Specimen ID:
Control ID:
TESTING

Acct#:

Phone:

Patient Details	Specimen Details	Physycian Details
DOB:	Date collected:	Ordering:
Age (yyy/mm/dd):	Date received:	Referring:
Gender:	Date entered:	ID:
Patient ID:	Date reported:	NPI:

POSITIVE

At least one clinically significant variant was detected.

RESULTS AND INTERPRETATION

	GENE	CLASSIFICATION	ZYGOSITY	VARIANT DETECTED	AMINO ACID CHANGE	CANCER RISK
+	**BRIP1**	**LIKELY PATHOGENIC**	Het	c.2765T>G	p.Leu922X	**HIGH**

Variant Summary: A heterozygous c.2765T>G (p.Leu922X) likely pathogenic variant was detected in exon 19 of BRIP1. This nonsense variant is predicted to result in a premature termination codon and has been previously reported in ClinVar, in general population databases, and in the literature in an individual with breast cancer as well as in a high-risk unaffected control (Couch 2015, Ramus 2015). A recent publication by Easton (2016) suggests some truncating BRIP1 variants may not be associated with a substantial increase in breast cancer risk, however they suggest there is clinical utility for predicting ovarian cancer risk. Therefore, this variant has been classified as likely to be associated with an increased risk for breast and/or ovarian cancer. (NM_032043; hg19 chr17:g.59763337)

BRIP1 (BRCA1-interacting protein 1 ; OMIM 605882) encodes a DNA helicase that functions as a tumor suppressor via its interaction with BRCA1. BRIP1 is essential for normal DNA repair and genomic stability. Heterozygous germline mutations in BRIP1 have been identified and associated with familial breast and ovarian cancers. Biallelic germline BRIP mutations may cause Fanconi anemia.

Clinical Significance: High Cancer Risk

This mutation is clinically significant and is associated with an increased cancer risk. Current NCCN guidelines for BRIP1 mutation carriers suggest consideration of risk reduction surgery at age 45-50 or earlier based on family history (www.nccn.org). In addition to this individual being at increased risk, other family members may also be at risk. There is a 50% (1 in 2) chance of a first-degree relative having this mutation. Please call (800) 345-4363 to speak to a Labcorp Genetic Counselor to discuss if targeted analysis for other family members is appropriate.

This result is associated with the following cancer risks:

Lifetime High Risk	8.3% Ovarian
Lifetime Increased Risk	10-20% Female breast

*See table below for additional risk information

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RECOMMENDATIONS

Genetic counseling is recommended to discuss the clinical implications of this result. Genetic counselors are available for health care providers to discuss this result further at (800) 345-GENE. To refer your patient for genetic counseling through Integrated Genetics, please call the scheduling line at (855) 422-2557.

CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION	RELATED TO
Ovarian			
To age 70	8.3%	1.3%	BRIP1
Breast			
To age 70	10-20% Females	12% Females	BRIP1

LIST OF ALL GENES IN PANEL					
MLH1	MSH6	PTEN	BRCA1	CHEK2	
MSH2	PMS2	TP53	BRCA2	EPCAM	MUTYH (biallelic)

ADDITIONAL INFORMATION

Specimen Type: Whole Blood

Indication for Testing: The indication for testing for this patient is a reported personal and/or family history of ovarian cancer.

Variant Classification: Variant classification is a weighted assessment that incorporates but is not limited to the following components: prevalence of a variant in the unaffected (general) population, evidence of co-segregation in affected individuals, review of locus specific databases and observed/reported co-occurrence with other deleterious variants within the gene, published functional evidence linking a variant to phenotypes, and predicted functional impact as determined using in-silico analyses. Variants classified within each gene are reported in accordance to the ACMG standards and guidelines. Evidence affecting a variant classification that alters its clinical significance will be reported via an amended report. **Pathogenic variants** negatively affect normal gene function, are associated with disease, and should be used in clinical decision making. **Likely pathogenic variants** are strongly suggestive of normal gene function being negatively affected, and when combined with other evidence of cancer, may be used in clinical decision making. **Variants of uncertain significance (VUS)** have unknown effects on gene function, have not been previously reported or have been reported with inadequate or conflicting evidence regarding pathogenicity, clinical relevance, or cancer risk. A VUS should not be used in clinical decision making but additional monitoring may be considered. **Likely benign variants** are strongly suggestive of having no effect on gene function and are unlikely to have an increased risk for cancer. **Benign variants** have sufficient evidence to be considered of no clinical significance. Likely benign, benign and synonymous variants are not reported, but are available upon request.

METHODOLOGY AND LIMITATIONS

Next generation sequencing is used to examine the entire gene coding regions, as well as flanking non-coding regions, of genes known to be involved in the development, progression, and susceptibility of cancer. Flanking regions for the BRCA1 and BRCA2 genes include +/- 20bp and +/-10bp for all other genes. Copy number variations are assessed by microarray or multiple-ligation-probe amplification assay (MLPA) to detect gross deletions and duplications. Due to inherent limitations in the sequence analysis methods used, some variants may be missed. The presence of pseudogenes can interfere with the ability to detect variants in certain genes. Results are reported using nomenclature recommended by the Human Genome Variation Society (HGVS http://www.hgvs.org/). Each gene sequence is interpreted independently of all other gene sequences. However, variants in different genes may sometimes interact to cause or modify a typically monogenic disease phenotype. The occurrence of cancer due to genes not analyzed with this test is possible. Additional details regarding technical specifications and limitations of this assay are available on our websites, www.labcorp.com, www.integratedgenetics.com, and www.integratedoncology.com.

METHODOLOGY AND LIMITATIONS (cont)

This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.

REFERENCES

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology, genetic/familial high-risk assessment: breast and ovarian. Available at: www.nccn.org. 2010. Accessed 5.29.13.
2. Rehm H. et al. Working Group of the American College of Medical Genetics and Genomics Laboratory Quality Assurance Commitee. ACMG clinical laboratory standards for next-generation sequencing. Genet Med. 2013 Sep;15(9):733-47.
3. Tung N. et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. Cancer. 2015 Jan 121(1):25-33.
4. LaDuca H. et al. Utilization of multigene panels in hereditary cancer predisposition testing. Genet Med. 2014 Nov;16(11):830-7.

Released By:

PERFORMING LABORATORIES

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For inquiries, the physician may contact the lab using the numbers indicated above.