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Title: Moderate Risk Genes Matter: Multigene Testing for Hereditary Breast Cancer

Background: Many genes have been associated with hereditary breast cancer (BC). For some genes, the associated cancer risks have been debated; however, recent studies have helped resolve some uncertainties. For example, *ATM*, *BARD1*, *CHEK2*, and *RAD51D* were associated with a moderate risk of BC (odds ratio (OR) 2- to 5-fold) in a recent study by Couch *et al.* Though many BC susceptibility genes have NCCN[®] management guidelines for at least one cancer type, some lack recommendations for BC risk management and others are missing altogether due to limited data. We aim to examine the mutation frequencies of genes on a BC focused multigene panel test (MGPT) and the possible clinical impact of these findings.

Methods: Sequential BC cases submitted to our laboratory for a BC focused MGPT between March 2012 and December 2016 were retrospectively reviewed. De-identified medical and family history data from test request forms and accompanying medical records as well as MGPT results were analyzed. Panel yield was assessed based on history of single or multiple primary diagnoses (MPD), level of BC risk, and clinical impact of test results.

Results: Of 30,161 BC cases tested, 3,174 (10.5%) were positive for a mutation, and 143 (0.5%) had more than one mutation identified. Mutations in high (>5-fold risk) and moderate risk (<5-fold risk) BC genes were detected in 3.9% and 6.6% of BC patients, respectively. Furthermore, 80.0% of the gene mutations identified (8.4% of all BC patients) occurred in genes with NCCN[®] management guidelines for at least one cancer type. Detection rate also varied based on personal history, with mutations detected in 10.2% of single BC cases only, 12.7% of BC cases with MPD only, and 14.0% of cases with breast and other cancers (see Table for gene specific frequencies).

	Breast Cancer Only N(%)	MPD Only N(%)	Breast + Other N(%)
<i>ATM</i>	246 (1.0%)	62 (1.5%)	33 (1.9%)
<i>BARD1</i>	58 (0.2%)	19 (0.5%)	3 (0.2%)
<i>BRCA1</i>	273 (1.2%)	65 (1.7%)	13 (0.8%)
<i>BRCA2</i>	336 (1.4%)	68 (1.8%)	36 (2.2%)
<i>BRIP1</i>	69 (0.3%)	6 (0.1%)	7 (0.4%)
<i>CDH1</i>	12 (0.1%)	5 (0.1%)	1 (0.1%)
<i>CHEK2</i>	412 (1.7%)	105 (2.6%)	58 (3.3%)
<i>CHEK2</i> (p.I157T)	122 (0.5%)	28 (0.7%)	13 (0.7%)
<i>MRE11A</i>	31 (0.1%)	6 (0.1%)	2 (0.1%)
<i>MUTYH</i> Carrier	312 (1.3%)	44 (1.1%)	31 (1.8%)
<i>NBN</i>	44 (0.2%)	5 (0.1%)	5 (0.3%)
<i>NF1</i>	39 (0.2%)	9 (0.3%)	6 (0.4%)

<i>PALB2</i>	221 (0.9%)	43 (1.1%)	14 (0.8%)
<i>PTEN</i>	14 (0.1%)	4 (0.1%)	1 (0.1%)
<i>RAD50</i>	57 (0.2%)	8 (0.2%)	9 (0.5%)
<i>RAD51C</i>	32 (0.1%)	13 (0.3%)	2 (0.1%)
<i>RAD51D</i>	17 (0.1%)	5 (0.1%)	2 (0.1%)
<i>TP53</i>	47 (0.2%)	16 (0.4%)	12 (0.7%)

Discussion: Findings from this large clinical testing cohort indicate that clinicians can expect approximately 3.9% and 6.6% of BC patients to have mutations in high and moderate risk genes, respectively. Though these values may shift as gene-specific BC risks continue to be refined, it is clear that moderate risk genes play a significant role in BC susceptibility. Five genes recently added to NCCN® management guidelines (*BRIP1*, *NBN*, *NF1*, *RAD51C*, and *RAD51D*) accounted for 9.9% of mutations identified (1.0% of all BC cases). Including these genes in MGPT provides patients and their families clinically relevant information about cancer risks and management options. Further studies are needed on genes such as *BARD1* and *RAD51D* that have recently been shown to predispose to BC but lack guidelines for BC risk management.