# Breast cancer susceptibility tests still valid, companies argue

Companies offering commercial screening for mutations in breast cancer susceptibility genes remain insistent that their tests are helpful to women, despite new research suggesting that these mutations may not carry as high a risk of disease as previously thought. Jeffrey Struewing and his colleagues at the National Cancer Institute recently published a study suggesting that previous research may have overestimated the risk of breast and ovarian cancer in women who carry mutations in the *BRCA1* and *BRCA2* cancer susceptibility genes. Their results show that the probability of developing breast cancer for women who carry one of the three most common mutations may be as low as 56 percent at age 70 — much lower than the 85-per-cent risk reported in earlier studies (*New Eng. J. Med.*, **336**; 1401, 1997). These findings once again raise the question of whether commercial companies are acting prematurely in offering the tests to women who have no strong family history of breast or ovarian cancer.

Three companies that offer screening — Myriad Genetics in Salt Lake City, Utah, OncorMed in Gaithersburg, Maryland and the Genetics & IVF Institute in Fairfax, Virginia — remain defiant in the face of the new data. "A 56 percent risk of breast cancer is four times higher than the national average and is still a significant risk," says Harvey Stern of the Genetics & IVF Institute. Leslie Alexandre, vice-president of OncorMed, points out that the NCI study differed from previous studies in that it sampled individuals in the general population, rather than those from families with a strong history of disease. "Our testing is restricted to women with a strong family history who are believed to have up to an 85 percent risk of developing breast cancer if they test positive for a *BRCA1* or *BRCA2* mutation," says Alexandre.

These companies have a slightly different policy on who they test: the Genetics & IVF Institute only tests Ashkenazi Jewish women with a strong family history of breast or ovarian cancer, whereas Myriad Genetics, although recommending testing for women at high risk, does not exclude those without a family history of disease. Alexandre is concerned that some women with a high risk of breast or ovarian cancer may no longer wish to be tested in light of the lowered estimate. But Stern is doubtful that the new data will cause a sharp decline in demand.

Some scientists feel that the NCI study is flawed. "It is difficult to make accurate estimates of breast cancer risk in the absence of any genetic analysis of family members of those testing positive," says Mary-Claire King, a medical geneticist at the University of Washington in Seattle. Preliminary results from a study of nine cancer centers in New York City — coordinated by King and others — will be available at the end of this year. In this study, all family members of those testing positive for *BRCA1* and *BRCA2* mutations are to be genotyped, and the possible role of environmental factors investigated. King hopes the study will help to clarify the true strength of the link between the *BRCA1* and *BRCA2* mutations and disease.

The companies are quick to point out what they see as further flaws. Peter Meldrum, president of Myriad Genetics, says the researchers asked the study's participants to fill in self-administered questionnaires on their family history of breast and ovarian cancer. He believes that the information from these questionnaires should have been confirmed by a follow-up interview and analysis of medical records.

Struewing defends his team's report. Indeed, he says, it may still overestimate the impact of *BRCA1* and *BRCA2* mutations on a woman's risk of disease. "The true risk estimate may be lower than 56 percent because families reported more breast cancer than expected." Meanwhile, he has agreed to make the data available for others to examine. Francis Collins of the National Human Genome Research Institute hopes that companies offering testing will "interpret the new results responsibly". The companies, not surprisingly, are keen to show that they will. Despite the apparent dissent, all agree that the decision on whether or not to be tested should only be taken by the well-informed and counselled woman.

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## Myriad's rationale for wider testing

In the midst of the debate over testing for breast cancer susceptibility, Myriad Genetics has done its own analysis to assess exactly which women stand to gain from being screened for mutations in the *BRCA1* gene. The results, announced at a recent meeting of the American Society of Clinical Oncology in Denver, seem set to increase the number of women who might be encouraged to take the test.

Last year, the Society issued guidelines that advocated testing individuals for a mutation linked with susceptibility to cancer if the probability of detecting it is 10 percent or more. Myriad has now calculated that this threshold is reached for *BRCA1* for women whose families have had two cases of breast cancer before the age of 50. This assessment includes older women than the company's previous estimates, so it lowers the threshold for those who could be considered appropriate for testing. The company also reported that the chance of detecting the mutation rises to 30 percent in women who have one relative with ovarian cancer and one with breast cancer under age 50.

At the same meeting, researchers from the Columbia-Presbyterian Medical Center reported estimates of how much longer a woman could expect to live if she took the difficult decision to have her breasts and ovaries surgically removed on learning that she was positive on the test. Based on a computer model constructed from 1.6 million cases of cancer survival, a 30-year-old woman from a family with a high risk of the disease and a positive result could expect an increase in lifespan of about 8.5 years following such radical surgery.

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