A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer

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IMPORTANCE Moving to multigene testing for all women with breast cancer (BC) could identify many more mutation carriers who can benefit from precision prevention. However, the cost-effectiveness of this approach remains unaddressed.

OBJECTIVE To estimate incremental lifetime effects, costs, and cost-effectiveness of multigene testing of all patients with BC compared with the current practice of genetic testing (BRCA) based on family history (FH) or clinical criteria.

DESIGN, SETTING, AND PARTICIPANTS This cost-effectiveness microsimulation modeling study compared lifetime costs and effects of high-risk BRCA1/BRCA2/PALB2 (multigene) testing of all unselected patients with BC (strategy A) with BRCA1/BRCA2 testing based on FH or clinical criteria (strategy B) in United Kingdom (UK) and US populations. Data were obtained from 11 836 patients in population-based BC cohorts (regardless of FH) recruited to 4 large research studies. Data were collected and analyzed from January 1, 2018, through June 8, 2019. The time horizon is lifetime. Payer and societal perspectives are presented. Probabilistic and 1-way sensitivity analyses evaluate model uncertainty.

INTERVENTIONS In strategy A, all women with BC underwent BRCA1/BRCA2/PALB2 testing. In strategy B, only women with BC fulfilling FH or clinical criteria underwent BRCA testing. Affected BRCA/PALB2 carriers could undertake contralateral preventive mastectomy; BRCA carriers could choose risk-reducing salpingo-oophorectomy (RRSO). Relatives of mutation carriers underwent cascade testing. Unaffected relative carriers could undergo magnetic resonance imaging or mammography screening, chemoprevention, or risk-reducing mastectomy for BC risk and RRSO for ovarian cancer (OC) risk.

MAIN OUTCOMES AND MEASURES Incremental cost-effectiveness ratio (ICER) was calculated as incremental cost per quality-adjusted life-year (QALY) gained and compared with standard £30 000/QALY and $100 000/QALY UK and US thresholds, respectively. Incidence of OC, BC, excess deaths due to heart disease, and the overall population effects were estimated.

RESULTS BRCA1/BRCA2/PALB2 multigene testing for all patients detected with BC annually would cost £10 464/QALY (payer perspective) or £7216/QALY (societal perspective) in the United Kingdom or $65 661/QALY (payer perspective) or $61 618/QALY (societal perspective) in the United States compared with current BRCA testing based on clinical criteria or FH. This is well below UK and US cost-effectiveness thresholds. In probabilistic sensitivity analysis, unselected multigene testing remained cost-effective for 98% to 99% of UK and 64% to 68% of US health system simulations. One year’s unselected multigene testing could prevent 2101 cases of BC and OC and 633 deaths in the United Kingdom and 9733 cases of BC and OC and 2406 deaths in the United States. Correspondingly, 8 excess deaths due to heart disease occurred in the United Kingdom and 35 in the United States annually.

CONCLUSIONS AND RELEVANCE This study found unselected, high-risk multigene testing for all patients with BC to be extremely cost-effective compared with testing based on FH or clinical criteria for UK and US health systems. These findings support changing current policy to expand genetic testing to all women with BC.
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urrent national and international guidelines recommend genetic testing in women with breast cancer (BC) who fulfill recognized or established family history (FH) or clinical criteria. These criteria are surrogates for BRCA (BRCA1 [OMIM 113705] and BRCA2 [OMIM 600185]) probability, with genetic testing usually offered at approximately a 10% probability threshold of being a BRCA carrier.\(^1\)\(^2\) Being a BRCA (mutation) carrier refers to carrying an inheritable genetic pathogenic variant that predisposes to development of BRCA-associated cancers. However, patients with BC and genetic pathogenic variants do not always have a positive FH, and these criteria miss a large proportion (approximately 50%) of pathogenic variant carriers.\(^3\)\(^5\) A genetic testing strategy based on clinical criteria or FH depends on the patient and their physician’s awareness and understanding of the importance of FH, FH accuracy, communication within or between families, and timely referrals to clinical genetics departments. Limited awareness by health care professionals and the public, complexity of the current structure, restricted genetic counseling services, and current testing pathways have fostered restricted access and massive underuse of genetic testing services.\(^6\)\(^8\) Only 20% to 30% of eligible patients are referred and access testing, and 97% of estimated carriers in the population remain unidentified,\(^7\) missing substantial opportunities for precision prevention.\(^6\) Testing all patients with BC at diagnosis can increase testing access and uptake and identify many more pathogenic variant carriers for screening and prevention. We herein evaluate the cost-effectiveness of this alternative approach of providing genetic testing to all patients with BC regardless of FH.

Knowing a patient’s genetic pathogenic variant status is important for the management and prognosis of BC. After unilateral BC, pathogenic variant carriers can choose contralateral prophylactic mastectomy (CPM) to reduce their risk of developing contralateral BC and opt for surgical prevention of ovarian cancer (OC). Cancer-affected carriers may become eligible for novel drugs (eg, poly [adenosine diphosphate ribose] polymerase [PARP] inhibitors) and other precision medicine–based therapeutics through clinical trials.\(^9\)\(^10\) A major advantage of genetic testing is enabling testing among relatives of BC pathogenic variant carriers in order to identify unaffected relatives carrying pathogenic variants for early diagnosis and cancer prevention. BRCA1/BRCA2 carriers have a 17% to 44% risk of developing OC and 69% to 72% risk of BC to 80 years of age.\(^10\) PALB2 (OMIM 610355) is a recently established high-penetrance BC gene associated with a 44% BC risk.\(^11\) A number of risk management options are available for unaffected relatives with pathogenic variants. To reduce OC risk, BRCA1/BRCA2 pathogenic variant carriers can undergo risk-reducing salpingo-oophorectomy (RRSO).\(^12\)\(^13\) To reduce BC risk, BRCA1/BRCA2/PALB2 pathogenic variant carriers can be offered enhanced magnetic resonance imaging and mammography screening,\(^14\)\(^15\) risk-reducing mastectomy (RRM),\(^16\) or chemoprevention with selective estrogen receptor modulators.\(^17\)

Current restricting of testing to FH- or clinical criteria–based selection misses important opportunities to prevent BC and OC in unaffected individuals. In this study, we obtained data from 4 large BC clinical trials and/or research cohorts in the United States, United Kingdom, and Australia. We used modeling to estimate downstream health effects and costs and explore the cost-effectiveness of multigene BRCA1/BRCA2/PALB2 testing for all cases with BC compared with current BCRA testing based on clinical criteria or FH alone. We restrict this analysis to BRCA1/BRCA2/PALB2, keeping in mind the principles of the ACCE framework (analytic validity, clinical validity, clinical utility and associated ethical/legal/social implications)\(^18\)\(^19\) advocated for clinical applicability of genetic testing.

### Methods

This analysis received full ethics approval from the Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee as well as the London School of Hygiene and Tropical Medicine Ethics Committee, waiving informed consent for the use of anonymized data. A patient and public involvement statement is found in eMethods 4 in the Supplement.

Data were collected and analyzed from January 1, 2018, through June 8, 2019. We obtained data on FH by age from 11 836 women diagnosed with invasive BC, including (1) 1389 unselected patients with BC older than 45 years who were identified among 57 902 women in the Predicting Risk of Breast Cancer Screening study, a large-scale study within the Greater Manchester UK National Health Service Breast Screening Programme\(^20\); (2) 2885 patients with BC younger than 40 years from 127 UK hospitals in the Prospective Outcomes in Sporadic vs Hereditary Breast Cancer study\(^21\); (3) 5892 unselected patients with BC older than 40 years among 132 139 women enrolled in the Kaiser Permanente Washington Breast Cancer Surveillance Consortium registry who underwent mammography screening from 1996 to 2014\(^22\); and (4) 1670 patients with BC younger and older than 40 years who were randomly selected from the unselected population–based BC cases...
from the Australian Breast Cancer Family Study. The proportion of cases fulfilling FH or clinical criteria for testing based on at least a 10% BRCA1/BRCA2 probability threshold was estimated using standard risk models (eg, BOADICEA [UK and Australian data] and BRCAPRO [US data]). We thus obtained the proportion fulfilling FH or clinical criteria (herein referred to as FH positive) for BRCA testing by age group among unselected BC cases in each setting (eTable 1 in the Supplement). The women in these cohorts are predominantly white and representative of a Western population ethnicity (details in eTable 1 in the Supplement). We obtained population-based BC incidence data by age from Cancer Research UK 2015 for the UK analysis and from US Cancer Statistics 2015 for the US analysis. Then we estimated the total number of FH-positive BC cases based on the number of new invasive BC cases by age group in the UK and US populations.

Model and Genetic Testing Strategy
We developed an individual-level microsimulation model (illustrated and described in Figure 1 and Figure 2) to analyze costs and effects of BRCA1/BRCA2/PALB2 testing for all patients with BC (strategy A) compared with the current practice of BRCA testing using clinical- or FH-based criteria (≥10% pathogenic variant risk) (strategy B). Microsimulation permits individual heterogeneity in gene types and ages and can track individual patient history if the memory of events (eg, risk-reducing options) affects future cycles. The model assumes all patients in the unselected testing arm (strategy A) and only those fulfilling clinical or FH criteria in strategy B are offered genetic counseling and testing. We assume all eligible patients undergo genetic testing in our base-case analysis. If patients had a BRCA1/BRCA2/PALB2 pathogenic variant, their first-degree relatives undergo testing for the familial pathogenic variant. If the first-degree relative had a BRCA1/BRCA2/PALB2 pathogenic variant, second-degree relatives undergo testing. We incorporate a 6.4% variant of uncertain significance (VUS) rate (BRCA1, 1.23%; BRCA2, 3.29%; and PALB2, 1.86%) and an 8.7% pathogenic or likely pathogenic reclassification rate for VUS.

Figure 1 provides a schema of the model with respect to patients with BC. In the unselected testing arm, all patients with BC are offered genetic testing and are classified as pathogenic.
variant carriers, VUS carriers, or noncarriers. A proportion (8.7%) of patients with VUS results will subsequently get reclassified as pathogenic variant carriers. Identified BRCA1/BRCA2 pathogenic variant carriers are offered options of CPM and RRSO, and identified PALB2 pathogenic variant carriers are offered CPM. Depending on the probability of patients undertaking a CPM and/or RRSO, they may progress to germline contralateral BC or both BC and OC. They also have a probability of dying due to germline BC. Patients who do not progress or die would stay in the state of germline ipsilateral BC and undertake the next cycle. Patients with negative findings for BRCA1/BRCA2/PALB2 have sporadic BC. Age-dependent probabilities allow them to develop sporadic OC and progress to the health state of BC and OC. They also have a probability of dying due to sporadic BC. Women who do not progress to BC and OC or die would stay in the health state of sporadic BC to undertake the next cycle.

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 carriers, or noncarriers. A proportion of patients with VUS results will subsequently be reclassified as pathogenic variant carriers. Patients with negative FH do not undertake genetic testing. They can be undetected BRCA1/BRCA2 pathogenic variant carriers, undetected PALB2 pathogenic variant carriers, or negative for BRCA1/BRCA2/PALB2. Options of CPM and/or RRSO and disease progression for identified BRCA1/BRCA2/PALB2 pathogenic variant carriers and disease progression for patients who are BC negative for BRCA1/BRCA2/PALB2 is the same as those in the unselected testing arm described above. Undetected BRCA1/BRCA2 pathogenic variant carriers are not offered CPM or RRSO, and undetected PALB2 pathogenic variant carriers are not offered CPM. Depending on the baseline risk (no risk-reducing options), they progress to germline contralateral BC or both BC and OC. They also have a probability of dying due to germline BC. Patients who do not progress or die would stay in the state of germline ipsilateral BC and undertake the next cycle.

Figure 2 provides a schema of the model with respect to unaffected relatives identified through cascade testing. Progression through the model depends on the probabilities provided in eTable 2 in the Supplement. In the unselected testing arm, relatives of pathogenic variant carriers with BC are offered BRCA1/BRCA2/PALB2 genetic testing and classified as pathogenic variant carriers or noncarriers. Relatives of patients with BC and VUS (8.7%) who are reclassified as pathogenic variant carriers are also offered predictive BRCA1/BRCA2/PALB2 testing. Relatives identified with BRCA1/BRCA2
pathogenic variants are offered options of RRM and RRSO, and those identified with PALB2 pathogenic variants are offered RRM. Unaffected relatives can also opt for chemoprevention for BC. Depending on the probability of pathogenic variant carriers undertaking an RRM and/or RRSO (with or without chemoprevention), they progress to germline BC (BRCA1/BRCA2/PALB2) or germline OC (BRCA1/BRCA2) or stay in the health state of no cancer. They have a probability of background all-cause mortality. Women who are negative for BRCA1/BRCA2/PALB2 progress to sporadic BC or sporadic OC or stay in the health state of no cancer. They have a probability of background all-cause mortality.

In the clinical criteria/FH testing arm, relatives of identified patients with BRCA1/BRCA2 mutation undergo predictive BRCA1/BRCA2 genetic testing. They are classified as pathogenic variant carriers or noncarriers. Relatives of patients with BC and VUS who are reclassified as pathogenic variant carriers also undergo predictive BRCA1/BRCA2 testing. PALB2 pathogenic variant carriers cannot be detected when only FH-based BRCA1/BRCA2 genetic testing is offered. Relatives of patients with negative FH may be undetected BRCA1/BRCA2 pathogenic variant carriers, undetected PALB2 pathogenic variant carriers, or negative for BRCA1/BRCA2/PALB2. The options of RRM and RRSO for identified carriers are the same as in the unselected testing arm. For identified BRCA1/BRCA2/PALB2 pathogenic variant carriers and noncarriers (BRCA1/BRCA2/PALB2 negative), the disease progression is the same as in relatives in the unselected testing arm. Undetected BRCA1/BRCA2 pathogenic variant carriers are not offered RRM or RRSO, and undetected PALB2 pathogenic variant carriers are not offered RRM. Depending on the baseline risk, they progress to germline BC or germline OC or stay in a no cancer health state. They also have a probability of background all-cause mortality.

As shown in the model, unaffected BRCA1/BRCA2/PALB2 pathogenic variant carriers can choose RRM and/or chemoprevention to reduce BC risk and RRSO (BRCA1/BRCA2 only) to reduce OC risk in addition to undertaking enhanced BC screening. Patients with BC found to have pathogenic variants can opt for CPM. Although initial studies suggested that premenopausal RRSO is associated with reduced BC risk, more recent data contradict this observation, especially in BRCA1, raising uncertainty around this issue. We explored no reduction in BC risk in our scenario analysis. We incorporated the excess risk and mortality due to coronary heart disease (CHD) after premenopausal oophorectomy (after RRSO) for premenopausal women who do not take hormone replacement therapy (HRT) (absolute mortality increase, 3.03%).

In our model, a hypothetical cohort of patients with BC and their cancer-free relatives can transition to different health states, including no cancer, germline ipsilateral BC, germline contralateral BC, sporadic BC, germline OC, sporadic OC, and both BC and OC. Cancer incidence was estimated by summing the probabilities of pathways ending in OC or BC. The potential population effect was calculated by estimating additional reduction in BC and OC incidence obtained through testing the entire population of BC cases occurring annually in UK and US women. In line with the National Institute of Health and Clinical Excellence (NICE) economic evaluation guidelines, costs and outcomes are discounted at 3.5%.35

Probabilities
Model probabilities for the different pathways are shown in eTable 2 in the Supplement. The age-specific incidences of BC and OC among the general population are obtained from Cancer Research UK 201526,36 and US Cancer statistics 2015.27 The age-specific incidence of BC and OC for BRCA1/BRCA2 carriers and of BC for PALB2 carriers,11 along with the incidence of contralateral BC after first BC diagnosis,10 are obtained from the literature.

Number and Age Distribution of Relatives
We used the number of new BC cases by age groups in the United Kingdom and United States to calibrate the age distribution of patients in the model.26,27 The mean number of first- or second-degree relatives and their ages relative to index cases are derived from data from the Office for National Statistics (in the United Kingdom)37 and the National Center for Health Statistics (in the United States)38 (details in eTable 3 in the Supplement). We used life tables based on age and sex to estimate the probability of being alive for relatives at different ages and to calculate the number and age distribution of relatives who need to undergo testing.

Life-Years
Our analysis incorporates lifetime risks and long-term consequences to provide a lifetime horizon. Female life tables from the Office of National Statistics (UK women)42 and the National Center for Health Statistics (US women)43 were used to estimate life expectancy by 80 years for women who did not develop OC or BC. We assumed the median age for undergoing RRM and RRSO in unaffected pathogenic variant carriers was 37 and 40 years, respectively.43 We also explored older age at RRM (42 years) and RRSO (46 years) reported in a scenario analysis.44 Survival after BC and OC (from diagnosis to death) was modeled using 10-year survival data. Details of survival estimates used are given in eMethods 2 in the Supplement.

Quality-Adjusted Life-Years
A quality-adjusted life-year (QALY) is a measurement of health outcomes in economic evaluations recommended by NICE. An explanation of QALY and utility scores in the model is given in eMethods 3 in the Supplement.
Cost-effectiveness of Multigene Testing for All Patients With Breast Cancer

Original Investigation Research

In the microsimulation model, we used the number of annual new BC cases (United Kingdom, 54 483; United States, 242 463) and corresponding female relatives (United Kingdom, 215 401; United States, 993 757) by age for running simulations. Internal validation of the model was undertaken through a process of descriptive, technical, and face validity.45 We calculated the incremental cost-effectiveness ratio (ICER) by dividing the difference in lifetime costs by the difference in lifetime effects (QALYs) between the 2 strategies as follows: (Cost of Strategy A − Cost of Strategy B)/(Effect of Strategy A − Effect of Strategy B). By comparing the ICER with the willingness-to-pay (WTP) threshold of €30 000/QALY (UK analysis)46 and $100 000/QALY (US analysis),47,48 we determined whether genetically testing all patients with BC is cost-effective compared with testing based on clinical criteria or FH alone. We undertook a number of scenario analyses, including (1) no reduction in BC risk due to RRSo; (2) nil HRT adherence; (3) lower genetic testing uptake rate (70%) in patients with BC and relatives; (4) 15% BRCA1/2 pathogenic variant prevalence in patients with BC fulfilling clinical criteria or FH; (5) double cost of genetic counseling (United Kingdom, £40; United States, $80); (6) higher median age for RRm (42 years) and RRSo (46 years) in unaffected pathogenic variant carriers; and (7) the maximum values of cost(s) of genetic testing at which the ICERs reach the WTP thresholds to maintain cost-effectiveness of unselected multigene testing (strategy A).

We performed extensive 1-way and probabilistic sensitivity analyses to explore model parameter uncertainty. In the 1-way sensitivity analysis, each variable or parameter was varied individually to assess the effect on results. Probabilities and utility scores were varied by their 95% CIs or range where available or by ±10%, and costs were varied by ±30%. In the probabilistic sensitivity analysis, all of the input variables were varied simultaneously (as recommended by NICE).49 As suggested in the literature,50 costs were given a γ distribution; quality of life, a log-normal distribution; and probability, a β distribution. For probabilistic sensitivity analysis, we obtained 1000 estimates of incremental costs and effects by sampling from the distributions of each variable. A cost-effectiveness acceptability curve was then plotted to show the probability of genetically testing all patients, with BC (strategy A) being cost-effective at different WTP thresholds.

Results

Compared with the current practice of genetic testing based on clinical criteria or FH, offering unselected multigene testing for all patients diagnosed annually with BC (54 483 in the United Kingdom and 242 463 in the United States) and subsequent predictive/cascade testing of relatives (strategy A) was highly cost-effective. The ICER for the UK payer perspective was £10 464/QALY (credible interval, £8 347/QALY to £28 965/QALY) and for the societal perspective, £7 216/QALY (credible interval, £6 194/QALY to £23 575/QALY). The ICER for the US payer perspective was $65 661 per QALY (credible interval, $46 613/QALY to $248 185/QALY) and for the societal perspective, $61 618/QALY (credible interval, $42 927/QALY to $221 781/QALY). The lifetime costs, QALYs, and population effects (reduced cancer incidence and deaths) for UK and US women are shown in Table 1 and Table 2. Strategy A was associated with an additional 419-day increase in life expectancy for UK and 298 days for US BRCA1/BRCA2/PALB2 pathogenic variant carriers. One year’s unselected genetic testing of all patients with BC could prevent an additional 1142 BC cases and 959 OC cases in the United Kingdom and 5478 BC cases and 4255 OC cases in the United States (Table 2). This finding corresponds to averting 633 deaths due to cancer in UK populations and 2406 deaths due to cancer in US populations during a lifetime horizon (Table 2). The corresponding excess deaths due to heart disease were 8 in UK and 35 in US women annually.

The 1-way sensitivity analysis (eFigure 1A-D in the Supplement) indicates that pathogenic variant prevalence, costs, utility scores, and transition probabilities had little individual influence on the cost-effectiveness of unselected genetic testing (strategy A) from a payer or societal perspective. Scatterplots for the UK and US analyses are given in eFigure 2 in the Supplement and show that all simulations and iterations lie in the northeast quadrant, indicating unselected testing was always more effective. The ICERs are lower than the UK and US WTP thresholds at the upper and lower limits of these variables. Probabilistic sensitivity analysis (Figure 3) shows that at the €30 000/QALY or $100 000/QALY thresholds, 98% (UK payer perspective), 99% (UK societal perspective), 64% (US payer perspective), and 68% (US societal perspective) of simulations indicate that unselected genetic testing is cost-effective compared with testing based on FH or clinical criteria.

The number of pathogenic variant carriers among unaffected female relatives identified through cascade testing was 1.41 in the United Kingdom and 1.46 in the United States per index pathogenic variant carrier with BC (details in eTable 4 in the Supplement). Scenario analyses are presented in Table 1. Unselected testing was cost-effective from payer and societal perspectives, even with alternative scenarios of no reduction in BC risk due to RRSo (ICER payer perspective, £10 532/QALY or $66 136/QALY; ICER societal perspective, £7 291/QALY or $62 102/QALY); nil HRT adherence (ICER payer perspective, £11 303/QALY or $89 705/QALY; ICER societal perspective, £7 870/QALY or $85 337/QALY); and lower (70%) genetic testing uptake rate in patients with BC and relatives (ICER payer perspective, £10 991/QALY or $71 006/QALY; ICER societal perspective, £8 046/QALY or $67 285/QALY). Although the probability of being a BRCA1/BRCA2 carrier in those fulfilling FH or clinical genetic testing criteria was reported at approximately 10%,51,52 we also explored a scenario of over 15% BRCA1/BRCA2 carrier probability. This variable had only a minimal effect on ICERs from the payer (£10 585/QALY) and societal (£7 332/QALY) perspectives among UK women and from the payer ($66 694/QALY) and societal ($62 646/QALY) perspectives among US women. The upper limit of genetic testing costs at which unselected genetic testing for all patients with BC would still remain cost-effective at the established WTP thresholds was approximately £1626 from the payer perspective and £1868 from the societal perspective for the UK health
Table 1. Lifetime Discounted Costs and Effects per Woman and ICER After Genetic Testing for All Patients With BC\(^a\)

| Country                  | Testing All Patients With BC | Testing Based on Family History | ICER |
|-------------------------|------------------------------|---------------------------------|------|
|                         | Health Effects               | Costs\(^b\)                     |      |
|                         | LGYs QALYs Payer Societal    | LGYs QALYs Payer Societal       |      |
| Baseline                |                              |                                 |      |
| United Kingdom          | 18.772 17.941 7213 11 147   | 18.755 17.922 7016 11 011       | 11 817 8149 10 464 7216 |
| United States           | 18.652 17.813 32 721 36 561 | 18.639 17.798 31 724 35 625     | 82 789 77 691 65 661 61 618 |
| No Reduction in BC Risk Due to RRSO\(^c\) |                              |                                 |      |
| United Kingdom          | 18.772 17.941 7214 11 148   | 18.755 17.922 7016 11 011       | 11 846 8201 10 532 7291 |
| United States           | 18.652 17.813 32 724 36 564 | 18.639 17.798 31 724 35 625     | 82 902 77 844 66 136 62 102 |
| No HRT Adherence\(^d\)  |                              |                                 |      |
| United Kingdom          | 18.771 17.940 7218 11 152   | 18.755 17.922 7016 11 011       | 12 706 8846 11 303 7870 |
| United States           | 18.651 17.812 33 013 36 852 | 18.639 17.798 31 751 35 652     | 113 342 107 823 89 705 85 337 |
| Lower Uptake Rate of Genetic Testing in Patients and Relatives\(^e\) |                              |                                 |      |
| United Kingdom          | 18.766 17.934 7132 11 096   | 18.755 17.922 7009 11 007       | 11 363 8319 10 991 8046 |
| United States           | 18.644 17.804 32 299 36 170 | 18.637 17.796 31 691 35 595     | 80 043 75 849 71 006 67 285 |
| 15% Probability of Being a BRCA Carrier in Patients With Positive FH\(^f\) |                              |                                 |      |
| United Kingdom          | 18.771 17.941 7213 11 147   | 18.755 17.923 7022 11 015       | 11 973 8293 10 585 7332 |
| United States           | 18.653 17.814 32 723 36 563 | 18.641 17.800 31 759 35 657     | 84 453 79 326 66 694 62 646 |
| Double Cost of Counseling\(^g\) |                              |                                 |      |
| United Kingdom          | 18.772 17.941 7220 11 154   | 18.755 17.922 7016 11 011       | 12 189 8521 10 794 7546 |
| United States           | 18.652 18.713 32 734 36 574 | 18.639 17.798 31 725 35 625     | 83 798 78 701 66 462 62 419 |
| Older Ages for RRM and RRSO in Unaffected Pathogenic Variant Carriers\(^h\) |                              |                                 |      |
| United Kingdom          | 18.770 17.938 7216 11 165   | 18.755 17.922 7016 11 013       | 13 181 10 043 12 214 9306 |
| United States           | 18.650 17.811 32 722 36 578 | 18.639 17.798 31 720 35 622     | 92 304 88 063 77 715 74 144 |

Abbreviations: BC, breast cancer; FH, family history; HRT, hormone replacement therapy; ICER, incremental cost-effectiveness ratio; LGY, life-years gained; QALY, quality-adjusted life-year; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy.
\(^a\) Costs and outcomes are discounted at 3.5%. Data are given at baseline (for the base case) and for separate scenarios.
\(^b\) Costs are given in dollars for the United States and pounds sterling for the United Kingdom.
\(^c\) Probability P15 = 1 (eTable 2 in the Supplement).
\(^d\) Probability P21 = 0 (eTable 2 in the Supplement).
\(^e\) Indicates a genetic testing uptake rate of 70%.
\(^f\) Probability P4 = 0.15 (eTable 2 in the Supplement).
\(^g\) Indicates £40 in the United Kingdom and $80 in the United States.
\(^h\) Indicates ages 42 and 46 years for RRM and RRSO, respectively.

Table 2. Population Effect of Genetic Testing for Patients With BC

| Estimated Effect | Testing in All Patients With BC | Testing Based on FH | Differences |
|------------------|---------------------------------|---------------------|-------------|
|                  | Patients Relatives              | Patients Relatives | Patients Relatives Total |
| UK germline cancer | No. of BC cases 364* 1965 | 684* 2787 | 320* 822 | 1142 |
|                  | No. of OC cases 447 1882 | 871 2417 | 424 535 | 959 |
|                  | No. of BC and OC deaths 451 988 | 748 1325 | 296 337 | 633 |
| US germline cancer | No. of BC cases 1639* 8727 | 3230* 12 614 | 1591* 3887 | 5478 |
|                  | No. of OC cases 2087 8655 | 3916 11 081 | 1829 2426 | 4255 |
|                  | No. of BC and OC deaths 1555 4168 | 2621 5508 | 1066 1340 | 2406 |

Abbreviations: BC, breast cancer; FH, family history; OC, ovarian cancer.
\(^*\) Indicates contralateral BC cases in patients with unilateral BC.
Lower RRSO and RRM rates are reported in some populations. The minimum RRSO uptake rate to maintain cost-effectiveness was 29% from the payer perspective or 28% from the societal perspective for the United States (ICER, $100,000/QALY), but unselected BC genetic testing was cost-effective in the United Kingdom even if the RRSO rate was nil (ICER from the payer perspective, £28,392/QALY; ICER from the societal perspective, £23,802/QALY). The strategy was cost-effective even if RRM rates in unaffected relatives approached 0 (UK ICER from the payer perspective, £99,691/QALY; UK ICER from the societal perspective, £70,641/QALY; US ICER from the payer perspective, $67,235/QALY; US ICER from the societal perspective, $63,643/QALY). However, if RRM uptake was 0, then the minimum RRSO uptake rate to maintain cost-effectiveness at the WTP thresholds (United States, $100,000/QALY; United Kingdom, £30,000/QALY) was 33% (payer perspective) or 32% (societal perspective) in the US health system and 5% (payer perspective) or 4% (societal perspective) in the UK health system.

**Discussion**

Our analysis addresses a topical and important issue of unselected multigene testing for all patients with BC. We show for the first time, to our knowledge, that multigene testing for high-penetrance BC pathogenic variants of well-established clinical utility is more cost-effective and outperforms standard...
BRCA testing driven by clinical criteria or FH alone. Moving toward such a program could lead to 142 fewer BC cases, 959 fewer OC cases, and 663 fewer deaths due to BC or OC in UK women and 5478 fewer BC cases, 4255 fewer OC cases, and 2406 fewer deaths due to BC or OC in US women annually. Our study provides QALY-based health outcomes that justify the cost differences between the 2 strategies that are needed for health care professionals, providers, and policy makers to guide or direct resource allocation. The ICERs (£10 464/QALY and £7216/QALY in the United Kingdom and $65 661/QALY and $61 618/QALY in the United States) lie well below the established cost-effectiveness thresholds for the UK (£20 000/QALY and £30 000/QALY) and the US ($100 000/QALY) health systems. Continuing with the current FH- or clinical criteria-based policy reflects important opportunities missed for BC and OC prevention.

Comparison With Other Studies
Although earlier studies have reported cost-effectiveness of BRCA testing at the 10% pretest probability threshold, we report cost-effectiveness of unselected BRCA/PALB2 testing irrespective of a priori mutation probability. Our findings are in line with a recent, small Norwegian study (535 patients) showing cost-effectiveness of BRCA testing for all patients with BC. Our study is broader in scope and draws on a much larger sample size of population-based UK, US, and Australian patients with BC. Testing at cancer diagnosis has now moved toward multigene testing. PALB2 is associated with nonsyndromic, quasi-mendelian BC susceptibility (BC risk, 44%), and magnetic resonance imaging screening and RRM are now offered for pathogenic variants. Other high-risk genes are identifiable as pleiotropic syndromic (STK11, PTEN, or p53) or associated with only a small subset (lobular), and all are very rare. In addition, reliable risk estimates corrected for ascertainment bias are lacking. Although ATM and CHEK2 are included in some commercial panels, clinical testing for these genes is not routine in most centers. Risks conferred by these pathogenic variants are lower (relative risk, approximately 1.5-2.0), and although National Comprehensive Cancer Network guidelines support breast screening, RRM is not routinely offered, FH needs incorporation into risk assessment and management, and many health care professionals believe that they fall below the clinical intervention threshold. Hence, we incorporated PALB2 along with BRCA but excluded other genes.

Implications
The current health care model of testing based on clinical criteria or FH has numerous limitations. It misses a large proportion of pathogenic variant carriers who fall below the current clinical threshold. The current system is plagued by massive underuse of genetic testing and missed opportunities for BC and OC screening and prevention. Moving toward unselected BC testing may give an impetus for prevention in unaffected family members along with clinical implications for the patient with BC. Pathogenic variant carriers with newly diagnosed BC can opt for bilateral mastectomy rather than breast conservation at initial BC surgery. Bilateral mastectomy reduces contralateral BC risk, may provide better options for breast reconstruction, and may obviate the need for adjuvant radiotherapy. The patients also become eligible for therapeutic options, such as PARP inhibitors. Addressing the increasing burden of long-term and chronic disease, including cancer, is one of the world’s greatest public health challenges and is important for future viability of health systems across the world. The Milken Institute estimates that improving prevention can cut billions of cases of chronic disease and reduce treatment costs by billions. The applicability of genomics to medicine is growing and expanding. Moving toward unselected multigene testing for patients with BC can provide a huge stimulus for precision prevention.

Existing genetic counseling services operating through high-risk cancer genetics clinics do not have the resources or manpower to deliver unselected genetic testing for all patients with BC given the large numbers of patients who receive a diagnosis annually. Hence, newer context-specific delivery models will be needed for implementing this approach. These models may require pretest counseling to be undertaken by nongenetic health care professionals who will need to be trained for this. This approach of mainstreaming genetic counseling and testing has recently been successfully implemented in OC treatment pathways. Oncologists, surgeons, and clinical nurse specialists have provided pretest counseling and genetic testing, with genetic services focusing on posttest counseling and support for women carrying pathogenic variants. A similar approach could work for patients with BC. Examples of other delivery options include a genetics service–coordinated nurse-led model, a genetics-embedded model (genetics health care professional or counselor embedded in the cancer clinic), and telemedicine counseling for genetic counseling and testing.

Going forward, most health care professionals who practice medicine will need an increased understanding of genetics and ability to counsel patients about this topic. As the volume of testing rises, the number of mutations and VUS being diagnosed along with the need for correct interpretation and management will increase. Implementation will need to be accompanied by a process of training and education for relevant physicians and other health care professionals involved in the care pathway so that they can understand the implications for management, including that of VUS. This process is critical to ensure best evidence-based care and to avoid unintended or inappropriate management, such as downstream predictive testing, screening, or prevention in VUS cases. Updated guidelines need to reflect the importance of appropriate management. Appropriate clinical decision support tools can facilitate this transformation. Another potential bottleneck to address is laboratory infrastructure to manage increased sample throughput. Although some health systems have adequate capacity, others may lack this infrastructure. Future research needs to evaluate the effects and downstream outcomes of various context-specific genetic testing implementation and management pathways for patients with BC.
Cost-effectiveness of Multigene Testing for All Patients With Breast Cancer

Our study has several strengths. The model incorporates unselected BC data from large population-based studies, up-to-date information from the Genetics Cancer Prediction Through Population Screening study,69 published literature, and public databases such as those of the Office for National Statistics (United Kingdom),37,41 National Center for Health Statistics (United States),38,42 and Cancer Research UK.26,36 We use the current standard of clinical care (approach based on clinical criteria or FH) as the comparator and present analyses from the payer and societal perspectives. Our analysis follows NICE recommendations: QALYs to measure health outcomes; cost-effectiveness analysis for health economic evaluation,49 integration of utility scores, discounting costs and outcomes (rate, 3.5%), sufficiently long horizon (lifetime) to uncover important differences in costs and outcomes, and extensive and thorough 1-way and probabilistic sensitivity analyses that support robustness and accuracy of results (eFigure 1 in the Supplement and Figure 2). We include a detriment for CHD mortality.33 Our costs include genetic testing, VUS management, pretest and posttest genetic counseling, HRT use, and protection from osteoporosis.

Our study has limitations related to modeling assumptions. Our baseline model assumes that all women with BC and their unaffected relatives undergo genetic testing. Although very high (>98%) genetic testing rates are reported in unselected genetic testing at OC diagnosis, and corresponding genetic testing uptake data in unselected patients with BC are not well established. Our scenario analysis reconfirms cost-effectiveness at lower (70%) uptake rates. Although our base model incorporates reduction in BC risk with premenopausal oophorectomy in keeping with many initial analyses,13,30,31,70 recent uncertainty surrounds this.32 Our scenario analysis reconfirms cost-effectiveness even without this benefit. Although genetic testing costs have fallen drastically, some health care providers charge higher prices than our base-case assumption. Nevertheless, unselected BC testing would remain cost-effective even at £1626 to £1868 in the United Kingdom or $2432 to $2679 in the United States, which is many times greater than costs charged by most health care providers today. Another limitation is that our model incorporates data predominantly from white women, which can limit interpretation of generalizability to nonwhite populations.

Although we have incorporated disutility for RRSO and RRM, surgical prevention might have associated complications (RRSO, approximately 3%–4%27; RRM, approximately 2%)72,73 that need to be factored into the informed consent and decision-making process. Although premenopausal RRSO is not associated with worsening general quality of life, poorer sexual function is reported (despite HRT).74,75 This outcome is compensated by extremely high satisfaction rates and reduction in perceived cancer risk and/or worry with RRSO,74,76 Risk-reducing mastectomy is negatively associated with sexual pleasure and body image. These disadvantages may be offset by reduced anxiety, improved social activity,77 good cosmetic satisfaction rates,26,79 and lack of negative impact on sexual activity/habit/discomfort,77 anxiety/depression, or generic quality of life.77-81 We confirmed that unselected multigene testing remains cost-effective at recently reported older ages of RRM and RRSO.44 The surgical prevention (RRM and RRSO) rates used are based on established UK and US data.43,82 However, these rates can vary, with lower rates reported in some populations.53 Those ascertained from population testing may have lower BC risks and result in lower uptake, particularly in the absence of death due to BC and heavy cancer burden in the family. Our scenario analyses show that unselected testing remains cost-effective at lower RRSO and RRM rates.

Conclusions

This study’s findings suggest that unselected multigene testing for BC susceptibility genes BRCA1/BRCA2/PALB2 can substantially reduce future BC and OC cases and related deaths compared with the current clinical strategy. Our analysis suggests that an unselected testing strategy is extremely cost-effective for UK and US health systems and provides a basis for change in current guidelines and policy to implement this strategy.

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