

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
+ TP53	LIKELY PATHOGENIC	Het	c.845G>A	p.Arg282Gln	HIGH

Variant Summary: A heterozygous c.845G>A (p.Arg282Gln) likely pathogenic variant was detected in exon 8 of TP53. This variant was reported in one patient with neuroblastoma whose family history was not suggestive of Li-Fraumeni Syndrome. Other amino acid changes at this location have been classified as pathogenic, and functional studies suggest that this change negatively affects but does not abolish normal TP53 function. Therefore, this variant has been classified as likely to be associated with an increased risk for Li-Fraumeni syndrome associated cancers. (NM_000546; hg19 chr17:g.7577093)

TP53 (Tumor Protein P53; OMIM 191170) is DNA-binding protein that functions as a tumor suppressor, with critical roles in normal cell division, DNA repair, apoptosis, and metabolism. Germline TP53 mutations are associated with Li-Fraumeni syndrome, which is characterized by predisposition to a variety of early onset cancers including breast, brain, colon, adrenal gland cancers, sarcomas, and leukemia.

Clinical Significance: High Cancer Risk

This mutation is clinically significant and is associated with an increased cancer risk. Current NCCN guidelines emphasize earlier and more comprehensive screening for TP53 mutation carriers, such as semiannual clinical breast exams starting at age 20-25 in women and age 35 in men, annual mammography and whole body MRI screening, discussion of risk reduction surgery, colonoscopy every 2–5 years starting no later than age 25 and consideration of full body skin exams for melanoma screening. Additionally, modification of surveillance should be based on a patient's personal and/or family history for specific associated cancers (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 Up to 73% males, Nearly 100% females for various cancers (Breast, Colon, Sarcoma, Brain, Adrenal gland, Leukemia)

*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
Sarcoma			
To age 70	≤73% Males, ≤100% Females	0.1-2%	TP53
Breast			
To age 70	≤73% Males, ≤100% Females	12% Females, 0.13% Males	TP53
Brain			
To age 70	≤73% Males, ≤100% Females	0.6%	TP53
Adrenal gland			
To age 70	≤73% Males, ≤100% Females	<1%	TP53
Leukemia			
To age 70	≤73% Males, ≤100% Females	1.5%	TP53
Colon			
To age 70	≤73% Males, ≤100% Females	4.5%	TP53

LIST OF ALL GENES IN PANEL

ALK	NF1	VHL	MSH2	SUFU	PHOX2B
APC	NF2	MEN1	MSH6	TP53	SMARCB1
NBN	RB1	MLH1	PMS2	PTCH1	

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 neuroblastoma and other 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.

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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, www.integratedgenetics.com, and 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. 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.