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The Role of Testing for *BRCA1* and *BRCA2* Mutations in Cancer Prevention

Anne Marie McCarthy, ScM, PhD and

Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

Katrina Armstrong, MD, MSCE

Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

In May 2013, Angelina Jolie,¹ the actress and director, announced in an op-ed in the *New York Times* that she carried a *BRCA1* mutation and had had a preventive double mastectomy. Jolie's message was striking—by identifying a mutation in a cancer susceptibility gene, one of the most famous actresses of our generation dramatically reduced her risk of dying from cancer.

Widely available for more than a decade, clinical testing for mutations in the breast and ovarian cancer genes, *BRCA1* and *BRCA2*, remains the most prominent example of the use of human genetic variation to reduce disease risk. *BRCA1* and *BRCA2* are tumor suppressor genes involved in DNA repair, and therefore a defective copy of either gene sensitizes cells to mutations and cancer development. *BRCA1/2* mutations substantially increase the risks of breast and ovarian cancer. The average US woman has a 12% lifetime risk of breast cancer, whereas *BRCA1/2* mutation carriers have a 50% to 60% lifetime risk. The increase in ovarian cancer risk is even greater—from a 1.4% lifetime risk without the mutations to over 40% among *BRCA1* carriers and nearly 20% among *BRCA2* carriers.²

The benefit of *BRCA1/2* testing comes from linking test results to interventions to reduce cancer risk. For women who are found to carry a mutation, the most dramatic—and also most effective—risk reduction intervention is prophylactic surgery, which Jolie chose. Prophylactic mastectomy reduces the risk of breast cancer by over 90%. Prophylactic oophorectomy has a similar effect on the risk of ovarian cancer and also reduces the risk of breast cancer. For women who do not undergo prophylactic surgery, yearly screening with mammography and breast magnetic resonance imaging and biannual pelvic ultrasonography with cancer antigen 125 (CA-125) testing is often used,³ although definitive evidence of a mortality benefit is lacking. The oral medications tamoxifen and raloxifene reduce the risk of developing breast cancer and are included in current recommendations for risk management among women who carry mutations.³

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Corresponding Author: Katrina Armstrong, MD, MSCE, Department of Medicine, Massachusetts General Hospital, 55 Fruit St, GRB 740, Boston, MA 02114 (karmstrong6@partners.org).

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BRCA1/2 test results also have implications in other settings. In families with hereditary breast and/or ovarian cancer where a mutation is found, individuals who test negative for the mutation may be spared increased surveillance and anxiety. In women with newly diagnosed breast cancer, the identification of a *BRCA1/2* mutation can influence the extent of surgery, such as the choice of contralateral mastectomy or breast-conserving surgery. Poly ADP-ribose polymerase (PARP) inhibitors are a new class of cancer drugs that target a DNA repair pathway different from the pathway targeted by *BRCA1/2*. PARP inhibitors may be particularly effective in women whose tumor cells already lack one DNA repair mechanism. PARP inhibitors are being studied in clinical trials involving patients with breast and ovarian cancer with *BRCA1/2* mutations.

It is not surprising that Jolie's decision has raised interest in *BRCA* testing, including the potential role of population-based *BRCA1/2* screening programs. Public response to her story was overwhelmingly positive. Genetic testing centers reported an influx of interested patients—a phenomenon that could be termed the *Angelina Jolie effect*. The reality, however, is that testing for *BRCA1/2* mutations is far more complicated than screening for elevated serum cholesterol levels or high blood pressure, or screening for breast cancer with mammography. *BRCA* mutations are very rare in the general population, with a prevalence of 2 to 3 per 1000 individuals.⁴ Even if a mutation is found, finding a variant of unknown significance (where there are not enough data to determine whether the genetic sequence change is associated with cancer risk) is common. Variants of unknown significance are found in about 10% to 15% of *BRCA1/2* tests.

None of the available risk reduction strategies fully eliminate the risk of developing cancer and all have potential complications. Removing the breasts and/or ovaries of a healthy woman has implications for fertility and body image. When performed in young women, oophorectomy causes immediate menopause, which can lead to weight gain, an increased risk of cardiovascular diseases, bone loss, and sexual problems. Tamoxifen and raloxifene have rare but serious adverse effects, such as uterine cancer, blood clots, and stroke. In addition, genetic testing has implications for an individual's family members; women found to carry a *BRCA* mutation may require additional counseling to facilitate communication within a family about these implications.

BRCA1/2 testing is also expensive. The current charge for full gene sequencing is over \$3000. That charge is likely to decrease now that the US Supreme Court has invalidated Myriad Genetics' patents on the *BRCA1/2* genes and opened the testing market to other companies.⁵ Nonetheless, testing for *BRCA* mutations in low-risk individuals may substantially increase health care utilization and costs, including physician visits, imaging studies, and additional testing when gene variants of unknown significance are found.

Given these considerations, how should *BRCA1/2* testing be used? It is clear that *BRCA1/2* testing has the greatest value among populations of women at increased risk of carrying a mutation. Current guidelines recommend that testing be considered among women with a high probability of breast and ovarian cancer, as defined by a personal or family history, and women with Ashkenazi Jewish ancestry, of whom 1 in 40 carry a mutation.³ When possible, the greatest information is obtained by first testing a family member who has been

diagnosed as having breast or ovarian cancer; if that family member does not have a *BRCA* mutation, further *BRCA1/2* testing in the family is unlikely to be useful. If a mutation is found in the family member with cancer, relatives can be tested for the specific familial mutation. This approach is less expensive than sequencing whole genes.

The higher prevalence of mutations in Ashkenazi women has recently led to debates in Israel about whether to institute a population-based screening program.⁶ Three “founder mutations” in *BRCA1* and *BRCA2* comprise 80% to 95% of mutations, respectively, in Ashkenazi populations,^{7,8} and therefore Ashkenazi Jews can be tested with a 3-variant test that is less expensive than full gene sequencing. However, even in Israel, population-based *BRCA1/2* screening is complicated because a woman’s decision about whether and when to be tested and how to respond to a positive test result remains difficult.⁶ Some women may feel empowered by knowing whether they have a *BRCA1/2* mutation; others, however, may find this knowledge a great burden and prefer not to know. *BRCA* testing has the most benefit when test results can be used to reduce a woman’s risk of developing cancer. If a woman is uncomfortable with the available options for reducing cancer risk, such as preventive surgery, testing makes less sense.

Underuse of *BRCA1/2* testing is a substantial concern. Limited uptake in high-risk women, such as young women with breast cancer,⁹ makes it more difficult to prevent cancer in family members. Relevant family history information should be collected in primary care practices, and patients with a strong family history of breast or ovarian cancer should be advised by genetic counselors with expertise and experience. Genetic risk assessment should also be a routine component of the management of patients with newly diagnosed breast or ovarian cancer. Access to genetic counseling services is vital, requiring investment in training genetic counselors, the continued development of long distance, telehealth approaches, and the expansion of insurance coverage.

By raising public awareness of the role of testing for *BRCA1/2* mutations in preventing cancer, Angelina Jolie has performed a great public service. The challenges of *BRCA1/2* testing should not impede the appropriate use of this genomic test to prevent breast and ovarian cancer.

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