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A Multigene Test Could Cost-Effectively Help Extend Life Expectancy for Women at Risk of Hereditary Breast Cancer

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ABSTRACT

Background: The National Comprehensive Cancer Network recommends that women who carry gene variants that confer substantial risk for breast cancer consider risk-reduction strategies, that is, enhanced surveillance (breast magnetic resonance imaging and mammography) or prophylactic surgery. Pathogenic variants can be detected in women with a family history of breast or ovarian cancer syndromes by multigene panel testing. **Objectives:** To investigate whether using a seven-gene test to identify women who should consider risk-reduction strategies could cost-effectively increase life expectancy. **Methods:** We estimated effectiveness and lifetime costs from a payer perspective for two strategies in two hypothetical cohorts of women (40-year-old and 50-year-old cohorts) who meet the National Comprehensive Cancer Network–defined family history criteria for multigene testing. The two strategies were the usual test strategy for variants in *BRCA1* and *BRCA2* and the seven-gene test strategy for variants in *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *STK11*, and *PALB2*. Women found to have a pathogenic variant were assumed to undergo either prophylactic surgery or enhanced surveillance. **Results:** The incremental cost-effectiveness ratio for the seven-gene test strategy compared with the *BRCA1/2* test strategy was $42,067 per life-year gained or $69,920 per quality-adjusted life-year gained for the 50-year-old cohort and $23,734 per life-year gained or $48,328 per quality-adjusted life-year gained for the 40-year-old cohort. In probabilistic sensitivity analysis, the seven-gene test strategy cost less than $100,000 per life-year gained in 95.7% of the trials for the 50-year-old cohort. **Conclusions:** Testing seven breast cancer–associated genes, followed by risk-reduction management, could cost-effectively improve life expectancy for women at risk of hereditary breast cancer.

Keywords: *BRCA*, breast cancer, cost-effectiveness, multigene panel testing.

Introduction

Breast cancer is the most commonly diagnosed noncutaneous cancer and the second leading cause of cancer death among women in the United States. An estimate for 2015 predicted 231,840 new cases of breast cancer and 40,290 breast cancer deaths [1]. Women with a family history of breast cancer are at increased risk, with about 13% of women with breast cancer having one or more first-degree relatives with the disease [2]. Pathogenic variants in the *BRCA1* and *BRCA2* genes explain approximately 15% of the breast cancer familial relative risk (i.e., the ratio of the risk of an individual with an affected relative to the risk of individuals in the general population), whereas pathogenic variants in other genes, including *TP53*, *PTEN*, *CDH1*, and *PALB2*, contribute further to the familial relative risk for breast cancer [3].

Women with a pathogenic variant in *BRCA1* have a 65% chance of developing breast cancer by age 70 years, whereas those with a *BRCA2* pathogenic variant have a 45% chance [4]. In contrast, women in the general population have a 7% chance of developing breast cancer [1]. Pathogenic variants in other breast cancer–associated genes can also confer substantial risk. For example, a recent study reported that women with a pathogenic variant in *PALB2* have a 33% to 58% chance of developing breast cancer by age 70 years, a risk similar to that of women with a pathogenic variant in *BRCA2* [5]. Pathogenic variants in breast cancer–associated genes also increase the risk of developing ovarian and other cancers [3].

For women whose lifetime risk of breast cancer is greater than 20%, the National Comprehensive Cancer Network (NCCN) guidelines recommend enhanced breast cancer surveillance by magnetic resonance imaging (MRI). The NCCN guidelines also recommend risk-reducing oophorectomy for *BRCA1/2* carriers, and the NCCN Breast Cancer Risk Reduction Panel supports "the use of RRM [risk-reducing mastectomy] in carefully selected women at high risk for breast cancer who desire this intervention (*e.g.* women with a *BRCA1/2*, *TP53*, *PTEN*, *CDH1* or *STK11* mutation …)" [6]. These recommended procedures have been shown to confer substantial survival benefits on at-risk individuals [7–10]. For example, clinical studies have found that risk-reducing mastectomy can decrease the risk of developing breast cancer by more than 90% for women with a family history of breast

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cancer or with a pathogenic variant in *BRCA1* or *BRCA2* [7–9]. And decision-analytic modeling has predicted that enhanced surveillance could increase life expectancy by 1.4 years for 50-year-old women who carry a pathogenic variant in *BRCA1* and by 1.0 year if they carry a pathogenic variant in *BRCA2* [10]. Similarly, risk-reducing mastectomy could increase life expectancy by 2.8 years for *BRCA1* carriers and by 2.0 years for *BRCA2* carriers; younger women would receive greater survival benefits [10].

Genetic analysis is recommended for individuals at risk of hereditary breast cancer [11,12]. Basic genetic testing for breast cancer detects pathogenic germline variants in the *BRCA1* and *BRCA2* genes, and the test results are used to guide the assessment and management of breast cancer risk. Newer testing options allow for the simultaneous analysis of expanded panels of genes, which include *BRCA1/2* as well as other genes whose pathogenic variants confer moderate to high risk for breast cancer [13,14]. Recent clinical studies have found that testing with expanded gene panels identifies substantially more individuals with pathogenic variants in breast cancer–associated genes than does *BRCA1/2* testing alone, and that the detection of these pathogenic variants in these genes can lead to clinical action [15,16].

For women at high risk of breast or ovarian cancer, *BRCA1/2* testing followed by prophylactic surgery when test-positive has been found to be cost-effective compared with no *BRCA1/2* testing [17–19]. This raises the question of whether testing with an expanded panel of breast cancer–associated genes is cost-effective compared with *BRCA1/2* testing alone. In this study, we used a decision-analytic model to compare the relative cost and effectiveness of a seven-gene panel test strategy with a *BRCA1/2* test strategy for women at risk of hereditary breast cancer.

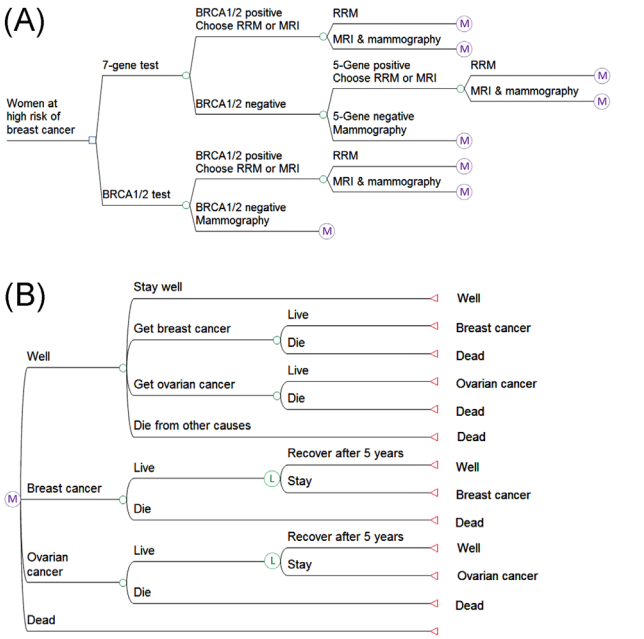

Fig. 1 – Decision-analytic model with Markov nodes. (A) Women at increased risk of breast cancer enter one of two test strategies and receive clinical recommendations on the basis of the test results. (B) The Markov model shows the four health states: well (no breast or ovarian cancer), breast cancer, ovarian cancer, and death. The logic nodes indicate that if patients survive in the breast cancer or ovarian cancer state for 5 years, they will return to the well state. The circle with an M indicates the Markov node, and the circle with an L indicates the logic node. MRI, magnetic resonance imaging; RRM, risk-reducing mastectomy.

Methods

Model

The objective of this study was to inform the risk-reduction decisions of women at risk of hereditary breast cancer by comparing the effectiveness and lifetime costs of the use of either *BRCA1/2* testing or seven-gene testing from a payer perspective. To this end, a decision-analytic model with Markov nodes was developed for hypothetical cohorts of 50-year-old and 40-year-old asymptomatic women with a family history of breast or ovarian cancer or other hereditary syndromes such as Li-Fraumeni syndrome and Cowden syndrome that predispose to breast cancer (Fig. 1). The model compares two strategies for detecting pathogenic genetic variants and using the test results to select appropriate breast cancer risk reduction: the usual care strategy tests for variants in the *BRCA1* and *BRCA2* genes (*BRCA1/2* testing) and the other strategy tests for variants in the *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *STK11*, and *PALB2* genes (seven-gene testing). Individuals who carry a pathogenic variant in any one of these genes are considered test-positive; otherwise, they are considered test-negative. Women who test positive were assumed to receive genetic counseling and recommendations to follow the NCCN breast cancer risk-reduction guidelines [11]. Specifically, women who test positive were assumed to either undergo annual surveillance by mammography and MRI till age 75 years or immediately undergo prophylactic risk-reducing mastectomy. Individuals who test negative were assumed to undergo annual surveillance by mammography till age 75 years.

Patient outcomes were evaluated using a Markov model with a lifetime time horizon (lifetime limited to age 100 years) with a cycle length of 1 year (Fig. 1). The patients enter the model in the well state (i.e., no breast or ovarian cancer) and can remain in the well state, progress to breast or ovarian cancer, or die. Patients who survive breast or ovarian cancer for 5 years return to the well state and were assumed to have the same probability of developing breast or ovarian cancer (recurrent cancer rate) as did those in the well state who never had cancer. This recurrent cancer rate affects the model outcome only for the five-gene test-positive subgroup (groups that are *BRCA1/2* test-positive or test-negative for all seven genes cancel out between the two strategies; see Fig. 1). This recurrent cancer rate is consistent with the rate (5%) reported by Bosco et al. [20] for the period between 5 and 10 years after breast cancer diagnosis, a rate that is on an annual basis similar to the base-case assumption (0.01196) for the five-gene test-positive group. The model does not allow patients to develop both breast and ovarian cancer because we assumed that this is a rare event. In health economics literature for breast cancer (e.g., [21]), co-occurrence of breast and ovarian cancer is often not included in the modeling. Other studies (e.g., [22]) considered that the risk of developing the two types of cancer is independent and consequently co-occurrence of breast and ovarian cancer is rare.

Model Parameters

Model parameters were based on peer-reviewed literature, Medicare fee schedules, and government agency program databases, as presented in Table 1 for the cohort of 50-year-old women. The frequencies of *BRCA1* and *BRCA2* carriers among the high-risk women were taken from a cross-sectional study of 46,276 women in the United States [23]; the seven-gene panel test (BRCAvantage Plus, Quest Diagnostics) and the *BRCA1/2* test were assumed to have equal sensitivity and specificity for the detection of