 20% are non-invasive DCIS and 80% invasive.^{4, 67}

Yearly cost of breast cancer treatment: includes costs of sentinel lymph node biopsy and axillary lymph node dissection as recommended in NICE guideline.¹⁶ Breast conserving surgery and mastectomy costs with reconstruction are included in treatment costs.⁵⁶ Radiotherapy costs are included that are offered for early invasive/locally advanced cancer whilst chemotherapy is offered alongside radiotherapy for advanced cancers.

Chemotherapy costs are taken from NICE guidelines based on 1st and 2nd line^{15, 16} polychemotherapy.⁶⁸ Costs take into account the difference in stage at presentation with 20% of cancers being non-invasive.

Costs are also taken into account for the testing cancers that are ER positive and HER2 positive in the general and BRCA carrier population. 70% general population invasive breast cancers are ER positive; 15% early invasive breast cancers and 25% advanced breast cancers are HER2 positive.¹⁵ ¹⁶ ER positive cancers receive Tamoxifen at 20mg/day if premenopausal or Anastrozole 1mg/day is postmenopausal for 5 years, costs of both are from the BNF.⁵⁷ To offset the risk of developing 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% receiving oral clodronate and ibandronic acid. As per NICE guidelines, HER2 positive patients are given trastuzumab at 3 weekly intervals for a year or until disease recurrence.¹⁶ Recurrence rates are included for breast cancer as obtained through the USA National Surgical Adjuvant Breast and Bowel Project.^{69, 70}

Follow up costs for breast cancer include, six monthly consultations and annual mammograms with MRI scans for stage 4 cancers. Costs take into account a 35% progression rate from early and locally advanced to advanced disease¹⁶ and 66% relapse rate in advanced disease.⁷¹ Terminal cancer care costs were obtained from a report published by the National Audit Office, UK.⁶¹

USA Breast Cancer Costs: The cost of breast cancer diagnosis and treatment is taken from Grann 2011⁶⁰ and inflated using the medical component of the USA consumer price index. Cost of breast screening in non-carriers: assumes mammograms are conducted every two years from the age of 50 (CDC guidelines)⁶⁴. Cost of breast screening in carriers: assumes USA women are offered a yearly mammography and MRI from the age of 30 years and then from 50 years onwards women are only offered an annual mammography.⁶⁴

Terminal breast cancer costs are taken from Grann 2011⁶⁰ and inflated using the medical component of the USA consumer price index.

Table 3: Model outcomes for costs, life-years and quality adjusted life-years (QALYs), for UK and USA

AJ grand parents	Screening arms	UK Results			USA Results		
		Cost, £	Life years*	QALYs	Cost, \$	Life years*	QALYs
4	Average population screening	1861	52.26	23.15	7254	52.59	23.24
	Average family history screening	1955	52.17	23.12	7775	52.51	23.22
	Incremental (difference)	-94	0.090	0.032	-522	0.072	0.027
	ICER per QALY	-2960			-19587		
3	Average population screening	1813	52.27	23.16	7038	52.60	23.25
	Average family history screening	1875	52.19	23.13	7413	52.53	23.22
	Incremental (difference)	-62	0.075	0.027	-375	0.061	0.022
	ICER per QALY	-2327			-16788		
2	Average population screening	1766	52.28	23.16	6822	52.61	23.25
	Average family history screening	1792	52.22	23.14	7033	52.56	23.23
	Incremental (difference)	-26	0.060	0.021	-212	0.048	0.018
	ICER per QALY	-1254			-12013		
1	Average population screening	1718	52.29	23.17	6606	52.62	23.26
	Average family history screening	1705	52.25	23.15	6637	52.58	23.24
	Incremental (difference)	13	0.042	0.015	-31	0.034	0.012
	ICER per QALY	863			-2542		

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

*Undiscounted outcomes shown for life years. Costs and QALY outcomes are discounted

Figure1: Decision Model Structure

Figure 1:

The upper part of the model structure reflects a population-based approach to BRCA testing and the lower part of the model depicts a FH-based approach. Each decision point in the model is called a 'node' and each path extending from a node is called a decision 'branch'. Each branch represents a mutually exclusive course or outcome. Each decision is given a probability (probabilities 'p1 to p14' used in the model are explained in Table1) highlighted in a white box along the decision branch. Values for each outcome are calculated. Cancer incidence was estimated by summing the probabilities of pathways ending in ovarian or breast cancer. Final outcomes (blue boxes on the right of the figure) of each path include development of breast cancer (BC), ovarian cancer (OC) and no breast/ovarian cancer (no OC or BC). BC- Breast Cancer, OC-Ovarian Cancer; No OC or BC- No Ovarian Cancer or Breast Cancer developed., RRSO –Risk reducing salpingo-oophorectomy; RRM – Risk reducing mastectomy.

Manchanda, R et al; Cost-effectiveness of Population Screening for BRCA Mutations in Ashkenazi Jewish Women Compared With Family History–Based Testing, Journal of the National Cancer Institute, 2014, 107, 1, by permission of Oxford University Press.

Figure 2: UK Probabilistic Sensitivity Analysis for varying Ashkenazi Jewish grandparent ancestry

Figure 2: Cost-effectiveness acceptability curves 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 four scenarios (4, 3, 2, 1 grandparents) were simulated 10,000 times and the results shown are the proportion of these simulations which would be cost-effective at different willingness-to-pay thresholds. X-axis: Incremental cost-effectiveness ratio (ICER) in terms of Cost (£s)/QALY; Y-axis: Proportion of simulations. The solid red line marks the proportion of simulations found to be cost-effective at the £20,000 threshold used by NICE. ≥95% simulations are cost effective for varying levels of Jewish ancestry in this analysis.

Figure 3: USA probabilistic Sensitivity Analysis for varying Ashkenazi Jewish grandparent ancestry

Figure 3: USA cost-effectiveness acceptability curves 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 four scenarios (4, 3, 2, 1 grandparents) were simulated 10,000 times and the results shown are the proportion of these simulations which would be cost-effective at different willingness-to-pay thresholds. X-axis: Incremental cost-effectiveness ratio (ICER) in terms of Cost (\$s)/QALY; Y-axis: Proportion of simulations. The solid red line marks the proportion of simulations found to be cost-effective at the \$100,000 threshold. $\geq 95\%$, simulations are cost effective for varying levels of Jewish ancestry in this analysis.

Fig 1

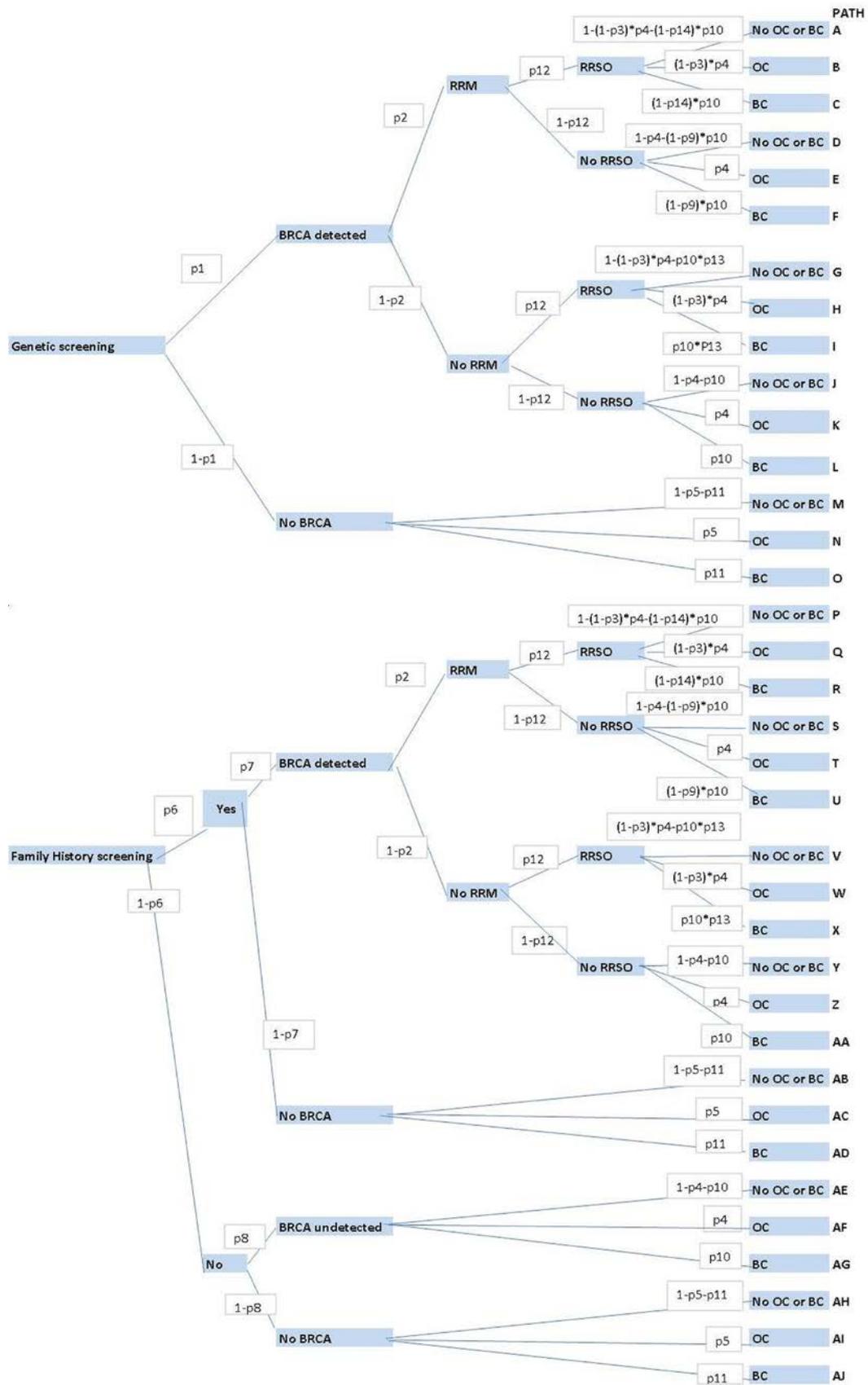


Fig 2

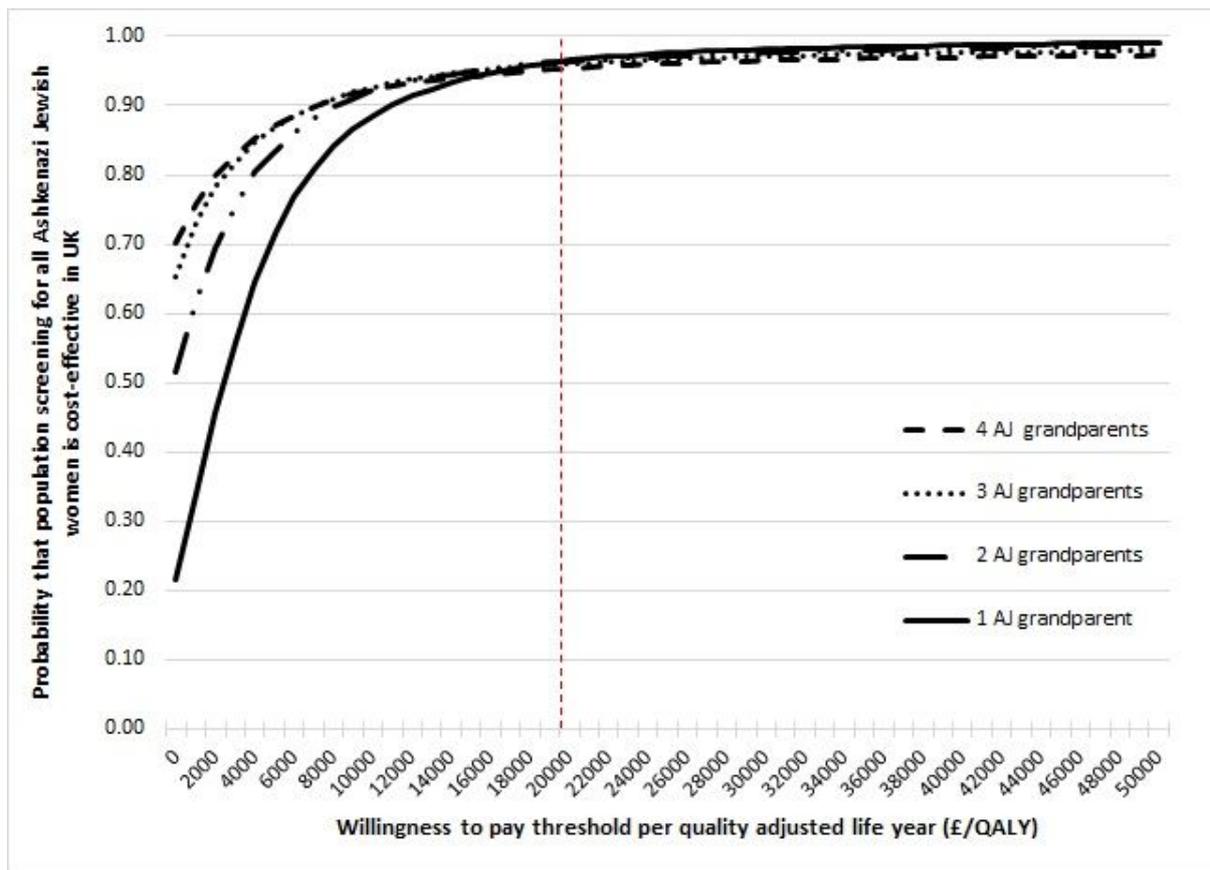


Fig 3

