UTSW Clinical NGS Laboratory
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CLIA ID 45D0861764
Director: Ravi Sarode, MD

Clinical NGS Laboratory

UTSouthwestern Medical Center

1385-Gene Pan-Cancer Mutation Test

PATIENT RECORD

Name	[redacted]	Order #	375042672	Order Date	2019-04-16
MRN	[redacted]	Lab Accession #	[redacted]	Tumor Collection Date	2019-04-16
DOB	[redacted]	Tumor Specimen #		Lab Received Date	2019-04-18
Sex	Male	Germline Specimen #	N/A	Report Date	2019-05-13
Institution	UTSW	Tumor Tissue	Bone Marrow	Pct. Over 100X	99.23%
Ordered By	Dr. Shahan,Jaim	Germline Tissue	Saliva	Avg. Depth	1845
Authorized By	Dr. Shahan,Jaim	OncoTree Diagnosis	PMF	Tumor Percent	%
ICD10	D75.81 Myelofibrosis (*);			Tumor Mutation Burden (Mutations/MB)	0.41
				Report Electronically Signed By	Dr. Jeffrey Gagan

CASE SUMMARY

Consistent with previous testing, variants in CALR and IDH1 were found. The CALR is generally prognostically favorable versus other drivers, such as JAK2. The IDH1 mutation is associated with shorter time to leukemic progression, but may also be an avenue of treatment through targeted inhibitors.

BIOMARKERS	INDICATED THERAPIES	CLINICAL TRIALS	VARIANT TIERS	CNVs	FUSIONS
CALR			Tier 1		
IDH1	1	1	Tier 1		
DDX6			Tier 3		
chr20q				Loss	

INDICATED THERAPIES

DRUGS	VARIANT	LEVEL	INDICATION
Ivosidenib	IDH1 p.Arg132Ser	Weak Evidence	Treatment with IDH1 inhibitors, such as Ivosidenib, are FDA approved in AML, but are still in clinical investigation in other IDH1 mutated hematologic malignancies.

CLINICAL TRIALS

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase Ib/II Investigator Sponsored Study of the IDH1-Mutant Inhibitor Ivosidenib (AG120) With the BCL2 Inhibitor Venetoclax in IDH1-Mutated Hematologic Malignancies	Phase 1/Phase 2	IDH1	Courtney DiNardo, MD 713-794-1141 cdinardo@mdanderson.org Houston, TX	NCT03471260

TIER 1 - VARIANTS OF STRONG CLINICAL SIGNIFICANCE

VARIANT	COMMENT
CALR p.Lys385fs **Pos:** chr19:12943813 **ENST:** ENST00000316448.9 **VAF:** 34.67% **Depth:** 1814	**Gene Function:** CALR encodes calreticulin, is a Ca2+ binding chaperone protein that plays a role in multiple biological processes, including protein folding and quality control, calcium homeostasis, immune response, cell adhesion and migration, and cell signaling (PMID: 19940256, 28470469, 22959412) **Prognosis:** PMF patients with CALR mutation have a lower risk of developing anemia, thrombocytopenia, and marked leukocytosis compared with other molecular subtypes (PMID: 24986690). CALR mutations are generally subdivided, and Type 2-like CALR mutations, such as this, were preferentially associated with an essential thrombocythemia phenotype, low risk of thrombosis despite very-high platelet counts and indolent clinical course (PMID: 26449662). **Variant Function:** This insertion is referred to as a Type II CALR mutation. The frameshift generate a novel C-terminus of the mutant protein in which the negatively charged amino acids are variably replaced by neutral and positively charged amino acids (PMID: 24325356).
IDH1 p.Arg132Ser **Pos:** chr2:208248389 **ENST:** ENST00000345146.6 **VAF:** 38.63% **Depth:** 2154	**Gene Function:** The IDH1 (isocitrate dehydrogenase 1) protein is an enzyme that catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG), a crucial step in the tricarboxylic acid (TCA) cycle. IDH1 utilizes NADP(+) as an electron acceptor and it is predominantly expressed in the cytosol and peroxisomes, playing a role in the cytoplasmic production of NADPH. **Prognosis:** In a study of a large cohort of PMF patients, leukemia-free survival was negatively affected by IDH1 mutations (PMID: 23619563). **Variant Function:** IDH1 R132S lies within the active site of the IDH1 protein (PMID: 19228619). R132S confers a gain of function to IDH1, as indicated by increased conversion of alpha-ketoglutarate to the onco-metabolite 2-hydroxyglutarate in cell culture (PMID: 19935646, 21326614).

TIER 2 - VARIANTS OF POSSIBLE CLINICAL SIGNIFICANCE

No variant to report at this level.

TIER 3 - VARIANTS OF UNKNOWN CLINICAL SIGNIFICANCE

VARIANT	POSITION	ENST	VAF	DEPTH
DDX6 p.Ile170Thr	chr11:118765346	ENST00000526070.2	38.47%	2290

COPY NUMBER ALTERATIONS

CHR:START-END	COPY #	CYTOBAND	COMMENT
chr20:37,241,915-58,686,405	1	q11.23-q13.32	Loss of 20q is a common abnormality in PMF, and it does not change the prognosis of the patient compared to comparable normal karyotype patients (PMID: 19131547).

GENE FUSIONS

No additional fusion

PUBMED REFERENCES

Somatic mutations of calreticulin in myeloproliferative neoplasms.
Int J Hematol. 2017 May 3;105(6):743-747.
PMID: 28470469

The role of cytogenetic abnormalities as a prognostic marker in primary myelofibrosis: applicability at the time of diagnosis and later during disease course.
Blood. 2009 Apr 30;113(18):4171-8.
PMID: 19131547

Calreticulin: non-endoplasmic reticulum functions in physiology and disease.
FASEB J. 2009 Nov 25;24(3):665-83.
PMID: 19940256

Differential clinical effects of different mutation subtypes in CALR-mutant myeloproliferative neoplasms.
Leukemia. 2015 Oct 9;30(2):431-8.
PMID: 26449662

Calreticulin in the immune system: ins and outs.
Trends Immunol. 2012 Sep 7;34(1):13-21.
PMID: 22959412

IDH1 and IDH2 mutations in gliomas.
N Engl J Med. 2009 Feb 19;360(8):765-73.
PMID: 19228619

Clinical effect of driver mutations of JAK2, CALR, or MPL in primary myelofibrosis.
Blood. 2014 Aug 14;124(7):1062-9.
PMID: 24986690

2-hydroxyglutarate production, but not dominant negative function, is conferred by glioma-derived NADP-dependent isocitrate dehydrogenase mutations.
PLoS One. 2011 Feb 4;6(2):e16812.
PMID: 21326614

Cancer-associated IDH1 mutations produce 2-hydroxyglutarate.
Nature. 2009 Dec 10;462(7274):739-44.
PMID: 19935646

Mutations and prognosis in primary myelofibrosis.
Leukemia. 2013 Apr 26;27(9):1861-9.
PMID: 23619563

Somatic mutations of calreticulin in myeloproliferative neoplasms.
N Engl J Med. 2013 Dec 19;369(25):2379-90.
PMID: 24325356

INFORMATION ABOUT THE TEST

Test Characteristics and Performance:

DNA and RNA are isolated from peripheral blood, bone marrow aspirate or formalin-fixed, paraffin-embedded tissues. Sequencing libraries are generated using Kapa Biosystems and Illumina chemistry. A custom panel of DNA probes is used to produce an enriched library containing all exons from over 1,425 cancer-related genes, which are sequenced on Illumina NextSeq 550 or MiSeq instruments. DNA and RNA sequence analyses are done using custom germline, somatic and mRNA bioinformatics pipelines run on the UTSW Bio-High Performance Computer cluster and optimized for detection of single nucleotide variants, indels and known gene fusions.

Reports are generated in Answer, which was developed at UTSW. Annotations are written either by a PhD variant curation scientist, UTSW residents and fellows, or MD medical directors. Interpretations can be revaluated upon request.

Median target exon coverage for the assay is 900X with 94% of exons at >100X. The minor allele frequency limit of detection is 5% for single nucleotide variants and 10% for indels and known gene fusions. The assay is not informative for mutations outside the 1,425 cancer-related genes or for those regions for which the assay achieves limited coverage. Full details of the genes tested, exon coverage and the bioinformatics pipeline are available at http://www.utsouthwestern.edu/sites/genomics-molecular-pathology/.

Disclaimer:
This is a laboratory developed test, and its performance characteristics have been determined by the Next Generation Sequencing Clinical Lab, Department of Pathology, UTSW. It has not been cleared or approved by the U.S. Food and Drug Administration. The U.S. Food and Drug Administration does not require this test to go through premarket review. This test is used for clinical purposes. It should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments (1988) as qualified to perform high complexity testing.