# 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 genetic testing of all patients with ovarian cancer (OC) can identify more pathogenic variants (PVs) that would benefit from PARP inhibitor (PARPi) therapy, and allow for precision prevention in unaffected relatives with PVs. In this study, we estimate the cost-effectiveness and population impact of parallel panel germline and somatic *BRCA* testing of all patients with OC incorporating PARPi therapy in the United Kingdom and the United States compared with clinical criteria/family history (FH)–based germline *BRCA* testing. We also evaluate the cost-effectiveness of multigene panel germline testing alone. **Methods:** Microsimulation cost-effectiveness modeling using data from 2,391 (UK: n=1,483; US: n=908) unselected, population-based patients with OC was used to compare lifetime costs and effects of panel germline and somatic *BRCA* testing of all OC cases (with PARPi therapy) (strategy A) versus clinical criteria/FH-based germline *BRCA* testing (strategy B). Unaffected relatives with germline *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* PVs identified through cascade testing underwent appropriate OC and breast cancer (BC) risk-reduction interventions. We also compared the cost-effectiveness of multigene panel germline testing alone (without PARPi therapy) versus strategy B. Unaffected relatives with PVs could undergo risk-reducing interventions. Lifetime horizon with payer/societal perspectives, along with probabilistic/one-way sensitivity analyses, are presented. Incremental cost-effectiveness ratio (ICER) and incremental cost per quality-adjusted life year (QALY) gained were compared with £30,000/QALY (UK) and $100,000/QALY (US) 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 of all patients with OC incorporating PARPi therapy had a UK ICER of £51,175/QALY (payer perspective) and £50,202/QALY (societal perspective) and a US ICER of $175,232/QALY (payer perspective) and $174,667/QALY (societal perspective), above UK/NICE and US cost-effectiveness thresholds in the base case. However, strategy A becomes cost-effective if PARPi costs decrease by 45% to 46% or if overall survival with PARPi reaches a hazard ratio of 0.28. Unselected panel germline testing alone (without PARPi therapy) is cost-effective, with payer-perspective ICERs of £11,291/QALY or $68,808/QALY and societal-perspective ICERs of £6,923/QALY or $65,786/QALY. One year's testing could prevent 209 UK BC/OC cases and 192 deaths, and 560 US BC/OC cases and 460 deaths. **Conclusions:** Unselected panel germline and somatic *BRCA* testing can become cost-effective, with a 45% to 46% reduction in PARPi costs. Regarding germline testing, unselected panel germline testing is highly cost-effective and should replace *BRCA* testing alone.

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## Background

Ovarian cancer (OC) is the most common cause of gynecologic cancer deaths worldwide annually (324,603 new cases, 206,956 deaths),[1] with approximately 90% of cases being epithelial OC.[2] By 2045, OC cases are predicted to increase by 24% in the United Kingdom, 28% in the United States, and 47% worldwide.[1] Germline pathogenic and likely pathogenic variants (henceforth termed "pathogenic variants" [PVs]) in *BRCA1/BRCA2* comprise most of the known inheritable component of OC risk and are found in 10% to 15% of epithelial OC.[3–5] *BRCA1/BRCA2* PVs are associated with a 17% to 44% OC risk and a 69% to 72% breast cancer (BC) risk by 80 years of age.[6] PARP inhibitor (PARPi) therapy is recommended for patients with OC with germline or somatic *BRCA1/2* PVs because it increases overall survival (OS) and progression-free survival (PFS) in both primary and recurrence

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settings.[7–13] Determining *BRCA* status helps decide treatment options, with olaparib being the first PARPi recommended for first-line maintenance treatment of platinum-sensitive, *BRCA*-mutated advanced OC.[14] However, approximately 50% of *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 somatic testing.[19–21] Lately, women with other cancer-susceptibility genes (CSGs) in the homologous recombination repair 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. Although 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 multigene panel germline testing itself can, through cascade testing, identify more unaffected relatives with PVs who can benefit from BC/OC screening and prevention, as well as identify women with OC themselves who can benefit from screening and prevention of secondary BC. Wide implementation and sustainability of changes in clinical practice requires that they be cost-effective for the health system. Unselected *BRCA* testing at OC diagnosis is cost-effective compared with no testing, but comparison with the clinical comparator of clinical criteria/FH-based testing is lacking, and these earlier analyses excluded PARPi treatment.[29] Both PARPi costs and OS results are critical parameters affecting cost-effectiveness. However, cost-effectiveness data on multigene panel germline testing at OC diagnosis are lacking. Additionally, the cost-effectiveness of parallel panel germline and somatic testing has not yet been established.

Using data from 4 OC cohorts in the UK and US along with modeling, we estimated, for the first time, the incremental lifetime effects, costs, and cost-effectiveness of parallel panel germline and somatic *BRCA* testing of all patients with OC compared with the earlier standard of clinical criteria/FH-based genetic (*BRCA*) testing in the UK and US health systems. Our analysis incorporates PARPi therapy and explores a range of PARPi costs and OS results to establish thresholds for the 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" patients with OC from 4 cohort studies: (1) North-East London Cancer Network cohort (n=298 from the SIGNPOST study [ISRCTN-16988857])[4]; (2) Manchester cohort (Manchester University NHS Foundation Trust; n=751)[30]; (3) Scottish cohort (n=434)[31]; and (4) Washington cohort (n=908 from University of Washington Medical Center). We obtained the proportion fulfilling standard FH/clinical criteria for genetic testing (henceforth termed FH-positive) by age group (see Table S1 in the supplementary material, available online with this article) and CSG PV prevalence among unselected OC cases in each setting. We obtained population-based OC incidence by age from Cancer Research UK 2015[32] (UK analysis) and US Cancer Statistics 2015[33] (US 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/US women (Supplementary Table S1).

### Model and Testing Strategy

Using TreeAge Pro software, we developed an individual-level microsimulation model (Supplementary Figure S1) to analyze the lifetime costs and health effects of parallel *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* panel germline testing and *BRCA1/BRCA2* somatic testing of all patients with OC incorporating PARPi therapy (strategy A). This strategy was compared with the historical clinical comparator of clinical criteria/FH-based *BRCA1/BRCA2* germline testing (strategy B). Because unselected multigene 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 underwent counseling and panel germline and somatic testing. In strategy B, only those fulfilling clinical/FH criteria underwent counseling and *BRCA* germline testing. For the base case, we presumed that all eligible patients underwent genetic testing. If patients had a *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* PV, their first-degree relatives (FDR) were tested for the familial PV, and the second-degree relatives were tested if the FDR was found to have a *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* PV. We assumed that all eligible relatives were tested in the base case but also undertook a scenario analysis with lower (70%) uptake of cascade testing. We incorporated an 8.8% variant of uncertain significance (VUS) rate (*BRCA1/BRCA2*, 4.86%; *RAD51C/RAD51D/BRIP1*, 3.93%)[4,30,31] and an 8.7% pathogenic/likely pathogenic VUS reclassification rate.[34]

Unaffected *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* PV carriers could choose risk-reducing salpingo-oophorectomy (RRSO) to reduce their OC risk,[35,36] and unaffected *BRCA1/BRCA2* PV carriers could choose risk-reducing mastectomy (RRM)[37] or chemoprevention with selective estrogen receptor modulators (SERM) for BC risk reduction[38] and MRI-based/mammography-based enhanced BC screening. OC cases with germline/somatic *BRCA1/BRCA2* PVs could opt for PARPi therapy. We assumed that 71% of patients with *BRCA*-mutated OC received PARPi therapy given that 88% of patients with *BRCA*-mutated OC have been shown to experience a response to first-line platinum-based chemotherapy,[39] and 81% have been shown to present in advanced stages.[40]

Although initial studies suggested that premenopausal RRSO reduced BC risk,[36,41,42] more recent data contradict this.[43–45] Hence, conservatively, we assumed no BC risk reduction from RRSO. We included an excess risk and mortality from coronary heart disease (CHD) in premenopausal women who do not take hormone-replacement therapy (HRT) following RRSO (absolute mortality increase, 3.03%).[46,47] Patients with OC 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 and OC. Cancer incidence

**Table 1.** Lifetime Discounted Costs and Effects per Woman, ICER of Panel Germline Testing, and Somatic *BRCA* Testing for All Patients With OC

| | Multigene Testing and Somatic *BRCA* Testing of All Patients With OC | | | | Testing Based on Family History | | | | ICER | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Health Effects | | Costs | | Health Effects | | Costs | | Cost/LYG | | Cost/QALY | |
| | LYGs[a] | QALYs[a] | Payer | Societal | LYGs[a] | QALYs[a] | Payer | Societal | Payer | Societal | Payer | Societal |
| **Baseline** | | | | | | | | | | | | |
| UK | 16.58 | 16.07 | £15,047 | £21,377 | 16.52 | 16.01 | £12,325 | £18,706 | £49,587 | £48,645 | £51,175 | £50,202 |
| US | 17.08 | 16.55 | $48,600 | $51,887 | 17.03 | 16.51 | $40,891 | $44,203 | $169,344 | $168,798 | $175,232 | $174,667 |
| **Scenario: Panel germline testing with no PARPi[b]** | | | | | | | | | | | | |
| UK | 16.49 | 15.99 | £10,157 | £16,441 | 16.48 | 15.97 | £9,953 | £16,316 | £19,944 | £12,229 | £11,291 | £6,923 |
| US | 16.99 | 16.48 | $35,303 | $38,576 | 16.99 | 16.47 | $34,628 | $37,931 | $306,981 | $293,499 | $68,808 | $65,786 |
| **Scenario: Half HRT adherence (40%), with PARPi** | | | | | | | | | | | | |
| UK | 16.58 | 16.06 | £15,057 | £21,386 | 16.52 | 16.01 | £12,331 | £18,712 | £50,483 | £49,524 | £52,272 | £51,278 |
| US | 17.08 | 16.55 | $49,128 | $52,415 | 17.03 | 16.51 | $41,190 | $44,502 | $179,097 | $178,536 | $186,175 | $185,592 |
| **Scenario: Half HRT adherence (40%), panel germline testing with no PARPi** | | | | | | | | | | | | |
| UK | 16.48 | 15.99 | £10,167 | £16,451 | 16.47 | 15.97 | £9,960 | £16,323 | £22,258 | £13,788 | £12,195 | £7,554 |
| US | 16.99 | 16.48 | $35,831 | $39,104 | 16.99 | 16.47 | $34,928 | $38,231 | $908,681 | $878,878 | $106,956 | $103,448 |
| **Scenario: 70% uptake rate of germline testing in unaffected relatives, with PARPi** | | | | | | | | | | | | |
| UK | 16.57 | 16.05 | £14,899 | £21,278 | 16.52 | 16.00 | £12,248 | £18,662 | £51,467 | £50,808 | £55,239 | £54,531 |
| US | 17.08 | 16.55 | $48,015 | $51,326 | 17.03 | 16.50 | $40,569 | $43,896 | $159,424 | $159,068 | $174,014 | $173,626 |
| **Scenario: 70% uptake rate of germline testing in unaffected relatives, with no PARPi** | | | | | | | | | | | | |
| UK | 16.48 | 15.98 | £10,087 | £16,421 | 16.47 | 15.97 | £9,919 | £16,313 | £21,683 | £13,940 | £12,377 | £7,957 |
| US | 16.99 | 16.48 | $34,933 | $38,229 | 16.98 | 16.47 | $34,408 | $37,726 | $112,451 | $107,834 | $54,555 | $52,315 |
| **Scenario: Parallel testing in patients with OC aged <70 y and sequential somatic testing followed by germline testing in patients aged ≥70 y** | | | | | | | | | | | | |
| UK | 16.58 | 16.07 | £15,037 | £21,367 | 16.52 | 16.01 | £12,325 | £18,706 | £49,413 | £48,471 | £50,995 | £50,022 |
| US | 17.08 | 16.55 | $48,589 | $51,876 | 17.03 | 16.51 | $40,891 | $44,203 | $169,111 | $168,565 | $174,992 | $174,426 |
| **Scenario: Panel germline testing with no PARPi[b] and half RRM uptake in unaffected PV carriers (23.5% uptake of RRM)** | | | | | | | | | | | | |
| UK | 16.48 | 15.99 | £10,114 | £16,422 | 16.47 | 15.97 | £9,928 | £16,303 | £20,347 | £12,996 | £11,616 | £7,419 |
| US | 16.99 | 16.48 | $35,221 | $38,504 | 16.99 | 16.47 | $34,584 | $37,892 | $296,743 | $285,274 | $70,859 | $68,120 |
| **Scenario: Panel germline testing with no PARPi[b] and half RRSO uptake in unaffected PV carriers (27.5% uptake of RRSO)** | | | | | | | | | | | | |
| UK | 16.48 | 15.98 | £10,175 | £16,500 | 16.47 | 15.97 | £9,963 | £16,350 | £34,458 | £24,437 | £17,153 | £12,165 |
| US | 16.98 | 16.47 | $35,232 | $38,525 | 16.98 | 16.47 | $34,625 | $37,941 | $1,006,182 | $967,912 | $90,849 | $87,394 |
| **Scenario: Panel germline and somatic testing vs "unselected" *BRCA* germline testing (PARPi treatment included)** | | | | | | | | | | | | |
| UK | 16.58 | 16.07 | £15,047 | £21,377 | 16.57 | 16.06 | £14,089 | £20,425 | £81,053 | £81,732 | £105,934 | £105,433 |
| US | 17.08 | 16.55 | $48,600 | $51,887 | 17.07 | 16.55 | $46,002 | $49,290 | $433,598 | $433,661 | $553,422 | $553,240 |

Discounted at 3.5%.
Abbreviations: HRT, hormone replacement therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OC, ovarian cancer; PARPi, PARP inhibitor; PV, pathogenic variant; QALY, quality-adjusted life year; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy.
[a]This is the average weighted life expectancy or QALY for all the women (patients and relatives) modeled for each strategy. It will be higher for unaffected relatives than for patients.
[b]No somatic testing is undertaken in this scenario.

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 and OC incidence following testing of all OC cases occurring annually in UK/US women.

## Probabilities

Model pathway probabilities are provided in Supplementary Table S2. The age-specific general population BC/OC incidences were obtained from Cancer Research UK 2015[32,48] (UK analysis) and US Cancer Statistics 2015[33] (US analysis), and BC/OC incidence for *BRCA1/BRCA2* carriers were obtained from the literature.[6] *RAD51C* confers an increased relative risk of 7.55 (CI, 5.60-10.19),[23] *RAD51D* a relative risk of 7.60 (CI, 5.61–0.30),[23] and *BRIP1* a relative risk of 3.41 (CI, 2.12–5.54).[22]

## Number and Age Distribution of Relatives

The new OC cases by age groups in the UK and US calibrated the age distribution of patients in the model. The Office for National Statistics (UK)[49] and the National Center for Health Statistics (US)[50] data helped estimate FDRs/second-degree relatives and their ages relative to index cases for UK and US women, respectively (see Supplementary Table S3). Lifetables helped estimate probabilities for relatives at different ages being alive and to compute the age distribution and number of relatives that undergo genetic testing.

## Costs

Costs are reported as 2019 prices. Both payer/societal-perspective analyses were undertaken. We included costs of germline testing, somatic testing, pretest and posttest genetic counseling,[51,52] BC and OC treatment, excess CHD, and productivity loss. UK costs were obtained from National Health Service (NHS) reference costs[53,54] and converted wherever needed using the Hospital and Community Health Services Index.[55] US costs from the literature were inflated to 2019 US dollars using the medical component of the Consumer Price Index. The list-price cost

of olaparib (PARPi) was £2,317.5 per 14-day pack (UK) and $13,886 per 30-day pack (US).[14,56] Germline testing cost was £150/$200 and somatic testing cost was £360/$480. As per National Institute for Health and Care Excellence (NICE) recommendations, future health care costs not associated with BC/OC/CHD were excluded.[57] See Supplementary Table S4 for an explanation of costs, and Supplementary Methods S1 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 Methods S2 for survival estimates. We assumed that the median age was 37 years for RRM and 40 years for RRSO.[58] BC and OC survival were modeled using 5-year survival data from the global surveillance of cancer survival.[59] No significant overall long-term survival differences between germline and sporadic BC/OC have been found.[40,60,61] Patients with OC with germline/somatic *BRCA* receiving first-line PARPi therapy have improved OS (hazard ratio [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

NICE recommends quality-adjusted life years (QALYs) for measuring health outcomes. See Supplementary Methods S3 for QALYs/utility scores within the model.

### Statistical Analysis

Annual new OC cases (UK: n=7,424; US: n=20,413) with corresponding female relatives (UK: n=29,854; US: n=86,928) by age were used for simulations within the microsimulation model. We discounted future costs and health effects by 3.5%.[57] Model internal validation was undertaken using descriptive validity, technical validity, and face validity.[62] The incremental cost-effectiveness ratio (ICER) was estimated by dividing the difference in lifetime costs by the difference in lifetime effects (QALYs):

$$\text{ICER} = \frac{(\text{cost}^{\text{strategy A}} - \text{cost}^{\text{strategy B}})}{(\text{effect}^{\text{strategy A}} - \text{effect}^{\text{strategy B}})}$$

ICERs obtained were compared with presumed willingness-to-pay (WTP) thresholds: UK analysis = £30,000/QALY[63] and US analysis = $100,000/QALY.[64] We evaluated the cost-effectiveness of unselected panel germline testing alone (without somatic testing/PARPi) compared with FH-based *BRCA* testing through a scenario analysis. We undertook a number of other scenario analyses: (1) half HRT compliance (40%) with and without PARPi therapy; (2) lower uptake rate (70%) of germline testing in unaffected relatives; (3) parallel germline and somatic testing in patients aged <70 years, and sequential somatic testing followed by germline testing if somatic PV was identified in patients aged ≥70 years as recent data highlight this possibility[65]; (4) 50% reduced RRM/RRSO rates; and (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 maintain cost-effectiveness of offering panel germline and *BRCA* somatic testing (strategy A) across various OC survival estimates, where ICERs of strategy A equal the WTP thresholds in the UK and US, respectively.

Wide-ranging one-way and probabilistic sensitivity analyses (PSAs) were undertaken to evaluate model uncertainty. Model parameters are varied individually in one-way analyses and simultaneously in the PSAs.[63] 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 was given a log-normal distribution, and probability was given a $\beta$ distribution, as recommended.[66] For PSAs, 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 patients with OC are cost-effective across varying WTP thresholds.

## Results

Overall lifetime costs, QALYs, and ICERs for UK/US women are presented in Table 1. Unselected parallel panel germline and *BRCA* somatic testing with PARPi therapy for all patients with OC diagnosed annually (strategy A) compared with clinical criteria/FH-based *BRCA* testing was not cost-effective in the base-case analysis. UK ICERs were £51,175/QALY from the payer perspective and £50,202/QALY from the societal perspective, and US ICERs were $175,232/QALY from the payer perspective and $174,667/QALY from the societal perspective. However, unselected panel germline testing is cost-effective compared with FH-based *BRCA* testing (without PARPi therapy). UK ICERs were £11,291/QALY from the payer perspective and £6,923/QALY from the societal perspective, and US ICERs were $68,808/QALY from the payer perspective and $65,786/QALY from the societal perspective. This would remain cost-effective even if genetic testing costs increased to £1,321/£1,594 (UK payer perspective/societal perspective) or $1,626/$1,765 (US payer perspective/societal perspective). Parallel panel germline and *BRCA* somatic testing with PARPi therapy was not cost-effective compared with unselected *BRCA* germline testing alone, with UK ICERs being £105,934/QALY from the payer perspective and £105,433/QALY from the societal perspective, and US ICERs being $553,422/QALY from the payer perspective and $553,240/QALY from the societal perspective. Strategy A is extremely sensitive to both PARPi costs and OS estimates from PARPi treatment. Panel germline and somatic testing with PARPi (strategy A) can become cost-effective for both the UK and the US if the OS HR improves from 0.55 (base case) to 0.28. The yearly PARPi list price is £60,462 in the UK, and $169,067 in the US. Strategy A becomes cost-effective if annual PARPi treatment costs decrease by 45% (UK cost, £33,006) or 46% (US cost, $90,841). The maximum PARPi costs for strategy A to remain cost-effective at different OS HRs (0.3–0.7) from payer/societal perspectives for the UK and US (see Figure 1) show that the HR for OS is inversely related to PARPi costs. Annual PARPi costs from payer/societal perspectives need to decrease to £24,030/£25,565 in the UK and $54,438/$55,042 in the US if the OS HR is 0.7. Various scenario analyses are illustrated in Table 1.

The population effects of reductions in BC/OC incidence and deaths are presented in Table 2. The unaffected female relative PV carriers identified through cascade testing were 1.41 (UK) and 1.49 (US) per index PV carrier with OC (see Supplementary Table S3). Unselected panel germline and somatic testing

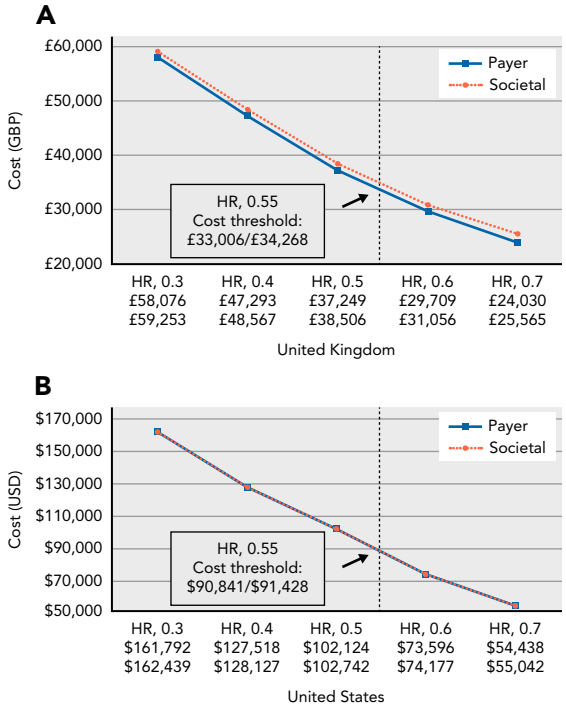


**Figure 1.** Maximum yearly PARP costs to remain cost-effective. The yearly cost of PARPi therapy is £60,462 in the UK and $169,067 in the US in the base-case analysis. The maximum yearly PARPi costs for unselected panel germline and somatic testing with PARPi therapy to remain cost-effective from the payer and societal perspectives, at WTP thresholds of **(A)** £30,000/QALY in the UK and **(B)** $100,000/QALY in the US. Different scenarios for the HR for ovarian cancer survival from PARPi were explored, ranging from 0.3 to 0.7.
Abbreviations: HR, hazard ratio; PARPi, PARP inhibitor; QALY, quality-adjusted life year; WTP, willingness-to-pay.

(strategy A) can lead to an average additional 348-day 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 US CSG PV carriers (380-day increase for PV carrier patients and 207-day increase for PV carrier unaffected relatives). For unaffected relatives identified as PV carriers, those who underwent RRM or RRSO had 529-day (UK) and 445-day (US) increases in life expectancy compared with those who did not undergo RRM or RRSO. One year's unselected panel germline and somatic testing for all patients with OC could prevent an additional 171 BC cases and 38 OC cases in UK women and 461 BC cases and 99 OC cases in US women (Table 2). Annually, strategy A translates to averting 192 UK cancer deaths and 460 US cancer deaths across a lifetime horizon (Table 2).

The PSA results (Figure 2) show that unselected panel germline testing and *BRCA1*/*BRCA2* somatic testing for patients with OC incorporating PARPi is cost-effective at the WTP thresholds for 29% (UK payer), 4% (US payer), or 8% (US societal) of simulations. However, unselected panel germline testing alone without PARPi therapy is cost-effective at the WTP thresholds for 99% (UK payer), 96% (US payer), and 100% (US societal) of simulations.

One-way sensitivity analyses (Supplementary Figure S2) show that PARPi cost is the main variable having the biggest impact on the cost-effectiveness results, and 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 patients with OC incorporating PARPi therapy has higher ICERs than the established cost-effectiveness thresholds for UK/US health systems. However, this can become cost-effective if PARPi treatment costs decrease by 45% in the UK and 46% in the US, or if the final OS following PARPi treatment reaches an HR of 0.28 rather than the established base-case HR of 0.55. This is critically important because implementation of such a program has significant clinical benefit, leading annually to 209 fewer cases of and 192 fewer deaths from BC and OC in UK women and 560 fewer cases of and 460 fewer deaths from BC and OC in US women.

Notably, unselected panel germline testing for patients with OC alone (excluding PARPi) is cost-effective, with ICERs well below considered WTP thresholds. This remains cost-effective even at higher genetic costs of up to £1,321 to £1,594 or $1,626 to

**Table 2.** Lifetime Population Impact of Multigenetic Testing and Somatic *BRCA* Testing for All Patients With OC

| | Patients | | Relatives | | Differences | | |
|---|---|---|---|---|---|---|---|
| Impact | Unselected | FH-Based | Unselected | FH-Based | Patients | Relatives | Total |
| UK estimates | | | | | | | |
| Total | 7,439 | 7,439 | 29,839 | 29,839 | 0 | 0 | 0 |
| Identified germline PV carriers | 1,408 | 735 | 1,983 | 1,010 | 673 | 973 | 1,646 |
| Identified somatic *BRCA1/2* carriers | 300 | 0 | 0 | 0 | 300 | 0 | 300 |
| Germline BC cases | 191 | 173 | 379 | 567 | 18 | −189 | −171 |
| Germline OC cases | 1,408 | 1,408 | 188 | 226 | 0 | −38 | −38 |
| Death from germline BC and germline/somatic OC | 1,269 | 1,370 | 200 | 291 | −101 | −91 | −192 |
| US estimates | | | | | | | |
| Total | 20,400 | 20,400 | 86,941 | 86,941 | 0 | 0 | 0 |
| Identified germline PV carriers | 3,907 | 2,033 | 5,656 | 2,827 | 1,874 | 2,829 | 4,703 |
| Identified somatic *BRCA1/2* carriers | 850 | 0 | 0 | 0 | 850 | 0 | 850 |
| Germline BC cases | 612 | 565 | 1,233 | 1,741 | 47 | −508 | −461 |
| Germline OC cases | 3,907 | 3,907 | 524 | 623 | 0 | −99 | −99 |
| Death from germline BC and germline/somatic OC | 3,210 | 3,502 | 475 | 643 | −292 | −168 | −460 |

Abbreviations: BC, breast cancer; FH, family history; OC, ovarian cancer; PV, pathogenic variant.

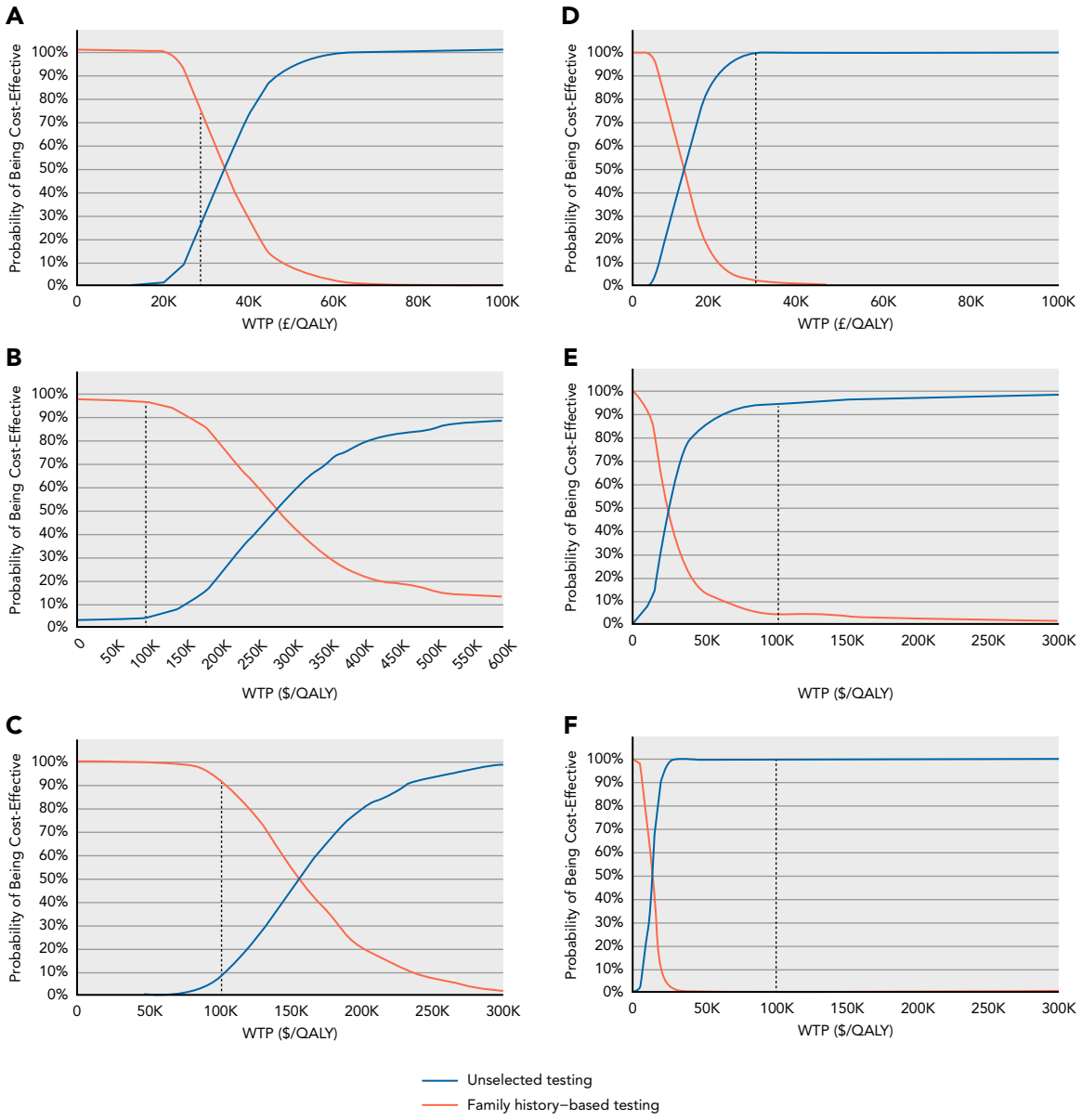


**Figure 2.** Probabilistic sensitivity analysis results. All model parameters/variables are varied simultaneously across their distributions to further explore model uncertainty in probabilistic sensitivity analysis. The results of 1,000 simulations were plotted on a cost-effectiveness acceptability curve showing the proportion of simulations (*y* axis) that indicated that the intervention was cost-effective at different WTP thresholds (*x* axis). Results are presented for comparison of both strategies: parallel panel germline and somatic testing with PARPi from the **(A)** UK payer perspective, **(B)** US payer perspective, and **(C)** US societal perspective, and panel germline testing without somatic testing or PARPi from the **(D)** UK payer perspective, **(E)** US payer perspective, and **(F)** US societal perspective.
Abbreviations: PARPi, PARP inhibitor; QALY, quality-adjusted life year; WTP, willingness-to-pay.

$1,765 (well within the costs of most providers) and even if RRM or RRSO rates decline by 50%. Our results support unselected panel germline testing at OC diagnosis, which can identify 3% to 4% more PV carriers (compared with *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 recommendations are expanded to include a panel of OC genes that have clear clinical utility. Besides *RAD51C/RAD51D/BRIP1* genes, a recommended OC panel should also include moderate-risk *PALB2*[67] and Lynch syndrome genes found in 1% patients with OC.[68–70] This can provide greater stimulus for early diagnosis/prevention in unaffected family members, preventing more cancers and saving more lives.

Earlier studies demonstrating the cost-effectiveness of germline *BRCA1/BRCA2* testing in patients with OC[29,71] compared unselected genetic testing with no testing, rather than clinical criteria/FH-based testing, which is a better clinical comparator. Our study uses a more appropriate comparator for evaluating cost-effectiveness. Our study also used a large sample of population-based UK and US patients with OC and is broader in scope through incorporating more ovarian CSGs (*RAD51C/RAD51D/BRIP1*), somatic *BRCA1/BRCA2* testing, and PARPi treatment.

Prior PARPi cost-effectiveness studies have predominantly evaluated its use in a recurrent (not first-line) setting and used surrogate outcomes, such as progression-free life years or progression-free QALYs, to draw conclusions.[72] 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 PARPi cost-effectiveness in this manner. Most studies suggest that PARPi is not cost-effective as maintenance therapy for platinum-sensitive recurrent OC, with high drug acquisition costs[73,74] being a major factor. An initial health technology assessment evaluation by NICE following a pharmaceutical company submission indicated that 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 overestimation of OS, the overestimation of eligibility, and limited flexibility of costs, leading to ICERs higher than the current WTP threshold. The group concluded that NICE was unable to recommend olaparib for routine NHS use but supported its use through the Cancer Drugs Fund pending OS results given its future cost-effectiveness potential.[14] Our results lend further credence to high PARPi 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 PARPi therapy (Table 1).

We evaluated unselected parallel germline panel testing and somatic *BRCA* testing because this approach arguably maximizes PV identification for patient benefit and precision prevention.[4] We preferred this to a sequential somatic first strategy because somatic testing may miss large genomic rearrangements, which in some populations (including in the UK) can comprise approximately 10% of PVs.[4] This parallel approach is recommended in UK guidelines and is part of routine NHS care.[75] 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.[57] We used QALYs for health outcomes, discount for costs/outcomes, presented a lifetime horizon, performed extensive sensitivity and scenario analyses to support the strength/accuracy of results, covered societal/payer perspectives, incorporated a detriment for CHD mortality,[46] and detailed a comprehensive range of costs. We used 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 (progression-free survival 2 [PFS-2], defined as the time from randomization to progression on first subsequent therapy) due to the immature clinical effectiveness data. We also provide the maximum PARPi costs to maintain cost-effectiveness at different HRs of OS, which is useful for providers and decision-makers.

A potential limitation of our analysis was the exclusion of HRD testing; however, HRD tests are extremely expensive, making this approach not cost-effective.[76] They are not universally available or implemented, and the SOLO-1 study,[13] whose survival data were used in our analysis, did not include HRD testing. We have also not evaluated the combination of PARPi with other drugs or agents,[77] which will need to be explored in other studies.

Randomized trial results have led to the US FDA, European Medicines Agency, and other countries approving PARPi for first-line maintenance treatment of *BRCA*-mutated advanced OC, bringing about a paradigm shift in the clinical management of this population of women. The skyrocketing costs of new oncology drugs, leading to financial toxicity, restricted availability, rising out-of-pocket costs, and inequality in access among 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 that 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.

## Conclusions

Our findings suggest that unselected panel germline and somatic testing for patients with OC can substantially reduce future BC and OC cases and related deaths compared with a clinical criteria/FH-based strategy. This approach can become cost-effective if PARPi costs decrease by 45% to 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 toward a multigene panel testing approach.

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