JNCI 17-0764R2

Article

Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women

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ABSTRACT

BACKGROUND

The cost-effectiveness of population-based panel-testing for high and moderate penetrance ovarian cancer (OC)/breast cancer (BC) gene mutations is unknown. We evaluate cost-effectiveness of population-based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* mutation testing compared to clinical-criteria/family history (FH) testing in unselected general population women.

METHODS

A decision-analytic model compared lifetime costs and effects of Criteria/FH-based *BRCA1/BRCA2* testing is compared with *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* testing in those fulfilling Clinical-criteria/strong FH of cancer (≥10% *BRCA1/BRCA2* probability), and all women ≥30 years. Analyses are presented for UK and USA populations. Identified carriers undergo risk-reducing salpingo-oophorectomy. *BRCA1/BRCA2/PALB2* carriers can opt for MRI/mammography, chemoprevention or risk-reducing mastectomy. One-way and probabilistic sensitivity analysis (PSA) enabled model uncertainty evaluation. Outcomes include OC, BC, and additional heart disease deaths. Quality-adjusted life-years (QALYs), OC incidence, BC incidence, and incremental cost-effectiveness ratio (ICER) were calculated. . The time horizon is lifetime and perspective is payer

RESULTS

Compared to Clinical-criteria/FH-based *BRCA1/BRCA2* testing, Clinical-criteria/FH-based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* testing is cost-effective: ICER=£7629.65/QALY or $49,282.19/QALY (0.04 days life-expectancy gained). Population-based testing for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* mutations is the most cost-effective strategy compared to current policy: ICER=£21,599.96/QALY or $54,769.78/QALY (9.34 or 7.57days life-expectancy gained). At £30,000/QALY and

$100,000/QALY willingness-to-pay thresholds population-based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* panel-testing is the preferred strategy in 83.7% and 92.7% PSA simulations; and Criteria/FH-based panel testing is preferred in 16.2% and 5.8% simulations respectively**.** Population-based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* testing can prevent 1.86%/1.91% BC and 3.2%/4.88% OC in UK/USA women: 657/655 OC-cases and 2420/2386 BC cases prevented per million.

CONCLUSIONS

Population-based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* testing is more cost-effective than any Clinicalcriteria/FH-based strategy. Clinicalcriteria/FH-based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* testing is more cost-effective than *BRCA1/BRCA2* testing alone.

INTRODUCTION

Our existing healthcare structure is directed predominantly towards treatment rather than illness prevention. Advances in genomic medicine are being used to guide novel cancer treatment strategies. However, it also offers the opportunity to deliver a new population-based predictive, preventive, personalized, and participatory (P4) medicine strategy for cancer prevention. Traditionally ovarian cancer (OC)/breast cancer (BC) prevention has been targeted at high-risk individuals like *BRCA1/BRCA2* mutation carriers. At-risk mutation carriers can opt for: risk-reducing salpingo-oophorectomy (RRSO) to reduce their OC-risk (1,2), MRI/mammography screening, risk-reducing mastectomy (RRM) (3), or chemoprevention with selective estrogen-receptor-modulators (SERM) to reduce their BC-risk (4), as well as pre-implantation genetic-diagnosis (PGD) (5). Identification of mutation carriers (e.g. *BRCA1/BRCA2*) at high-risk of OC/BC has involved genetic-testing affected individuals or those from high-risk families in specialised genetics clinics. Clinical-criteria/family-history (FH) are surrogates for *BRCA* probability with testing offered above a certain threshold. However, clinical-criteria/FH-based testing is only moderately effective at identifying mutations and has poor ability to rule out the absence of one (6). We (7) and others (8,9) have shown that this approach misses >50% mutation carriers. Given the effective options available for OC and BC risk management/prevention, this raises serious questions about the adequacy of a Clinical-criteria/FH-based approach. Additionally lately, newer intermediate/moderate risk OC-genes *RAD51C*,(10) *RAD51D(11)* and *BRIP1(12)* (OC-risks ~5-9%), have been identified and their penetrance estimates validated (13,14). Furthermore, our recent modelling work strongly suggests that RRSO would be cost-effective at ≥4-5% OC-risk (15,16). This enables clinical-utility and supports implementation of clinical testing for these gene mutations. Amongst the newer moderate-risk BC-genes, *PALB2* is the one that confers non-syndromic quasi-Mendelian susceptibility to BC (BC-

risk=44%) (17) for which equivalent interventions (RRM/breast-MRI) are now offered to mutation carriers. ATM, CHEK-2 have lower moderate risks (RR~1.5-2) which don't justify RRM. Testing for these though commercially available, is not currently routinely undertaken in clinical practice (18,19).

The limitations of Clinical-criteria/FH-based ascertainment can be overcome by population-based testing. Next-generation sequencing technologies (20,21) with high-throughput multiplex panel-testing, falling costs, and advances in computational bioinformatics has made population-testing feasible. In a prospective randomised trial we showed that compared to FH-based testing, population-based *BRCA1/BRCA2* testing in Ashkenazi-Jews(AJ) is acceptable, feasible, can be undertaken in a community setting, doesn't harm psychological health/quality-of-life, identifies >50% additional carriers, reduces BC-&-OC incidence, and is extremely cost-effective (incremental-cost-effectiveness-ratio (ICER)=-£2079/quality-adjusted-life-year (QALY)) (7,22). While, there is good evidence to support a change in the clinical paradigm from Clinical-criteria/FH to population-based testing in Ashkenazi-Jews (23), a population-based approach has not yet been properly evaluated in the non-Jewish general population. A health-economic assessment is crucial for evaluating and comparing the efficacy of different health interventions. This helps allocate resources across interventions, and set policy to improve population health. Here we use a decision-analysis model to compare the costs-&-effects of Clinical-criteria/FH and population-testing approaches for the known high and moderate penetrance OC/BC gene mutations: *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1* and *PALB2*.

METHODS

Ethics approval: This analysis was approved under the ethics approval obtained for the Genetic Cancer Prediction through Population Screening (GCaPPS) study, from the Institute

of Child Health/ Great Ormond Street Hospital Research Ethics Committee: REC Reference number 08/H0713/44.

Decision Model

A decision-analytic model (**Figure 1**) was developed to compare the lifetime costs-&-effects of genetically testing all non-Jewish women ≥30 years for *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1* and *PALB2* mutations compared with the current practice of clinical-criteria/FH-based testing (based on ≥10% *BRCA1/BRCA2* mutation probability alone) (19). We present separate analyses for both UK and USA populations. The standard clinical-criteria/FH-based testing for *BRCA1/BRCA2* mutations is compared in an incremental fashion to (Strategy-A): Clinical-criteria/FH-based panel testing for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* mutations and (Strategy-B): Population-testing for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* mutations. The model assumes all women in the population-screening arm and only those fulfilling clinical/FH-criteria in the FH-arm are offered genetic-counselling and genetic-testing. We assume 71% will uptake genetic-testing (from GCaPPS study) (7). The cost of pre-test counselling is included (24,25). *BRCA1/BRCA2* negative women are tested for *RAD51C/RAD51D/BRIP1/PALB2* mutations (from the same DNA sample). A detailed description of all model assumptions is given in **Supplementary Table 1**. The model incorporates the increased risk of cardiovascular mortality (absolute increase=3.03%) reported with pre-menopausal bilateral-oophorectomy in women who don't take hormone replacement therapy (HRT) (26,27). Model outcomes included OC, BC and excess deaths from heart disease. As per National Institute of Health and Care Excellence(NICE) economic evaluation guidelines, costs and outcomes are discounted at 3.5% (28).

Probabilities

We use the most up-to date prevalence estimates for *BRCA1/BRCA2* (29) and *RAD51C*, *RAD51D* (14), *BRIP1* (13), and *PALB2* (30). The probability of having a positive FH or fulfilling clinical criteria for non-AJ genetic testing is obtained from previously unpublished unselected control population data from the Australian Breast Cancer Family Registry (ABCFR). The different pathway probabilities are specified in **Table 1** (explanation in **Supplementary Table 2**). Cancer incidence was estimated by summing the probabilities of pathways ending in OC or BC. The possibility of both OC and BC occurring simultaneously is rare and presumed close to zero. The potential population impact was calculated by translating reduction in BC and OC incidence obtained across the population of non-AJ UK/USA women.

Costs

All costs (**Supplementary Table 3**) are reported at 2014 prices (31) and derived from a healthcare system/payer's perspective. Costs were converted wherever needed using the Hospital and Community Health Service Index (32). As per NICE recommendations future healthcare costs not associated with OC/BC or cardiovascular disease were not considered (28).

Life-years

The analysis has a lifetime time-horizon covering lifetime risks as well as long-term consequences. Female lifetables from the Office of National Statistics (UK women) and SEER (USA women) were used for life expectancy data for women not developing OC/BC (33). To simplify the analysis we used average estimates for ages of onset and survival for *BRCA1/BRCA2* related BC and OC. Details of ages of onset and survival estimates used are

in **Supplementary Table 4**. The average ages for BC/OC were 44.4/59.6 years respectively for *BRCA1+BRCA2* carriers (34). The median ages of onset of sporadic OC/BC were 68/60 and 63/62 years in the UK and USA populations respectively (from CRUK/SEER) (35-37). OC/BC outcomes were modelled using 10-year survival data.

Quality-adjusted-life-years (QALYs)

QALYs are recommended by NICE as the most suitable summary measure for economic evaluation of health outcomes. It adjusts changes in length-of-life, by potential alterations in quality-of-life and thus reflects both mortality and health-related quality-of-life effects (28). QALY=(Survival in life-years)x(Utility-weight). Calculating QALYs requires knowledge of utility weights for each health state in the model. 'Utility weight' is an adjustment for quality-of-life. It indicates an individual's preference for specific health state where '1'=perfect health and '0'=death. The utility-scores used are described in **Supplementary-Table 5**.

Analysis

Figure 1 illustrates the decision-model. Path probabilities (**Supplementary-Figure 1**) were multiplied to calculate each branch probability. The total costs-and-effects in terms of life-years and QALYs were estimated by weighting the values for each branch by the branch probability. The ICER was estimated by dividing the difference in cost by the difference in effect between strategies. ICER=(Cost A–Cost B)/(Effect A–Effect B). This ICER obtained is compared with the cost-effectiveness willingness-to-pay (WTP) thresholds of NICE <£30000/QALY (38) (UK analysis) and USA $100,000/QALY (39,40) (USA analysis) to determine whether or not population screening for all women can be cost effective compared with clinical-criteria/FH-based testing. Additional scenario analyses were also undertaken: (a) no benefit of reduction in BC-risk; (b) varying genetic-testing costs to define UK and USA

cost-thresholds for cost-effectiveness; (c) higher all-cause mortality from premenopausal oophorectomy, and (d) lower RRSO/RRM uptake.

Sensitivity analyses explored uncertainty in results and robustness of the model. In a one-way sensitivity analysis, each model parameter is varied individually to evaluate impact on results. Probabilities/utility weights were varied according to 95% confidence-intervals/range, where available, or by +/-10%. Costs were varied by +/-30%. Given, model parameters/variables are likely to vary in parallel rather than independently, probabilistic sensitivity analysis (PSA) was also undertaken (28,41). It permits variables to be varied simultaneously across their distributions and is recommended by NICE (28). The PSA was fitted with appropriate distributions recommended in the literature (probabilities=beta; costs=gamma; utilities=log-normal) (42). A cost-effectiveness acceptability curve plotted the result of 10,000 simulations for all strategies. It depicts the proportion of cost-effective simulations for each strategy at the various WTP thresholds. The sum of the (cost-effective) proportions for all strategies taken together at any given WTP threshold is always=1.

RESULTS

The comparison of decision model outcomes of the three different testing strategies for undiscounted and discounted lifetime costs, life-years(survival), and QALYs is given for both UK and US women in **Table 2**. Discounting reduces the overall cost difference as well as gain in life-years/QALYs. This is because future costs/outcomes are adjusted by discounting and cost-savings which are generated through preventing future BC/OC are considered lower in value. Our results show that both newer strategies are cost-effective compared to the current clinical-criteria/FH-based *BRCA1/BRCA2* testing policy. Compared to Clinical-criteria/FH-based *BRCA1/BRCA2* testing, Clinical-criteria/FH-based panel testing for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* mutations is highly cost-effective:

ICER=£7,629.65/QALY or $49,282.19/QALY (0.04days life-expectancy gained). A population-based panel-testing strategy for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* mutations is the most cost-effective strategy compared to current policy: ICER=£21,599.96/QALY (9.34days life-expectancy gained) or $54,769.78/QALY (7.57days life-expectancy gained).

Results of the one-way sensitivity-analysis (**Figure 2**; **Supplementary Figures 2 and 3**) indicate that for Strategies-B and A, model-outcomes are not impacted that much by different model parameters (**Supplementary Tables 2 and 3**), mutation prevalence, surgical prevention costs, utility-scores or treatment of OC/BC or cardiovascular disease. Despite varying parameters at extremes of their CIs/range, the model remains cost-effective at the <£30,000/QALY or $100,000/QALY thresholds. The model is cost-effective at the lower limits of RRSO (30%) and RRM (34%).

PSA results (**Figures 3 and 4**) show that at £30,000/QALY WTP-threshold population-testing for all gene mutations (strategy-B) is the preferred strategy in 83.7% simulations and Clinical-criteria/FH-based panel-testing for all gene mutations (strategy-A) is preferred only in 16.2% simulations. Correspondingly, in American women, strategy-B is the preferred strategy at $100,000/QALY WTP threshold in 92.7% simulations. A population-testing strategy is more cost-effective than any clinical-criteria/FH-testing strategy, with strategy-B emerging as the most cost-effective. Taken together, this clearly indicates cost-effectiveness and overall preference for a population testing approach for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* mutations in the general population.

Scenario analyses are presented in **Table 3**. The alternative strategies-A and B still remain cost-effective at the UK/USA WTP-thresholds compared to the current clinical strategy, even if there is no reduction in BC-risk from RRSO (ICER=£27,632.95/QALY or

$72,221.37/QALY) and for lower RRM and RRSO rates. Population-testing remains cost-effective until the genetic-testing costs rise to £250/test or $772/test.

BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2 testing can prevent 1.86%/1.91% BC and 3.2%/4.88% OC in UK/USA women: 657/655 OC cases and 2420/2386 BC cases prevented per million. The overall proportion and number of BC/OC cases prevented as well as excess cardiovascular deaths from general (non-Jewish) population-based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* testing is given in **Table 4**.

DISCUSSION

Our analysis for the first time addresses the important topical issue of cost-effectiveness of a population-based strategy for testing moderate/high-penetrance OC/BC gene mutations in the general population. It justifies cost differences for different interventions by providing QALY-based health outcomes. This is required to guide policy decisions on healthcare resource allocation for disease prevention. Our findings that a population-based genetic testing strategy for OC/BC gene mutations outperforms any clinical-criteria or FH-strategy, with 84%-93% simulations cost-effective on PSA (£30,000/QALY and $100,000/QALY thresholds) are extremely noteworthy. Such a population-based program implemented in women >30years could result in 17,505/65,221 fewer OC and 64,493/237,610 fewer BC cases in British/American women respectively. This can have a much greater impact on the burden of disease than any current treatment strategy. Our data also highlight the need to move from *BRCA1/BRCA2* testing to panel-testing incorporating additional *RAD51C/RAD51D/BRIP1/PALB2* mutations within a clinical-criteria/FH-based strategy itself. These results have important implications for clinical care and OC/BC prevention. They could also be valuable to program evaluators/managers, policy makers, and healthcare commissioners.

Long and Ganz (43) used our AJ decision-analysis model (22) to evaluate systematic *BRCA1/BRCA2* testing in the general non-Jewish population and found it not to be cost-effective (43). However, AJ estimates/parameters should not be used to evaluate general population-testing, which may be a reason their analysis gives apparently incorrect/different results. For example, they use AJ estimates for prevalence of FH of cancer. However, clinical/FH-criteria are far more stringent and prevalence of such individuals is much lower in the general compared to the AJ-population. These data were previously unpublished and obtained from the ABCFR control population for our analysis. Additionally our current model and analysis is different, more comprehensive; uses general non-AJ estimates and compares two new panel testing strategies to the current gold-standard of Clinical-criteria/FH-based *BRCA1/BRCA2*-testing.

Our analysis has several advantages. It fulfils various principles listed by NICE for economic analyses including preferred type of economic evaluation (28). We use NICE guideline and clinical criteria-based current *BRCA1/BRCA2* testing policy as the best practice comparator. Additionally, QALYs are used to measure health effects, utilities are incorporated and costs and outcomes discounted at 3.5%. Model parameters are derived from well-established/proven information from the literature and up-to-date data from the PROMISE programme, GCaPPS study, and Australian BC registry. The time-horizon is sufficient to reveal important differences in costs and outcomes, and costs of pre-test counselling plus testing are included. Besides OC/BC outcomes we also included excess coronary deaths from premenopausal oophorectomy (26). To avoid over-estimating the advantages of population testing, we used conservative costs for OC/BC diagnosis, treatment and management of recurrence (44). The extensive sensitivity analysis presented adds rigour to the results. Costs of counselling, RRSO, chemoprevention and treatment of OC/BC/coronary disease do not influence overall results. Results remain cost-effective even

at extremes of *BRCA1/BRCA2* prevalence/penetrance estimates. Our analysis also highlights the need for better precision around prevalence and penetrance estimates of *RAD51C/RAD51D/BRIP1/PALB2* mutations as the CIs for these are extremely wide. This requires further research.

A limitation may be considering only cardiovascular mortality (not morbidity) from early oophorectomy. However, we include costs for all excess cardiovascular disease and one-way sensitivity-analysis shows these parameters don't substantially impact results. Another limitation may be our exclusion of increased lung/colorectal cancer mortality from premenopausal oophorectomy reported in the Nurses Health Study (26). However, this finding was not validated/reproduced in the 337,802 women EPIC study (45). Additionally, this excess mortality is confounded by smoking/risk related behaviors. The NIH-AARP Diet and Health Study found oophorectomy associated increased lung cancer risk was limited to smokers (46). Additionally, cardiovascular risk can also be confounded by smoking. Besides cohort data show that RRSO is associated with an overall 77% reduction in all-cause mortality (47), which will further improve cost-effectiveness. Nevertheless, even if we assumed a higher all-cause mortality (1:8), the model remains cost-effective for population-screening (ICER=£22,820/QALY and $58,561/QALY, 8.7 and 6.9 days life-expectancy gained).

We assume a 71% uptake of genetic-testing. However, the true uptake in non-AJ women needs to be addressed in future studies. Acceptability/uptake of population-based panel-testing is being assessed by us in the PROMISE pilot study (48). Premature surgical menopause is associated with worse sexual-functioning and vasomotor symptoms without decreasing generic quality-of-life (49-52). While HRT ameliorates detrimental consequences of premature menopause, symptom levels are still higher than those retaining their ovaries (51). This can be offset by reduced cancer worry, decrease in perceived risk, and high

satisfaction rates found with surgical prevention (49,50). These issues along with a small (~3-4%) complication rate(53) should be part of informed consent and RRSO decision making process. While we assume 80% HRT compliance, the true compliance in a larger population-based cohort remains to be determined. It is important for these women to have long-term follow-up and monitoring of bone/cardiovascular health and receive psychosexual support.

The utility of concomitant hysterectomy along-with RRSO has been debated. Proponents of hysterectomy cite the benefits of estrogen-alone HRT (no increased BC/heart disease risk) (54) and avoiding cervical smears. The impact and context of HRT in women undergoing premenopausal oophorectomy is completely different to that of older post-menopausal WHI women. Short-term HRT in *BRCA1/BRCA2* carriers undergoing premenopausal oophorectomy doesn't increase BC-risk (55). HRT is protective for heart disease in premenopausal oophorectomized women (26,27), will be stopped at 50years (age of menopause), and does not increase cardiovascular risk in the post-menopausal post-intervention phase (54). Hysterectomy has higher morbidity, complication rates, costs, longer operating time and hospital stay/recovery. Hysterectomy is not routinely offered as an alternative to progesterone HRT or to Tamoxifen in BC. With Tamoxifen (the absolute increase in endometrial-cancer (EC) risk is small (56), and ACOG/RCOG guidelines only recommend urgent investigation of unscheduled/abnormal bleeding.(57,58). Recent reports suggest increased 'serous'-EC risk in *BRCA1* (59,60). However, serous-EC comprises ~7% of overall-EC (61), number of cases were small, CIs wide, absolute EC-risk (~3%) remains small, and overall EC-risk is not statistically significantly increased (59,60).. A recent cost-effectiveness analysis had limitations. It only included women undergoing mastectomy and lacked a disutility for hysterectomy (62). Further corroborating data are needed and the issue of hysterectomy may then need revisiting. The risk-benefit profile doesn't currently justify

routine hysterectomy at RRSO for OC-risk reduction(63), and most centres don't practice this.

In line with a number of analyses in high (2,64,65) and low-risk (66) women our base-model incorporates a reduction in BC-risk with pre-menopausal oophorectomy. Conversely, a recent Dutch article (67) found no such effect. However, the follow-up was short (3.2years)(67), and longer follow-up data are awaited.. Nevertheless, our scenario analysis reconfirms cost-effectiveness of strategy-A and strategy-B even if pre-menopausal oophorectomy doesn't decrease BC-risk. RAD51C/RAD51D/PALB2 have been considered as single cancer genes only. However, should future evidence show both increased OC and BC, it would increase cost-effectiveness of population-testing.

Our model incorporates the impact of breast screening already prevalent and RRM. While RRM is weighted for a 21% complication rate, any reduction in QALYs is not included. Although RRM is linked with a negative impact on body-image and sexual pleasure, no detrimental impact on sexual-activity, habit, discomfort (68), anxiety, depression or quality-of-life was reported (68-70). Besides, adverse consequences may be balanced by decreased anxiety, increased social activity(68) and high cosmetic satisfaction rates (69,71-73).

Genomic, clinical and biological information is being combined through precision-medicine initiatives like the 100,000-Genomes (74) and Moonshot (75) projects to optimise clinical decisions for personalized treatment. . Importantly these advances also offer the opportunity for personalised cancer prevention. This can have a much bigger impact on reducing burden of disease but requires a shift in focus to the unaffected population. We show for the first time that introduction of systematic genetic-testing in the general population for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* mutations is a cost-effective strategy that can reduce OC and BC incidence and save lives. This form of panel-

testing can potentially be expanded to include other gene mutations with established 'clinical-utility' for cancer prevention. Our findings pave the way for research studies in carriers ascertained through population means to evaluate and understand impact on psychological-health, quality-of-life, long-term health behaviour and reconfirm uptake rates of screening/surgical prevention strategies. Additionally big services re-design and implementation issues affecting major system change/intervention outcomes (76,77) need addressing before introducing such a programme. Furthermore, a robust system/platform for monitoring and re-classifying (as required) variants of uncertain-significance (VUS) detected needs establishing. Other issues that need addressing include raising public/health professional awareness, education, delivery logistics, quality-control, call-recall mechanisms and fail-safe checks/processes for quality assurance. All these have additional costs. Further development/expansion of co-ordinated/integrated clinical pathways between primary and tertiary care involving GPs, geneticists, gynaecologists, breast teams are needed for managing high-risk women. Given extreme cost-effectiveness (78), of AJ-population *BRCA*-testing, panel-testing incorporating additional OC/BC genes would be cost-effective too and should be considered. The global cancer burden is expected to rise by 75%(79) and the number of BC/OC cases by 24%/27% in the UK and 34%/39% in the USA respectively by 2035 (80). Cancer prevention is key to achieve long-term transformational change and cost-efficiencies in our health-system. It is important we seize the opportunity offered to facilitate implementation of genomics for cancer prevention in healthcare.

Funding

The study was funded by 'The Eve Appeal' charity. The study is supported by researchers at the Barts Cancer Institute Cancer Research UK Centre for Excellence, Queen Mary University of London (C16420/A18066).

Notes

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.

Contribution to authorship

RM developed concept and design of the study. RM and RL developed the model. RM, RL, SP, VSG, AA, SS, RJM, JH, CT were involved in the health-economic and statistical analysis. JH, RJM, AA, AL, SG, SR, PP contributed data to the analysis. RM, RL, SP, VSG prepared the tables and figures. RM, RL prepared initial draft of the manuscript. All authors critically contributed to writing the manuscript and approved final version of the manuscript.

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, a Director of Women's Health Specialists Ltd and received consultancy from Beckton Dickinson. RM declares research funding from The Eve Appeal and Cancer Research UK into population testing and from Barts & the London Charity outside this work, as well as an honorarium for grant review from Israel National Institute for Health Policy Research. The other authors declare no conflict of interest.

References

1. 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(2):185-92.

2. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 2009;101(2):80-7.

3. 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(6):1055-62.

4. Cuzick J, Sestak I, Bonanni B*, et al.* Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet 2013;381(9880):1827-34.

5. Menon U, Harper J, Sharma A*, et al.* Views of BRCA gene mutation carriers on preimplantation genetic diagnosis as a reproductive option for hereditary breast and ovarian cancer. Hum Reprod 2007, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17428877.

6. Kang HH, Williams R, Leary J*, et al.* Evaluation of models to predict BRCA germline mutations. Br J Cancer 2006;95(7):914-20.

7. 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(1):379.

8. 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(39):14205-10.

9. 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(3):387-91.

10. Loveday C, Turnbull C, Ruark E*, et al.* Germline RAD51C mutations confer susceptibility to ovarian cancer. Nat Genet 2012;44(5):475-6; author reply 476.

11. Loveday C, Turnbull C, Ramsay E*, et al.* Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet 2011;43(9):879-82.

12. Rafnar T, Gudbjartsson DF, Sulem P*, et al.* Mutations in BRIP1 confer high risk of ovarian cancer. Nat Genet 2011;43(11):1104-7.

13. Ramus SJ, Song H, Dicks E*, et al.* Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. J Natl Cancer Inst 2015;107(11).

14. Song H, Dicks E, Ramus SJ*, et al.* Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol 2015;33(26):2901-7.

15. Manchanda R, Legood R, Antoniou C*, et al.* Defining the risk threshold of premenopausal risk reducing salpingo-oophorectomy for ovarian cancer prevention: a cost-effectiveness analysis. J Med Genet 2016:In Press.

16. Manchanda R, Legood R, Pearce L*, et al.* Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women. Gynecol Oncol 2015; 10.1016/j.ygyno.2015.10.001.

17. Antoniou AC, Casadei S, Heikkinen T*, et al.* Breast-cancer risk in families with mutations in PALB2. N Engl J Med 2014;371(6):497-506.

18. Lerner-Ellis J, Khalouei S, Sopik V*, et al.* Genetic risk assessment and prevention: the role of genetic testing panels in breast cancer. Expert Rev Anticancer Ther 2015;15(11):1315-26.

19. 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. In. NICE clinical guideline CG164 ed. London, UK: National Institute for Health and Care Excellence; 2013.

20. Shendure J, Ji H. Next-generation DNA sequencing. Nat Biotechnol 2008;26(10):1135-45.

21. Walsh T, Casadei S, Lee MK*, et al.* Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A 2011;108(44):18032-7.

22. 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(1):380.

23. Manchanda R, Jacobs I. Genetic screening for gynecological cancer: where are we heading? Future Oncol 2015; 10.2217/fon.15.278.

24. 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; 10.1136/jmedgenet-2015-103740.

25. 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(7):618-26.

26. Parker WH, Feskanich D, Broder MS*, et al.* Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. Obstet Gynecol 2013;121(4):709-16.

27. Rivera CM, Grossardt BR, Rhodes DJ*, et al.* Increased cardiovascular mortality after early bilateral oophorectomy. Menopause 2009;16(1):15-23.

28. NICE. Guide to the methods of technology appraisal. In. N1618 ed. London: National Institute for Health and Clinical Excellence (NICE); 2008.

29. 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; 10.1136/jmedgenet-2015-103077.

30. Slavin TP, Maxwell KN, Lilyquist J*, et al.* The contribution of pathogenic variants in breast cancer susceptibility genes to familial breast cancer risk. NPJ Breast Cancer 2017;3:22.

31. Department of Health. NHS Reference Costs 2012-2013. 2013, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/261154/nhs_reference_costs_2012-13_acc.pdf:https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/261154/nhs_reference_costs_2012-13_acc.pdf. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/261154/nhs_reference_costs_2012-13_acc.pdf.

32. Curtis L. Unit Costs of Health and Social Care 2011. In. Canterbury, Kent: Personal Social Services Research Unit (PSSRU); 2011.

33. Office of National Statistics. *Lifetable for females in the UK*. http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables.

34. Mavaddat N, Peock S, Frost D*, et al.* Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 2013;105(11):812-22.

35. CRUK. Ovarian Cancer Incidence Statistics: 2011. 2014, http://www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/incidence/uk-ovarian-cancer-incidence-statistics#age:accessed from http://www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/incidence/uk-ovarian-cancer-incidence-statistics#age , access date 10/03/2015. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/incidence/uk-ovarian-cancer-incidence-statistics#age.

36. SEER. Cancer Stat Facts: Ovary Cancer. 2014:http://seer.cancer.gov/statfacts/html/ovary.html (accessed 10/01/2017).

37. SEER. Cancer Stat Facts: Female Breast Cancer. 2014, https://seer.cancer.gov/statfacts/html/breast.html:https://seer.cancer.gov/statfacts/html/breast.html (date accessed: 20.01.2017). https://seer.cancer.gov/statfacts/html/breast.html.

38. NICE. Social value judgements: principles for the development of NICE guidance. In: (NICE) NIfHaCE, (ed). 2nd ed: National Institute for Health and Clinical Excellence (NICE); 2008.

39. Ubel PA, Hirth RA, Chernew ME*, et al.* What is the price of life and why doesn't it increase at the rate of inflation? Arch Intern Med 2003;163(14):1637-41.

40. 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(9):796-7.

41. 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(29):iii, ix-xi, 1-61.

42. Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2005;8(1):1-2.

43. Long EF, Ganz PA. Cost-effectiveness of Universal BRCA1/2 Screening: Evidence-Based Decision Making. JAMA Oncol 2015;1(9):1217-8.

44. Manchanda R, Legood R, Pearce L*, et al.* Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women. Gynecol Oncol 2015;139(3):487-94.

45. Tsilidis KK, Allen NE, Key TJ*, et al.* Oral contraceptives, reproductive history and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 2010;103(11):1755-9.

46. Brinton LA, Gierach GL, Andaya A*, et al.* Reproductive and hormonal factors and lung cancer risk in the NIH-AARP Diet and Health Study cohort. Cancer Epidemiol Biomarkers Prev 2011;20(5):900-11.

47. Finch AP, Lubinski J, Moller P*, et al.* Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol 2014;32(15):1547-53.

48. PROMISE 2016. https://www.eveappeal.org.uk/about/research/promise/:https://www.eveappeal.org.uk/about/research/promise/. https://www.eveappeal.org.uk/about/research/promise/.

49. 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(1):163-8.

50. 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(28):6890-8.

51. Madalinska JB, van Beurden M, Bleiker EM*, et al.* The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. J Clin Oncol 2006;24(22):3576-82.

52. 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(2):281-7.

53. Manchanda R, Abdelraheim A, Johnson M*, et al.* Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. BJOG : an international journal of obstetrics and gynaecology 2011;118(7):814-24.

54. Manson JE, Chlebowski RT, Stefanick ML*, et al.* Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 2013;310(13):1353-68.

55. Rebbeck TR, Friebel T, Wagner T*, et al.* Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2005;23(31):7804-10.

56. Fisher B, Costantino JP, Wickerham DL*, et al.* Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97(22):1652-62.

57. Committee Opinion No. 601: Tamoxifen and uterine cancer. Obstet Gynecol 2014;123(6):1394-7.

58. RCOG. Management of Endometrial Hyperplasia. *Green-top Guideline No. 67,* 2016, https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg_67_endometrial_hyperplasia.pdf. https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg_67_endometrial_hyperplasia.pdf.

59. Saule C, Mouret-Fourme E, Briaux A*, et al.* Risk of Serous Endometrial Carcinoma in Women With Pathogenic BRCA1/2 Variant After Risk-Reducing Salpingo-Oophorectomy. J Natl Cancer Inst 2018;110(2).

60. Shu CA, Pike MC, Jotwani AR*, et al.* Uterine Cancer After Risk-Reducing Salpingo-oophorectomy Without Hysterectomy in Women With BRCA Mutations. JAMA Oncol 2016;2(11):1434-1440.

61. Ueda SM, Kapp DS, Cheung MK*, et al.* Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol 2008;198(2):218 e1-6.

62. Havrilesky LJ, Moss HA, Chino J*, et al.* Mortality reduction and cost-effectiveness of performing hysterectomy at the time of risk-reducing salpingo-oophorectomy for prophylaxis against serous/serous-like uterine cancers in BRCA1 mutation carriers. Gynecol Oncol 2017;145(3):549-554.

63. Manchanda R, Legood R, Antoniou AC*, et al.* Commentary on changing the risk threshold for surgical prevention of ovarian cancer. BJOG 2017; 10.1111/1471-0528.14763.

64. 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 : the journal of the American Medical Association 2010;304(9):967-75.

65. Chai X, Domchek S, Kauff N*, et al.* 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(9).

66. Parker WH, Jacoby V, Shoupe D*, et al.* Effect of bilateral oophorectomy on women's long-term health. Womens Health (Lond Engl) 2009;5(5):565-76.

67. 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(5).

68. Brandberg Y, Sandelin K, Erikson S*, et al.* Psychological reactions, quality of life, and body image after bilateral prophylactic mastectomy in women at high risk for breast cancer: a prospective 1-year follow-up study. J Clin Oncol 2008;26(24):3943-9.

69. Isern AE, Tengrup I, Loman N*, et al.* Aesthetic outcome, patient satisfaction, and health-related quality of life in women at high risk undergoing prophylactic mastectomy and immediate breast reconstruction. J Plast Reconstr Aesthet Surg 2008;61(10):1177-87.

70. Nelson HD, Fu R, Goddard K*, et al.* In. *Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation*. Rockville (MD); 2013.

71. Brandberg Y, Arver B, Johansson H*, et al.* Less correspondence between expectations before and cosmetic results after risk-reducing mastectomy in women who are mutation carriers: a prospective study. Eur J Surg Oncol 2012;38(1):38-43.

72. Metcalfe KA, Esplen MJ, Goel V*, et al.* Psychosocial functioning in women who have undergone bilateral prophylactic mastectomy. Psychooncology 2004;13(1):14-25.

73. Wasteson E, Sandelin K, Brandberg Y*, et al.* High satisfaction rate ten years after bilateral prophylactic mastectomy - a longitudinal study. Eur J Cancer Care (Engl) 2011;20(4):508-13.

74. Genomics England. The 100,000 Genomes Project. 2015, http://www.genomicsengland.co.uk/the-100000-genomes-project/:http://www.genomicsengland.co.uk/the-100000-genomes-project/. http://www.genomicsengland.co.uk/the-100000-genomes-project/.

75. Lowy DR, Collins FS. Aiming High--Changing the Trajectory for Cancer. N Engl J Med 2016;374(20):1901-4.

76. Burnett S, Mendel P, Nunes F*, et al.* Using institutional theory to analyse hospital responses to external demands for finance and quality in five European countries. J Health Serv Res Policy 2016;21(2):109-17.

77. Fulop NJ, Ramsay AI, Perry C*, et al.* Explaining outcomes in major system change: a qualitative study of implementing centralised acute stroke services in two large metropolitan regions in England. Implement Sci 2016;11(1):80.

78. Manchanda R, Patel S, Antoniou AC*, et al.* Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. Am J Obstet Gynecol 2017; 10.1016/j.ajog.2017.06.038.

79. Bray F, Jemal A, Grey N*, et al.* Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol 2012;13(8):790-801.

80. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. *Online Analysis > Prediction,* 2016, http://globocan.iarc.fr/Pages/burden_sel.aspx:http://globocan.iarc.fr/Pages/burden_sel.aspx. http://globocan.iarc.fr/Pages/burden_sel.aspx.

81. 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(8):2318-24.

82. Antoniou AC, Cunningham AP, Peto J*, et al.* The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 2008;98(8):1457-66.

83. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25(11):1329-33.

84. CRUK. Cancer incidence for common cancers. *The 10 Most Common Cancers in Females, UK, 2012,* 2015, http://www.cancerresearchuk.org/content/cancer-incidence-for-common-

cancers#heading-Two:http://www.cancerresearchuk.org/content/cancer-incidence-for-common-cancers#heading-Two. http://www.cancerresearchuk.org/content/cancer-incidence-for-common-cancers#heading-Two.

85. SEER. Lifetime Risk (Percent) of Being Diagnosed with Cancer by Site and Race/Ethnicity. 2016, https://seer.cancer.gov/csr/1975_2013/results_merged/topic_lifetime_risk.pdf https://seer.cancer.gov/csr/1975_2013/results_merged/topic_lifetime_risk.pdf https://seer.cancer.gov/csr/1975_2013/results_merged/topic_lifetime_risk.pdf

86. 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 : an international journal of obstetrics and gynaecology 2012; 10.1111/j.1471-0528.2011.03257.x.

87. Parker WH, Broder MS, Chang E*, et al.* Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol 2009;113(5):1027-37.

88. Read MD, Edey KA, Hapeshi J*, et al.* Compliance with estrogen hormone replacement therapy after oophorectomy: a prospective study. Menopause Int 2010;16(2):60-4.

89. Cuzick J, Sestak I, Cawthorn S*, et al.* Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol 2015;16(1):67-75.

90. Smith SG, Sestak I, Forster A*, et al.* Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. Ann Oncol 2016;27(4):575-90.

91. Buys SS, Sandbach JF, Gammon A*, et al.* A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. Cancer 2017;123(10):1721-1730.

92. Graham D, Schmool M, Waterman S. Jews in Britain: a snapshot from the 2001 Census. In. London: Institute for Jewish Policy Research; 2007.

93. Office of National Statistics. Census 2001: National report for England and Wales, Part1, Section-2. Table S149: Sex and age by religion. In. London: Office of National Statistics; 2003, 182-183.

94. Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2016

2017:https://www.census.gov/data/datasets/2016/demo/popest/nation-detail.html.

95. Pew Research Center. A Portrait of Jewish Americans. *Findings from a Pew Research Center Survey of U.S. Jews,* 2013, http://www.pewforum.org/files/2013/10/jewish-american-full-report-for-web.pdf. http://www.pewforum.org/files/2013/10/jewish-american-full-report-for-web.pdf.

Tables

Table-1: Probabilities of different pathways in the model*

Probability	Value	(95%CI) [Range]	Description	Source
P1	0.00677	(0.0059-0.0077)	BRCA1/BRCA2 mutation prevalence in a general population	Jervis 2015(29)
P2	0.47	(0.34-0.56)	Probability that carrier will undergo RRM	Evans 2009(81)
P3	0.96	[0.8-0.96]	Reduction in risk of ovarian cancer from RRSO	Finch 2006,(1) Rebbeck 2009(2)
P4	0.202	[0.17-0.28]	Probability that BRCA1/BRCA2 carrier without RRSO will get ovarian cancer	Antoniou 2008 BOADICEA,(82) Chen 2007(83)
P5	0.02	(0.001, 0.06)	Probability that a non-carrier will get ovarian cancer	CRUK 2015(84)
	0.0128	(0.0126-0.0130)	Probability that a non-carrier will get ovarian cancer – USA estimate	SEER(85)
P6	0.0098	(0.0047, 0.0179)	Probability of having a positive FH fulfilling non-AJ genetic testing criteria	ABCFR data
P7	0.1		BRCA1/BRCA2 prevalence in those fulfilling clinical criteria or FH positive individuals	Current testing guideline
P8	0.0056	(0.0049, 0.0066)	BRCA1/2 Mutation prevalence in FH negative individuals	Jervis 2015,(29) ABCFR data
P9	0.911	(0.62-0.98)	Reduction in breast cancer risk from RRM without RRSO in BRCA1/2 carriers	Rebbeck 2004(3)
P10	0.644	[0.42-0.67]	Probability that BRCA1/2 carrier without RRM will get breast cancer	Antoniou 2008 BOADICEA,(82) Chen 2007(83)
P11	0.129	[0.11-0.14]	Probability that a non-BRCA1/2 carrier will get breast cancer with screening	CRUK 2015(84)
	0.124	(0.1236-0.1249)	Probability that a non-BRCA1/2 carrier will get breast cancer with screening – USA estimate	SEER(85)
P12	0.55	(0.30-0.75)	Probability that mutation carrier will follow-up with RRSO	Manchanda 2012(86)
P13	0.49	(0.37-0.65)	HR for breast cancer from RRSO alone in BRCA1/BRCA2 carrier	Rebbeck 2009(2)
P14	0.95	(0.78-0.99)	Reduction in risk of breast cancer from RRM with RRSO in BRCA1/BRCA2 carriers	Rebbeck 2004(3)

P15	0.002	(0.0003, 0.0036)	RAD51C, RAD51D, BRIP1 Mutation prevalence in unselected general population controls	Song 2015,(14) Ramus 2015(13)
P16	0.089	(0.05, 0.17)	Probability that RAD51C, RAD51D, BRIP1 carrier without RRSO will get ovarian cancer	Loveday 2012,(10) Loveday 2011,(11) Ramus 2015(13)
P17	0.94	(0.83-0.98)	Reduction in ovarian cancer risk from RRSO in RAD51C, RAD51D, BRIP1	Parker 2013(26)
P18	0.62	(0.53-0.74)	HR of breast cancer from RRSO alone in RAD51C, RAD51D, BRIP1	Parker 2009(87)
P19	0.0122	(0.0074, 0.017)	RAD51C, RAD51D, BRIP1 Mutation prevalence in FH positive (BRCA1/2 negative) individuals	Song 2015,(14) Ramus 2015(13)
P20	0.00186	(0.00023, 0.0034)	RAD51C, RAD51D, BRIP1 Mutation prevalence in FH negative individuals	Song 2015,(14) Ramus 2015(13) and ABCFR data
P21	0.0303	(0.011,0.043)	Risk of mortality from CHD after RRSO	Parker 2013(26)
P22	0.8	(0.76,0.83)	Compliance with HRT	Read 2010(88)
P23	0.71	(0·60–0·83)	HR of breast cancer risk from chemoprevention	Cuzick 2015(89)
P24	0.163	(0.136, 0.19)	Uptake of breast cancer chemoprevention	Smith 2016(90)
P25	0.00125	(0.0008, 0.0017)	PALB2 Mutation prevalence in unselected general population controls	Slavin 2017(30)
P26	0.44	(0.34, 0.55)	Probability that PALB2 carrier without RRM will get breast cancer	Antoniou 2014(17)
P27	0.0089	(0.0079, 0.0099)	PALB2 Mutation prevalence in FH positive (BRCA1/2 negative) individuals	Buys 2017(91)
P28	0.0012	(0.00073, 0.0016)	PALB2 Mutation prevalence in FH negative individuals	ABFCR data, Buys 2017(91), Slavin 2017(30)
P29	0.0072	(0.0068, 0.0076)	Excess risk of CHD after RRSO	Parker 2013(26)

*95%CI- 95% confidence interval, ABCFR- Australian Breast Cancer Family Registry, CHD- Coronary heart disease, CRUK- Cancer Research UK, FH- family history, HRT- hormone replacement therapy , RRSO- risk reducing salpingo-oophorectomy, RRM: Risk reducing Mastectomy. A detailed explanation of the various probabilities is given in **Supplementary Table 1**

Table 2. Model Outcomes for the different genetic testing strategies: undiscounted and discounted Costs, Quality Adjusted Life Years (QALYs) and Incremental Cost-effectiveness Ratio (ICER) per QALY

		Undiscounted			Discounted			
	Strategy	**Cost (UK=£, USA=$)**	**Life years**	**QALYs**	**Cost (UK=£, USA=$)**	**Life years**	**QALYs**	**ICER in £/QALY or $/QALY**
UK Estimates	*Standard FH based testing for BRCA1/BRCA2 mutations	£4423.25	52.2850	52.0822	£1586.11	23.7621	23.6909	-*
	FH based testing for BRCA1/BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutations	£4423.23	52.2851	52.0823	£1586.38	23.7621	23.6909	£7629.65
	Population testing for BRCA1/BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutations	£4586.86	52.3107	52.1116	£1779.73	23.7693	23.6999	£21599.96
USA Estimates	*Standard FH based testing for BRCA1/BRCA2 mutations	$19252.85	52.5063	52.3139	$6795.73	23.8127	23.7478	-*
	FH based testing for BRCA1/BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutations	$19253.14	52.5064	52.3140	$6797.35	23.8128	23.7479	$49282.19
	Population testing for BRCA1/BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutations	$19515.76	52.5271	52.3386	$7207.90	23.8185	23.7553	$54769.78

*Reference strategy. FH- family history, QALY- Quality Adjusted Life Years, ICER- Incremental Cost-effectiveness Ratio

Table-3: Scenario Analysis: UK and USA model outcomes for different scenarios

SCENARIO ANALYSIS								
		UK Estimates				USA Estimates		
		Strategy A		Strategy B		Strategy A		Strategy B	
	SCENARIOS	ICER/QALY (£)	LE gained (days)	ICER/QALY (£)	LE gained (days)	ICER/QALY ($)	LE gained (days)	ICER/QALY ($)	LE gained (days)
	No reduction in BC risk from RRSO (p13=1, p18=1)	9,540.39	0.04	27,632.95	7.8	57,693.62	0.04	72,221.37	6.5
	Lowest cost-effective RRM (p2) uptake rate: p2=19% (UK), p2= 8% (USA)	16,564.53	0.03	29,985.08	7.3	151,005.84	0.024	99,851.74	5.6
	Lowest cost-effective RRSO (p12) uptake rate: p12= 22% (UK), p2= 13% (USA)	7,298.79	0.03	29,970.42	6.4	71,788.24	0.024	99,969.56	4.1
	Lower RRM (p2) plus RRSO (p12) cost-effective rates: UK (p2 = 36% & p12 = 36%); (p2 = 32% & p12 = 32%)	9,965.86	0.03	29,984.88	6.8	93,684.20	0.03	99,653.60	4.8
	Genetic Testing cost £250 or $772 (thresholds at which population testing remains cost-effective)	7,629.65	0.04	29,896.23	9.4	49,282.19	0.04	99,947.44	7.6

Strategy-A: FH based testing for BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, and PALB2 mutations

Strategy-B: Population testing for BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, and PALB2 mutations

QALY- Quality Adjusted Life Years, ICER- Incremental Cost-effectiveness Ratio; LE – Life expectancy; RRM – Risk reducing mastectomy; RRSO – Risk reducing salpingo-oophorectomy; BC- breast cancer

Table 4. Overall impact of General (non-Jewish) Population Testing for *BRCA1/BRCA2/ RAD51C/RAD51D/BRIP1/PALB2* mutations in women >30 years*

Population Testing for *BRCA1/BRCA2/ RAD51C/RAD51D/BRIP1/PALB2* mutations	**UK women**	**USA women**
Proportion of BC cases prevented	1.86%	1.91%
Number of BC cases prevented per million women	2420	2386
Number of BC cases prevented in the total population (26.65M UK and 99.6M USA women)	64493	237610
Number of deaths from BC prevented per million women	523	367
Number of deaths from BC prevented in the total female population	13930	36591
Proportion of OC cases prevented	3.20%	4.88%
Number of OC cases prevented per million women	657	655
Number of OC cases prevented in the total population (26.65M UK and 99.6M USA women)	17505	65221
Number of OC deaths prevented per million	461	460
Number of OC deaths prevented in the total female population	12298	45857
Number of excess deaths from heart disease per million women	25	25
Number of excess deaths from heart disease in the total population (26.65M UK and 99.6M USA women)	666	2490

*The estimated female population (non-Jewish) >30years ~26.65M in the UK(92,93) and 99.6M in USA.(94,95). BC – breast cancer, OC – ovarian cancer, M – million

Figure Legends

Figure 1. Decision Analysis Model. The Right half of the model reflects a population-based approach to testing from *BRCA1, BRCA2, RAD51C, RAD51D,BRIP1* and *PALB2* mutations. The left half of the model reflects a clinical criteria/ family history based testing approach for the same. 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 highlighted along the decision branch. The probabilities used in the model are explained in Table-1 and Supplementary Table-S1. Values for each outcome are calculated. Cancer incidence was estimated by summing the probabilities of pathways ending in ovarian or breast cancer. Final outcomes of each path include development of breast cancer (BC), ovarian cancer (OC), no breast/ovarian cancer (no OC or BC) and excess deaths from coronary heart disease (CHD).
Abbreviations: BC- Breast Cancer, CHD- Coronary heart disease; OC-Ovarian Cancer; No OC or BC- No Ovarian Cancer or Breast Cancer developed., RRSO –Risk reducing salpingo-oophorectomy; RRM – Risk reducing mastectomy; BRCA- BRCA1 & BRCA2; RAD+ - RAD51C, RAD51D & BRIP1

Figure 2. One way Sensitivity Analysis: Population screening for BRCA1, BRCA2, RAD51C, RAD51D, BRIP1 and PALB2 mutations in UK & USA women. One-way sensitivity analysis for all probabilities, costs and utilities in terms of ICER of UK and USA Population-based screening for *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1* and PALB2 mutations, compared to a Clinical-criteria / FH-based approach for *BRCA1* and *BRCA2* testing. Y-axis: Incremental cost-effectiveness ratio (ICER): Cost (£s or $s) per quality adjusted life year (QALY) (discounted). X-axis: Probability, cost and utility parameters in the

model. The model is run at both lower and upper values/limits of the 95% confidence interval or range of all probability parameters described in Table-1/methods; and both lower and upper values/limits of the cost and utility-score parameters given in Table 2. Costs are varied by +/- 30%. 'Maximum value' represents outcomes for upper limit and 'minimum value' represents outcomes for lower limit of the parameter.

Figure 3. Probabilistic Sensitivity Analysis: UK women. Probabilistic sensitivity analysis in which all model parameters/ variables are varied simultaneously across their distributions to further explore model uncertainty. X-axis: Incremental cost-effectiveness ratio (ICER) in terms of Cost (£s))/QALY; Y-axis: Proportion of simulations. The results of 10,000 simulations were plotted on a cost-effectiveness acceptability curve showing the proportion of simulations (Y-axis) that indicated that the intervention was cost-effective at different willingness to pay thresholds (X-axis). The dotted line in Fig 4, marks the proportion of simulations found to be cost-effective at the £30,000 UK threshold used by NICE. Bold line Curve – Standard Clinical-criteria/ Family-history based testing for *BRCA1/BRCA2* mutations.

Curve A- Clinical-criteria/ Family-history based testing for *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1* and *PALB2* mutations

Curve B - Population-based screening for *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1* and *PALB2* mutations

At any given point on the WTP-threshold scale, the sum of proportion of cost-effective simulations for all three strategies is always =1.

At the £30,000/QALY willingness to pay threshold, 16.2% simulations are cost-effective for Clinical-criteria/ Family-history based testing for all gene mutations (Curve A) and 83.7% simulations are cost-effective for population-testing for all gene mutations (Curve B).

A population-testing strategy is more cost-effective than any Clinical-criteria/FH-testing strategy

Figure 4. Probabilistic Sensitivity Analysis: USA women. Probabilistic sensitivity analysis in which all model parameters/ variables are varied simultaneously across their distributions to further explore model uncertainty. X-axis: Incremental cost-effectiveness ratio (ICER) in terms of Cost ($s))/QALY; Y-axis: Proportion of simulations. The results of 10,000 simulations were plotted on a cost-effectiveness acceptability curve showing the proportion of simulations (Y-axis) that indicated that the intervention was cost-effective at different willingness to pay thresholds (X-axis). The dotted line marks the proportion of simulations found to be cost-effective at the $100,000 USA willingness to pay (WTP) threshold.

Curve with Bold Line – Standard Clinical-criteria/ Family-history based testing for *BRCA1/BRCA2* mutations

Curve A- Clinical-criteria/ Family-history based testing for *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1* and *PALB2* mutations

Curve B - Population-based screening for *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1* and *PALB2* mutations

At any given point on the WTP-threshold scale, the sum of proportion of cost-effective simulations for all three strategies is always =1.

At the $100,000/QALY willingness to pay threshold, 5.8% simulations are cost-effective for Clinical-criteria/ Family-history based testing for all gene mutations (Curve A) and 92.7% simulations are cost-effective for population-testing for all gene mutations (Curve B).

A population-testing strategy is more cost-effective than any Criteria/FH-testing strategy