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
+	**MSH6**	**LIKELY PATHOGENIC**	Het	c.3646+1G>T	NA	**HIGH**

Variant Summary: A heterozygous c.3646+1G>T likely pathogenic variant was detected in intron 7 of MSH6. This splice-site variant has not been previously reported in the literature or databases but is predicted to negatively affect normal gene splicing. Therefore, this variant has been classified as likely to be associated with an increased risk for Lynch syndrome associated cancers. (NM_000179; hg19 chr2:g.48032847)

MSH6 (mutS homolog 6; OMIM 600678) encodes an essential component of the DNA mismatch repair system (MMR), repairing errors occuring during DNA replication. Germline mutations in MSH6 have been associated with Lynch syndrome, which is characterized by an increased risk for early-onset colorectal cancer and other tumors including the GI, urological, female reproductive tracts, CNS and skin. Muir-Torre syndrome can also be caused by mutations in the MSH6 gene.

Clinical Significance: **High Cancer Risk**
This mutation is clinically significant and is associated with an increased cancer risk. Current NCCN guidelines emphasize additional screening for MSH6 mutation carriers such as annual/biennial colonoscopy starting at age 25-30 (or 2-5 years prior to the earliest onset of colon cancer reported before age 30 in the family) and discussion of risk reduction surgery such as prophylactic hysterectomy and bilateral salpingo-oophorectomy in women (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	10-44% Colon, 16-44% Endometrial, 1-11% Ovarian

*See table below for additional risk information

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.

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CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION	RELATED TO
Colon			
To age 70	10-44%	4.5%	MSH6
Endometrial			
To age 70	16-44%	2.8%	MSH6
Ovarian			
To age 70	1-11%	1.3%	MSH6

LIST OF ALL GENES IN PANEL

FH	WT1	MITF	**MSH6**	SDHB	TP53	EPCAM
MET	FLCN	MLH1	PMS2	SDHC	TSC1	
VHL	GPC3	MSH2	PTEN	SDHD	TSC2	

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 renal, ovarian, and gastric cancers.

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 include +/-10bp for all 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.

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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.