# New Tests Urged for Breast Cancer Gene Mutations

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Patients at high risk for breast cancer are not getting the full story from the genetic tests now being carried out in the United States, according to a study by Tom Walsh, Ph.D, and his associates.

Genetic testing is recommended for women with family histories of breast and ovarian cancer that suggest they may have inherited *BRCA1* or *BRCA2* gene mutations. To determine the frequency and type of cancer-predisposing gene mutations that are undetected by the most commonly used genetic tests, Dr. Walsh and his associates enrolled 300 representatives of cancer-afflicted families, or "probands" (JAMA 2006;295:1379-88).

"The clinical dilemma is what to offer to women with a high probability of carrying a mutation in *BRCA1* and *BRCA2* but with negative commercial test results," the researchers wrote. The U.S. probands comprised 291 women with invasive breast cancer, three males with invasive breast cancer, and six women with ovarian cancer; 95% were of European ancestry. All participants had family histories of four or more cases of breast and ovarian cancer, and all had negative (wild-type) genetic test results for *BRCA1* and *BRCA2*.

Participants were tested for complete "inherited rearrangements" of *BRCA1* and *BRCA2*—and for other major breast cancer susceptibility genes, including *CHEK2* (a cell cycle regulator), *PTEN,* and *TP53*—using multiplex ligation-dependent probe amplification (MLPA), a testing method available in Europe through a commercial firm in Amsterdam. The test is not available in the United States, and the researchers disclosed no financial interest in any company involved in this study.

"We believe that for families testing negative (wild type) for *BRCA1* and *BRCA2* by conventional sequencing, MLPA … is the current best choice," Dr. Walsh and associates wrote.

Of the 300 probands with negative (wild-type) *BRCA1* and *BRCA2* commercial test results, 12% carried "cancer-predisposing genomic deletions or duplications in one of these genes," the investigators reported. Additionally, 4% had inherited *CHEK2* mutations, and 1% carried *TP53* mutations. Of these probands, 52 (17%) carried inherited mutations in *BRCA1, BRCA2, CHEK2,* and *TP53*. This included 31 probands with rearrangements of *BRCA1*, four with rearrangements of *BRCA2*, 14 with *CHEK2* mutations, and three with *TP53* mutations. No *PTEN* inherited rearrangements were found.

The inherited *BRCA1* rearrangements were more frequently found in probands younger than 40 years of age (16%). Additionally, inherited rearrangements of *BRCA1* and *BRCA2* were found in larger proportions in families with ovarian cancer, male breast cancer, or both (16%), compared with families with only female breast cancer (4.2%). According to the researchers, "the 52 mutation-positive families harbored 28 different mutations," which are extremely rare, and included 14 previously unreported rearrangements.

Currently, conventional genetic testing for *BRCA1* and *BRCA2* mutations are done almost exclusively in the United States by one commercial laboratory in Utah. According to the researchers, this lab uses short-range polymerase chain reaction (PCR) followed by genomic sequencing to test for five specific larger mutations in *BRCA1*. However, recent evidence has shown that many mutations go undetected by PCR, and as a result many high-risk patients are given a negative (wild-type) genetic test result, noted Dr. Walsh of the departments of medicine and genome sciences at the University of Washington, Seattle, and colleagues.

The lifetime risk of breast cancer may be as high as 80% among U.S. women with *BRCA1* and *BRCA2* mutations; the lifetime risk of ovarian cancer is greater than 40% for women with *BRCA1* mutations, and greater than 20% for those with *BRCA2* mutations. Mutations of *CHEK2* may double the risk of breast cancer, and—although extremely rare—inherited mutations of *TP53* in families with Li-Fraumeni syndrome, and *PTEN* in families with Cowden syndrome are tied to high risk of early-onset breast cancer.

"As more breast cancer susceptibility genes of different penetrances are identified, clinicians will be increasingly challenged to offer the most appropriate genetic tests, to assist patients in interpreting the results, and to optimize risk reduction strategies," the researchers concluded. ■