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. Pathogenic variants in breast cancer genes explain approximately 15% of 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.

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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
cancer or with a pathogenic variant in BRCA1 or BRCA2 [7–9]. And
decision-analytic modeling has predicted that enhanced surveil-
ance 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 assess-
ment 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 individu-
als 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 test-
ing [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.

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
Specifically, women who test positive were assumed to undergo
annual surveillance by mammography and MRI till age 75 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 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 devel-
oping 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, Medi-
care 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

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.
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