New Test Predicted Presence of Harmful BRCA Mutations

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- Profile test demonstrated high sensitivity and specificity.
- Test results could aid in clinical decision making.
- May provide a quick, affordable alternative to current genetic testing.

PHILADELPHIA — A new multiple gene expression profile test was able to predict the presence of harmful BRCA1 or BRCA2 mutations in otherwise healthy women carrying the mutations, according to data published in *Cancer Prevention Research*, a journal of the American Association for Cancer Research.

“This novel technology aims to provide a layer of information regarding the cell functionality aspect of BRCA mutations that could greatly enhance the doctor’s ability to identify high-risk carriers,” said Asher Y. Salmon, M.D., a breast cancer specialist at the Hadassah Hebrew University Medical Center in Jerusalem, Israel.

Women with a mutation in their BRCA1 or BRCA2 gene have a significantly increased risk for developing breast cancer or ovarian cancer, and for many of those at risk disease may develop at an early age. Researchers are investigating ways to detect these genetic mutations so women carrying the genes can consider taking measures to reduce their cancer risk or increase the chance for detecting cancer in its early stages.

“The current tool for mutation detection is gene sequencing, which is expensive, time-consuming and, in many cases, lacking clear and decisive clinical decision making information,” said Salmon. “In many cases, the current sequencing tool identifies a mutation, but we do not know if the mutation is neutral or harmful.”

According to Salmon, emerging evidence has revealed that cells with a mutation in one of the two copies of the BRCA1 or BRCA2 genes have a distinct gene expression profile when exposed to causes of DNA damage, such as radiation.

After collecting white blood cells from blood samples donated by nine healthy women with a mutated BRCA1 gene and eight healthy women with a mutated BRCA2 gene, Salmon and his colleagues cultured the cells and exposed them to radiation. They then extracted the total RNA from these cells and compared it to the total RNA from identically treated white blood cells from 10 healthy, noncarrier women.

About 1,500 genes were differentially expressed between carriers and noncarriers. They narrowed this list to 18 genes that were the most significantly differentiated

between the two groups of women. The final narrowing was done with a validation study of a model using 21 of the newly identified genes and five control genes to predict the risk for carrying a mutation. They used blood samples from an independent group of 40 women who were carriers of mutated BRCA1 and/or BRCA2 and 17 noncarrier women. The model had a sensitivity of 95 percent and a specificity of 88 percent.

According to Salmon, this test can portray whether a patient carries a harmful mutation regardless of the patient's ethnic origin or specific mutation. In addition, it is affordable and quick, he said.

"In wealthy societies, it can become a screening tool for identifying individuals with a very high susceptibility for carrying a mutation, and full sequencing can be reserved only for them," Salmon said. "In societies in which sequencing is not feasible, this test can substitute for it with a very high accuracy rate."

Salmon and colleagues are assembling a large validation study in Europe and North America to analyze the efficacy of the test in heterogeneous populations.

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