Center for Clinical Genetics and Genomics Newsletter

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http://pittgenomics.org/

MESSAGE FROM THE DIRECTOR:

The Center for Clinical Genetics and Genomics (CCGG) introduces a uniquely UPMC tailored genetic testing for hereditary breast and ovarian cancer. This test was developed in collaboration with cancer genetics counselors, physicians and laboratory genomics directors at UPMC. The UPMC crafted test offers the highest resolution and interrogates both larger deletions/duplications as well as single nucleotide changes. Individuals with concerns about their personal or family history of cancer should be referred to the Cancer Genetics Program for cancer risk assessment, genetic counseling, and genetic testing. The Program is headed by Dr. Phuong Mai and five experienced cancer genetic counselors led by Darcy Thull. Our cancer program will work with insurance companies to obtain appropriate authorization for genetic testing and will strive for a seamless patient experience. Moreover, the program will work with at-risk family members to receive appropriate genetic counseling and testing. Please contact Dr. Mai for any additional information at maip@mail.magee.edu.

CCGG consists of physicians, Genetic Counselors, laboratory directors and laboratory personnel that strive to provide diagnostic and risk assessment services at UPMC and beyond. We hope to address topics that are of interest to the referring providers and their patients. Please contact us with specific topic or issues that you would like to see addressed at rajkovic@upmc.edu.

You may also want to visit our recent website for additional information regarding genetic services across UPMC: http://pittgenomics.org/

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WHERE TO REFER THE PATIENTS

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For more information, see the video presentation at the CME UPMC Physician Resources:
"Cancer Risk Assessment and Genetic Counseling: Hereditary Breast and Ovarian Cancer"

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HEREDITARY BREAST/OVARIAN CANCER TESTING

Next Generation Sequencing and Deletion/Duplication Analysis

Test Background: The general population risk for breast and ovarian cancers is 12% and 1.5%, respectively. Inherited pathogenic variants in high-risk breast cancer-predisposing genes account for approximately 5-10% of breast cancer and 15-20% of ovarian cancer. The *BRCA1* and *BRCA2* genes are responsible for the majority of cases. Patients with pathogenic variants in *BRCA1* and *BRCA2* have a 50-80% lifetime risk of developing breast cancer and a 20-40% risk of developing ovarian cancer. Variants in DNA-repair genes as well as genes associated with syndromes may also cause hereditary breast and ovarian cancer (see Gene Table below).

Inheritance:

- Autosomal dominant;
- Offspring have a 50% chance of inheriting a disease-causing allele.

Reasons for Referral:

- Individuals with a clinical/family history consistent with hereditary breast/ovarian cancer.
- To establish appropriate clinical management based on genetic findings.
- Identify family members at-risk for hereditary breast/ovarian cancer.

Upcoming Gene Panels: Three panels with increasing gene coverage are available as reflex orders to optimize the identification of pathogenic variants and minimize the detection of variants of uncertain significance. Genes are sequenced and analyzed for deletions and duplications.

PANELS	GENES TESTED
Hereditary Breast/Ovarian Cancer: *BRCA1/2**	*BRCA1, BRCA2*
Hereditary Breast Cancer High & Moderate Risk Panel: High and moderate risk genes for hereditary breast cancer as designated by the National Comprehensive Cancer Network.	*BRCA1, BRCA2, ATM, CHD1, CHEK2, NBN, PALB2, PTEN, STK11, TP53*
Hereditary Breast/Ovarian Cancer Expanded Panel: Genes for hereditary breast and ovarian cancer including the genes for Lynch syndrome.	*BRCA1, BRCA2, ATM, CHD1, CHEK2, NBN, PALB2, PTEN, STK11, TP53, BRIP1, EPCAM, MLH1, MSH2, MSH6, PMS2, RAD51C, RAD51D*
Familial variants: Testing for familial variants is available.	Variant in a single gene

*Reanalysis of results from the *BRCA1/2* gene panel to the High & Moderate or Expanded Breast/Ovarian Cancer gene set may be initiated by the clinical genetics provider without collection of an additional sample from the patient.

Gene Descriptions:

Gene	Breast Cancer Estimated Lifetime Risk	Ovarian Cancer Estimated Lifetime Risk
ATM	17-52%	Unknown
BRCA1	57-65% by age 70	39-44% by age 70
BRCA2	45-55% by age 70	11-18% by age 70
BRIP1	OR:<2.0	~6% by age 80
CDH1	42% by age 80	Low or none
CHEK2	37% by age 70	Unknown
EPCAM	Unknown	Elevated. Uterine: 12-55%
MLH1	19% by age 70	20% by age 70
MSH2	11% by age 70	24% by age 70
MSH6	Unknown	Elevated: 6-8%, Uterine: up to 71%
NBN	OR: 3.0	Low or none
PALB2	Up to 58%	Low or none
PMS2	SIR:3.8	SIR: 12.0
PTEN	85% by age 70	Low or none
RAD51C	Unknown	9% by age 80
RAD51D	Unknown	OR: 12
STK11	32% by age 60	Gynecological: 13% by age 60
TP53	54%	Unknown

OR: Odds ratio, SIR: standardized incidence ratio

Data from Nielsen et al, Nat Rev Cancer (2016) 16:599-612 except for ATM, MSH6, PALB2, TP53 and EPCAM (EPCAM: PMID 18398828, 23901106, 19177550, 21145788; MSH6: PMID 18398828, 23091106, 15236168, 22619739; ATM, PALB2: https://www.ncbi.nlm.nih.gov/books/NBK1247/; TP53: PMID: 27496084).

Reportable Results: (The testing could have the following results)

- **Positive - Pathogenic variant(s) identified.** A pathogenic or likely pathogenic variant in a gene was identified that is consistent with having the condition or being at risk for developing the condition. Family members may be at risk of inheriting this pathogenic variant.
- **Negative – No causal variant identified.** A pathogenic variant was not identified in the genes tested. This does not completely rule out the possibility of hereditary breast/ovarian cancer as not all sequence variant types are detectable and other genes not included in the assay may be involved in risk of hereditary breast/ovarian cancer.
- **VUS - Variant of uncertain significance was identified.** A variant of uncertain significance was identified in a gene that is associated with hereditary breast/ovarian cancer. At the present level of evidence, it is not known whether the variant causes hereditary breast/ovarian cancer or is a benign variant. Additional testing of family members may be necessary to understand the significance of the result.

Variant Classification:
Results will be interpreted and reported following recommendations of the American College of Medical Genetics guideline (www.acmg.net). Based on current scientific knowledge including literature and databases, variations detected by sequencing or del/dup analysis will be analyzed and classified into the following categories:

- **Pathogenic Variant:** Pathogenic variants include frameshift/nonsense variants that are predicted to result in premature protein truncation or mRNA decay, consensus splice site variants, and previously reported missense variants that are recognized as disease-causing.
- **Likely Pathogenic Variant:** Variants with significant, but not conclusive, evidence supporting pathogenicity.
- **Variant of Uncertain Significance:** Sequence variants with insufficient evidence to classify whether they are pathogenic or benign. Rare missense variants frequently fall into this category.
- **Negative:** No sequence variant of clinical or uncertain significance was detected. Any variation detected and classified as a likely benign or benign variant based on population data, review of the literature and appropriate locus-specific databases will not be reported.

Test Method:
Genomic DNA is enriched for the complete coding regions and splice sites for the genes in the panel using a custom oligonucleotide-based target capture followed by next generation sequencing (MiSeq, Illumina) with 2x150 pair-end reads, mapping to human genome reference hg19 and variant calling. Average sequence coverage is >250x and 100% of targets have at least 10x coverage. Sanger sequencing is used to confirm all clinically significant variants and to provide data for bases with insufficient coverage when needed. Sequence variants classified as likely benign/benign are not confirmed or reported. The genes in this panel are also analyzed for copy number variants using an Agilent 8x60K custom microarray that detects most single-exon deletions and duplications.

Test Performance and Limitations:
This test is designed to detect nucleotide substitutions, small deletions (≤ 25bp), small insertions (≤10bp), small indels, and gross deletions/duplications for a targeted set of genes. The microarray has an average genomic resolution of 1 Mb and an enhanced resolution of 1-2 Kb resolution for the genes in the panel. Deletions or duplications <500-1000 bp may not be reliably detected. Sequence and microarray analysis is expected to be >99% sensitive with a false positive rate <1%. This assay is not intended to detect gross rearrangements, deep intronic variants, insertions of repetitive elements, and other unknown abnormalities. Some complex areas of the genome may result in suboptimal data that could increase the chance of a variant not being detected. This assay is not designed to detect mosaicism and its accuracy detecting mosaicism has not been established.

Turn Around Time (TAT): 2-4 weeks

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