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Cost-effectiveness analysis of germ-line *BRCA* testing in women with breast cancer and cascade testing in family members of mutation carriers

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Purpose: To evaluate the cost-effectiveness of *BRCA* testing in women with breast cancer, and cascade testing in family members of *BRCA* mutation carriers.

Methods: A cost-effectiveness analysis was conducted using a cohort Markov model from a health-payer perspective. The model estimated the long-term benefits and costs of testing women with breast cancer who had at least a 10% pretest *BRCA* mutation probability, and the cascade testing of first- and second-degree relatives of women who test positive.

Results: Compared with no testing, *BRCA* testing of affected women resulted in an incremental cost per quality-adjusted life-year (QALY) gained of AU$18,900 (incremental cost AU $1,880; incremental QALY gain 0.10) with reductions of 0.04 breast and 0.01 ovarian cancer events. Testing affected women and cascade testing of family members resulted in an incremental cost per QALY gained of AU$9,500 compared with testing affected women only (incremental cost AU$665; incremental QALY gain 0.07) with additional reductions of 0.06 breast and 0.01 ovarian cancer events.

Conclusion: *BRCA* testing in women with breast cancer is cost-effective and is associated with reduced risk of cancer and improved survival. Extending testing to cover family members of affected women who test positive improves cost-effectiveness beyond restricting testing to affected women only.

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Key Words: *BRCA* testing; breast cancer; cascade testing; cost-effectiveness; ovarian cancer

INTRODUCTION

A germ-line mutation in the breast cancer susceptibility genes *BRCA1* and *BRCA2* is associated with an increased risk of breast and ovarian cancers. Women with a *BRCA* mutation have a 40 to 80% lifetime breast cancer risk and a 10 to 40% risk of ovarian cancer.[1–3] The prevalence of *BRCA* mutations varies based on a number of factors such as type of cancer, age at diagnosis, family history of cancer, and ethnicity.[4,5] For instance, women with breast cancer diagnosed before the age of 40 have almost 10% risk of carrying a *BRCA* mutation regardless of family history of breast or ovarian cancer, 20% risk if they have a family history, and 30% risk if they are Ashkenazi.[6–9]

Various interventions have been found to be effective in reducing the risk of cancer in *BRCA* mutation carriers including risk-reducing mastectomy (RRM) and/or bilateral salpingo-oophorectomy (RRBSO).[10–12] Women who do not wish to pursue or would rather delay risk-reducing surgery may benefit from other interventions such as enhanced cancer surveillance. In the presence of effective strategies to reduce the incidence of *BRCA*-related cancers, genetic testing has been recommended to identify carriers who would benefit from cancer prevention interventions.[13,14] Given the high cost of the test and the potentially large number needed to test to detect a mutation, though, there has been an increasing interest in the cost-effectiveness of *BRCA* mutation testing to inform which genetic testing program would deliver value for money. One option is to have a population-based genetic screening whereby individuals without cancer are screened if they belong to a group with high prevalence of *BRCA* mutation based on ethnicity such as the Ashkenazi Jewish. Another approach is to test people who have a family history of cancer but in whom a familial mutation has not been identified. A more focused approach entails testing affected individuals (i.e., individuals diagnosed with cancer) who have disease characteristics suggesting a high probability of carrying a mutation (e.g., early-onset breast cancer) to determine whether a germ-line *BRCA* mutation is present, followed by *BRCA* testing of the relatives (i.e., cascade testing) of those affected individuals who test positive for the mutation. The latter strategy is an efficient approach that is supported by the recent international guidelines for *BRCA* mutation testing.[12–15]

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The cost-effectiveness of the different *BRCA* testing programs has been recently reviewed.[16] Population-based *BRCA* mutation screening is too expensive unless it is targeted at Ashkenazi Jewish women.[16] Family history–based testing programs appeared to be cost-effective in two studies;[17,18] however, the results of these economic evaluations should be considered with caution because they did not model cascade testing among the relatives of mutation carriers.[16] For the programs that are based on testing affected individuals, two studies concluded that testing women with ovarian cancer followed by the cascade testing of their family members was cost-effective.[5,19] Nevertheless, the two studies assumed that only the relatives of the affected individual benefit from *BRCA* testing and that the affected woman herself would not benefit (directly) from testing because RRM would not be a reasonable option for patients diagnosed with ovarian cancer.[19] Only one economic evaluation included women affected with breast cancer; however, that study did not consider the cascade testing of their family members.[20] Thus, there is a need for more evidence on the cost-effectiveness of *BRCA* testing in women diagnosed with breast cancer followed by cascade testing of relatives of mutation carriers.

The aim of this study was to assess the cost-effectiveness of germ-line *BRCA* testing in women with breast cancer, and the cascade testing for the relevant mutation in first- and second-degree relatives of affected women who test positive for the mutation, compared with no *BRCA* testing.

MATERIALS AND METHODS

Model description

A decision analytic model (**Figure 1**) was developed using TreeAge Pro 2015 (TreeAge Software 2015, Massachusetts, USA) to compare the costs and effects of germ-line *BRCA* testing with no testing for the following populations: (i) high-probability affected women, defined as women with unilateral breast cancer whose personal or family history of cancer using a mutation prediction score predicts a combined mutation carrier probability of $>10\%$ according to either BOADICEA, *BRCA*PRO, or pathology-adjusted Manchester score; (ii) first-degree family members (i.e., siblings and children) of the affected women who test positive; and (iii) second-degree family members who are the children of siblings who test positive. The mothers of affected women were excluded because, at an age of >65 years on average, there is little utility of genetic testing to prevent future development of cancer.[1,3] Based on the epidemiology of breast cancer in women younger than 50 years old, the base case model assumes the mean age of affected women and their siblings is 40 years.[2,21,22] The average age of mothers giving birth (i.e., childbearing) in Australia is 30 years,[23] and therefore the model assumes that the average age of children, for a 40-year-old affected woman, is 10 years.

The model starts with a decision tree where affected women will be either tested for a *BRCA* mutation (i.e., the intervention group) or not tested (i.e., the comparator group). A positive test will prompt a cascade of testing of first-degree relatives. The model assumes that the affected women belong to an average first-generation household of 2.6 children (i.e., the affected woman and her siblings), based on the data from the Australian Institute of Family Studies.[23] Thus, the number of siblings at risk of a *BRCA* mutation is 1.6 (0.8 female and 0.8 male siblings). Assuming that the affected woman now lives in an average more modern household with two children, she will have two children at risk, one male child and one female child. Accordingly, for each affected woman, an average of 1.6 siblings and 2 children will be tested for *BRCA* mutation. The chance of a sibling testing positive is 50% because *BRCA* mutations are autosomal dominant, which means that 0.8 siblings (of 1.6) will test positive. With an average of 2 children per sibling, the number of second-degree relatives at risk is 1.6 (0.8 female and 0.8 male).

The long-term outcomes and costs were modeled for females only. Thus, for each affected woman, 0.8 female sibling and 1.8 female children (one affected woman's female child and 0.8 sibling's female child) were followed using Markov modeling. This is because, unlike men, women can derive utility from genetic testing by undertaking risk-reducing surgery. Therefore, male family members were not followed in the model but were only tested to inform the need to test their children (i.e., second-degree relatives). We set the cycle length in the Markov model to 1 year and female individuals were followed for lifetime (i.e., until the age of 90 years). Female individuals who test positive would choose one of the following interventions: RRM alone, RRBSO alone, or RRM plus RRBSO. Chemoprevention or surveillance alone was not considered in the model given the very low uptake rate of these interventions compared with surgery.[21,24] Standard cancer screening (e.g., annual mammogram) was offered to the individuals in the comparator arm and to those who test negative for the *BRCA* mutation. The model assumed that affected women and their siblings would make a decision on a strategy to reduce the risk of future cancer within 1 year after they know that they carry a *BRCA* mutation. It is unlikely that those individuals would delay their decisions because, at the age of 40, they have an increased risk of cancer relative to the normal population, and they have probably completed their families. On the other hand, the model assumed female children would not be tested until they turn 20 years. Further, the model assumed that the children who test positive would not take an immediate decision to undertake a preventive strategy because the risk of developing cancer at the age of 20 is relatively small, and they may wish to have their own children before undergoing any risk-reducing surgery. Therefore, children who carry the mutation would stay in the *BRCA*-positive health state until the age of 30 years when they might act on cancer risk reduction (e.g., undergo risk-reducing surgery).

Individuals in the model may die of any cause, stay alive without a new cancer, or develop either breast cancer or ovarian cancer. Those who develop cancer may die of that cancer or stay alive. Individuals who remain alive in the cancer health states for 5 years are considered cured. In this

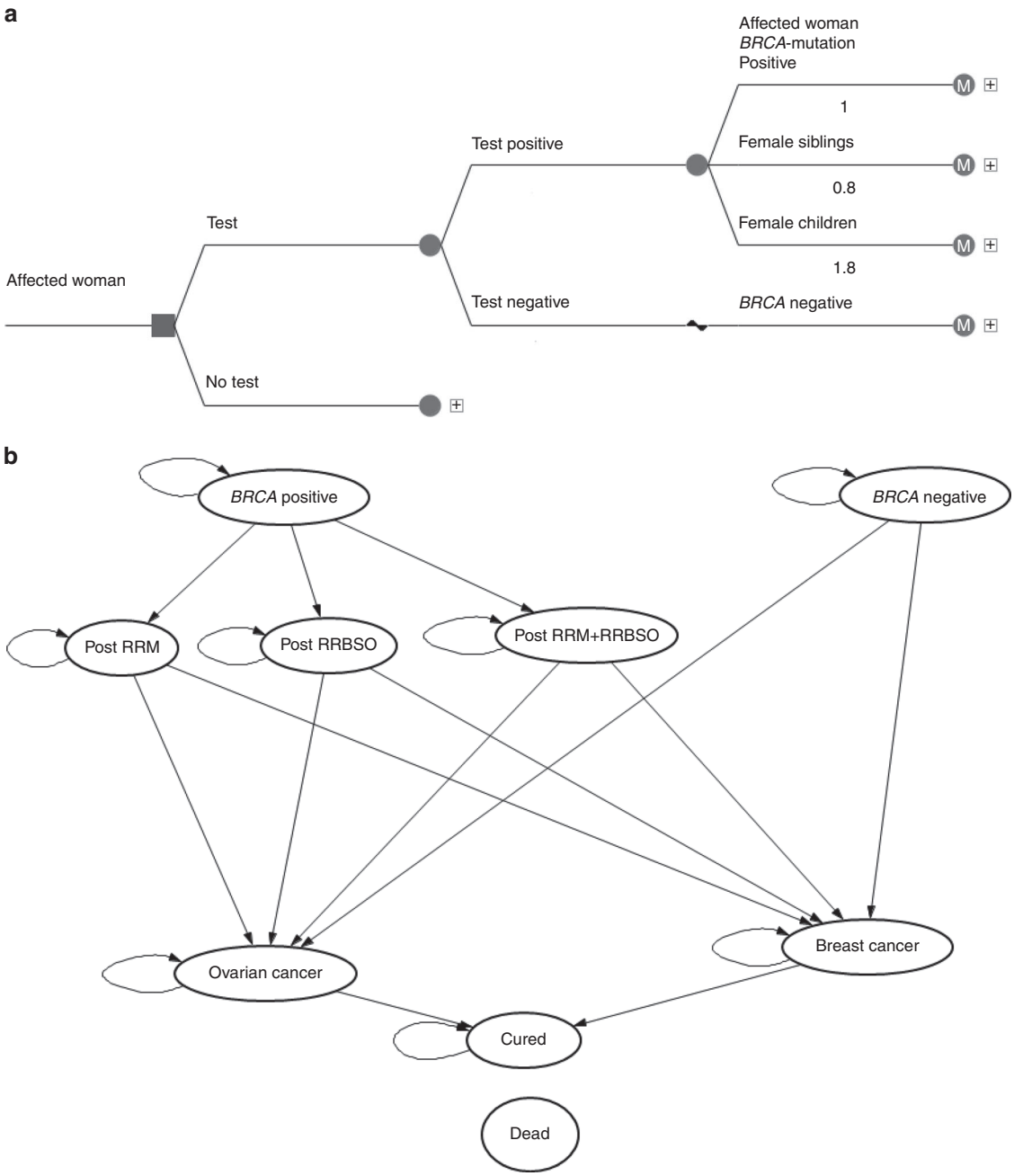

Figure 1 Model structure. (**a**) Decision tree. (**b**) Markov model. RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRM, risk-reducing mastectomy.

model, it was possible for a woman to develop ovarian cancer after breast cancer. However, breast cancer after ovarian cancer was not included, because the incidence is expected to be low given the relatively low probability but high mortality rate of ovarian cancer.

Model inputs

Table 1 summarizes the key model inputs with their values, ranges, and sources. The probability of an affected woman having a *BRCA* mutation was set at 15% because this included affected women who have a minimum 10% probability of a *BRCA* mutation.[5,9,15,20] The breast and ovarian cancer risks assumed for those not tested were based on a 15% probability that they carried a *BRCA* mutation. Population annual risk of breast cancer and ovarian cancer, obtained from current reports by the Australian Institute of Health and Welfare, was used for women who do not carry a *BRCA* mutation.[25,26]

For risks associated with *BRCA1* or *BRCA2* mutations, the weighted average risk for the two mutations was calculated assuming 54% prevalence for *BRCA1* and 46% prevalence for *BRCA2*.[27,28] We assumed that affected women had undergone breast-conserving surgery after their original diagnosis (e.g.,

Table 1 Summary of key input parameters values and sources

Variable	Base value	SE/Range	Distribution	Source
Transition probabilities				
Starting age	Affected = 40 years	2.5	Normal	Collins et al.[21]; Hayes et al.[23]
	Siblings = 40 years	2.5	Normal	
	Children = 10 years	2.0	Normal	
Probability of *BRCA* mutation positive in affected individuals	15%	10–20%	Uniform	Konstantopoulou et al.[9]; Palma et al.[4]; Malone et al.[6]
Probability to undergo RRM alone if positive	30%	—	Dirichlet	Collins et al.[21]
Probability to undergo RRBSO only if *BRCA*-positive	54%	—	Dirichlet	Collins et al.[21]
Probability to undergo RRM +RRBSO if *BRCA*-positive	16%	-	Dirichlet	Collins et al.[21]
Annual risk of contralateral breast cancer if *BRCA*-positive	20–29 years = 0.000	0.010	Beta	Mavaddat et al.[3]
	30–39 years = 0.050	0.010	Beta	
	40–49 years = 0.040	0.010	Beta	
	50–59 years = 0.030	0.020	Beta	
	60–69 years = 0.030	0.020	Beta	
Annual risk of new incidence of breast cancer if *BRCA*-positive	20–29 years = 0.005	0.001	Beta	Mavaddat et al.[3]
	30–39 years = 0.015	0.010	Beta	
	40–49 years = 0.030	0.010	Beta	
	50–59 years = 0.026	0.020	Beta	
	60–69 years = 0.012	0.020	Beta	
Annual risk of new incidence of ovarian cancer if *BRCA*-positive	20–29 years = 0.000	0.020	Beta	Mavaddat et al.[3]
	30–39 years = 0.002	0.001	Beta	
	40–49 years = 0.005	0.001	Beta	
	50–59 years = 0.012	0.010	Beta	
	60–69 years = 0.040	0.010	Beta	
	70–79 years = 0.020	0.010	Beta	
Population annual risk of breast cancer	20–29 years = 0.000	0.001	Beta	Australian Institute of Health and Welfare[25]
	30–39 years = 0.001	0.001	Beta	
	40–49 years = 0.002	0.001	Beta	
	50–59 years = 0.003	0.002	Beta	
	60–69 years = 0.003	0.002	Beta	
Population annual risk of ovarian cancer	20–29 years = 0.000	0.001	Beta	Australian Institute of Health and Welfare[26]
	30–39 years = 0.0000	0.0001	Beta	
	40–49 years = 0.0001	0.0001	Beta	
	50–59 years = 0.0002	0.0001	Beta	
	60–69 years = 0.0003	0.0002	Beta	
	70–79 years = 0.0004	0.0002	Beta	
RR of ovarian cancer with RRBSO only	0.166	0.030	Log-normal	Ludwig et al.[10]
RR of breast cancer with RRBSO only	0.550	0.060	Log-normal	Li et al.[11]
RR of breast cancer with RRM only	0.110	0.030	Log-normal	Li et al.[11]
RR of ovarian and breast cancer with RRM+RRBSO	0.110	0.030	Log-normal	Clinical expert advice

Table 1 Continued

Variable	Base value	SE/Range	Distribution	Source
Annual mortality of breast cancer	0.021	0.010	Beta	Australian Institute of Health and Welfare[25]
Annual mortality of ovarian cancer	0.15	0.060	Beta	Australian Institute of Health and Welfare[26]
Utility values				
Utility for normal population	0.90	0.010	Beta	Clemens et al.[31]
Utility with breast cancer	0.79	0.100	Beta	Peasgood et al.[32]; Manchanda et al.[26]
Utility with ovarian cancer	0.63	0.250	Beta	Manchanda et al.[26]
Costs in AU$				
Cost of *BRCA* test	Gene sequencing = 1,200	600	Gamma	MBS item 73295
	Single-site = 230	100	Gamma	MBS item 73291
Cost of genetic counseling	264	130	Gamma	MBS item 132
Cost of breast cancer treatment	Year 1 = 24,510	12,000	Gamma Gamma	MSAC application no 1098.1, February 2014
	Years 2–5 = 550	250		
Cost of ovarian cancer treatment	Year 1 = 20,000	10,000	Gamma Gamma	Gordon 2010 [35]
	Years 2–5 = 5,000	2,500		
Cost of RRBSO	8,621	400	Gamma	Weighted value of AR-DRG N05A and N05B in Round 17 of National Hospital Cost Data Collection
Cost of risk-reducing contralateral mastectomy	8,747	4,000	Gamma	AR-DRG J06B in Round 17 of National Hospital Cost Data Collection
Cost of risk-reducing bilateral mastectomy	15,586	7,000	Gamma	AR-DRG J06B from Round 17 of National Hospital Cost Data Collection

AR-DRG, Australian refined diagnosis-related group; AU$, Australian dollar; MBS, Medicare Benefits Schedule; MR, magnetic resonance imaging; MSAC, Medical Services Advisory Committee; RCPA, Royal College of Pathologists of Australia; RR, relative risk; RRBSO, risk-reducing salpingo-oophorectomy; RRM, risk-reducing mastectomy.

lumpectomy), so they remained at risk for subsequent ipsilateral and contralateral breast cancer. The age-specific incidence of breast, ovarian, and contralateral breast cancer and the corresponding cumulative risks in mutation carriers were obtained from the results of the Epidemiological Study of *BRCA1* and *BRCA2* Mutation Carriers.[3] The average cumulative risk by age 70 years for *BRCA1* carriers was 60% for breast cancer, 59% for ovarian cancer, and 83% for contralateral breast cancer.[3] For *BRCA2* carriers, the corresponding risks were 55% for breast cancer, 17% for ovarian cancer, and 62% for contralateral breast cancer.[3] Background mortality rates in the general Australian female population, by age, were based on Australian Bureau of Statistics life tables.[29] The 5-year mortality rates were 10% and 57% for breast cancer and ovarian cancer, respectively, based on the data from Australian Institute of Health and Welfare.[25,26] All rates were converted into annual probabilities using the rate to probability formula $(1 - e^{-\text{rate} \times \text{time}})$ where relevant.

The probability of an individual with a *BRCA* mutation choosing a risk-reducing strategy was based on the study by Collins et al.[21] with 54% for RRBSO alone, 30% for RRM alone, and 16% for RRM plus RRBSO. Cancer risk reduction rates for the different preventive interventions were obtained from recent meta-analyses.[10,11] RRM will have no effect on reducing ovarian cancer risk but will reduce breast cancer risk by 90%, as reported in the meta-analysis by Li et al.[11] According to the meta-analysis by Ludwig et al.,[10] RRBSO alone reduces breast cancer risk by 50% and ovarian cancer risk by 80%. Based on clinical experts' advice, RRM plus RRBSO was assumed to reduce both breast cancer risk and ovarian cancer risk by 90%.

The utilities for the health states in the model were based on EuroQoL 5D-3L scores. These scores range from zero to one with zero meaning worst state or death and one for best possible health.[30] Utility weights were based on the preferences of the Australian population. We set the background utility value for women without cancer at 0.9, based on a study by Clemens et al.[31] Given that the majority of cases of breast cancer are diagnosed at an early stage, the utility weight for breast cancer was set to 0.79 based on the studies by Manchanda et al.[27] and Peasgood et al.[32] Assuming that 70% of women with ovarian cancer have advanced stage disease at diagnosis, the utility weight for ovarian cancer was set at 0.63 based on Manchanda et al.[27] and Havrilesky et al.[33] We did not assign disutilities to risk-reducing surgery because we considered that any reduction in the health-related quality of life would likely be offset by the assurance attained from the reduction in the risk of developing cancer.

The cost-effectiveness analysis was from the perspective of health-care payers (i.e., the direct costs to the Australian health-care system). Results were presented in 2016 Australian dollars (AU$). Prices for medical and hospital services were obtained from the 2016 Australian Medicare Benefits Schedule fees and the Australian refined diagnosis-related groups data.[34] Based on the best laboratory practice in Australia,[35] we assumed that duplicate and independent blood samples were collected from affected individuals to perform gene sequencing followed by a single-site test (i.e.,

confirmatory testing) in women who tested positive prior to family cascade testing. For the cascade testing, we assumed that the family members of *BRCA*-positive cases had single-site testing. Thus, the cost of *BRCA* testing was AU$1,200 for the initial test (i.e., gene sequencing) and AU$230 for the single-site test. Two sessions of genetic counseling before and after *BRCA* testing were offered at a total cost of AU$264. An annual cost of AU$90 for mammography was applied to cancer surveillance. The cost of surgery was set at AU$8,747 for contralateral mastectomy, AU$15,586 for bilateral mastectomy, and AU$8,621 for RRBSO. We assumed that the cost of cancer management would be the highest in the year in which cancer was diagnosed considering the costs of testing, procedures, and chemotherapy. Accordingly, the first year after diagnosis would cost around AU$25,000 for breast cancer and AU$20,000 for ovarian cancer. Subsequent years (i.e., years 2 to 5) of management would cost around AU$550 per year for breast cancer and approximately AU$5,000 for ovarian cancer.[36]

Analysis

Two scenarios were analyzed: (i) *BRCA* mutation testing of affected women only compared with no testing; and (ii) testing affected women and the cascade testing of the first-and second-degree family members of affected women who test positive compared with no testing.

The model aggregated the probabilities and values assigned to the health states and generated mean expected values for costs and effects. We calculated the incremental cost-effectiveness ratio (ICER), which is the incremental effectiveness (i.e., the difference in effectiveness between the two options of genetic testing or not) divided by the incremental cost. The main effectiveness estimate was the quality-adjusted life-year (QALY) gained, which adjusts the length of survival gained through an intervention by the utility values of the associated health states.[30] For this analysis, we set the willingness-to-pay per incremental QALY gained at AU $50,000. An annual discount rate of 5% was applied to QALYs gained and costs. We also estimated other outcomes including survival, cumulative breast cancer risk, and cumulative ovarian cancer risk, in each cohort. To address the uncertainty in our results, we performed one-way sensitivity analyses in which we varied key parameters through a range of plausible values and observed changes to the base case estimates. In addition, we conducted a probabilistic sensitivity analysis whereby parameter values were randomly sampled using Monte Carlo simulation (10,000 times) from a priori defined probability distributions.[37] In general, we assigned beta distributions to transition probabilities and utilities, gamma distributions to costs and length of hospital stay, and log-normal distributions to relative risk.

RESULTS

Compared with no testing, *BRCA* mutation testing of affected women only (i.e., scenario 1) resulted in an incremental cost of AU$1,880 and 0.10 QALYs gained, with an ICER of $18,900 per QALY. For each affected woman tested, the model predicted 0.09 gain in life-years and reductions of 0.04 and 0.01 breast and ovarian cancer events respectively. Assuming a willingness-to-pay threshold of AU$50,000 per QALY gained, a *BRCA* mutation testing of affected individuals only appears to be cost-effective compared with no testing. Compared with no testing, testing affected women followed by testing family members of mutation-positive affected women (i.e., scenario 2) resulted in a mean incremental cost of AU$2,535 and 0.17 QALYs gained, with an estimated ICER of around AU$14,900 per QALY compared with no testing. For each affected woman tested followed by the cascade testing of family members, there were 0.70 life-years gained and around 0.10 breast cancer events and 0.02 ovarian cancer events avoided. Thus, compared with testing affected women only, testing affected women followed by the cascade testing of family members would incur a mean additional cost of AU$665 for an additional 0.07 QALYs gained (i.e., AU$9,500 per QALY) together with an additional 0.06 breast cancer and 0.01 ovarian cancer events avoided. **Table 2** summarizes the cost-effectiveness analysis results.

The model predicted that cumulative risks by age 70 years for *BRCA* carriers was 53% for breast cancer, 25% for ovarian cancer, and 59% for contralateral breast cancer. With *BRCA* testing, the corresponding risks were 24% for breast cancer, 19% for ovarian cancer, and 28% for contralateral breast cancer. **Figure 2** shows the cumulative risks for breast and

Table 2 Results of cost-effectiveness analysis

	Scenario 1			Scenario 2			Scenario 2 vs. scenario 1
	Testing	No testing	Increment	Testing	No testing	Increment	
Cost (discounted)	AU$5,955	AU$4,076	AU$1,880	AU$8,602	AU$6,067	AU$2,535	AU$665
QALYs (discounted)	15.83	15.73	0.10	22.54	22.37	0.17	0.07
ICER/QALY			AU$18,900			AU$14,900	AU$9,500
Life-years	17.47	17.38	0.09	66.81	66.11	0.70	0.61
Breast cancer events	0.23	0.28	−0.04	0.31	0.41	−0.10	−0.06
Ovarian cancer events	0.04	0.05	−0.01	0.08	0.10	−0.02	−0.01

Scenario 1, testing affected individuals only compared with no testing; scenario 2, testing affected individuals and cascade testing in family members of mutation carriers compared with no testing; scenario 2 vs. scenario 1, testing affected individuals and cascade testing in family members of mutation carriers versus testing affected individuals only. AU$, Australian dollar; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

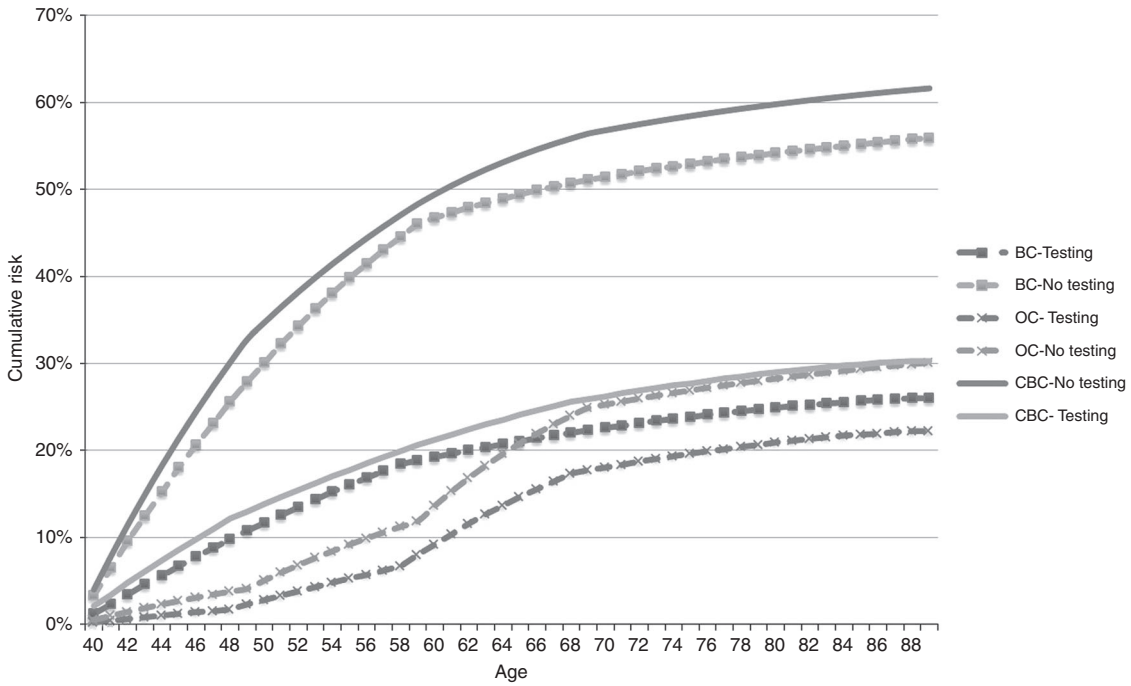

Figure 2 Cumulative risk of breast and ovarian cancer with and without *BRCA* testing. BC, new breast cancer in a family member; CBC, contralateral breast cancer; OC, ovarian cancer.

ovarian cancers for the cohorts included in the model with and without *BRCA* testing.

In the sensitivity analyses summarized in **Table 3**, the results were most sensitive to the discount rate, the probability of *BRCA* mutation positive in the affected individuals, the start age of affected individuals, and the uptake rate of the genetic testing and the preventive surgeries. However, the ICER remained below AU$50,000 per QALY over the range of plausible values and observed changes to the base case estimates. In the probabilistic sensitivity analysis, the probability of *BRCA* testing being cost-effective was 85% for testing affected women only and 90% for testing affected women followed by cascade testing of family members of mutation carriers.

DISCUSSION

Our cost-effectiveness analysis demonstrates that testing of women with breast cancer who have at least 10% risk for *BRCA* mutation is cost-effective compared with no testing. Our results support the recommendations from the international guidelines on *BRCA* testing in women with cancer. The National Institute for Health and Care Excellence in England also recommends that patients with cancer at more than 10% risk of having a *BRCA* mutation should be offered testing.[15] Likewise, the National Comprehensive Cancer Network recommends testing affected individuals with a personal history of breast cancer if they were diagnosed at age 45 or younger, diagnosed with triple-negative breast cancer (i.e., estrogen-, progesterone-, and HER2-negative), have a family history of breast or ovarian cancer, or have Ashkenazi Jewish heritage.[14] Importantly, the integrated model used in our analysis allowed us to estimate the downstream costs and benefits of testing family members who wish to be tested to prevent future cancers. Although testing family members would result in additional costs, the benefits of testing and risk-reducing surgery would offset the additional costs of genetic testing. Compared with testing affected women only, testing affected women and the cascade testing of family members incurred a mean additional cost of AU$665 for 0.07 QALYs gained together with an additional 0.06 breast cancer and 0.01 ovarian cancer events avoided, i.e., AU$9,500 per QALY gained. This suggests that extending testing beyond affected women to cover family members of affected women who test positive for the mutation is better value for money than restricting testing to affected women only.

It is not straightforward to compare our results with other studies because our analysis is the first to assess the cost-effectiveness of testing both affected women and the family members of women who tested positive for the mutation. Nevertheless, our results of testing affected women only are in line with the results of the only published cost-effectiveness analysis of *BRCA* testing of women with breast cancer by Kwon et al.[20] In that study, testing affected women younger than 40 years old resulted in an incremental cost in 2006 prices of 908 United States dollars (US$) and 0.08 QALYs gained with an ICER of approximately US$11,000 per QALY. Furthermore, the predicted cumulative cancer risk in our model for *BRCA* carriers was 53% for breast cancer and 25% for ovarian cancer, which is within the ranges of 50–60% for breast cancer and 20–30% for ovarian cancer risks reported in

Table 3 Results of the one-way sensitivity analyses

Scenario	Incremental cost	Incremental QALYs	ICER/QALY
Scenario 1: Testing affected women only			
Base case	AU$1,880	0.10	AU$18,900
Mean age affected individual 30 years	AU$1,837	0.08	AU$22,209
Mean age affected individual 50 years	AU$1,811	0.14	AU$13,221
Probability of *BRCA* mutation 5%	AU$1,427	0.03	AU$43,039
Probability of *BRCA* mutation 20%	AU$2,106	0.13	AU$15,886
Breast and ovarian cancer risks in women tested negative obtained from BOADICEA model	AU$1,880	0.10	AU$18,900
Uptake rate of *BRCA* testing is 50%	AU$1,450	0.05	AU$29,161
Uptake of RRM alone 24%, RRBSO 43%, RRBSO+RRM 13%, and surveillance 20%	AU$1,770	0.08	AU$21,898
Discount rate 3%	AU$1,755	0.15	AU$11,853
Disutility of mastectomy 0.05	AU$1,880	0.10	AU$19,095
Disutility of oophorectomy 0.05	AU$1,880	0.10	AU$19,703
Surveillance using annual MRI	AU$2,312	0.10	AU$23,257
Scenario 2: Testing affected individuals and cascade testing in family members of mutation carriers			
Base case	AU$2,535	0.17	AU$15,011
Start age affected 30	AU$2,571	0.14	AU$18,225
Start age affected 50	AU$2,430	0.22	AU$11,767
Probability of *BRCA* mutation 5%	AU$1,645	0.06	AU$29,225
Probability of *BRCA* mutation 20%	AU$2,979	0.23	AU$13,233
Breast and ovarian cancer risks in women tested negative obtained from BOADICEA model	AU$2,535	0.17	AU$15,011
Uptake rate of *BRCA* testing is 50%	AU$1,777	0.08	AU$21,052
Uptake of RRM alone 24%, RRBSO 43%, RRBSO+RRM 13%, and surveillance 20%	AU$2,260	0.14	AU$16,394
Discount rate 3%	AU$2,308	0.28	AU$8,363
Disutility of mastectomy 0.05	AU$2,535	0.16	AU$15,300
Disutility of oophorectomy 0.05	AU$2,535	0.16	AU$15,883
Surveillance using annual MRI	AU$3,208	0.17	AU$18,868

AU$, Australian dollar; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year; RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRM, risk-reducing mastectomy.

two large meta-analyses by Antoniou et al.[1] and by Chen and Parmigiani.[2]

The results of our analysis were stable over a range of plausible estimates for the input parameters. In the base case analysis, we set the pretest probability of having a *BRCA* mutation at 15%; however, the ICER remained below the willingness-to-pay threshold of AU$50,000 per QALY when the pretest probability varied from 5 to 20%. The higher the probability that an affected woman carries a *BRCA* mutation, the lower the ICER, indicating better value for money. A pretest probability of having a *BRCA* mutation of greater than 20% is expected in women with breast cancer diagnosed with triple-negative disease or having Ashkenazi Jewish ancestry.[38] Another major driver of costs and benefits was the rate of uptake of cancer prevention strategy. We assumed that the majority of women who tested positive for the *BRCA* mutation would opt for risk-reducing surgery. This was based on the results of the Australian study by Collins et al.,[21] which are corroborated by international studies.[24,39] However, applying uptake rates, based on an expert advice, of 80% surgery and 20% surveillance alone did not significantly alter the ICER. Expectedly, altering the uptake rate of the genetic testing to reflect possible reduced uptake in practice increased the ICER significantly. This emphasized the need to ensure high uptake of the program to maximize expected benefits.

Our analysis was from the perspective of health-care payers in Australia, which means that some of the costs used in the model may not be applicable to other jurisdictions; nevertheless, the results of our study regarding the effectiveness of *BRCA* testing (i.e. life-years gained, cancer events avoided) are generalizable. We used the best available evidence from high-quality international studies and meta-analyses to inform key parameters in the model; nevertheless, a number of assumptions were made based on local evidence and expert advice. These include the age of affected women as well as the age and number of family members of women who tested positive. We also adopted realistic estimates of the timing of testing and the uptake of surgical interventions. For instance, we assumed that affected women who test positive and their siblings will act within 1 year of knowing the results, whereas their children will (i) wait until they are of an age where they become eligible for testing, and (ii) complete their families before they undertake risk-reducing surgical procedures. We assumed that women with a *BRCA* mutation who chose not to receive risk-reducing surgery would still be eligible for increased surveillance. Furthermore, we assumed that male first-degree relatives were tested for the

BRCA mutation to identify any second-degree female relatives for testing but with no direct benefit to the tested males.

We assumed that women with breast cancer who have at least a 10% pretest *BRCA* mutation probability will be identified based on family history and clinical features, and referred to testing by their treating specialist. This approach is more focused compared with a broader approach whereby the population is screened to identify women at high risk for hereditary breast and ovarian cancer syndrome. The screening approach would require special programs at potentially high costs to detect and screen women in the general population. Another aspect that was not considered in our analysis was the value of identifying a *BRCA* mutation in guiding treatment with targeted agents (e.g., polyadenosine diphosphate ribose polymerase inhibitors).[40] However, the analysis was conservative because including this consideration in the model would increase the expected benefits of *BRCA* testing and lower the estimated ICER.

Implementing a *BRCA* testing program in women with breast cancer who have at least a 10% pretest probability of having a *BRCA* mutation is likely to be cost-effective compared with no testing. However, expanding the program to test affected women followed by cascade testing of family members of affected women who test positive for the mutation maximizes clinical benefits and improves value for money beyond testing affected women only.

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DISCLOSURE

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