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**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 ( $\geq 10\%$  *BRCA1/BRCA2* probability), and all women  $\geq 30$  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 7.57 days 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  $\geq 4$ -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  $\geq 30$  years for *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1* and *PALB2* mutations compared with the current practice of clinical-criteria/FH-based testing (based on  $\geq 10\%$  *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).  $QALY = (\text{Survival in life-years}) \times (\text{Utility-weight})$ . 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.  $ICER = (\text{Cost A} - \text{Cost B}) / (\text{Effect A} - \text{Effect B})$ . 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.

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## 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.

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## 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**

	Strategy	Undiscounted			Discounted			ICER in £/QALY or \$/QALY
		Cost (UK=£, USA=\$)	Life years	QALYs	Cost (UK=£, USA=\$)	Life years	QALYs	
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\***

<b>Population Testing for <i>BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2</i> mutations</b>	<b>UK women</b>	<b>USA women</b>
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

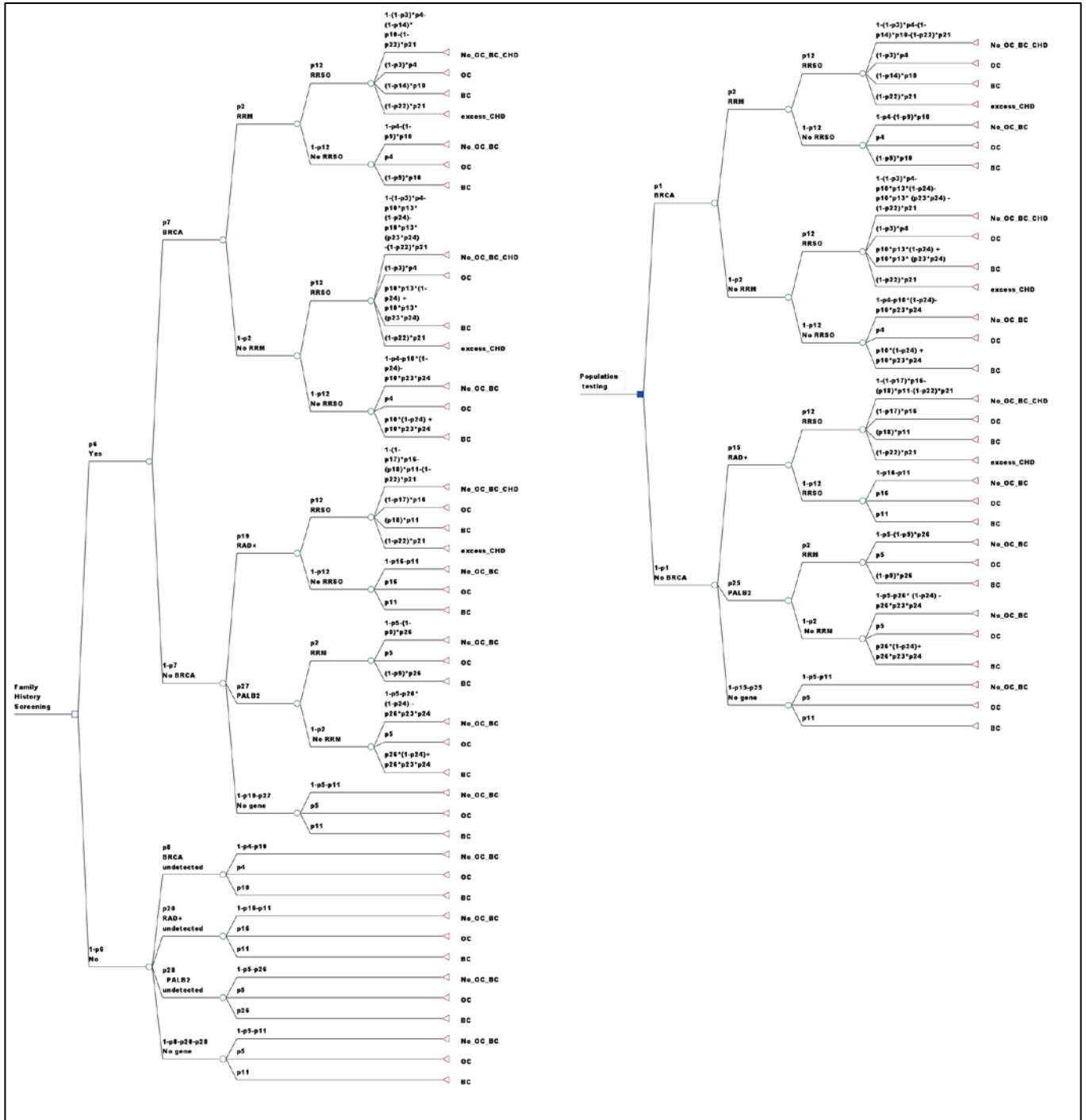
Curve B - Population-based screening for *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1* and *PALB2* mutations

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

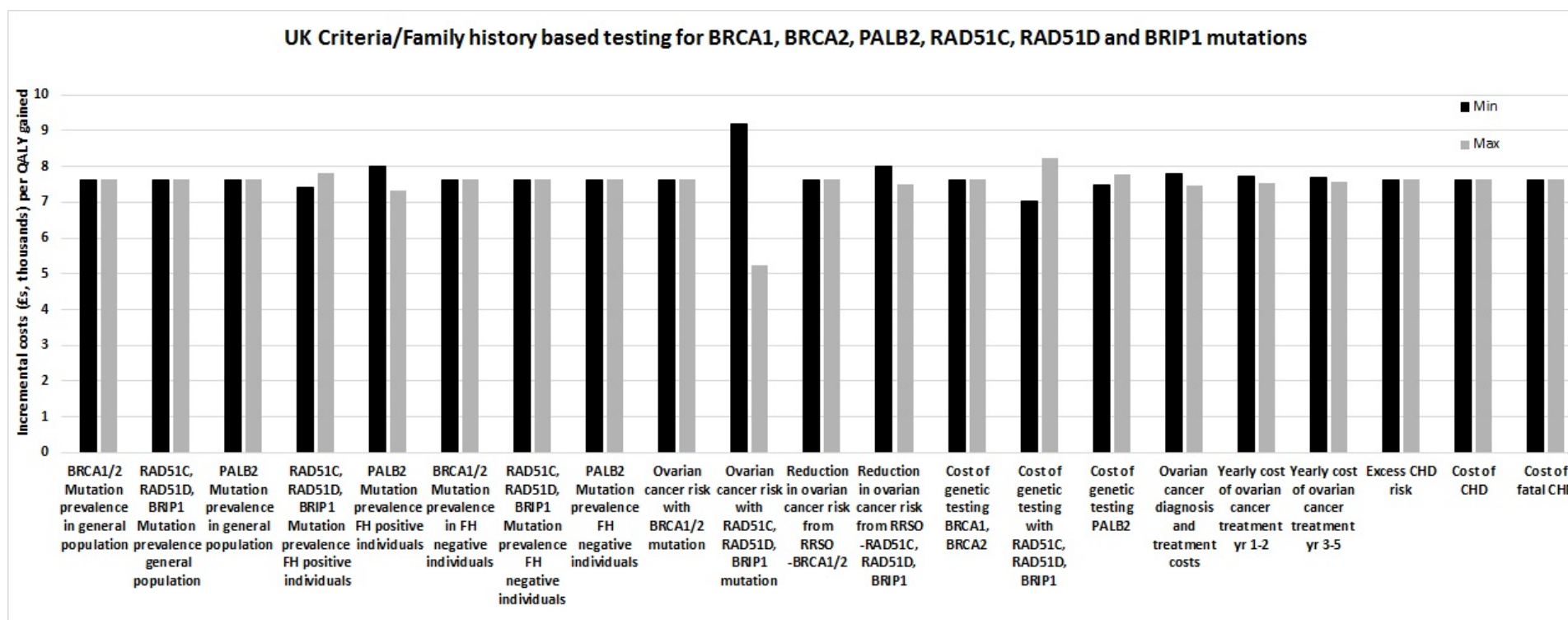
At the \$100,000/QALY willingness to pay threshold, 5.8% simulations are cost-effective for Clinical-criteria/ Family-history based testing for all gene mutations (Curve A) and 92.7% simulations are cost-effective for population-testing for all gene mutations (Curve B).

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

# Supplementary Figures



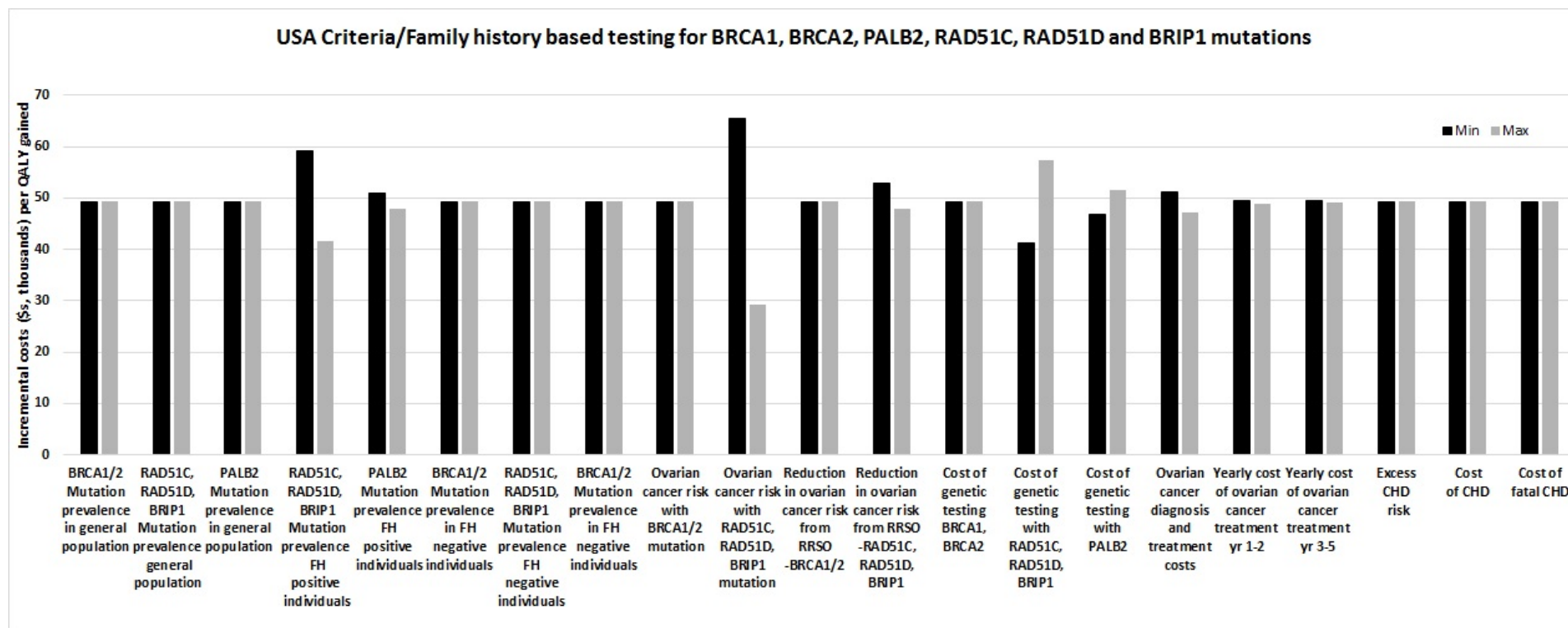
**Supplementary Figure 1: Decision Analysis Model.** The right half of the model reflects a population based approach to testing from BRCA1, BRCA2, PALB2, RAD51C, RAD51D, BRIP1 and PALB2 mutations. The left half of the model reflects a clinical criteria/ family history based testing approach for the 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 (p1 to p29) used in the model are explained in **Table 1** and **Supplementary Table 1**. The path probabilities are given for each branch of the model. 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



**Supplementary Figure 2. One way Sensitivity Analysis: Clinical-criteria/Family-history screening for BRCA1, BRCA2, RAD51C, RAD51D, BRIP1 and PALB2 mutations in UK women.** One-way sensitivity analysis for all probabilities, costs and utilities in terms of ICER of – UK Clinical-criteria/Family-history based screening for *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1* mutations, compared to a Clinical-criteria / FH-based approach for *BRCA1* and *BRCA2* testing. Y-axis: Incremental cost-effectiveness ratio (ICER): Cost (£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.



**Supplementary Figure 3. One way Sensitivity Analysis: Clinical-criteria/Family-history screening for BRCA1, BRCA2, RAD51C, RAD51D, BRIP1 and PALB2 mutations in USA women.** One-way sensitivity analysis for all probabilities, costs and utilities in terms of ICER of – USA Population-based screening for *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1* mutations, compared to a Clinical-criteria/ FH-based approach for *BRCA1* and *BRCA2* testing. Y-axis: Incremental cost-effectiveness ratio (ICER): Cost (\$) 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.

## SUPPLEMENTARY TABLES

### SUPPLEMENTARY TABLE 1: DECISION ANALYSIS MODEL ASSUMPTIONS

#### Detailed description of Model Assumptions:

The decision-analysis 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) (1). The cost of pre-test counselling is included (2,3). *BRCA1/BRCA2* negative women are tested for *RAD51C/RAD51D/BRIP1/PALB2* mutations (from the same DNA sample). Genetic-testing is undertaken in a research laboratory with repeat confirmatory testing for all pathogenic mutations in identified carriers being performed in an accredited Health Service genetics laboratory. This approach has been accepted and is being currently implemented within the UK 100,000 genome project for delivering personalised medicine across the UK National Health Service (NHS) (4). This has also been adopted in a pilot study on acceptability of general population testing in the PROMISE-programme (5). In line with current guidelines/literature (6,7), women testing positive are offered RRSO to reduce their OC risk (8,9). *BRCA1/BRCA2/PALB2* mutation carriers are also offered options for BC-risk reduction: MRI/mammography screening; chemoprevention with SERM (10) or RRM (11) to reduce their BC-risk as appropriate (7). The model incorporates the increased risk of cardiovascular mortality (absolute increase=3.03%) reported with pre-menopausal bilateral-oophorectomy, particularly in women <45-50years who don't take hormone replacement therapy (HRT) (12,13). The increased risk of heart disease and associated costs are modelled over an individual's lifetime. Women undergoing RRSO are given HRT till 51years. We assume HRT compliance of 80% (CI:76%,83%) (14). We include costs of bone health monitoring using Dual Energy X-ray Absorptiometry (DEXA) scans as well as calcium and vitamin D3 and HRT supplementation. Short-term HRT following RRSO does not affect BC-risk (15). OC-screening was excluded, as a conclusive mortality benefit has not been demonstrated (16). Model outcomes included OC, BC and excess deaths from coronary heart disease. As per National Institute of Health and Care Excellence(NICE) economic evaluation guidelines, costs and outcomes are discounted at 3.5% (17).

**SUPPLEMENTARY TABLE 2. PROBABILITIES OF DIFFERENT PATHWAYS IN THE MODEL**

<b>Probability</b>	<b>Value</b>	<b>(95%CI) [Range]</b>	<b>Description</b>	<b>Source</b>
<b>P1</b>	<b>0.00677</b>	<b>(0.0059-0.0077)</b>	<b>BRCA1/BRCA2 mutation prevalence in a general population</b>	Jervis 2015 (18)
<b>P2</b>	<b>0.47</b>	<b>(0.34-0.56)</b>	<b>Probability that carrier will undergo RRM</b>	Evans 2009 (19)
<b>P3</b>	<b>0.96</b>	<b>[0.8-0.96]</b>	<b>Reduction in risk of ovarian cancer from RRSO</b>	Finch 2006 (8), Rebbeck 2009 (9)
<b>P4</b>	<b>0.202</b>	<b>[0.17-0.28]</b>	<b>Probability that BRCA1/BRCA2 carrier without RRSO will get ovarian cancer</b>	Antoniou 2008 BOADICEA (20), Chen 2007 (21)
<b>P5</b>	<b>0.02</b>	<b>(0.001, 0.06)</b>	<b>Probability that a non-carrier will get ovarian cancer</b>	CRUK 2015 (22)
	<b>0.0128</b>	<b>(0.0126-0.0130)</b>	<b>Probability that a non-carrier will get ovarian cancer – USA estimate</b>	SEER (23)
<b>P6</b>	<b>0.0098</b>	<b>(0.0047, 0.0179)</b>	<b>Probability of having a positive FH fulfilling non-AJ genetic testing criteria</b>	ABCFR data
<b>P7</b>	<b>0.1</b>		<b>BRCA1/BRCA2 prevalence in those fulfilling clinical criteria or FH positive individuals</b>	Current testing guideline
<b>P8</b>	<b>0.0056</b>	<b>(0.0049, 0.0066)</b>	<b>BRCA1/2 Mutation prevalence in FH negative individuals</b>	Jervis 2015 (18), ABCFR data
<b>P9</b>	<b>0.911</b>	<b>(0.62-0.98)</b>	<b>Reduction in breast cancer risk from RRM without RRSO in BRCA1/2 carriers</b>	Rebbeck 2004 (11)
<b>P10</b>	<b>0.644</b>	<b>[0.42-0.67]</b>	<b>Probability that BRCA1/2 carrier without RRM will get breast cancer</b>	Antoniou 2008 BOADICEA (20), Chen 2007 (21)
<b>P11</b>	<b>0.129</b>	<b>[0.11-0.14]</b>	<b>Probability that a non-BRCA1/2 carrier will get breast cancer with screening</b>	CRUK 2015 (22)
	<b>0.124</b>	<b>(0.1236-0.1249)</b>	<b>Probability that a non-BRCA1/2 carrier will get breast cancer with screening – USA estimate</b>	SEER (23)

<b>P12</b>	<b>0.55</b>	<b>(0.30-0.75)</b>	<b>Probability that mutation carrier will follow-up with RRSO</b>	Manchanda 2012 (24)
<b>P13</b>	<b>0.49</b>	<b>(0.37-0.65)</b>	<b>HR for breast cancer from RRSO alone in BRCA1/BRCA2 carrier</b>	Rebbeck 2009 (9)
<b>P14</b>	<b>0.95</b>	<b>(0.78-0.99)</b>	<b>Reduction in risk of breast cancer from RRM with RRSO in BRCA1/BRCA2 carriers</b>	Rebbeck 2004 (11)
<b>P15</b>	<b>0.002</b>	<b>(0.0003, 0.0036)</b>	<b>RAD51C, RAD51D, BRIP1 Mutation prevalence in unselected general population controls</b>	Song 2015 (25), Ramus 2015 (26)
<b>P16</b>	<b>0.089</b>	<b>(0.05, 0.17)</b>	<b>Probability that RAD51C, RAD51D, BRIP1 carrier without RRSO will get ovarian cancer</b>	Loveday 2012 (27), Loveday 2011 (28), Ramus 2015 (26)
<b>P17</b>	<b>0.94</b>	<b>(0.83-0.98)</b>	<b>Reduction in ovarian cancer risk from RRSO in RAD51C, RAD51D, BRIP1</b>	Parker 2013 (12)
<b>P18</b>	<b>0.62</b>	<b>(0.53-0.74)</b>	<b>HR of breast cancer from RRSO alone in RAD51C, RAD51D, BRIP1</b>	Parker 2009 (29)
<b>P19</b>	<b>0.0122</b>	<b>(0.0074, 0.017)</b>	<b>RAD51C, RAD51D, BRIP1 Mutation prevalence in FH positive (BRCA1/2 negative) individuals</b>	Song 2015 (25), Ramus 2015 (26)
<b>P20</b>	<b>0.00186</b>	<b>(0.00023, 0.0034)</b>	<b>RAD51C, RAD51D, BRIP1 Mutation prevalence in FH negative individuals</b>	Song 2015 (25), Ramus 2015 (26) and ABCFR data
<b>P21</b>	<b>0.0303</b>	<b>(0.011,0.043)</b>	<b>Risk of mortality from CHD after RRSO</b>	Parker 2013 (12)
<b>P22</b>	<b>0.8</b>	<b>(0.76,0.83)</b>	<b>Compliance with HRT</b>	Read 2010 (14)
<b>P23</b>	<b>0.71</b>	<b>(0.60–0.83)</b>	<b>HR of breast cancer risk from chemoprevention</b>	Cuzick 2015 (30)
<b>P24</b>	<b>0.163</b>	<b>(0.136, 0.19)</b>	<b>Uptake of breast cancer chemoprevention</b>	Smith 2016 (31)
<b>P25</b>	<b>0.00125</b>	<b>(0.0008, 0.0017)</b>	<b>PALB2 Mutation prevalence in unselected general population controls</b>	Slavin 2017 (32)
<b>P26</b>	<b>0.44</b>	<b>(0.34, 0.55)</b>	<b>Probability that PALB2 carrier without RRM will get breast cancer</b>	Antoniou 2014 (33)

<b>P27</b>	<b>0.0089</b>	<b>(0.0079, 0.0099)</b>	<b>PALB2 Mutation prevalence in FH positive (BRCA1/2 negative) individuals</b>	Buys 2017 (34)
<b>P28</b>	<b>0.0012</b>	<b>(0.00073, 0.0016)</b>	<b>PALB2 Mutation prevalence in FH negative individuals</b>	ABFCR data, Buys 2017 (34), Slavin 2017 (32)
<b>P29</b>	<b>0.0072</b>	<b>(0.0068, 0.0076)</b>	<b>Excess risk of CHD after RRSO</b>	Parker 2013 (12)

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-S1

Explanation:

P1: The probability of carrying a BRCA1/BRCA2 mutation in the non-AJ population (P1= 0.00677) is taken from Jervis et al 2015. It provides the most up to date estimates for BRCA1/BRCA2 prevalence using contemporary sequencing technologies and knowledge of pathogenicity (18).

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 (19). A composite uptake rate (P2=0.47) for BRCA1 (60% RRM rate) and BRCA2 (43% RRM rate) carriers weighted for the relative prevalence of BRCA1 and BRCA2 mutations was computed (19).

P3: The reduction in ovarian cancer risk obtained from RRSO (P3= 0.96) is taken from previous studies which report a 4% residual-risk of primary peritoneal cancer following RRSO (8).

P4: A wide range of ovarian cancer risks have been reported for BRCA1/BRCA2 carriers, with higher penetrance estimates found in carriers ascertained from high-risk families with multiple cancer cases (35). Our analysis uses ovarian cancer penetrance figures till age 80 years from Antoniou 2008, which are corrected for ascertainment (20). To simplify the analysis we have used a composite risk for BRCA1 and BRCA2 carriers (P4= 0.202) weighted for the relative prevalence of BRCA1 and BRCA2 mutations.

P5: The risk of ovarian cancer in a low-risk population is obtained from Cancer Research UK (22) for UK women and SEER (23) data for USA women.

P6: the probability of having a positive FH fulfilling non-AJ genetic testing criteria is obtained from the unselected control population of the Australian Breast Cancer Family Registry database (unpublished data).

P7: This is the BRCA1/2 mutation probability in FH positive individuals i.e., individuals who have a strong family history of cancer. P7=0.1 which is the threshold for genetic testing.

P8: The probability of BRCA1/2 Mutation prevalence in FH negative individuals (individuals without a strong family history of cancer who do not fulfil the threshold of genetic testing is estimated from population mutation prevalence (Jervis et al) (18) and Australian Breast Cancer Family Registry control data.

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 (11).

P10: The breast cancer penetrance estimates for BRCA1/BRCA2 carriers till age 80 years which are corrected for ascertainment are obtained from Antoniou 2008 (20). To simplify the analysis we have used a composite risk for BRCA1 and BRCA2 carriers ( $P_{10}=0.644$ ) weighted for the relative prevalence of BRCA1 and BRCA2 mutations.

P11: The risk of breast cancer in a low risk population is taken from Cancer Research UK and UK Office for National Statistics data for UK women (22,36) and from SEER (23) data for USA women.

P12: Decision making regarding RRSO can be a complex process. RRSO rates ranging from 0.3 to 0.75 have been reported in the literature (19,24,37,38). We have used the RRSO rate reported in high-risk women from London ( $P_{12}= 0.55$ ), as it reflects the views of carriers from a UK population and is within the range reported in the literature (24).

P13: The reduction in breast cancer risk in pre-menopausal BRCA1/BRCA2 women undergoing RRSO alone is taken from a meta-analysis by Rebbeck et al 2009 (9).

P14: Reduction in breast cancer risk in BRCA1/BRCA2 women undergoing RRM and RRSO is taken from the PROSE study data by Rebbeck et al 2004 (11).

P15: The mutation prevalence RAD51C, RAD51D, BRIP1 in unselected general population controls is obtained from recent publications by Song et al 2015 (RAD51C, RAD51D) (25) and Ramus et al 2015 (BRIP1) (26). A composite prevalence for all three mutations is calculated.

P16: The ovarian cancer penetrance for RAD51C, RAD51D, and BRIP1 mutations is obtained from recent publications by Loveday 2011 (RAD51D) (28), Loveday 2012 (RAD51C) (27) and Ramus 2015 (BRIP1) (26). A composite penetrance weighted for the relative prevalence of RAD51C, RAD51D, and BRIP1 mutations was computed.

P17: Reduction in ovarian cancer risk from RRSO in RAD51C, RAD51D, BRIP1 carriers is obtained from risk reduction observed in the general population (non-BRCA1/BRCA2 carriers) reported by Parker 2013 (12), as no specific data for RAD51C, RAD51D, BRIP1 exist.

P18: Reduction in breast cancer risk from RRSO in RAD51C, RAD51D, BRIP1 carriers is obtained from risk reduction observed in the general population (non-BRCA1/BRCA2 carriers) reported by Parker (29), as no specific data for RAD51C, RAD51D, BRIP1 exist.

P19: RAD51C, RAD51D, BRIP1 mutation prevalence in FH positive (BRCA1/2 negative individuals with a strong family history of cancer) is obtained from UKFOCSS data (Song 2015, Ramus 2015) (25,26).



P20: RAD51C, RAD51D, BRIP1 mutation prevalence in FH negative individuals (those with a strong family history of cancer) is obtained from Song 2015, Ramus 2015 (25,26) and Australian Breast Cancer Family Registry control data.

P21: The risk of CHD mortality is obtained from the Nurses Health Study (Parker et al 2013) (12). Death from CHD is reported in 1 in 33 pre-menopausal women undergoing RRSO and not taking HRT (12).

P22: HRT compliance rate is obtained from a UK cohort (Read et al, 2010) (14).

P23: The level of breast cancer risk reduction obtained from chemoprevention in high risk women is obtained from the recent published extended long term follow-up of the IBIS-I breast cancer prevention trial. The HR of breast cancer is reported as 0.71 (0.60–0.83) (Cuzick et al 2015)(30).

P24: the breast cancer chemoprevention uptake rate is obtained from a recent meta-analysis by Smith et al meta-analysis. The pooled uptake estimate was 16.3% [95% CI 13.6%–19.0%] (31).

P25: The probability of carrying a PALB2 mutation in the general population is taken from control data used in a study by Slavin 2017 (32).

P26: The breast cancer penetrance estimates for PALB2 carriers till the age 80 years are obtained from Antoniou 2014 (33).

P27: Mutation prevalence of PALB2 in FH positive carriers is obtained from a study of 35,000 women with breast cancer by Buys 2017 (34).

P28: Australian Breast Cancer Family Registry control data along with population prevalence estimates above inform the PALB2 mutation prevalence in FH negative carriers.

P29: Excess risk of CHD after oophorectomy is estimated using data from Parker 2013 (12). The absolute excess CHD incidence is obtained by subtracting CHD in women with oophorectomy from those without oophorectomy.

**SUPPLEMENTARY TABLE 3. SUMMARY OF COSTS USED IN MODEL (2015 PRICES)\***

<b>Item</b>	<b>Cost UK (£)</b>	<b>Cost USA (\$)</b>	<b>Source</b>
Cost of genetic testing	175	330	PROMISE programme and NHS clinical genetics laboratory
Cost of counselling	27	43	GCaPPS (1,2), PSSRU Unit costs of Health and Social Care (39), Schwartz et al 2014 (3), Eggington 2014 (40).
Cost of RRSO (and HRT and osteoporosis prevention)	3,570	8,144	NHS Reference costs (41), BNF (42), Grann 2011 (43), Williams-Frame 2009 (44)
Cost of ovarian cancer diagnosis and initial treatment	14,201	127,995	NHS Reference costs (41), NICE guideline (45), Grann 2011 (43)
Yearly cost of ovarian cancer treatment and follow-up: years 1-2	5,394	14,071	NHS Reference costs (41), NICE guideline (45), Grann 2011 (43), CRUK 2014 report (46)
Yearly cost of ovarian cancer treatment and follow-up: years 3-5	5,024	14,071	NHS Reference costs (41), NICE guideline (45), Grann 2011 (43), CRUK 2014 report (46)
Terminal care cost with ovarian cancer	15,588	89,424	National Audit office (47), Grann 2011 (43)
Cost of breast cancer screening general	350	1534	Robertson 2011 (48), NHS reference cost (41), CDC guideline (49)
Cost of breast cancer screening BRCA1/BRCA2/PALB2 carriers	4,623	33,530	NHS reference cost (41), NICE guideline Familial breast cancer (7), CDC guidelines (49), Grann 2011 (43)
Cost of RRM	4,059	12,596	NHS reference cost (41), weighted for 21% complication rate (6,50), Grann 2011(43)
Cost of breast cancer diagnosis and treatment (Sporadic, PALB2)	15,923	82,030	NHS Reference costs (41), NICE guideline Advanced breast cancer (51), NICE guidelines Early and locally advanced breast cancer (52), Grann 2011 (43)
Cost of breast cancer diagnosis and treatment (BRCA1/BRCA2)	14,476	75,873	NHS Reference costs (41), NICE guideline Advanced breast cancer (51), NICE guidelines Early and locally advanced breast cancer (52), Grann 2011 (43)

Yearly cost of breast cancer follow-up and adjuvant treatment if any (e.g. Tamoxifen): years 1-5 (Sporadic breast cancer)	2,027	7,738	BNF (42), Robertson 2011 (48), NHS Reference costs (41), NICE guidelines Early and locally advanced breast cancer (52), NICE guideline Advanced breast cancer (51). National Costing report. Implementing NICE guidance 2009 (53), Grann 2011 (43)
Yearly cost of breast cancer follow-up and adjuvant treatment if any (e.g. Tamoxifen): years 1-5 (BRCA1, BRCA2)	1,748	7,738	BNF (42), Robertson 2011 (48), NHS Reference costs (41) NICE guidelines Early and locally advanced breast cancer (52) NICE guideline Advanced breast cancer (51) National Costing report. Implementing NICE guidance 2009 (53) Grann 2011 (43)
Yearly cost of breast cancer follow-up and adjuvant treatment if any (e.g. Tamoxifen): years 1-5 (PALB2)	1,852	7738	BNF (42), Robertson 2011 (48), NHS Reference costs (41) Antnoiou 2014 (33), NICE guidelines Early and locally advanced breast cancer (52), NICE guideline Advanced breast cancer (51), National Costing report. Implementing NICE guidance 2009 (53), Grann 2011 (43)
Terminal care cost with breast cancer	15,588	65,403	Grann 2011 (43)
Cost of fatal CHD	3,343	23,012	NHS Reference costs (41,47), Afana 2015 (54)
Cost of excess CHD	3,380	188,787	NIH (55), Townsend 2015 (56), CDC 2017 (57), Parker 2013 (12), American Heart Association 2017 (58), World Bank 2017 (59)
<p>*All costs were varied by +/-30% in one way sensitivity analysis</p> <p>BNF- British National Formulary, CDC- Centers for Disease Control and Prevention, CHD- Coronary heart disease, GCaPPS- Genetic Cancer Prediction through Population Screening study, HRT- hormone replacement therapy, NHS- National Health Service, NICE-National Institutes for Health and Care Excellence, PSSRU- Personal Social Services Research Unit, RRSO- risk reducing salpingo-oophorectomy, RRM- risk reducing mastectomy, UK- United Kingdom, USA- United States of America</p>			

Costs obtained from Grann 2011 were inflated using the medical component of the USA consumer price index to 2015 US\$.

A detailed explanation of the costs is given in Supplementary Table-S2

### **Explanation**

Cost of genetic counselling/ testing: based on pre-test counselling in the population based GCaPPS study, 71% genetic testing uptake (GCaPPS study). The UK national unit cost assumed for genetic counseling= £44/hr of client contact from PSSRU Unit costs of Health and Social Care 2010 (1,2,39). The USA costs of genetic counselling are taken from Schwartz et al 2014, which includes ancillary preparation (scheduling/administration), counsellor preparation and counselling (3). We also include the cost of post-test counselling for VUS in 2% cases (40).

The cost of BRCA1/BRCA2 and RAD51C, RAD51D, BRIP1 and PALB2 testing is based on testing costs for these genes in the PROMISE research programme as well as confirmatory testing costs in an accredited national genetics laboratory for those testing positive.

RRSO costs: UK costs are based on national reference costs for an upper genital tract laparoscopic/endoscopic intermediate procedure (41), and USA costs are from Grann 2011 (43) which were inflated using the medical component of the USA consumer price index to 2015 US\$. Costs of HRT for the UK are taken from BNF (42) and for the USA from Williams-Frame 2009 (44). Costs assume HRT is given from average age of RRSO to the average age of menopause (51 years). These costs are calculated for the 80% assumed to be compliant with HRT. Costs include the cost of three follow up DEXA scans for monitoring bone health and calcium and vitamin-D3 for additional osteo-protection.

### Ovarian Cancer Costs:

We assumed that the cost of diagnosis to include a pelvic examination, ultrasound scan, CA125 test, CT scan, percutaneous biopsy and peritoneal cytology.

The cost of treatment included the reference cost for a lower and upper genital tract very complex major procedure and administration of chemotherapy based on 6 cycles of carboplatin and paclitaxel treatment. It was assumed that in years-1 and -2 treated survivors would have a further three consultant visits, a CT scan and 4 CA125 tests each year. In years 3 to 5 post-surgery it was assumed that survivors would have 2 consultant visits and 2 CA125 tests.

Costs for ovarian cancer diagnosis and treatment in the UK were derived from national reference costs and a recent ovarian cancer guideline developed by NICE (41,45). Annual costs of ovarian cancer treatment in the USA are taken from Grann et al 2011 (43), and inflated using the medical component of the USA consumer price index to 2015 US\$.

We include costs of treatment of recurrence, taken from the Saving lives, averting costs report commissioned by CRUK (46) and Grann 2011 (43).

Costs for terminal care for ovarian cancer in the UK were derived from end-of-life costs for cancer patients based on a report from the National Audit Office (47). Terminal care costs for ovarian cancer in the USA are obtained from Grann, 2011 (43), and inflated using the medical component of the USA consumer price index to 2015 US\$.

In line with NICE recommendations future healthcare costs not associated with ovarian cancer were not considered (17).

#### Breast Cancer Costs:

Breast cancer diagnosis & treatment costs are predominantly derived from: 'National costing report- Implementing NICE guidance (Feb 2009)' which provides estimates of the national cost impact arising from implementation of NICE guidelines for diagnosis and treatment of early/locally advanced breast cancer and advanced breast cancer in England, UK (53); from UK Department of Health NHS reference costs 2012 (41); the BNF (42), and other relevant NICE guidelines on breast cancer care in general and high risk populations (7,51,52).

Cost of breast cancer screening for non-carriers: assumes routine mammography (8 mammograms between 50-70 years) as per UK NHS breast cancer screening program (60). Breast screening in the USA assumes mammography every two years starting at 50 years (49).

Cost of breast screening for BRCA1/2 carriers: for the UK it is based on annual mammogram from 40-69 years and annual MRI from 30-49 years as per NICE guidelines for familial breast cancer (7). For the USA it is based on yearly mammography and MRI starting at 30 years, then the cost of annual mammography only from age 50 years (49).

Cost of RRM: obtained from NHS reference costs (41) weighted for a 21% complication rate (6,50). For the USA this is obtained from Grann 2011 (43), and inflated using the medical component of the USA consumer price index to 2015 US\$.

Cost of breast cancer treatment: In the general population 10% breast cancer is non-invasive DCIS; 90% breast cancer is invasive; 95% of invasive breast cancer is early and locally advanced (41% Stage-1, 45% stage-2, 9% stage-3 (53,61-63)); 5% of invasive breast cancer is advanced breast cancer (stage 4) (53,61,62); 35% of early & locally advanced breast cancer will progress to advanced breast cancer (NICE costing report, 2009) (53). In BRCA1/2 carriers, 20% of cancers are DCIS and 80% invasive (61% stage1) (6,64).

Stage distribution in PALB2 carriers was assumed to be the same as in the general population, owing to a lack of robust PALB2 specific data.

The cost of diagnosis includes clinical examination, mammogram, ultrasound & biopsy.

Mean prevalence of Axillary lymph node metastasis in early invasive breast cancer is 31.4% (systematic reviews within the NICE breast cancer guideline (52) and breast cancer clinical outcome measures (BCCOM) project (65)). 30% node positive rate is assumed for BRCA1/2 breast cancer (based on screening studies in familial breast cancer, breast cancer case series and Early Breast Cancer Trialists' Collaborative Group data) (64,66-69). Annual breast cancer treatment costs in the USA are obtained from Grann et al 2011 (43), and inflated using the medical component of the USA consumer price index to 2015 US\$.

Cost of Sentinel lymph node biopsy (SLNB): is obtained from NICE national costing report (53). SLNB is used for staging axilla for early invasive breast cancer and no evidence of lymph node involvement on Ultrasound (US)/ negative US-guided biopsy (73% of invasive cancers).

Cost of axillary lymph node dissection (ALND): is assumed to be 25% of cost of breast surgery as per NICE guideline development group recommendation (53). ALND is undertaken for lymph node positive cancers (31% early & locally advanced invasive cancers) (52,53).

Breast Surgery Costs: This includes, costs of breast conserving surgery (assumed for all non-invasive cancers, and 75% of early/locally advanced (stage 1-3) invasive cancers); and costs of mastectomy with reconstruction (for 25% early/locally advanced cancers). Costs are obtained from the national NHS reference costs (41).

Radiotherapy and Chemotherapy: Invasive breast cancers who are not low risk (65,70,71) receive adjuvant treatment in line with NICE guidelines. Costs include, radiotherapy costs for 60% of early invasive/locally advanced, radiotherapy and chemotherapy costs for 40% early invasive/locally advanced and chemotherapy costs for all advanced cancers.

Radiotherapy costs include planning and 40Gy in 15 fractions over 3 week (NICE guidelines (52)) or palliative treatment, taken from national NHS reference costs (72).

Chemotherapy costs based on polychemotherapy (66), include administration costs, costs of 1<sup>st</sup> and 2<sup>nd</sup> line therapy and toxicity from NICE guidelines (51,53).

All costs are adjusted for BRCA1/2 breast cancers for difference in stage at presentation & 20% cancers being non-invasive.

70% general population invasive breast cancers are ER positive; 15% early invasive breast cancers and 25% advanced breast cancers are HER2 positive (51,52). 27% BRCA1 and 67% BRCA2 breast cancers are ER positive; 5% BRCA1 and 14% BRCA2 breast cancers are HER2 positive (67-69,73-75). ER & HER2 testing costs are obtained from a local NHS trust and included for all breast cancers. 74% of PALB2 breast cancers are ER positive (33).

Endocrine therapy costs: As per NICE guidelines (52,53), ER positive invasive breast cancers receive Tamoxifen 20mg/day (premenopausal)/ Anastrozole 1mg/day (postmenopausal) for 5 years: costed from the BNF (42). Rates are adjusted for BRCA1/2 and PALB2 carriers, ER positivity and menopause status.

Biphosphonate costs: 74% patients with advanced breast cancer will develop bone metastases and 65% patients with bone metastases are offered bisphosphonates (53,76,77).

As per NICE guidelines, costs (from BNF(42)) assume that 50% patients receive oral clodronate & ibandronic acid, and 50% receive intravenous zoledronic acid or pamidronate (53).

Cost of Trastuzumab: For HER2 positive patients, given at 3-week intervals for 1 year or until disease recurrence as per NICE guidelines. Costs obtained from NICE costing report (53).

35% of early/locally advanced breast cancer progress to advanced breast cancer (NICE guidelines) (53). Recurrence rates for early/locally advanced breast cancer (from the USA National Surgical Adjuvant Breast and Bowel Project (NSABP)): 15.9% for node positive (78) and 11% for node negative (79) breast cancer: composite recurrence rate= 12.6% (weighted for 31% node positive and 69% node negative disease). Recurrence rate for advanced/metastatic breast cancer is 66% (34% relapse free 5yr survival) (80).

Follow up Costs: Includes annual mammograms and six monthly consultations. MRI scan for all stage 4 cancers. Costs include a progression rate of 35% from early & locally advanced to advanced disease (53), and 66% relapse rate for advanced disease (80).

Costs for terminal care for breast cancer were derived from end-of-life costs for cancer patients based on a report from the National Audit Office, UK (47). For the USA terminal care costs are obtained from Grann 2011 (43), and inflated using the medical component of the USA consumer price index to 2015 US\$.

In line with NICE recommendations future healthcare costs not associated with breast cancer were not considered (17).

Chemoprevention: Tamoxifen/Raloxifene for 10 years (7,10), from BNF (UK) (42) and Grann et al 2011 (USA) (43). 16.3% uptake was assumed for chemoprevention (31).

#### Cost of CHD:

Cost of excess CHD: British Heart Foundation statistics reports costs per capita across four Commissioning Regions in England (London, Midlands and East, North and South) (56). The costs of CHD and stroke are averaged across the four regions. The prevalence of CHD is estimated at 12.0% in the UK (56) and 11.7% in the USA (57) with the onset of CHD estimated at 55 years of age (12,55).

The yearly cost of CHD in the UK is obtained by dividing the per capita cost by the population prevalence of CHD (56). Using the report published by the American Heart Association (58), the total cost of CHD, CHF and stroke were divided by the population with CHD (57,59) giving the yearly cost of CHD in the USA. This yearly cost is multiplied by the number of years between onset of CHD and average life expectancy to provide the cost attributed to excess CHD.

Cost of fatal CHD: This was costed on the basis of a fatal myocardial infarction using NHS reference costs (41). USA costs are obtained from Afana et al 2015 (54).

#### **SUPPLEMENTARY TABLE 4. ESTIMATES FOR AGE OF ONSET AND SURVIVAL FOR BREAST AND OVARIAN CANCERS**

The analysis has a lifetime time horizon covering lifetime risks as well as long-term consequences. Female life-tables from the Office of National-Statistics (UK-women) and SEER (USA-women) were used for life-expectancy data for women who did not develop OC/ BC (81).

To simplify the analysis we used average ages for BC (44.4 years) and OC (59.6 years) onset for BRCA1/BRCA2 carriers (82). These were obtained by assigning weights to the individual ages of onset for the relative population prevalence of BRCA1 and BRCA2  $((0.00158 * \text{Age}^{\text{BRCA1}}) / 0.00677 + (0.00519 * \text{Age}^{\text{BRCA2}}) / 0.00677)$ . 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) (83-85). OC/BC outcomes were modelled using 10-year survival data.

No statistically significant survival difference between BRCA1/BRCA2 and sporadic BC has been reported (86,87). For BC, 10-year survival rate=78.4% (CI: 78.3,78.4) (88).

Long-term survival outcomes for BRCA and sporadic OC have also recently been reported to be similar (89). For OC the 10 year survival rates for BRCA1 and BRCA2 are 34% and 28% respectively (89,90). Composite survival rates for BRCA1+BRCA2 OC are calculated by weighting the individual survival rates for the relative population prevalence of BRCA1 and BRCA2  $((0.00158 * \text{OC-Survival}^{\text{BRCA1}}) / 0.00677 + (0.00519 * \text{OC-Survival}^{\text{BRCA2}}) / 0.00677)$ . This gives composite BRCA1+BRCA2 survival rate at 10-years of 29%. For non-BRCA1/BRCA2 OC or sporadic OC: 10-year survival=34.5% (CI: 33.8,35.3) (91). After 10-years survival the probability of death was assumed to be the same as the general population.



## SUPPLEMENTARY TABLE 5. UTILITY SCORES

### Detailed Explanation of Utility Scores used in the analysis

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-weight for RRSO= 0.95 (SD=0.1, Grann, 2010) (92) and for ovarian cancer (OC) treatment were obtained from Havrilesky, 2009 (93). We preferred Time-Trade-Off (TTO) scores for comparing health state preferences as visual scales are generally less accurate due to inherent biases.(94) Utility-score for early stage OC= 0.81 (SD=0.26) while for advanced stage OC (70% women at presentation)= 0.55 (SD=0.29) (93,95,96). The end-stage of life utility-score (where OC patients don't survive the next year)= 0.16 (SD=0.25). Of those surviving initial chemotherapy, with early disease the chance of recurrence=10.5% annually,(97) and for advanced disease=20.6% annually (95). For women with recurrent disease the mean utility-score=0.5 (range=0.4-0.61) and for remission it's= 0.83 (SD=0.25) (93).

Of general population Breast Cancer (BC), 10%= non-invasive/DCIS; 90%= invasive; 95% of invasive cancer is early & locally advanced (41%= Stage-1, 45%=stage-2, 9%=stage-3)(53,61-63) and 5%=advanced (stage-4) (53,61,62).

In BRCA associated BC, 20%= DCIS and 80%= invasive (61%= stage1) (6,64). Utility-weights for BC were obtained from NICE guidelines (51,98) and assumed as follows: advanced BC= 0.65, early/locally advanced BC= 0.71, remission= 0.81 and recurrence= 0.45. For those who survived initial chemotherapy, the chance of BC recurrence/progression with early/locally advanced disease= 35% (53) and for recurrence with advanced disease= 66% (80).

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