The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. G701, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 702 9130
ucgslabs@genetics.uchicago.edu dnatesting.uchicago.edu
CLIA #: 14D0917593 CAP #: 18827-49

Hereditary Breast/Ovarian Cancer Panel Testing

Clinical Features:

Most cases of breast or ovarian cancer are sporadic; however, 5-10% of breast and ovarian cancers are considered hereditary. The *BRCA1* and *BRCA2* genes are responsible for approximately two thirds of all breast cancers among families in the United States and Europe that show a pattern of autosomal dominant transmission. The presence of a mutation in either *BRCA1* or *BRCA2* increases an individual's lifetime risk of developing cancer to up to 85% [1]. Breast cancer is also a common feature of Li-Fraumeni syndrome due to *TP53* mutations and of Cowden syndrome due to *PTEN* mutations. Other genetic syndromes may include breast cancer as an associated feature, including Peutz-Jeghers syndrome and heterozygous carriers of the ataxia telangiectasia [1]. Ovarian cancer has also been associated with Lynch syndrome [2].

Our Comprehensive Hereditary Breast/Ovarian Cancer Panel includes mutation analysis of the 18 genes listed below. Other smaller panels are also available, please see below for more details.

ATM	BARD1	BRCA1	BRCA2	BRIP1 (FANCJ)
CDH1	CHEK2 (CHK2)	EPCAM	MLH1	MSH2
MSH6	PALB2 (FANCN)	PMS2	PTEN	RAD51C (FANCO)
RAD51D	STK11	TP53		

Hereditary Breast/Ovarian Cancer Panel genes and associated cancer syndromes

Gene	Associated Syndrome	Cancer Risk	Management Guidelines	References
ATM	Biallelic mutations are associated with ataxia telangiectasia (A-T).	The lifetime risk for cancer for individuals with A-T is 30-40%, with leukemia and lymphoma accounting for the majority of malignancies. Breast cancer relative risk is 2.37 (95% CI 1.5–3.8). Other cancers include ovarian cancer, gastric cancer, and medulloblastoma.	NCCN-BR/OV, ACS Breast MRI	[3, 4]
BARD1	N/A	Increased risk of breast and ovarian cancer.	N/A	[5]
BRCA1 BRCA2	Hereditary breast and ovarian cancer syndrome	The lifetime risk of breast cancer or ovarian cancer is as high as 80%. The risk of other types of cancer is also increased, including fallopian tube cancer, prostate cancer, male breast cancer, and pancreatic cancer.	NCCN-BR/OV, CAPS	[6, 7]
BRIP1	Biallelic mutations are associated with Fanconi anemia complementation group J.	Heterozygous truncating mutations in *BRIP1* may be associated with a modest increased risk of breast cancer.	N/A	[8, 9]
CDH1	Hereditary Diffuse Gastric Cancer	The lifetime risk of lobular breast cancer is 39%. The risk of gastric cancer is 70% in men and 56% in women by the age of 80.	NCCN-Gastric	[1, 10]
CHEK2	N/A	The relative risk of breast cancer in male is 10.3, 95% (CI 3.5–30.0); in female is 1.70 (95% CI 1.3–2.2). The risk of other types of cancer is also increased including prostate and colon cancer.	NCCN-BR/OV, ACS Breast MRI	[1, 4]
EPCAM MLH1 MSH2 MSH6 PMS2*	Lynch syndrome, Turcot syndrome, Muir-Torre syndrome	The lifetime risk of colon cancer is 70-80%, endometrial cancer is 20-60%, ovarian cancer is 0.3-20%, gastric cancer is 5-10%, small bowel cancer is 0.4-12%, and urinary tract cancers is 0.2-25%.	NCCN-CRC, CAPS	[7, 11]

PALB2 (FANCN)	Biallelic mutations are associated with Fanconi anemia complementation group N.	The relative risk of breast cancer in women is 2.3 (95% CI 1.4–3.9). The risk of pancreatic cancer is increased.	NCCN-BR/OV, ACS Breast MRI, CAPS	[1, 4, 7, 12]
PTEN	PTEN Hamartoma Tumor Syndrome, Cowden Syndrome	The lifetime risk of breast cancer is 85%.	NCCN-BR/OV	[13]
RAD51C	Biallelic mutations in *RAD51C* have been identified in patients with Fanconi anemia complementation group O.	Heterozygous germline mutations in *RAD51C* have been identified as conferring a high penetrance susceptibility to breast and ovarian cancer [14].	N/A	[15]
RAD51D	N/A	A 10% risk of ovarian cancer by age 80.	N/A	[16]
STK11	Peutz-Jeghers Syndrome	The lifetime risk of breast cancer is 32% by age 60 and colorectal cancer is 39%-57%.	NCCN-CRC, CAPS	[1, 7, 17]
TP53	Li-Fraumeni syndrome (LFS)	The lifetime cancer risk for an individual with LFS is greater than 90%.	NCCN-BR/OV	[18]

N/A: Not available.
**Please note variations within exons 1-5, 9 and 11-15 of the PMS2 gene may not be analyzed or reported due to homology issues.*

Testing Options

BRCA1, BRCA2 and PALB2 Mutation Analysis

Cost: $2500
CPT codes: 81162, 81406
Turn-around time: 4 weeks

BRCA1, BRCA2 and TP53 Mutation Analysis

Cost: $2500
CPT codes: 81162, 81405
Turn-around time: 4 weeks

Hereditary Breast and Ovarian Cancer High Risk Panel (mutation analysis of *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53*)

Cost: $3500
CPT codes: 81162, 81321, 81405, 81406x2
Turn-around time: 6 weeks

Comprehensive Hereditary Breast/Ovarian Cancer Panel (mutation analysis of all 18 genes)

Cost: $3500
CPT codes: 81162, 81321, 81405, 81406x2
Turn-around time: 6 weeks

3 Ashkenazi BRCA1 and BRCA2 mutations

Cost: $500
CPT codes: 81212
Turn-around time: 3 weeks

Testing methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire panel. All abnormal results are reported by telephone.

References:

1. Shiovitz, S. and L.A. Korde, *Genetics of breast cancer: a topic in evolution.* Ann Oncol, 2015. **26**(7): p. 1291-9.
2. Toss, A., et al., *Hereditary ovarian cancer: not only BRCA 1 and 2 genes.* Biomed Res Int, 2015. **2015**: p. 341723.
3. Meyn, M.S., *Ataxia-telangiectasia, cancer and the pathobiology of the ATM gene.* Clin Genet, 1999. **55**(5): p. 289-304.
4. Saslow, D., et al., *American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography.* CA Cancer J Clin, 2007. **57**(2): p. 75-89.
5. De Brakeleer, S., et al., *Frequent incidence of BARD1-truncating mutations in germline DNA from triple-negative breast cancer patients.* Clin Genet, 2015.
6. Petrucelli, N., M. Daly, and G. Feldman, *BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer*, in *GeneReviews [Internet]*, R. Pagon, T. Bird, and C. Dolan, Editors. 1998, updated 2013, University of Washington: Seattle.
7. Canto, M.I., et al., *International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer.* Gut, 2013. **62**(3): p. 339-47.
8. Seal, S., et al., *Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles.* Nat Genet, 2006. **38**(11): p. 1239-41.
9. Minion, L.E., et al., *Hereditary predisposition to ovarian cancer, looking beyond BRCA1/BRCA2.* Gynecol Oncol, 2015. **137**(1): p. 86-92.
10. Colvin, H., et al., *Hereditary Gastric Cancer Syndromes.* Surg Oncol Clin N Am, 2015. **24**(4): p. 765-77.
11. Tiwari, A.K., H.K. Roy, and H.T. Lynch, *Lynch syndrome in the 21st century: clinical perspectives.* QJM, 2015.
12. Ghiorzo, P., *Genetic predisposition to pancreatic cancer.* World J Gastroenterol, 2014. **20**(31): p. 10778-89.
13. Eng, C., *PTEN Hamartoma Tumor Syndrome*, Nov 2001 [Last Updated Jan 23, 2014], GeneReviews [Internet]: Seattle, WA: University of Washington, Seattle.
14. Gevensleben, H., et al., Pathological features of breast and ovarian cancers in RAD51C germline mutation carriers. Virchows Arch, 2014. **465**(3): p. 365-9.
15. Vaz, F., et al., *Mutation of the RAD51C gene in a Fanconi anemia-like disorder.* Nat Genet, 2010. **42**(5): p. 406-9.
16. Baker, J.L., et al., *Breast cancer in a RAD51D mutation carrier: case report and review of the literature.* Clin Breast Cancer, 2015. **15**(1): p. e71-5.
17. Campos, F.G., M.N. Figueiredo, and C.A. Martinez, *Colorectal cancer risk in hamartomatous polyposis syndromes.* World J Gastrointest Surg, 2015. **7**(3): p. 25-32.
18. Apostolou, P. and F. Fostira, *Hereditary breast cancer: the era of new susceptibility genes.* Biomed Res Int, 2013. **2013**: p. 747318.

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDS