

Specimen ID:

Control ID:

Acct#:

Phone:

**TESTING**

**Patient Details**

DOB:  
 Age (yyy/mm/dd): 046/00/00  
 Gender:  
 Patient ID:

**Specimen Details**

Date collected:  
 Date received:  
 Date entered:  
 Date reported:

**Physician Details**

Ordering:  
 Referring:  
 ID:  
 NPI:

**POSITIVE**

At least one clinically significant variant was detected.

**RESULTS AND INTERPRETATION**

| + | GENE  | CLASSIFICATION           | ZYGOSITY | VARIANT DETECTED | AMINO ACID CHANGE | CANCER RISK      |
|---|-------|--------------------------|----------|------------------|-------------------|------------------|
|   | MUTYH | <b>LIKELY PATHOGENIC</b> | Het      | c.1163T>C        | p.Leu388Pro       | <b>INCREASED</b> |

**Variant Summary:** A heterozygous c.1163T>C (p.L388P) likely pathogenic variant was detected in exon 12 of MUTYH. This missense variant has been previously reported in ClinVar and in the literature in individuals with adenomatous polyposis and attenuated FAP (Aceto 2005, Lejeune 2006, Olschwange 2007). This variant alters a conserved nucleotide located within the catalytic core important for the MUTYH glycosylase activity and functional studies suggest this variant affects normal gene function (Goto 2010, Shinmura 2012, Komine 2015). However, additional studies are needed to fully classify this variant as pathogenic. Therefore, this variant has been classified as likely to be associated with an increased risk for colorectal and/or other cancers. (NM\_001128425; hg19 chr1:g.45797356)

MUTYH (MutY or MYH; OMIM 604933) encodes a DNA glycosylase essential in repairing oxidative DNA damage. Individuals who carry one altered MUTYH gene may have a small increase in risk of cancer compared to the general population. Biallelic germline mutations in MUTYH have been associated with MUTYH-associated polyposis (MAP), which is characterized by multiple colorectal adenomas and carcinomas.

**Clinical Significance: Increased Cancer Risk**

This mutation is clinically significant and is associated with an increased cancer risk. Current NCCN guidelines for unaffected heterozygous MUTYH mutation carriers emphasize additional screening such as colonoscopy every 5 years beginning at age 40, or 10 years prior to the age of onset of colorectal cancer in a first-degree relative. For heterozygous MUTYH carriers affected with colorectal cancer, see surveillance recommendations in the NCCN guidelines for Colon and Rectal Cancers. NCCN guidelines also emphasize additional screening for biallelic MUTYH mutation carriers such as colonoscopy beginning at age 25-30, repeating every 2-3 years if no polyps are detected, annually if polyps are present with polypectomy, and baseline upper endoscopy starting at age 30-35 (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 Increased Risk** Biallelic: 43-100% Colorectal, **Heterozygous: 3.4-10% Colorectal**

\*See table below for additional risk information

**No additional sequence or copy number variants of clinical significance were detected.**

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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 |
|-------------------|--|-----------------------------|------------|
| <b>Colorectal</b> |  |                             |            |
| To age 70         | Biallelic: 43-100%<br><b>Heterozygous: 3.4-10%</b> | 4.5%                        | MUTYH      |

| LIST OF ALL GENES IN PANEL |      |       |       |              |        |        |
|----------------------------|------|-------|-------|--------------|--------|--------|
| APC                        | MSH2 | TP53  | CHEK2 | PRKAR1A      | SMAD4  | RAD51C |
| ATM                        | MSH6 | CDH1  | PALB2 | BMPR1A       | EPCAM  | RAD51D |
| NBN                        | PMS2 | MLH1  | BARD1 | FAM175A      | CDKN2A |        |
| CDK4                       | PTEN | STK11 | BRIP1 | <b>MUTYH</b> |        |        |

**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 colorectal 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.

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## 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](http://www.labcorp.com), [www.integratedgenetics.com](http://www.integratedgenetics.com), and [www.integratedoncology.com](http://www.integratedoncology.com).

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](http://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 Committee. 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

TG LabCorp RTP 1912 T.W. Alexander Drive, RTP, NC 27709-0150 Lab: (800) 345-4363 Dir: Arundhati Chatterjee, MD  
For inquiries, the physician may contact the lab using the numbers indicated above.