

## Spectrum of Mutations in *BRCA1* and *BRCA2* in Families with Severe Family History for Breast/Ovarian Cancer

### Testing for Hereditary Breast and Ovarian Cancer is Highly Accurate

Mutations in *BRCA1* and *BRCA2* account for the majority of hereditary breast and ovarian cancer. Clinical testing is currently available and extremely accurate. The clinical test consists of comprehensive sequencing plus large rearrangement analysis that detects deleterious mutations in the DNA sequence, small insertions and deletions and approximately 1/2 of large rearrangements. In the entire population of patients currently tested at Myriad, it is estimated<sup>1,2,3</sup> that fewer than 1% have large rearrangements (either detected or undetected).

Walsh T et al. Spectrum of Mutations in *BRCA1*, *BRCA2*, *CHEK2* and *TP53* Families at High Risk of Breast Cancer. *JAMA* 2006;295(12):1379-1388.

**Purpose:** To determine the frequency and types of undetected mutations in *BRCA1*, *BRCA2*, *CHEK2* and *TP53* among high-risk patients with negative *BRCA1/2* sequencing results.

**Design and Methods:** All patients had a "severe family history" of breast or ovarian cancer. The study group was 300 women affected with breast cancer who had three or more relatives with either breast or ovarian cancer. All women were *BRCA1* and *BRCA2* sequence negative and some subjects were negative for the most common large rearrangements. These individuals were screened for large rearrangements in *BRCA1* and *BRCA2* as well as all classes of mutations in *CHEK2*, *TP53* and *PTEN* using various DNA and RNA-based methods.

**Results:** Within this severe risk group who had negative sequencing results, large rearrangements in *BRCA1* and *BRCA2* were detected in 12% of patients. (Note: A portion of the reported rearrangements include mutations detected by Myriad's large rearrangement panel - the publication does not allow further subdivision of this 12% number.)

**Conclusion:** "The US Preventive Services Task Force recently recommended that genetic testing be offered to women whose family history suggests inherited *BRCA1* or *BRCA2* mutations." "The mutational spectra of *BRCA1* and *BRCA2* include many high-penetrance, individually rare genomic rearrangements."

**Bottom Line:** This paper confirms that some large rearrangements can be found in patients with severe family history. In the entire population of patients currently tested at Myriad Genetic Laboratories Inc. for *BRCA1* and *BRCA2* mutations, all large rearrangements account for less than 1% of patients. Myriad's test currently detects about one-half of the patients with large rearrangements. Myriad is actively developing a test to detect all such large rearrangements and anticipates that the test will be available for patients with severe family history before the end of the year.

<sup>1</sup> Hartman C et al. *Human Mutation Research* 2004;24(6):534.

<sup>2</sup> Hendrickson BC et al. *Am Society Hum Gen* 2004, poster #518.

<sup>3</sup> Myriad Genetic Laboratories: Data base, 2006.

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