VIEWPOINT

Cost-effectiveness of Universal *BRCA1/2* Screening Evidence-Based Decision Making

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Of the 233 000 breast cancers diagnosed annually in the United States, 5% to 10% are attributable to mutations in the *BRCA1* or *BRCA2* genes.[1] Breast cancers in *BRCA* mutation carriers are characterized by younger age at onset, bilateral occurrence, and more aggressive subtypes, such as "triple-negative."[1] Female mutation carriers face a 45% to 65% breast cancer risk by age 70 years, and an ovarian cancer risk ranging from 10% to 17% (*BRCA2*) to 39% (*BRCA1*). Women found to be *BRCA* mutation carriers—either through genetic screening or following a cancer diagnosis—may choose to undergo bilateral risk-reducing mastectomy (RRM) and/or salpingo-oophorectomy (RRSO) as an alternative to increased surveillance or chemoprevention. Knowledge of a genetic mutation may have a further impact on fertility decisions, including oocyte retrieval and genetic testing prior to cryopreservation or embryo implantation.

Although the US Preventive Services Task Force advises *BRCA* genetic testing only for women with a known familial history of breast, ovarian, tubal, or peritoneal cancer, a recent Viewpoint in *JAMA*[2] called for universal *BRCA* testing of all women older than 30 years in the United States. One factor influencing this recommendation is that more than half of all women with *BRCA* mutations have no family history of breast cancer.[2,3] Although the announcement of a $249 genetic test offered by Color Genomics may induce more price competition, given the extraordinarily low prevalence of *BRCA* mutations, the potential value of population-based genetic testing is questionable.

Decision-analytic modeling is an established technique for estimating the potential costs and health benefits of population-based screening strategies. These models are especially useful for capturing a sequence of probabilities: proportion of women with a *BRCA* mutation, fraction of mutation carriers who elect RRM and/or RRSO, and conditional likelihood of breast or ovarian cancer with and without RRM or RRSO. Using a prior model (eFigure in the Supplement)[3] updated with current treatment costs for the United States (eTable 1 in the Supplement),[4] we estimated the cost-effectiveness of universal *BRCA* testing of all US women older than 30 years, and the potential number of cancers prevented and life-years saved (eTable 2 in the Supplement).

Assuming that 1 in 400 women carry a *BRCA* mutation, the cost-effectiveness of universal screening with Myriad's test exceeds $1.7 million per quality-adjusted life year (QALY) gained, compared with testing only women with a familial history of breast cancer. Ambry Genetics' slightly cheaper test still generates a cost-effectiveness ratio of more than $900 000 per QALY gained. In contrast, screening women of Ashkenazi Jewish descent—among whom 1 out of every 50 women carries a mutation—generates cost savings with Myriad's less expensive test for 3 founder mutations. Another study[3] has shown similarly favorable cost-effectiveness estimates for this population in the United Kingdom.

Universal *BRCA* screening could avert an additional 4 breast cancers and 2 ovarian cancers per 10 000 women screened compared with family history–based screening. This generates an additional 0.006 years of life expectancy, or 2.1 additional days, on average. For 99.75% of women screened, a negative genetic test result offers no gain in life expectancy, does not eliminate the need for regular mammograms, and may provide false reassurance. For the 0.25% with a *BRCA* mutation, universal screening extends life expectancy by 3.5 years vs family history-based screening, a relatively modest gain, because many women found to have a deleterious mutation opt for risk-reducing surgery, increased surveillance, or both. With population-level screening of only Jewish women, 62 breast and 34 ovarian cancers per 10 000 women are averted, and average gains in life expectancy are 16-fold higher than with universal screening because a larger fraction of women are identified as *BRCA* mutation carriers.

Other diagnostic techniques for breast cancer generate significantly more value for their cost (**Table**). Annual mammography for *BRCA* carriers costs less than $30 000 per QALY gained.[5] Augmenting mammography with magnetic resonance imaging costs less than $180 000 per QALY gained,[5,7] with superior cost-effectiveness in *BRCA1* carriers vs *BRCA2*.[5] Biennial mammograms for 40- to 49-year-old women with high breast density (Breast Imaging–Reporting and Data System [BI-RADS] categories 3-4), and therefore higher 10-year incidence of breast cancer, generate cost-effectiveness values of $75 000 to $89 000 per QALY gained.[6] Among women with less dense breasts, biennial mammograms cost $140 000 (BI-RADS category 2) to $363 000 (BI-RADS category 1) per QALY gained,[6] far less than universal *BRCA* genetic testing with Myriad or Ambry.

Is it possible for population-level *BRCA* screening to be cost-effective? Even if every woman with a detected mutation elects to have RRM and RRSO, universal screening still exceeds $1 million per QALY gained. We initially assumed that RRSO reduces ovarian cancer risk by 96%; RRSO alone halves breast cancer risk; RRM alone reduces breast cancer risk by 91%; and both procedures reduce breast cancer risk by 95%.[3] Under the optimistic assumption that risk-reducing surgery completely eliminates cancer risk,

Table. Cost-effectiveness[a] of Breast Cancer Testing Strategies in the United States

Source	Testing Strategy	Age Range of Female Population, y, and Risk Factor	Cost-effectiveness Ratio ($/QALY), $
Plevritis et al,[5] 2006	Annual mammography	25-69,*BRCA1* 25-69,*BRCA2*	19 000 28 400
	Annual mammography + MRI	35-54,*BRCA1* 35-54,*BRCA2*	55 400 130 700
	Semiannual mammography + MRI	35-54,*BRCA1* 35-54,*BRCA2*	176 400 481 800
Grann et al,[4] 2011	Annual mammography	30-65,*BRCA2*	88 100
	Annual mammography + MRI	30-65,*BRCA2*	247 600
Schousboe et al,[6] 2011	Biennial mammography	40-49, BI-RADS 1-2 40-49, BI-RADS 3-4 50-79, BI-RADS 1-2 50-79, BI-RADS 3-4	140 000-362 700 74 500-87 800 63 700-208 700 21 400-51 000
	Annual mammography	All ages	>340 000
Moore et al,[7] 2009	Annual MRI	High-risk women	179 600
Current study	*BRCA* mutation screening	>30, Universal >30, Universal >30, Universal >30, Ashkenazi Jewish	1.7 million (Myriad) 920 000 (Ambry Genetics) 53 000 (Color Genomics) Cost-saving

Abbreviations: BI-RADS, Breast Imaging–Reporting and Data System category; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

[a] Incremental cost-effectiveness ratios are relative to the comparator strategy; cost-saving implies that the strategy increases QALYs while saving money.

universal *BRCA* screening still exceeds $970 000 per QALY gained compared with screening based on family history.

If the price of *BRCA* genetic testing falls below $250 as indicated by Color Genomics, cost-effectiveness dramatically improves to $53 000 per QALY gained, far below the oft-cited $100 000 acceptable cost-effectiveness threshold based on hemodialysis treatment for end-stage renal disease. Given the potential market size of women interested in testing for *BRCA* and other genes, a drastically lower test price could simultaneously increase test utilization and profitability. Bundling *BRCA* testing with other cancer-associated genes, such as *p53* or *PALB2*, could further improve cost-effectiveness estimates, although more information is needed about the long-term risks of cancer associated with such rare mutations.

The logistics of genetically testing more than 100 million women pose additional challenges and would likely overwhelm the capacity of existing genetic counselors. Asking primary care physicians to counsel and test patients would further tax overburdened clinicians, so other avenues, such as mail-order testing and online counseling, would need to be explored.

Before a broad genetic testing program in the United States is realistically considered, understanding the relative value of such a program is important, especially because these resources may offer more health benefits if spent on earlier or more frequent breast imaging. Even though a very small percentage of women would benefit from universal *BRCA* testing, at $2000 to $4000 per test, such a strategy is an inefficient use of health care resources.

ARTICLE INFORMATION

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