Cost-effectiveness of unselected multigene germline and somatic genetic testing for epithelial ovarian cancer

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ABSTRACT

Background: Parallel panel-germline and somatic-testing all ovarian-cancer (OC) patients identifies more pathogenic-variants (PV) benefitting from poly-ADP-ribose (PARP) inhibitor (PARP-i) therapy, and unaffected PV-relatives for precision prevention. We estimate cost-effectiveness and population-impact of parallel panel-germline and somatic *BRCA*-testing all UK/USA OC-patients incorporating PARP-i therapy, compared with family-history (FH)/clinical-criteria based germline *BRCA*-testing. We also evaluate cost-effectiveness of multi-gene panel-germline testing alone.

Patient and Methods: Microsimulation cost-effectiveness modelling using data from 2,391(UK=1,483, USA=908) unselected population-based OC-patients compares lifetime costs-&-effects of panel-germline and somatic *BRCA*-testing all OC-cases (with PARP-i therapy) (Strategy-A) with clinical-criteria/FH-based germline *BRCA*-testing (Strategy-B). Unaffected relatives with germline *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* PVs identified through cascade-testing undergo appropriate OC and breast-cancer(BC) risk-reduction interventions. We also evaluated cost-effectiveness of multi-gene panel-germline testing alone (without PARP-i therapy) compared with Strategy-B. Unaffected relatives with PVs can undergo risk-reducing interventions. Lifetime horizon with payer/societal perspectives, along-with probabilistic/one-way sensitivity-analyses are presented. Incremental-cost-effectiveness-ratio (ICER), incremental-cost per quality-adjusted-life-year (QALY) gained, was compared to

£30,000/QALY(UK) and $100,000/QALY(USA) thresholds. OC-incidence, BC-incidence and prevented deaths were estimated.

Results: Compared with clinical-criteria/FH-based *BRCA*-testing, *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* germline-testing and *BRCA1/BRCA2* somatic-testing all OC-patients incorporating PARP-i therapy had UK-ICER=£51,175/QALY (payer-perspective), £50,202/QALY (societal-perspective); USA-ICER=$175,232/QALY (payer-perspective), $174,667/QALY (societal-perspective), above UK/NICE and USA cost-effectiveness thresholds in the base-case. However, Strategy-A becomes cost-effective if PARPi-costs fall by 45%-46% or overall-survival (OS) with PARP-i reaches HR=0.28. Unselected panel-germline testing alone (without PARP-i therapy) is cost-effective: payer-perspective ICER=£11,291/QALY or $68,808/QALY; and societal-perspective ICER=£6,923/QALY or $65,786/QALY. One year's testing could prevent 209 UK BC/OC-cases and 192 deaths; and 560 USA BC/OC-cases and 460 deaths.

Discussion: Implementing a panel-germline and somatic-testing programme has significant clinical benefit, reducing annual cases and deaths from BC/OC. The cost-effectiveness results are highly sensitive to costs of PARP-i therapy and its impact on OS results, but robust for other model parameters.

Conclusions: Unselected panel-germline and somatic *BRCA*-testing can become cost-effective with 45%-46% reduction in PARPi-costs. Regarding germline-testing, unselected panel-germline testing is highly cost-effective and should replace *BRCA*-testing alone.

Key words: Ovarian cancer; genetic-testing; *BRCA*; somatic; cost-effectiveness

INTRODUCTION

Ovarian cancer (OC) is the commonest cause of gynaecological cancer deaths (313,959 new cases, 207,252 deaths) worldwide annually,[1] with ~90% cases being epithelial OC.[2] OC-cases are predicted to rise in the UK by 23%, USA by 25% and worldwide by 42% by 2040.[1] Germline pathogenic and likely-pathogenic variants (here-forth termed 'pathogenic-variants' or 'PVs') in *BRCA1/BRCA2* comprise most of the known inheritable component of OC-risk, and are found in 10-15% epithelial-OC.[3-5] *BRCA1/BRCA2* PVs are associated with a 17-44% OC-risk and 69-72% breast-cancer (BC) risk by 80-years.[6] Poly-adenosine-diphosphate-ribose-polymerase (PARP) inhibitor' (PARP-i) therapy is recommended for OC-women with germline or somatic *BRCA1/2* PVs, as it increases overall survival (OS) and progression-free-survival (PFS) at both primary and recurrence settings.[7-13] Determining *BRCA*-status helps decide treatment options, with Olaparib being the first PARP-i recommended for first-line maintenance treatment of Platinum sensitive *BRCA*-mutated advanced OC.[14] However, ~50% *BRCA* PVs are missed by traditional family-history (FH)-based testing.[4,15-17] Guidelines now recommend mainstreaming unselected *BRCA*-testing at OC-diagnosis for initially germline[18] and subsequently also somatic-testing.[19-21] Lately, women with other cancer-susceptibility-genes (CSGs) in the homologous-recombination-repair (HRR) pathway, such as, *RAD51C, RAD51D* and *BRIP1* with validated moderate lifetime OC-risks of 5.8 to 13%,[22,23] are being offered surgical prevention.[24-27] Testing for these CSGs of clinical-utility[28] can enable wider therapeutic benefit and is now recommended. While CSG-testing at OC-diagnosis has been driven by increasing applicability for therapeutic oncology, arguably the major impact on disease burden overall may come from opportunities for precision-prevention. Unselected

multi-gene panel germline-testing itself can through cascade-testing identify more unaffected relatives with PVs who can benefit from screening and prevention of BC/OC in along-with screening/prevention for secondary BC in women with OC themselves. Wide implementation and sustainability of changes in clinical-practice requires they be cost-effective for the health-system. Unselected *BRCA*-testing at OC diagnosis is cost-effective compared to 'no' testing, but comparison with the clinical comparator of FH/clinical-criteria based testing is lacking, and these earlier analyses excluded PARP-i treatment.[30] Both PARP-i costs and OS results are critical parameters affecting cost-effectiveness. However, cost-effectiveness data on multi-gene panel germline-testing at OC-diagnosis are lacking. Additionally, cost-effectiveness of parallel panel-germline and somatic-testing has not yet been established.

Using data from four OC cohorts in the UK and USA along-with modelling, we for the first time, estimate the incremental lifetime effects, costs, and cost-effectiveness of parallel panel-germline and somatic *BRCA*-testing all OC-patients compared to the earlier standard of clinical-criteria/FH-based genetic (*BRCA*)-testing in the UK and USA health-systems. Our analysis incorporates PARP-i therapy and explores a range of PARP-i costs and OS results to establish thresholds for cost-effectiveness of this important clinical strategy. We also compared unselected panel *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* germline-testing itself with clinical-criteria/FH-based *BRCA*-testing to evaluate the potential benefit from unselected panel germline-testing.

METHODS

We obtained CSG and FH data by age from 2,391 'unselected' OC-patients from four cohort-studies: **[BLINDED]**. We obtained the proportion fulfilling standard FH/clinical-criteria for genetic-testing (hereinafter termed FH-positive) by age-group (Supplementary eTable-1) and CSG PV-prevalence among unselected OC-cases in each setting. We obtained population-based OC-incidence by age from Cancer-Research-UK 2015[31] (UK-analysis) and US Cancer-Statistics 2015[32] (USA-analysis). From this we calculated the total FH-positive and CSG PV-positive OC-cases depending on the annually newly diagnosed OC-cases by age-group in UK/USA women (Supplementary eTable-1).

Model and testing strategy

We developed an individual-level microsimulation-model (Figure-1a,1b) (TreeAge-Pro 2018-Williamson/MA) to analyse the lifetime costs and health-effects of parallel *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* panel germline-testing and *BRCA1/BRCA2* somatic-testing all OC-patients incorporating PARPi-therapy (Strategy-A). This was compared with the historical clinical comparator of FH/clinical-criteria based *BRCA1/BRCA2* germline-testing (Strategy-B). As unselected multi-gene panel germline testing itself can identify more unaffected relatives with PVs who can undergo risk-reducing interventions, we also compared unselected panel *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* germline-testing alone (excluding somatic-testing and PARPi-treatment) with Strategy-B. Additionally, we compared Strategy-A with unselected *BRCA*-germline testing in a scenario analysis. In Strategy-A all patients undergo counselling, panel-germline and somatic testing. In Strategy-B only those fulfilling clinical/FH-criteria undergo counselling and *BRCA* germline-testing. For the base-case we

presume all eligible patients undergo genetic-testing. If patients had a *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* PVs, their first-degree-relatives (FDR) are tested for the familial-PV, and the second-degree-relatives (SDR) are tested if the FDR is detected to have a *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* PV. We assume all eligible relatives are tested in the base case, but also undertake a scenario analysis with lower (70%) uptake of cascade testing. We incorporate a 8.8% Variant-of Uncertain-Significance (VUS) rate (*BRCA1/BRCA2*=4.86%, *RAD51C/RAD51D/BRIP1*=3.93%)[4,33,34] and 8.7% pathogenic/likely-pathogenic VUS re-classification rate.[35]

Unaffected *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* PV-carriers can choose risk-reducing salpingo-oophorectomy (RRSO) to reduce their OC-risk [36,37] and unaffected *BRCA1/BRCA2* PV-carriers can choose risk-reducing-mastectomy (RRM)[38], or chemoprevention with selective-estrogen-receptor-modulators (SERM) for BC-risk reduction[39] and MRI/mammography based enhanced BC-screening. OC-cases with germline/somatic *BRCA1/BRCA2* PVs can opt for PARP-i therapy. We assumed 71% *BRCA*-mutated OC-patients have PARPi-therapy given 88% *BRCA*-mutated OC-patients respond to first-line platinum-based chemotherapy[40] and 81% are advanced stages[41].

Although initial studies suggested premenopausal RRSO reduced BC-risk,[37,42,43] more recent data contradict this.[44-46] Hence, conservatively we assumed no BC-risk reduction from RRSO. We included an excess risk and mortality from coronary-heart-disease (CHD) in pre-menopausal women who don't take hormone-replacement-therapy (HRT) following RRSO (absolute mortality increase=3.03%).[47,48] OC-patients and their cancer-free relatives may pass through various health-states in the model: no-cancer, sporadic-OC, germline-OC, somatic-OC,

sporadic-BC, germline-BC, and both BC-&-OC. Cancer incidence was determined by summing the probabilities of pathways ending in OC or BC. The potential population-impact was estimated from the additional reduction in BC-&-OC incidence following testing all OC-cases occurring annually in UK/USA women.

Probabilities

Model pathway probabilities are in Supplementary-eTable-2. The age-specific general-population BC/OC incidences are obtained from Cancer-Research-UK 2015[31,49] (UK-analysis) and US Cancer-statistics 2015[32] (USA-analysis); and BC/OC incidence for *BRCA1/BRCA2*-carriers from the literature[6]. *RAD51C* confers an increased relative-risk=7.55 (CI:5.60,10.19)[23], *RAD51D* a relative-risk=7.60 (CI:5.61,10.30)[23], and *BRIP1* a relative-risk=3.41 (CI:2.12,5.54)[22].

Number and age distribution of relatives

The new OC-cases by age-groups in UK and USA calibrated the age-distribution of patients in the model. Office-for-National-Statistics (UK)[50] and the National-Centre-for-Health-Statistics (USA)[51] data helped estimate FDR/SDRs and their ages relative to index-cases for UK and USA women respectively (see Supplementary-eTable-3). Lifetables helped estimate probabilities for relatives at different ages being alive, and compute the age-distribution and relatives that undergo genetic-testing.

Costs

Costs are reported at 2019 prices. Both payer/societal-perspective analyses were undertaken. We included costs of germline-testing, somatic-testing, pre-&-post-test genetic-counselling,[52,53]

BC-&OC treatment, excess CHD, and productivity-loss. UK-costs were obtained from NHS-reference costs,[54,55] and converted wherever needed using the Hospital/Community Health-Service-Index.[56] USA-costs from the literature were inflated using the medical component of the USA consumer price-index to 2019 US$. The list-price cost of Olaparib (PARP-i) was £2,317.5/14-day pack (UK) and $13,886/30-day pack (USA).[14,57] The germline-testing cost=£150/$200 and somatic-testing=£360/$480. As-per NICE recommendations, future healthcare costs not associated with BC/OC/CHD were excluded.[58] For an explanation of costs see Supplementary-eTable-4, and Supplementary-eMethods-1 for costs from productivity-loss.

Life-years

Our analysis incorporates a lifetime time-horizon and relevant lifetables estimate life-expectancy in unaffected women. See Supplementary-eMethods-2 for survival-estimates. We assumed the median-age for RRM=37-years and RRSO=40-years respectively.[59] BC and OC survival were modelled using five-year survival-data from the global-surveillance of cancer survival.[60] No significant overall long-term survival differences between germline and sporadic BC/OC have been found.[41,61,62] OC-patients with germline/somatic *BRCA* receiving first line PARPi-therapy have improved OS (HR=0.55, CI:0.40,0.76),[13] and we additionally explored its uncertainty through a range of scenario and sensitivity analyses.

Quality-adjusted life-years (QALYs)

NICE recommends QALYs for measuring health-outcomes. See supplementary-eMethods-3 for QALYs/utility-scores within the model.

Statistical analysis

Annual new OC-cases (UK=7,424; USA=20,413) with corresponding female relatives (UK=29,854; USA=86,928) by age were used for simulations within the microsimulation-model. We discounted future-costs and health-effects by 3.5%.[58] Model internal validation was undertaken using descriptive-validity, technical-validity and face-validity.[63] The incremental-cost-effectiveness-ratio (ICER) was estimated by dividing the difference in lifetime-costs by difference in lifetime-effects (QALYs). ICER=($Cost^{Strategy-A}$–$Cost^{Strategy-B}$)/($Effect^{Strategy-A}$–$Effect^{Strategy-B}$). ICERs obtained were compared with presumed willingness-to-pay (WTP) thresholds: UK-analysis=£30,000/QALY[64] and USA-analysis=$100,000/QALY.[65] We evaluated the cost-effectiveness of unselected panel-germline testing alone (without somatic-testing/PARP-i) compared to FH-based *BRCA*-testing through a scenario analysis. We undertook a number of other scenario-analyses: (1) half HRT-compliance (40%), with/without PARP-i therapy; (2) lower uptake rate (70%) of germline testing in unaffected relatives; (3) parallel germline-&-somatic testing in patients <70-years, and sequential-somatic followed by germline-testing if somatic-PV identified in patients >70-years, as recent data highlight this possibility;[66] (4) 50% reduced RRM/RRSO-rates, (5) comparison of panel-germline and *BRCA*-somatic testing (Strategy-A) with unselected *BRCA* germline testing. Additionally, we evaluated the maximum cost(s) of PARPi-therapy to achieve ICERs=WTP-thresholds to maintain cost-effectiveness of offering panel-germline and *BRCA*-somatic testing (Strategy-A) across various OC-survival estimates.

Wide-ranging one-way and probabilistic sensitivity-analyses (PSA) were undertaken to evaluate model-uncertainty. Model parameters are varied individually in one-way, and simultaneously in the PSA.[64] Probabilities/utility-scores were varied by their 95% confidence-

intervals/range or by +/-10%, and costs by +/-30%. Costs were given a Gamma-distribution, quality-of-life a Log-normal distribution, and probability a Beta-distribution, as recommended.[67] For PSA we obtained 1,000 estimates of incremental-costs and effects by sampling from the distributions of each parameter. Cost-effectiveness acceptability curves demonstrated whether (1) panel-germline and *BRCA*-somatic testing with PARPi-treatment and (2) panel-germline testing alone (without somatic-testing/PARPi-treatment) for all OC-patients are cost-effective across varying WTP-thresholds.

RESULTS

The overall lifetime-costs, QALYs, and ICERs for UK/USA-women are in Table-1. Unselected parallel panel-germline and *BRCA*-somatic-testing with PARPi-therapy for all OC-patients diagnosed annually (Strategy-A) compared with FH/clinical-criteria *BRCA*-testing was not cost-effective in the base-case analysis. UK-ICERs are payer-perspective=£51,175/QALY; societal-perspective=£50,202/QALY. USA-ICERs are payer-perspective=$175,232/QALY; societal-perspective=$174,667/QALY. However, unselected panel-germline testing is cost-effective vs FH-based *BRCA*-testing (without PARPi-therapy). The UK-ICERs: payer-perspective=£11,291/QALY, societal-perspective=£6,923/QALY (UK); USA-ICERs: payer-perspective=$68,808/QALY; societal-perspective=$65,786/QALY. This will remain cost-effective even if genetic-testing costs increase to £1,321/£1,594 (UK payer-perspective/societal-perspective) or $1,626/$1,765 (USA payer-perspective/societal-perspective). Parallel panel-germline and *BRCA*-somatic-testing with PARPi-therapy was not cost-effective compared to unselected *BRCA*-germline testing alone, with UK-ICERs being payer-perspective=£105,934/QALY; societal-perspective=£105,433/QALY; and USA-ICERs

being payer-perspective=$553,422/QALY; societal-perspective=$553,240/QALY respectively. Strategy-A is extremely sensitive to both PARPi-costs and OS estimates from PARPi-treatment. Panel-germline and somatic-testing with PARP-i (strategy-A) can become cost-effective for both UK and USA if the OS HR improves from 0.55 (base-case) to 0.28. The yearly PARP-i list-price UK-cost=£60,462 and USA-cost=$169,067. Strategy-A becomes cost-effective if annual PARP-i treatment costs fall by 45% (UK-cost=£ 33,006) or 46% (USA-cost=$ 90,841). The maximum PARP-i costs for strategy-A to remain cost-effective at different OS HRs (0.3 to 0.7) from payer/societal perspectives for UK/USA (see Figure-2), shows the HR for OS is inversely related to PARP-i costs. Annual PARP-i costs need to fall to £24,030/£25,565 (UK) or $54,438/$55,042 (USA) if the OS HR=0.7. Various scenario analyses are illustrated in Table-1.

The population effects of reduction in BC/OC incidence and deaths are in Table-2. The unaffected female-relative PV-carriers identified through cascade-testing was 1.41 (UK) and 1.49 (USA) per-index PV-carrier with OC (see Supplementary-eTable-3). Unselected panel-germline and somatic-testing (Strategy-A) can lead to an average additional 348-days increase in life-expectancy for UK CSG PV-carriers (397-day increase for PV-carrier patients and 322-day increase for PV-carrier unaffected relatives) and 278 days for USA CSG PV-carriers (380-day increase for PV-carrier patients and 207-day increase for PV-carrier unaffected relatives). For unaffected relatives who are identified PV-carriers, those who underwent RRM and RRSO had 529-day (UK) and 445-day (USA) increase in life-expectancy compared to those did not undergo RRM or RRSO. One year's unselected panel-germline and somatic testing for all OC-patients could prevent an additional 171 BC-cases and 38 OC-cases in UK-women, and 461

BC-cases and 99 OC-cases in USA-women (Table-2). Annually, strategy-A translates to averting 192 UK cancer deaths and 460 USA cancer deaths across a lifetime-horizon (Table-2).

The PSA-results (Figure-3) show unselected panel-germline testing and BRCA1/BRCA2 somatic-testing for OC-patients incorporating PARP-i is cost-effective at the WTP-thresholds for 29% (UK-payer), 4% (USA-payer) or 8% (USA-societal) simulations. However, unselected panel-germline testing alone without PARP-i therapy, is cost-effective at the WTP-thresholds for 99% (UK-payer), 96% (USA-payer) and 100% (USA-societal) simulations.

One-way sensitivity analyses (Supplementary-eFigure-1) show that PARPi-costs is the main variable having the biggest impact on the cost-effectiveness results, while OS is also important. Without PARPi-therapy, individual variables such as PV-prevalence, costs, utility-scores, and transition probabilities have very minimal impact on the cost-effectiveness of unselected panel-germline testing.

DISCUSSION

We show for the first time that offering unselected parallel panel-germline testing and somatic *BRCA1/BRCA2*-testing for OC-patients incorporating PARPi-therapy has higher ICERs than the established cost-effectiveness thresholds for UK/USA health-systems. However, this can become cost-effective if PARPi-treatment costs fall by 45%-46% in the UK/USA or if the final OS following PARPi-treatment reaches a HR=0.28, rather than the established base-case HR=0.55. This is critically important as implementation of such a programme has significant

clinical benefit, leading annually to 209 fewer BC/OC-cases, 192 fewer BC/OC deaths in UK-women and 560 fewer BC/OC-cases, and 460 fewer BC/OC deaths in USA-women.

Notably, unselected panel germline-testing for OC-patients alone (excluding PARP-i) is cost-effective with ICERs well below considered WTP-thresholds. This remains cost-effective even at higher genetic-costs of up-to £1,321-£1,594 or $1,626-$1,765 (well within costs of most providers) and even if RRM or RRSO rates fall by 50%. Our results support unselected panel-germline testing at OC-diagnosis, which can identify 3-4% more PV-carriers (compared to *BRCA*-testing alone) who can benefit from precision-prevention.[4,5] Most current guidelines advocate *BRCA*-testing at OC-diagnosis only.[19,21] It is important that these are expanded to include a panel of OC-genes which have clear clinical-utility. Besides *RAD51C/RAD51D/BRIP1* genes, a recommended OC-panel should also include moderate-risk *PALB2* [68] and Lynch-Syndrome genes found in 1% OC patients[69-71]. This can provide greater stimulus for early diagnosis/prevention in unaffected family members preventing more cancers and saving more lives.

Earlier studies demonstrating cost-effectiveness of germline *BRCA1/BRCA2*-testing in OC-patients,[30,72] compared unselected genetic-testing with 'no testing', rather than FH/clinical-criteria based testing which is a better clinical comparator. Our study uses a more appropriate comparator for evaluating cost-effectiveness. Also, we use a large sample of population-based UK/USA OC-patients and are broader in scope by incorporating more ovarian CSGs (*RAD51C/RAD51D/BRIP1*), somatic *BRCA1/BRCA2* testing, and PARPi-treatment.Prior PARP-i cost-effectiveness studies have predominantly evaluated its use in a recurrent (not first-line) setting and used surrogate outcomes like progression-free life-years or progression-free

QALYs to draw conclusions.[73] However, there are no theoretical or empirical thresholds for cost-effectiveness using PFS as an effectiveness measure, and thus it is incorrect to draw conclusions on PARP-i cost-effectiveness in this manner. Most studies suggest PARP-i is not cost-effective as maintenance therapy for platinum-sensitive recurrent OC, with high drug acquisition costs,[74,75] being a major factor. An initial health-technology assessment evaluation by National-Institute of Health-&-Care Excellence (NICE) following a pharmaceutical company submission indicated Olaparib was not cost-effective for first line maintenance treatment of *BRCA*-mutated OC, though it could potentially become cost-effective in the future.[14] The NICE Evidence-Review-Group highlighted the significant uncertainty and potential over-estimation of OS, the over-estimation of eligibility, and limited flexibility of costs, leading to ICERs higher than the current WTP-threshold. It concluded NICE's inability to recommend Olaparib for routine NHS use but supported its use through the Cancer-Drug-Fund pending OS results, given its future cost-effectiveness potential.[14] Our results lend further credence to high PARP-i costs being a major factor in determining cost-effectiveness as evidenced from the one-way sensitivity-analysis and hugely different ICERs in the scenarios with and without PARP-i therapy (Table-1).

We evaluated unselected 'parallel' germline panel-testing and somatic *BRCA*-testing, as this approach arguably maximises PV identification for patient benefit and precision-prevention.[4] We preferred this to a sequential somatic first strategy, as somatic testing may miss large genomic rearrangements, which in some populations (including in the UK) can comprise around 10% of PVs.[4] This parallel approach is recommended in UK guidelines and is part of routine NHS care.[29] However, there may be countries or populations where LGR rates are

negligible or very low. These jurisdictions may choose to have a sequential somatic first (followed by germline) approach to mainstreaming genetic testing.

Our study has many strengths, including drawing data form large population-based cohorts, and adhering to NICE recommendations of cost-utility analysis for economic evaluation.[58] We use QALYs for health outcomes, discount for costs/outcomes, a lifetime horizon, extensive sensitivity and scenario analyses to support strength/accuracy of results, cover societal/payer-perspectives, incorporate a detriment for CHD-mortality,[47] and detailed comprehensive range of costs. We use the most recently published OS estimates from Olaparib therapy (HR=0.55, CI: 0.40, 0.76)[13], instead of the earlier surrogate of OS (PFS-2) due to the immature clinical effectiveness data. We also provide the maximum PARPi-costs to maintain cost-effectiveness at different HR of OS, which is useful for providers/decision-makers.

A potential limitation of our analysis was the exclusion of HRD-testing. HRD-tests are extremely expensive making this approach not cost-effective.[76] They are not universally available/implemented, and the SOLO-1 study whose survival data used in our analysis did not include HRD-testing. We have also not evaluated the combination of PARP-i with other drugs or agents,[77] and this will need to be explored in other studies.

Randomised trial results have led to US Food-&-Drug Agency (FDA), European-Medicines-Agency and other countries approving PARP-i, for first-line maintenance treatment for *BRCA*-mutated advanced OC, bringing about a paradigm shift in the clinical management of these women. The sky-rocketing costs of new oncology drugs leading to financial toxicity, restricted availability, rising out-of-pocket costs and inequality in access amongst patients has become a

major global problem.[78,79] For widescale implementation, and equitable access it is important that new drugs are priced at a level which is cost-effective and affordable for health-systems. Our analysis highlighting potential cost-effective price thresholds for Olaparib is an important pointer in this regard. For broadening equity and access even lower price thresholds will be needed for middle- and lower-income countries.

In conclusion, our findings suggest that unselected panel-germline and somatic testing for OC-patients can substantially reduce future BC/OC-cases and related deaths compared with a clinical-criteria/FH-based strategy. This approach can become cost-effective if PARP-i costs fall by 45%-46%%. Nevertheless, panel-germline testing alone is highly cost-effective and maximizes variant identification for precision-prevention. It is important for clinical germline/genetic-testing guidelines to move from single-gene (*BRCA1/2*) testing towards a multi-gene panel-testing approach.

TABLES

Table 1. Lifetime discounted costs and effects per woman, ICER of panel germline testing and somatic BRCA testing for all ovarian cancer patients

Table 2. Lifetime population impact of multigenetic testing and somatic BRCA testing for all ovarian cancer patients

FIGURES

Figure 1. Model structure

Figure 1a:

* *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* negative includes individuals testing negative and VUS not reclassified as pathogenic variants.

Figure 1b:

* *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* negative includes individuals testing negative, VUS not reclassified as pathogenic variants, and untested individuals in the clinical criteria/FH testing arm not found to carry *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* pathogenic variants.

** In the model structure for relatives, *RAD51C/RAD51D/BRIP1*-positive individuals are identified only through the unselected testing arm. Relatives in the clinical criteria/FH testing arm only undergo *BRCA1/BRCA2* testing.

*** Unaffected relatives can progress from no cancer to germline BC (*BRCA1/BRCA2*), germline OC (*BRCA1/BRCA2/RAD51C/RAD51D/BRIP1*), sporadic BC, or sporadic OC (or remain in that health state).

**** *BRCA1/BRCA2* relatives who develop germline OC can get PARP inhibitor therapy.

BC, breast cancer; FH, family history; OC, ovarian cancer; PARP-i, poly-ADP-ribose inhibitor; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy; path var-pathogenic variant; VUS, Variant of Uncertain Significance.

Figure 1 is a schematic diagram showing the microsimulation model structure for unselected panel germline and clinical-criteria/family-history (FH) based genetic testing for ovarian cancer (OC) patients and their relatives.

Figure 1a provides a schema of the model with respect to OC patients.

Figure 1b provides a schema of the model with respect to unaffected relatives identified through cascade testing.

Progression through the model is dependent on the probabilities provided in Supplementary eTable 2.

Figure 1a:

Patients in unselected testing arm:

In the unselected testing arm, all ovarian cancer (OC) patients are offered genetic testing and get classified as pathogenic variant carriers, VUS, or non-carriers. A proportion (8.7%) of patients with VUS results will subsequently get reclassified as pathogenic variant carriers.

Germline *BRCA1/BRCA2* OC carriers identified are offered PARP inhibitor therapy. Depending on the probability of patients undertaking PARP inhibitor therapy they may either stay in the state of germline OC or die from germline OC. Also they have a probability of

developing germline BC and progress to the health state of 'BC and OC'. Patients who do not progress or die would stay in the state of germline OC and undertake the next cycle.

Somatic *BRCA1/BRCA2* OC carriers identified are offered PARP inhibitor therapy. Depending on the probability of patients undertaking PARP inhibitor therapy they may either stay in the state of somatic OC or die from somatic OC. Age-dependent probabilities allow them to develop sporadic BC and progress to the health state of 'BC and OC'. Patients who do not progress or die would stay in the state of somatic OC and undertake the next cycle.

RAD51C/RAD51D/BRIP1 OC carriers may stay in the state of germline OC or die from germline OC. Age-dependent probabilities allow them to develop sporadic BC and progress to the health state of 'BC and OC'. Patients who do not progress or die would stay in the state of germline OC and undertake the next cycle.

BRCA1/BRCA2/RAD51C/RAD51D/BRIP1 negative patients have sporadic OC. Age-dependent probabilities allow them to develop sporadic BC and progress to the health state of 'BC and OC'. They also have a probability of dying from sporadic OC. Women who do not progress to 'BC and OC' or die would stay in the health state of sporadic OC to undertake the next cycle.

Patients in clinical criteria/FH testing arm

In the clinical criteria/FH testing arm, patients with positive FH (fulfilling clinical criteria) undergo genetic testing and are classified as pathogenic variant carriers, VUS, or non-carriers. A proportion of patients with VUS results will subsequently get reclassified as pathogenic variant carriers.

Patients with negative FH do not undertake genetic testing. They can be undetected somatic *BRCA1/BRCA2* carriers, undetected germline *BRCA1/BRCA2* carriers, undetected *RAD51C/RAD51D/BRIP1* carriers, or *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* negative.

Options of PARP inhibitor and disease progression for identified germline or somatic *BRCA1/BRCA2* OC carriers and disease progression for *RAD51C/RAD51D/BRIP1* OC carriers or *BRCA1/BRCA2/ RAD51C/RAD51D/BRIP1* negative OC patients, is the same as those in the unselected testing arm and are described above.

Undetected germline *BRCA1/BRCA2* carriers are not offered PARP inhibitor therapy. They may die from germline OC, or develop germline BC and progress to the health state of 'BC and OC'. Patients who do not progress or die would stay in the state of germline OC and undertake the next cycle.

Undetected somatic *BRCA1/BRCA2* carriers are not offered PARP inhibitor therapy. They may die from somatic OC, or develop sporadic BC and progress to the health state of 'BC and OC'. Patients who do not progress or die would stay in the state of somatic OC and undertake the next cycle.

Figure 1b

Relatives in the unselected testing arm:

In the unselected testing arm, relatives of OC pathogenic variant carriers are offered *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* predictive genetic testing (depending on the familial variant) and classified as pathogenic variant carriers, or non-carriers. Relatives of OC patients with VUS (8.7%) who get reclassified as pathogenic variant carriers are also offered

predictive *BRCA1/BRCA2/ RAD51C/RAD51D/BRIP1* testing.

Relatives identified with *BRCA1/BRCA2* pathogenic variants are offered options of risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO). Unaffected relatives can also opt for chemoprevention for BC. Those identified with *RAD51C/RAD51D/BRIP1* pathogenic variants are offered RRSO. Depending on the probability of pathogenic variant carriers undertaking an RRM and/or RRSO (+/- chemoprevention) they progress to either germline BC (*BRCA1/BRCA2*) or germline OC (*BRCA1/BRCA2/RAD51C/RAD51D/BRIP1*), or stay in the health state of no cancer. They have a probability of dying from the background all-cause mortality.

BRCA1/BRCA2/RAD51C/RAD51D/BRIP1 negative women progress to sporadic BC or sporadic OC, or stay in the health state of no cancer. They have a probability of dying from the background all-cause mortality.

Relatives in the clinical-criteria/FH testing arm:

In the clinical-criteria/FH testing arm, relatives of identified *BRCA1/BRCA2* germline mutation patients undergo predictive *BRCA1/BRCA2* genetic testing. They are classified as pathogenic variant carriers, or non-carriers. Relatives of BC patients with VUS who get reclassified as pathogenic variant carriers also undergo predictive *BRCA1/BRCA2* testing.

RAD51C/RAD51D/BRIP1 pathogenic variant carriers cannot be detected with only FH based *BRCA1/BRCA2* genetic testing being offered. Relatives of patients with negative FH may be undetected *BRCA1/BRCA2* path var carriers, undetected *RAD51C/RAD51D/BRIP1* path var carriers, or *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* negative.

The options of RRM and RRSO for identified carriers are the same as in the unselected testing arm. For identified *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* pathogenic variant carriers and non-carries (*BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* negative), the disease progression is the same as relatives in the unselected testing arm.

Undetected *BRCA1/BRCA2* pathogenic variant carriers are not offered RRM or RRSO, and undetected *RAD51C/RAD51D/BRIP1* pathogenic variant carriers are not offered RRSO. Depending on the baseline risk they progress to either germline BC or germline OC, or stay in 'no cancer' health state. Also they have a probability of dying from the background all-cause mortality.

Figure 2. Maximum yearly PARP costs to remain cost-effective

The yearly cost of PARP inhibitor therapy is £60,462 in the UK and 169,067 in the USA in the base case analysis.

Figure 2 shows the maximum yearly PARP inhibitor costs for unselected panel germline and somatic testing with PARP inhibitor therapy to remain cost-effective from the payer and societal perspectives, at willingness-to-pay (WTP) thresholds of £30,000/QALY in the UK (Figure 2a) and $100,000/QALY in the USA (Figure 2b). Different scenarios for the HR for ovarian cancer survival from PARP inhibitors were explored, ranging from 0.3 to 0.7. The HR of 0.55 for the base-case is annotated in red in the figures.

Figure 3 Probabilistic sensitivity analysis results

All model parameters/variables are varied simultaneously across their distributions to further explore model uncertainty in probabilistic sensitivity analysis. The results of 1,000 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). Results are presented for comparison of both strategies: parallel panel germline and somatic testing with PARP-i (Figure 3a – UK payer perspective; Figure 3b – USA payer perspective; Figure 3c – USA societal perspective); and panel germline testing (without somatic testing or PARP-i) (Figure 3d – UK payer perspective (no PARP-i); Figure 3e – USA payer perspective (no PARP-i); Figure 3f – USA societal perspective (no PARP-i)).

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