175 Technology Dr, Suite 100 Irvine, CA 92618
Tel: 1-949-450-9421 genomictestingcooperative.com

Clonal Hematopoiesis

Patient Name:		Ordered By	
Date of Birth:		Ordering Physician:	
Gender (M/F):		Physician ID:	
Client:		Accession #:	
Case #:		Specimen Type:	
Body Site:		Specimen ID:	

Ethnicity:				Family History:	
MRN:				Indication for Testing:	
Collected Date:		Time :		Reason for Referral:	Malignant Neoplasm of Lung
Received Date:		Time :		Tumor Type:	Lung
Reported Date:		Time :		Stage:	T2B

This is a next generation sequencing (NGS) test to identify molecular abnormalities in 177 genes implicated in hematologic cells. The assay is designed to detect genomic abnormalities in hematologic cells. The presence of genomic abnormalities indicates clonal hematopoiesis. Clonal hematopoiesis has implication on the development of hematologic neoplasms as well as cardiovascular diseases.

Clonal Hematopoiesis
Detected

Mutated Genes	
TET2	ASXL1

Diagnostic Implications	
Clonal hematopoiesis of Indeterminate Potential (CHIP)	Yes
Clonal Cytopenia of Unknown Significance (CCUS)	No
Risk of Cardio Vascular Disease	Yes
MDS	NO
Other	Non

Prognostic Implications	
Clonal hematopoiesis of Indeterminate Potential (CHIP)	May evolve into CCUS or MDS
Clonal Cytopenia of Unknown Significance (CCUS)	N/A

Cardio Vascular Disease	4 times greater
MDS	NA
Other	Neutral

Therapeutic Implications	
TET2	Monitor Hematologic indices/Check other CVD risk factors
ASXL1	Monitor Hematologic indices/Check other CVD risk factors

Results Summary

- Mutations in TET2 and ASXL1 genes are detected at very low levels.
- The presence of these mutations suggests the presence of abnormal clonal hematopoiesis. However, since no hematologic abnormality is detected, the findings are consistent with CHIP (Clonal Hematopoiesis of indeterminate potential).
- The presence of mutations in two genes suggests higher possibility of transformation into MDS or other hematologic neoplasm at perhaps earlier age as compared with the presence of a mutation in one gene.
- The presence of these abnormalities is also consistent with higher risk of developing cardiovascular disease and myocardial infarction.

Clinical Background:

Random somatic mutations occur in normal cells, but rarely these cells evolve into viable clone, but with aging, the possibility of a clone to accumulate increases. Clonal hematopoiesis of indeterminate potential (CHIP) is defined by the presence of low-level mutations in the peripheral blood in clinically normal individuals. CHIP is detected in 3-5% of normal individuals above the age of 50 and in approximately 10% of people aged 70 to 80. The most common mutation is on the *DNMT3A* gene, followed by *TET2* and *ASXL1*. The rate of transformation to a hematological neoplasia is 0.5–1% per year. Clonal cytopenias of undetermined significance (CCUS) is defined by the presence of cytopenia (anemia, low platelets or white cells) along with low level mutations but does not meet World Health Organization (WHO)-defined criteria for MDS and the mutations are detected in <40% of cells. Approximately 25% to 65% of patients with cytopenia will have mutation in one or more genes. These patients with mutations have significantly higher probability of developing MDS or other hematopoietic neoplasms (AML, MPN, lymphoma,…) within 5 years. Recent studies demonstrated that patients with acute myeloid leukemia (AML) had significantly high incidence of clonal hematopoiesis multiple years prior to developing AML. All patients with mutations in specific genes such as IDH1, IDH2, and TP53 developed AML within few years.

In addition, recent studies linked mutations in peripheral blood to cardiovascular disease (CVD). Recent data show that patients with CHIP have 4.0-times greater risk of myocardial infarction as compared to individuals without such clone. The prevalence of CHIP in patients with coronary artery disease is reported to be at 18.2%. In contrast, the prevalence of CHIP in centenarians is only at 2.5%. It has been shown that mutations in *TET2* gene, which is one of the commonly mutated genes in CHIP, are pro-inflammatory and lead to the development of atherosclerotic plaques. Based on that it has been suggested that anti-inflammatory agents might slow the progression of cardiovascular disease in patients with low level mutations in peripheral blood. Additional studies are needed to determine the clinical relevance of anti-inflammatory agents in reducing CVD or to determine the relationship between duration of the presence of CHIP or level of the mutated clone with progression of CVD or hematologic

neoplasms. In addition, studies are needed to determine if early therapy especially using targeted therapy (IDH1/IDH2 inhibitors) would prevent or delay the onset of hematologic neoplasms.

Biological Relevance of Detected Alterations

- TET2 (Tet Methylcytosine Dioxygenase 2) gene encodes a methylcytosine dioxygenase that catalyzes the conversion of methylcytosine to 5-hydroxymethylcytosine. The encoded protein is involved in myelopoiesis, and defects in this gene have been associated with several myeloproliferative disorders. In addition to its role in DNA demethylation, also involved in the recruitment of the O-GlcNAc transferase OGT to CpG-rich transcription start sites of active genes, thereby promoting histone H2B GlcNAcylation by OGT. No targeted therapy is available for this gene. However hypomethylation agents are considered to be relevant in treatment of diseases with abnormalities in this gene.
- ASXL1 (Additional Sex Combs Like 1, Transcriptional Regulator) gene encodes a protein that disrupt chromatin in localized areas, enhancing transcription of certain genes while repressing the transcription of other genes. The protein encoded by this gene functions as a ligand-dependent co-activator for retinoic acid receptor in cooperation with nuclear receptor coactivator 1. Mutations in this gene are associated with myelodysplastic syndromes and chronic myelomonocytic leukemia, but also reported in colorectal and other types of cancers.

Drug Information:

None

Potential Clinical Trials

None

Detailed Results

Single Nucleotide Variant (SNV)								
Gene name	Hgvsp	Hgvsc	Amino acids	Codons	Consequence	Allele frequency	Read depth	Predicted effect on protein
TET2	NP_001120680.1:p.Gln138Ter	NM_001127208.2:c.412C>T	Q/*	Caa/Taa	stop_gained	5.3	645	deleterious
ASXL1	NP_056153.2:p.Gly646TrpfsTer12	NM_015338.5:c.1934dupG	-/X	-/G	frameshift_variant	4.6	395	deleterious

Methodology and Test Background

This is next generation sequencing (NGS) test that analyzes DNA for abnormalities in 65 genes that are reported to be altered in hematopoietic cells. The assay is designed to detect single nucleotide variations (SNV) and indels. Our sequencing method has a typical sensitivity of 1% to 3% for detecting common specific mutations in hematopoietic cells. Performance of the assay may vary dependent on the quantity and quality of nucleic acid, sample preparation and sample age.

Tested genes

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Genes Tested for abnormalities

ABL1	BTK	CBLC	CIC	DNMT3A	FBXW7	H3F3A	KIT	MYC	PBRM1	PTPN11	SETD2	TP53
ASXL1	CALR	CD274	CSF1R	EP300	FLT3	IDH1	KMT2A	MYD88	PHF6	RHOA	SRSF2	TSC1
ATRX	CARD11	CD79A	CSF3R	ERG	GATA1	IDH2	KMT2B	NPM1	PIK3CA	RUNX1	STAG2	TSC2
B2M	CBL	CD79B	CUX1	ETV6	GATA2	JAK2	KRAS	NRAS	PIM1	SDHB	STAT3	WT1
BRAF	CBLB	CEBPA	CXCR4	EZH2	GATA3	KDR	MPL	PAX5	PPM1D	SETBP1	TERT	ZRSR2

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Electronic Signature

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The Technical Component Processing, Analysis and Professional Component of this test was completed at GTC Laboratories, 21 Technology Dr. #100, Irvine, CA / 92618/ Medical Director: Maher Albitar, M.D. .

The performance characteristics of this test have been determined by GTC Laboratories. This test has not been approved by the FDA. The FDA has determined such clearance or approval is not necessary. This laboratory is CLIA certified to perform high complexity clinical testing.