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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=£7,629.65/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 Clinical criteria/FH-based strategy. Clinical criteria/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 \textit{BRCA1/BRCA2} (29) and \textit{RAD51C}, \textit{RAD51D} (14), \textit{BRIP1} (13), and \textit{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 \textit{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 (0.04 days 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 (9.34 days life-expectancy gained) or $54,769.78/QALY (7.57 days 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 >30 years 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 (3.2 years)(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.
References


33. Office of National Statistics. Lifetable for females in the UK.


35. CRUK. Ovarian Cancer Incidence Statistics: 2011. 2014,


37. SEER. Cancer Stat Facts: Female Breast Cancer. 2014,


https://www.eveappeal.org.uk/about/research/promise/


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/.


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-


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


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

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
<th>(95%CI) [Range]</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.00677</td>
<td>(0.0059-0.0077)</td>
<td>BRCA1/BRCA2 mutation prevalence in a general population</td>
<td>Jervis 2015(29)</td>
</tr>
<tr>
<td>P2</td>
<td>0.47</td>
<td>(0.34-0.56)</td>
<td>Probability that carrier will undergo RRM</td>
<td>Evans 2009(81)</td>
</tr>
<tr>
<td>P3</td>
<td>0.96</td>
<td>[0.8-0.96]</td>
<td>Reduction in risk of ovarian cancer from RRSO</td>
<td>Finch 2006,(1) Rebbeck 2009(2)</td>
</tr>
<tr>
<td>P4</td>
<td>0.202</td>
<td>[0.17-0.28]</td>
<td>Probability that BRCA1/BRCA2 carrier without RRSO will get ovarian cancer</td>
<td>Antoniou 2008 BOADICEA,(82) Chen 2007(83)</td>
</tr>
<tr>
<td>P5</td>
<td>0.02</td>
<td>(0.001, 0.06)</td>
<td>Probability that a non-carrier will get ovarian cancer</td>
<td>CRUK 2015(84)</td>
</tr>
<tr>
<td></td>
<td>0.0128</td>
<td>(0.0126-0.0130)</td>
<td>Probability that a non-carrier will get ovarian cancer – USA estimate</td>
<td>SEER(85)</td>
</tr>
<tr>
<td>P6</td>
<td>0.0098</td>
<td>(0.0047, 0.0179)</td>
<td>Probability of having a positive FH fulfilling non-AJ genetic testing criteria</td>
<td>ABCFR data</td>
</tr>
<tr>
<td>P7</td>
<td>0.1</td>
<td></td>
<td>BRCA1/BRCA2 prevalence in those fulfilling clinical criteria or FH positive individuals</td>
<td>Current testing guideline</td>
</tr>
<tr>
<td>P8</td>
<td>0.0056</td>
<td>(0.0049, 0.0066)</td>
<td>BRCA1/2 Mutation prevalence in FH negative individuals</td>
<td>Jervis 2015,(29) ABCFR data</td>
</tr>
<tr>
<td>P9</td>
<td>0.911</td>
<td>(0.62-0.98)</td>
<td>Reduction in breast cancer risk from RRM without RRSO in BRCA1/2 carriers</td>
<td>Rebbeck 2004(3)</td>
</tr>
<tr>
<td>P10</td>
<td>0.644</td>
<td>[0.42-0.67]</td>
<td>Probability that BRCA1/2 carrier without RRM will get breast cancer</td>
<td>Antoniou 2008 BOADICEA,(82) Chen 2007(83)</td>
</tr>
<tr>
<td>P11</td>
<td>0.129</td>
<td>[0.11-0.14]</td>
<td>Probability that a non-BRCA1/2 carrier will get breast cancer with screening</td>
<td>CRUK 2015(84)</td>
</tr>
<tr>
<td></td>
<td>0.124</td>
<td>(0.1236-0.1249)</td>
<td>Probability that a non-BRCA1/2 carrier will get breast cancer with screening – USA estimate</td>
<td>SEER(85)</td>
</tr>
<tr>
<td>P12</td>
<td>0.55</td>
<td>(0.30-0.75)</td>
<td>Probability that mutation carrier will follow-up with RRSO</td>
<td>Manchanda 2012(86)</td>
</tr>
<tr>
<td>P13</td>
<td>0.49</td>
<td>(0.37-0.65)</td>
<td>HR for breast cancer from RRSO alone in BRCA1/BRCA2 carrier</td>
<td>Rebbeck 2009(2)</td>
</tr>
<tr>
<td>P14</td>
<td>0.95</td>
<td>(0.78-0.99)</td>
<td>Reduction in risk of breast cancer from RRM with RRSO in BRCA1/BRCA2 carriers</td>
<td>Rebbeck 2004(3)</td>
</tr>
<tr>
<td>Probability</td>
<td>Value</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
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<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P15</td>
<td>0.002</td>
<td>Song 2015,(14) Ramus 2015(13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P16</td>
<td>0.089</td>
<td>Probability that RAD51C, RAD51D, BRIP1 carrier without RRSO will get ovarian cancer Loveday 2012,(10) Loveday 2011,(11) Ramus 2015(13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P17</td>
<td>0.94</td>
<td>Reduction in ovarian cancer risk from RRSO in RAD51C, RAD51D, BRIP1 Parker 2013(26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P18</td>
<td>0.62</td>
<td>HR of breast cancer from RRSO alone in RAD51C, RAD51D, BRIP1 Parker 2009(87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P19</td>
<td>0.0122</td>
<td>Probability that RAD51C, RAD51D, BRIP1 carrier without RRSO will get ovarian cancer Song 2015,(14) Ramus 2015(13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P20</td>
<td>0.00186</td>
<td>Mutation prevalence in FH positive (BRCA1/2 negative) individuals Song 2015,(14) Ramus 2015(13) and ABCCFR data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P21</td>
<td>0.0303</td>
<td>Risk of mortality from CHD after RRSO Parker 2013(26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P22</td>
<td>0.8</td>
<td>Compliance with HRT Read 2010(88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P23</td>
<td>0.71</td>
<td>HR of breast cancer risk from chemoprevention Cuzick 2015(89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P24</td>
<td>0.163</td>
<td>Probability that PALB2 carrier without RRM will get breast cancer Antoniou 2014(17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P25</td>
<td>0.00125</td>
<td>PALB2 Mutation prevalence in unselected general population controls Slavin 2017(30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P26</td>
<td>0.44</td>
<td>Uptake of breast cancer chemoprevention Smith 2016(90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P27</td>
<td>0.0089</td>
<td>PALB2 Mutation prevalence in FH positive (BRCA1/2 negative) individuals Buys 2017(91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P28</td>
<td>0.0012</td>
<td>PALB2 Mutation prevalence in FH negative individuals ABFCR data, Buys 2017(91), Slavin 2017(30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P29</td>
<td>0.0072</td>
<td>Excess risk of CHD after RRSO Parker 2013(26)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*95%CI- 95% confidence interval, ABCCFR- 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

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Undiscounted</th>
<th>Discounted</th>
<th>ICER in £/QALY or $/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost (£,</td>
<td>Life</td>
<td>Cost (£,</td>
</tr>
<tr>
<td></td>
<td>USA=$)</td>
<td>QALYs</td>
<td>£, USA=$)</td>
</tr>
<tr>
<td>UK Estimates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Standard FH based testing for BRCA1/BRCA2 mutations</td>
<td>£4423.25</td>
<td>52.2850</td>
<td>£1586.11</td>
</tr>
<tr>
<td>FH based testing for BRCA1/BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutations</td>
<td>£4423.23</td>
<td>52.2851</td>
<td>£1586.38</td>
</tr>
<tr>
<td>Population testing for BRCA1/BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutations</td>
<td>£4586.86</td>
<td>52.3107</td>
<td>£1779.73</td>
</tr>
<tr>
<td>USA Estimates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Standard FH based testing for BRCA1/BRCA2 mutations</td>
<td>$19252.85</td>
<td>52.5063</td>
<td>$6795.73</td>
</tr>
<tr>
<td>FH based testing for BRCA1/BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutations</td>
<td>$19253.14</td>
<td>52.5064</td>
<td>$6797.35</td>
</tr>
<tr>
<td>Population testing for BRCA1/BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutations</td>
<td>$19515.76</td>
<td>52.5271</td>
<td>$7207.90</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>SCENARIOS</th>
<th>SCENARIO ANALYSIS</th>
<th>UK Estimates</th>
<th>USA Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Strategy A</td>
<td>Strategy B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICER/QALY (£)</td>
<td>LE gained (days)</td>
</tr>
<tr>
<td>No reduction in BC risk from RRSO (p13=1, p18=1)</td>
<td>9,540.39</td>
<td>0.04</td>
<td>27,632.95</td>
</tr>
<tr>
<td>Lowest cost-effective RRM (p2) uptake rate: p2=19% (UK), p2= 8% (USA)</td>
<td>16,564.53</td>
<td>0.03</td>
<td>29,985.08</td>
</tr>
<tr>
<td>Lowest cost-effective RRSO (p12) uptake rate: p12= 22% (UK), p2= 13% (USA)</td>
<td>7,298.79</td>
<td>0.03</td>
<td>29,970.42</td>
</tr>
<tr>
<td>Lower RRM (p2) plus RRSO (p12) cost-effective rates: UK (p2 = 36% &amp; p12 = 36%); (p2 = 32% &amp; p12 = 32%)</td>
<td>9,965.86</td>
<td>0.03</td>
<td>29,984.88</td>
</tr>
<tr>
<td>Genetic Testing cost £250 or $772 (thresholds at which population testing remains cost-effective)</td>
<td>7,629.65</td>
<td>0.04</td>
<td>29,896.23</td>
</tr>
</tbody>
</table>

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

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

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

*The estimated female population (non-Jewish) >30 years ~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.