Expanded gene panel utilization in women with breast cancer: identification and intervention beyond breast cancer risk

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Background

Clinicians ordering multi-gene next-generation sequencing (NGS) panels for hereditary breast cancer risk have a variety of test panel options. *BRCA1* and *BRCA2* (*BRCA1/2*) testing has been available for more than two decades, and multiple professional organizations have developed guidelines for testing individuals based on a suggestive personal or family history.[1-5] The clinical impact, cancer risks, and medical management guidelines are also well established.[1-3,6] However, multiple studies have demonstrated that compared with multi-gene NGS panels, traditional *BRCA1/2* tests miss potentially actionable findings in a substantial proportion of cases.[7-11] Medical management guidelines exist for many other hereditary breast cancer genes, including *PALB2*, *CHEK2*, and *ATM*[1,3]; however, no defined testing criteria have been established. In the absence of guidelines to assist in selecting among the increasing variety of panels, oncology providers must choose from high-risk panels limited to genes with established management guidelines or from larger panels that include genes for a variety of non-breast hereditary cancers.

We hypothesized that the use of broader gene panels increases the identification of incidental but clinically significant findings. We also examined clinician ordering patterns and compared the yield of pathogenic or likely pathogenic (P/LP) variants in non-*BRCA* genes in female breast cancer patients.

Methods

- We queried a consecutive series of 20,592 women with breast cancer undergoing multi-gene panel testing in our commercial laboratory between February 2015 and August 2016. Patients were tested for 2 to 79 genes as selected by the ordering clinician.
- Testing was performed with NGS as previously described,[11] and variant interpretation was carried out based on an expansion of the ACMG guidelines.[12]
- A total of 2105 individuals with P/LP variants were identified. Of these, 1020 individuals had variants in *BRCA1* or *BRCA2* and were excluded, leaving 1085 individuals with P/LP findings in other hereditary cancer genes.
- According to an IRB-approved study protocol, we analyzed de-identified personal and family history information from submitted requisition forms and medical records (when available) to create 3 groups by panel type:
  - (A) breast cancer, (B) commonly assessed cancers (breast, gynecologic, and gastrointestinal), and (C) expanded tumor types (Table 1).
- Testing indications were compared with published testing guidelines[1-5] to determine whether findings were consistent with the reported patient history information (expected findings) or not (incidental).
- We compared the frequency of P/LP variants in genes with established management guidelines and evaluated their consistency with personal and family histories.

Table 1. Genes included in groups A, B, and C

Group A	Group B	Group C
Breast-specifiic cancer panels	Common hereditary cancer panels	Large, comprehensive cancer panels
ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, FANCC, MRE11A, NBN, NF1, PALB2, PTEN, STK11, TP53	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, FANCC, MRE11A, NBN, NF1, PALB2, PTEN, STK11, TP53, APC, AXIN2, BMPR1A, CDKN2A, DICER1, EPCAM, GREM1, KIT, MEN1, MLH1, MSH2, MSH6, MUTYH, PDGFRA, PMS2, POLD1, POLE, RAD51C, RAD51D, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARCA4, TSC1, TSC2, VHL*	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, FANCC, MRE11A, NBN, NF1, PALB2, PTEN, STK11, TP53, APC, AXIN2, BMPR1A, CDKN2A, DICER1, EPCAM, GREM1, KIT, MEN1, MLH1, MSH2, MSH6, MUTYH, PDGFRA, PMS2, POLD1, POLE, RAD51C, RAD51D, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARCA4, TSC1, TSC2, VHL, ALK, BAP1, BLM, CASR, CDC73, CDK4, CDKN1B, CDKN1C, CEBPA, DIS3L2, EGFR, FH, FLCN, GATA2, GPC3, HOXB13, HRAS, MAX, MET, MITF, NF2, PDGFRA, PHOX2B, PRKAR1A, PTCH1, RAD50, RB1, RECQL4, RET, RUNX1, SDHAF2, SMARCB1, SMARCE1, SUFU, TERC, TERT, TMEM127, WRN, WT1*

Results

Among the 1085 cases reviewed, 1131 P/LP variants were identified; 44 patients (4%) had 2 or more variants. Overall, 92.3% of the variants identified in this cohort were in genes with medical management guidelines (Figure 1). Nearly 12% were in genes unrelated to personal or family history.

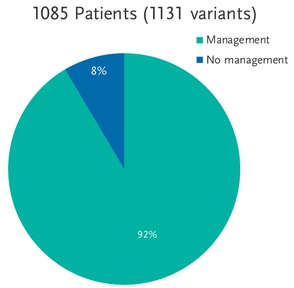

Figure 1. Percentage of identified pathogenic and likely pathogenic variants in the total cohort in genes with medical management guidelines.

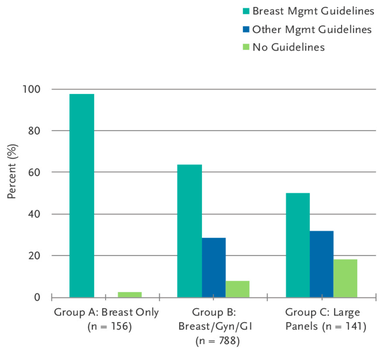

Figure 2. Comparison of variants identified according to test panel type (GI, gastrointestinal; Gyn, gynecologic).

As expected, the percentage of P/LP variants in genes with breast management guidelines was higher in group A (97.5%) than in groups B (63.6%) and C (50%). In groups B and C, a significant percentage of P/LP variants (28.5% and 31.8%, respectively) were identified in genes associated with increased risks for non-breast cancers and for which established management guidelines exist (Figure 2).

Approximately 13% and 15% of the P/LP variants identified in groups B and C, respectively, were defined as unexpected findings—that is, they were found in genes for which patients had no associated personal or family history.

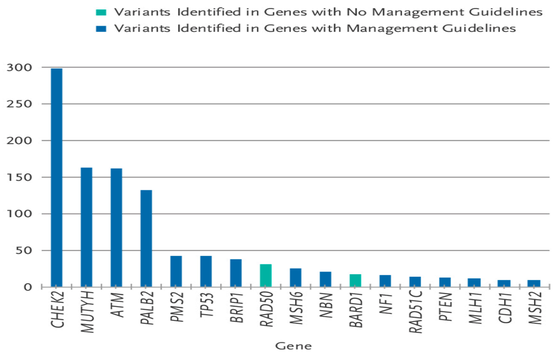

Figure 3. Most frequently identified pathogenic and likely pathogenic variants.

Discussion

The limitations of multi-gene panels are well known and include the following:
- undefined cancer risks associated with some hereditary cancer genes
- the need for more extensive pre-test genetic counseling[13]
- the lack of established screening guidelines for patients with positive findings in multiple genes[14]
- an increased risk of identifying variants of uncertain significance—findings that tend to increase proportionally with the number of genes ordered.

Despite these concerns, our results showed that

- **>85% of clinicians ordered larger, pan-cancer panels.**
- **Expanded panel testing increased the identification of P/LP findings in non-*BRCA* genes.**
- **>92% of P/LP variants were in genes with medical management guidelines.**
- **13%-15% of P/LP variants identified in groups B and C were incidental and unrelated to personal and familial histories.**
- ***CHEK2* and *MUTYH* heterozygotes accounted for a large proportion of P/LP results owing to the higher general population frequency of variants in these genes (Figure 3).**
- **Breast cancer–specific panels may miss clinically actionable findings in genes associated with hereditary predispositions for other cancers.**

Our results showed that expanded panel testing increased the identification of P/LP findings related to non-breast cancers. Notably, the majority of these findings occurred in genes with published management recommendations. Breast surgeons ordering panel testing can be reassured that resources are available to help guide patient care when such variants are identified.

The potential downsides of comprehensive panel testing must be weighed against the opportunity to discover actionable variants in cancer-related genes that may lead to earlier screening and detection, prevention, and decreased morbidity. Pre-test counseling should address the potential for incidental but actionable findings and findings that may have no medical management guidelines. Finally, further analysis is needed to determine the clinical impact and patient outcomes associated with the identification of P/LP variants in non-*BRCA1/2* genes.

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