

Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment

BACKGROUND:

Genetic testing for hereditary breast and ovarian cancer (HBOC) is evolving rapidly, owing to the recent introduction of multigene panels. Compared with testing for BRCA1/BRCA2 alone, these tests identify a greater number of individuals with genetic mutations. This study addresses how often and in which ways the identification of non-BRCA1/2 mutations would alter clinical management under current practice guidelines.

METHODS:

More than 1000 patients from three large medical centers (Stanford University School of Medicine, Massachusetts General Hospital, and Beth Israel Deaconess Medical Center) were prospectively enrolled. All patients met clinical criteria for HBOC evaluation and all were tested for BRCA1/2 and at least 23 other cancer risk genes. For the 63 patients found to have non-BRCA1/2 mutations, detailed clinical records and family histories were reviewed. We determined whether the positive test result would warrant consideration of a change in management in comparison with management recommendations based on personal and family history alone. These analyses were based on the most recent update (1.2015) to the National Comprehensive Cancer Network® (NCCN) guidelines for HBOC and other applicable current guidelines.

RESULTS:

- Consistent with other studies of comparable populations, 9.0% of all patients were positive for BRCA1 or BRCA2, and 3.8% of the BRCA1/2-negative patients had a mutation uncovered in another cancer risk gene.
- Most (92%) of the non-BRCA1/2 mutations were consistent with the spectrum of cancer(s) observed in the patient/family, suggesting that these results are clinically relevant and not incidental.
- Additional screening or prevention measures—over and above any recommendations based on personal and family history alone—would be considered for the majority (52%) of the non-BRCA1/2-positive patients (Table 1).
- Testing of most (72%) first-degree relatives of the non-BRCA1/2-positive patients would also be indicated based on the potential management changes for those individuals (Table 1).
- Clinical impact was not restricted to a few of the tested genes: most genes with positive results had the potential to change management for at least some patients in this study.

DISCUSSION:

In a clinically representative cohort, we found that multigene panel testing for HBOC yields clinically actionable findings across a broad spectrum of cancer risk genes. Compared with the results of BRCA1/2 testing alone, these findings are likely to change risk assessment and management for substantially more patients and their family members under current practice guidelines.

Table 1: Management change for patients and their family members following positive multigene panel patient findings

Intervention criteria	Relevant genes ^a	Intervention	Patients	Family testing ^b
High-risk genes, NCCN [®] management guidelines (n=20)	<i>CDH1</i> , <i>TP53</i> , <i>PTEN</i> , <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , <i>APC</i> , <i>MUTYH</i> (biallelic), <i>BMPR1A</i>	Guidelines-based surveillance, prevention	20	19/19
Breast cancer risk $\geq 40\%$ (<40% pre-test risk by IBIS ^{c,d}) (n=8)	<i>PALB2</i> ^d	Surgical prevention candidate	5 ^e	7/7
Breast cancer risk >20%/NCCN [®] 1.2015 recommendations ^f (<20% pre-test risk by IBIS ^{c,d}) (n=32)	<i>ATM</i> ^f , <i>CHEK2</i> ^f , <i>BRIP1</i> , <i>NBN</i> , <i>RAD51C</i>	Enhanced breast screening candidate	5	13/29
Other cancer risk (pancreas, melanoma) (n=3)	<i>CDKN2A</i>	Pancreas screening candidate	3	3/3

^a Listed genes are only those found to be mutated in this study.

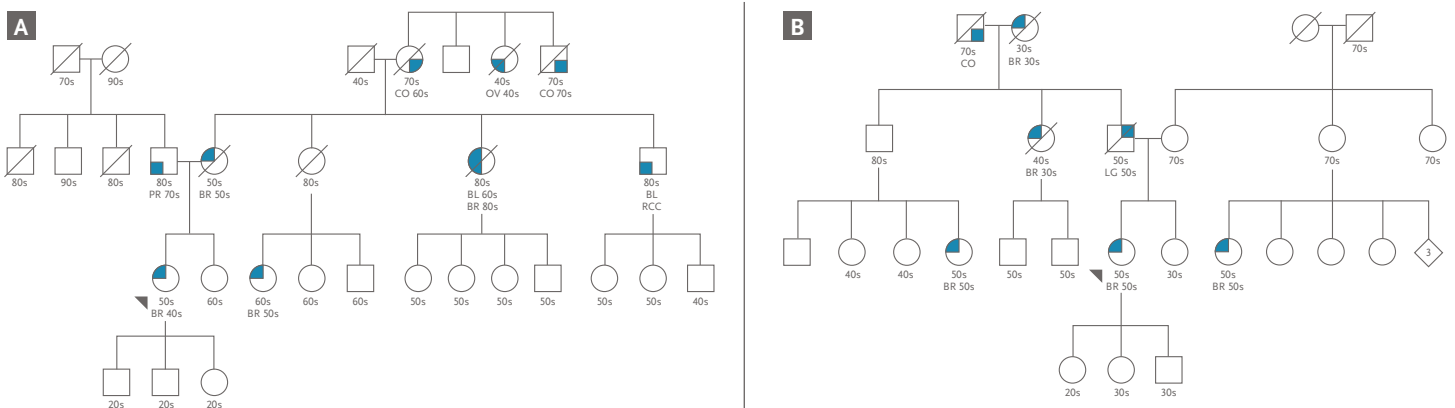
^b Family testing was recommended if positive result would change management. Only living first-degree relatives and families with same mutation were considered.

^c IBIS (Tyrer Cuzick model) only applies to breast cancer-unaffected individuals. Risk estimates consider both personal and family history.

^d Risk to age 70 years. For *PALB2*, risk estimate reflects that all had 1 or more first-degree relatives with breast cancer.

^e Three of 8 patients had undergone prior bilateral mastectomy.

^f Annual breast magnetic resonance imaging per NCCN[®] guidelines.

Figure 1: Representative pedigrees


A. With an *MSH6* mutation in this patient (indicated by black triangle) with breast cancer and a family history of breast, colon, uterine, and bladder cancer, screening for colorectal, gynecologic, and urologic cancers would be indicated; prophylactic gynecologic surgery could be considered, and additional family member testing is recommended and could provide indication for enhanced screening and possibly preventive surgery.

B. Presence of a *PALB2* mutation makes the patient (indicated by black triangle), who is already a candidate for enhanced (magnetic resonance imaging) breast screening, a possible candidate for prophylactic surgery, and makes the sister, 2 daughters, and potentially other paternal relatives candidates for testing, results of which may alter their recommended screening and prevention options.

Cancer types: BR, breast; BL, bladder; CO, colon; LG, lung; OV, ovarian; PR, prostate; RCC, renal cell. Symbols: circles, females; squares, males; quadrant shading, cancer affected; slash through circle or square, deceased; number alone, age by decade (current or at time of death); number following abbreviation, age by decade at time of cancer diagnosis. Not all ages were known.

PUBLICATION:

Andrea Desmond, Allison W Kurian, Michele Gabree, Meredith A Mills, Michael J Anderson, Yuya Kobayashi, Nora Horick, Shan Yang, Kristen M Shannon, Nadine Tung, James M Ford, Stephen E Lincoln, Leif W Ellisen, Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncology*. 2015.