SAMPLE REPORT, VISTASEQ

Patient Details		Specimen Details		Client Details	
DOB:	1/23/1967	Specimen ID:	SAMPLE 0080	Acct #:	CMBP - Test Ac
Age(y/m/d):	048/05/00	Date Collected:	6/23/2015	Ordering Physician:	PHY 1, F
Gender:	N	Date Reported:	7/14/2015		
Patient ID:	SAMPLE	Specimen Type:	Blood		

POSITIVE

At least one clinically significant variant was detected.

RESULTS AND INTERPRETATION

	GENE	CLASSIFICATION	ZYGOSITY	VARIANT DETECTED	AMINO ACID CHANGE	CANCER RISK
+	**PRKAR1A**	**LIKELY PATHOGENIC**	Heterozygous	c.307G>T	p.E103Ter	**POSSIBLY ELEVATED**

Variant Summary: A heterozygous c.307G>T (p.E103Ter) likely pathogenic variant was detected in exon 3 of PRKAR1A. This variant has not been previously reported but is predicted to result in a premature termination codon. Loss of function mutations in this gene have been shown to negatively effect normal protein function and result in disease. Therefore, this variant has been classified as associated with a possibly elevated risk for multiple neoplasias which includes thyroid and myxomatous tumors. (NM_002734; hg19 chr17:g.66519026).

PRKAR1A (Protein kinase A regulatory subunit-1-alpha; OMIM 188830) is a critical subunit of type I protein kinase A which has roles in regulation of metabolism, cell proliferation, differentiation, and cell death. Germline PRKAR1A mutations have been identified and associated with Carney complex type 1, a multiple neoplasia syndrome characterized by cardiac, endocrine, cutaneous, and neural myxomatous tumors which shows some similarities to multiple endocrine neoplasia (MEN) type 1 and Peutz-Jeghers syndromes.

Clinical Significance: Possibly Elevated Cancer Risk
This mutation is clinically significant and is associated with a possibly increased cancer risk. At this time there are no NCCN guidelines for individuals with PRKAR1A mutations. However, modification of surveilance should be based on a patient's personal and/or family history. Annual echocardiography for cardiac myxomas and additional baseline testing for testing thyroid, testicular and breast tumors may be warranted in PRKAR1A mutation carriers presenting with primary pigmented nodular adrenocortical disease (www.uptodate.com). 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 Possible Increased Risk	thyroid, myxomatous tumors

* 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
Thryoid			
To age 70	risk not yet determined	1.2%	PRKAR1A

LIST OF ALL GENES IN PANEL							
	APC	BRCA1	BRCA2	CDH1	CDKN2A	EPCAM	MLH1
	MSH2	MSH6	PMS2	PTEN	STK11	TP53	MUTYH (biallelic)
	ATM	BMPR1A	CDK4	CHEK2	PALB2	SMAD4	FAM175A
	BARD1	BRIP1	RAD51C	NBN	**PRKAR1A**	RAD51D	

ADDITIONAL INFORMATION

Indication for Testing: The indication for testing for this patient is a reported personal and/or family history of cancers related to Thyroid 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

The entire gene coding regions, as well as all flanking noncoding regions, of 27 cancer genes known to be involved in the development and progression of cancers is analyzed by next generation sequencing. 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 gene deletions and duplications. Results are reported using nomenclature recommended by the Human Genome Variation Society (HGVS http://www.hgvs.org/).

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METHODOLOGY AND LIMITATIONS (cont)

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. It cannot be excluded that pathogenic variants were missed due to limitations inherent in the sequence analysis method used here. In addition, the presence of a Inherited Cancer Syndrome due to a different genetic cause can also not be ruled out. Any interpretation given here should be clinically correlated with available information about presentation and relevant family history of the patient.

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. American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility. J Clin Oncol. 2003 Jun 15; 21(12):2397-406.
3. 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.

Released By: Director, PhD, Director

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.