GENOMIC TESTING COOPERATIVE

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CLIA # 05D2111917 CAP # 9441574

Hematology Profile Plus

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

MRN:				Indication for Testing:	R79.89 Other specified abnormal findings of blood chemistry
Collected Date:		Time:	12:00 AM		
Received Date:		Time:	12:28 PM		
Reported Date:		Time:	01:47 PM		

Detected Genomic Alterations

CDKN1B (?Germline)	TP53	PLCG1 (3 mutations)	CEBPA	MTOR
GRIN2A	NOTCH1 (3 mutations)	EP300	KMT2C (3 mutations)	GATA3
CCR4	TFPT	Autosomal chromosomes show : 8p-(distal), 8p+(proximal), 9q-, 13q-, +15, 18q+, +21	HTLV1 viral RNA : Detected (8239 copies)	B-cell clonality : Not detected
T-cell clonality : Detected (TRAV 9-2/TRBV 5-4)	-			

Results Summary

- **-Somatic mutations in TP53, PLCG1 (3 mutations), CEBPA, MTOR, GRIN2A, NOTCH1 (3 mutations), EP300, KMT2C (3 mutations), GATA3, CCR4, and TFPT genes**
  -Possible germline mutation in CDKN1B gene, heterozygous
  -EBV viral RNA: Not detected
  -HPV viral RNA: Not detected
  -TTV viral RNA: Not detected
  -HLA Genotyping:
  -HLA-A: A*01:01-A*68:02
  -HLA-B: B*49:01-B*58:01
  -HLA-C: C*07:01-C*07:01
  -Autosomal chromosomes show : 8p-(distal), 8p+(proximal), 9q-, 13q-, +15, 18q+, +21
  -T-cell markers RNA ratios:
  CD3D:CD3E Ratio : 1.88
  CD4:CD8A Ratio : 42.47
  CD4:CD8B Ratio : 74.99

CD4:CD26 Ratio : 1064.33
CD4:CD7 Ratio : 31.46
-Increased T-cell markers with abnormal expression pattern
-LowB-cell markers
-Low CD30 mRNA

-These findings are consistent with adult T-cell lymphoma with HTLVI positivity.

-The CDKN1B mutation is detected at high level, raising the possibility of a germline mutation. This mutation leads to early termination (loss of function). However, there is no data on its clinical relevance and should be classified as of "uncertain significance" at this time.

See additional report information at the end of the report.

Heterogeneity

There are abnormal clones with TP53, PLCG1 (3 mutations), CEBPA, MTOR, GRIN2A, NOTCH1 (3 mutations), EP300, KMT2C(3 mutations), GATA3, CCR4, and TFPT mutations.
The CDKN1B mutation is detected at a high level, possible germline abnormality.

Expression

Increased T-cell markers with abnormal expression pattern	Low B-cell markers

Diagnostic Implications

CDKN1B, TP53, PLCG1 (3 mutations), CEBPA, MTOR, GRIN2A, NOTCH1 (3 mutations), EP300, KMT2C (3 mutations), GATA3, CCR4, TFPT	-These findings are consistent with T-cell lymphoma with HTLVI positivity. -The CDKN1B mutation is likely a germline variant.

Therapeutic Implications

TP53	Aurora kinase A inhibitors, Wee1 inhibitors, Chk1 inhibitors, kevetrin, APR-246, nutlins, gene therapy
MTOR	MTOR inhibitors
GRIN2A	GRIN2A inhibitors
NOTCH1	NOTCH inhibitors
EP300	Bromodomain Extra-Terminal (BET) inhibitors

Prognostic Implications

TP53	Poor

PLCG1 (3 mutations)	Unknown
CEBPA	Neutral
MTOR	Poor
GRIN2A	Unknown
NOTCH1 (3 mutations)	Poor
EP300	Poor
KMT2C (3 mutations)	Unknown
GATA3	Unknown
CCR4	Unknown
TFPT	Unknown

Relevant Genes with NO Alteration
No evidence of mutation in SF3B1 or MYD88

Test Description:

This is a comprehensive molecular profile which uses next generation sequencing (NGS) to identify molecular abnormalities, including single nucleotide variants (SNVs), insertions/deletions (indels), copy number variants (CNVs), fusions, B- and T-cell clonality, IgVH mutation analysis, and viruses (HPV, EBV, and TTV), in DNA of 302 genes and RNA in greater than 1600 genes implicated in hematologic neoplasms, including leukemia, lymphoma, myeloma, myelodysplastic syndrome, and myeloproliferative neoplasms. Whenever possible, clinical relevance and implications of detected abnormalities are described below. If a gene is not reported, then no somatic mutations were detected. This assay facilitates myelodysplastic syndrome risk assessment as it includes evaluation for mutations and significant chromosomal gains and losses in all of the genes included in the IPSS-M risk calculator: ASXL1, BCOR, BCORL1, CBL, CEBPA, DNMT3A, ETNK1, ETV6, EZH2, FLT3, GATA2, GNB1, IDH1, IDH2, KMT2A (including KMT2A(MLL)-PTD), KRAS NF1, NPM1, NRAS, PHF6, PPM1D, PRPF8, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, TP53, U2AF1, and WT1.

Biological relevance of detected Alterations

- CDKN1B. This gene encodes a cyclin-dependent kinase inhibitor, which shares a limited similarity with CDK inhibitor CDKN1A/p21. The encoded protein binds to and prevents the activation of cyclin E-CDK2 or cyclin D-CDK4 complexes, and thus controls the cell cycle progression at G1. The degradation of this protein, which is triggered by its CDK dependent phosphorylation and subsequent ubiquitination by SCF complexes, is required for the cellular transition from quiescence to the proliferative state. Mutations in this gene are associated with multiple endocrine neoplasia type IV (MEN4). [provided by RefSeq, Apr 2014]

- TP53. This gene encodes a tumor suppressor protein containing transcriptional activation, DNA binding, and oligomerization domains. The encoded protein responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Mutations in this gene are associated with a variety of human cancers, including hereditary cancers such as Li-Fraumeni syndrome. Alternative splicing of this gene and the use of alternate promoters result in multiple transcript variants and isoforms. Additional isoforms have also been shown to result from the use of alternate translation initiation codons from identical transcript variants (PMIDs: 12032546, 20937277). [provided by RefSeq, Dec 2016]

- PLCG1. The protein encoded by this gene catalyzes the formation of inositol 1,4,5-trisphosphate and diacylglycerol from phosphatidylinositol 4,5-bisphosphate. This reaction uses calcium as a cofactor and plays an important role in the intracellular transduction of receptor-mediated tyrosine kinase activators. For example, when activated by SRC, the encoded protein causes the Ras guanine nucleotide exchange factor RasGRP1 to translocate to the Golgi, where it activates Ras. Also, this protein has been shown to be a major substrate for heparin-binding growth factor 1 (acidic fibroblast growth factor)-activated tyrosine kinase. Two transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Jul 2008]

- CEBPA. Acute myeloid leukemia (AML) with CEBPA mutation is characterized by CEBPA mutation that should be biallelic (biCEBPA) or, if single, must be located in the basic leucine zipper (bZIP) region of the gene (smbZIPCEBPA) (WHO 5th edition). For proper classification of AML, it is recommended to test for CEBPA and other recurrent, defining genetic abnormalities. CEBPA mutations are common in cytogenetically normal AML (CN-AML). AML with biCEBPA or smbZIP CEBPA has a favorable prognosis in children and adults up to 70 years old. Among cases with biCEBPA, approximately 5-10% have a germline N-terminal mutation. CEBPA is an intronless gene that encodes a DNA-binding protein that regulates myeloid differentiation and stem/progenitor cell function. The bZIP region is required for dimerization and DNA binding of this protein. N-terminal nonsense (frameshift) mutations result in a dominant negative C/EBP-alpha protein while C-terminal in-frame mutations in the b-ZIP domain reduce the DNA-binding potential of this transcription factor. The use of alternative in-frame non-AUG (GUG) and AUG start codons results in protein isoforms with different lengths. Differential translation initiation is mediated by an out-of-frame, upstream open reading frame which is located between the GUG and the first AUG start codons. [RefSeq (Dec 2013) and WHO Classification of Haematolymphoid Tumours, 5th edition online, IARC (accessed 01-31-2024)]

- MTOR. The protein encoded by this gene belongs to a family of phosphatidylinositol kinase-related kinases. These kinases mediate cellular responses to stresses such as DNA damage and nutrient deprivation. This kinase is a component of two distinct complexes, mTORC1, which controls protein synthesis, cell growth and proliferation, and mTORC2, which is a regulator of the actin cytoskeleton, and promotes cell survival and cell cycle progression. This protein acts as the target for the cell-cycle arrest and immunosuppressive effects of the FKBP12-rapamycin complex. Inhibitors of mTOR are used in organ transplants as immunosuppressants, and are being evaluated for their therapeutic potential in SARS-CoV-2 infections. Mutations in this gene are associated with Smith-Kingsmore syndrome and somatic focal cortical dysplasia type II. The ANGPTL7 gene is located in an intron of this gene. [provided by RefSeq, Aug 2020]

- GRIN2A. This gene encodes a member of the glutamate-gated ion channel protein family. The encoded protein is an N-methyl-D-aspartate (NMDA) receptor subunit. NMDA receptors are both ligand-gated and voltage-dependent, and are involved in long-term potentiation, an activity-dependent increase in the efficiency of synaptic transmission thought to underlie certain kinds of memory and learning. These receptors are permeable to calcium ions, and activation results in a calcium influx into post-synaptic cells, which results in the activation of several signaling cascades. Disruption of this gene is associated with focal epilepsy and speech disorder with or without cognitive disability. Alternative splicing results in multiple transcript variants. [provided by RefSeq, May 2014]

- NOTCH1. This gene encodes a member of the NOTCH family of proteins. Members of this Type I transmembrane protein family share structural characteristics including an extracellular domain consisting of multiple epidermal growth factor-like (EGF) repeats, and an intracellular domain consisting of multiple different domain types. Notch signaling is an evolutionarily conserved intercellular signaling pathway that regulates interactions between physically adjacent cells through binding of Notch family receptors to their cognate ligands. The encoded preproprotein is proteolytically processed in the trans-Golgi network to generate two polypeptide chains that heterodimerize to form the mature cell-surface receptor. This receptor plays a role in the development of numerous cell and tissue types. Mutations in this gene are associated with aortic valve disease, Adams-Oliver syndrome, T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, and head and neck squamous cell carcinoma. [provided by RefSeq, Jan 2016]

- EP300. This gene encodes the adenovirus E1A-associated cellular p300 transcriptional co-activator protein. It functions as histone acetyltransferase that regulates transcription via chromatin remodeling and is important in the processes of cell proliferation and differentiation. It mediates cAMP-gene regulation by binding specifically to phosphorylated CREB protein. This gene has also been identified as a co-activator of HIF1A (hypoxia-inducible factor 1 alpha), and thus plays a role in the stimulation of hypoxia-induced genes such as VEGF. Defects in this gene are a cause of Rubinstein-Taybi syndrome and may also play a role in epithelial cancer. [provided by RefSeq, Jul 2008]

- KMT2C. This gene is a member of the myeloid/lymphoid or mixed-lineage leukemia (MLL) family and encodes a nuclear protein with an AT hook DNA-binding domain, a DHHC-type zinc finger, six PHD-type zinc fingers, a SET domain, a post-SET domain and a RING-type zinc finger. This protein is a member of the ASC-2/NCOA6 complex (ASCOM), which possesses histone methylation activity and is involved in transcriptional coactivation. [provided by RefSeq, Jul 2008]

- GATA3. This gene encodes a protein which belongs to the GATA family of transcription factors. The protein contains two GATA-type zinc fingers and is an important regulator of T-cell development and plays an important role in endothelial cell biology. Defects in this gene are the cause of hypoparathyroidism with sensorineural deafness and renal dysplasia. [provided by RefSeq, Nov 2009]

- CCR4. The protein encoded by this gene belongs to the G-protein-coupled receptor family . It is a receptor for the CC chemokine - MIP-1, RANTES, TARC and MCP-1. Chemokines are a group of small polypeptide, structurally related molecules that regulate cell trafficking of various types of leukocytes. The chemokines also play fundamental roles in the development, homeostasis, and function of the immune system, and they have effects on cells of the central nervous system as well as on endothelial cells involved in angiogenesis or angiostasis. [provided by RefSeq, Jul 2008]

- TFPT. Predicted to enable DNA binding activity and protein kinase binding activity. Involved in apoptotic signaling pathway. Located in nucleoplasm. Part of Ino80 complex. [provided by Alliance of Genome Resources, Apr 2022]

Drug Information

APR-246

APR-246 is a first-in-class agent targeting mutant p53. In vitro and in vivo preclinical models have demonstrated that APR-246 has excellent efficacy in OC (both adenocarcinoma and squamous cell carcinoma) and potently synergises with chemotherapies used in the treatment of OC, restoring

sensitivity to chemotherapy-resistant tumours. An initial phase I clinical trial has shown APR-246 to be safe in humans and early results from a currently running phase Ib/II trial of APR-246 with carboplatin and liposomal doxorubicin in ovarian cancer have been promising. Together, these data provide a strong rationale for investigating the efficacy of APR-246 in OC.

APR-246 has been used in trials studying the treatment of Prostatic Neoplasms, Hematologic Neoplasms, and Platinum Sensitive Recurrent High-grade Serous Ovarian Cancer With Mutated p53.

APR-246 is an analogue of PRIMA-1, which modifies the core domain of mutant p53, resulting in restoration of wild-type p53 conformation and reactivation of normal p53 function, leading to increased cell cycle arrest and tumor cell death (PMID: 20498645).

Everolimus

Everolimus is a PI3K/Akt/mTOR pathway inhitior. The PI3K/Akt/mTOR plays a cruitial role in trastuzumab resistance, dysregulating the HER2 downstream signal. The mTOR inhibitor everolimus inhibits the mTOR/S6K signal, and therefore improves fluorouracil-induced apoptosis in gastric cancer cells with HER2 amplification. A concordant therapy using HER2-targeted agents and everolimus might lead to an improvement in therapy of HER2-positive gastric cancer.

Temsirolimus

Temsirolimus is an inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-drug complex inhibits the activity of mTOR that controls cell division. Inhibition of mTOR activity resulted in a G1 growth arrest in treated tumor cells. When mTOR was inhibited, its ability to phosphorylate p70S6k and S6 ribosomal protein, which are downstream of mTOR in the PI3 kinase/AKT pathway was blocked. In in vitro studies using renal cell carcinoma cell lines, temsirolimus inhibited the activity of mTOR and resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor.

Temsirolimus is indicated for the treatment of renal cell carcinoma (RCC). Also investigated for use/treatment in breast cancer, lymphoma (unspecified), rheumatoid arthritis, and multiple myeloma.

Brontictuzumab

Brontictuzumab is a humanized monoclonal antibody directed against the Notch-1 receptor with potential antineoplastic activity. Upon administration, brontictuzumab binds to Notch-1 on the cell surface, thereby inhibiting Notch-mediated signaling and tumor cell proliferation. Notch 1, a type 1 transmembrane protein belonging to the Notch family, functions as a receptor for membrane bound ligands and has various roles during development; dysregulated Notch signaling is associated with increased cell growth and chemoresistance in cancers.

Birabresib

Birabresib (OTX015 or MK-8628) is a potent BET bromodomian inhibitor, which targets the BET bromodomain proteins 2, 3, and 4 (BRD2/3/4). BRDs 2, 3, and 4 are considered potential cancer targets because of their pivotal role in regulating the transcription of growth-promoting genes and cell cycle regulators. OTX015 is the first BRD2/3/4 inhibitor to enter clinical trials. Upon administration, birabresib binds to the acetylated lysine recognition motifs on the bromodomain of BET proteins, thereby preventing the interaction between the BET proteins and acetylated histone peptides. This disrupts chromatin remodeling and gene expression.

Potential Clinical Trials

Trial URL	Status	Title	Disease	Drug	Sites
https://clinicaltrials.gov/study/NCT04068597	Recruiting	An Open-label Phase I/IIa Study to Evaluate the Safety and Efficacy of CCS1477 as Monotherapy and in Combination in Patients With Advanced Haematological Malignancies.	T-Cell Lymphoma	CCS1477, Pomalidomide, Dexamethasone, Azacitidine, Venetoclax	Emory Winship Cancer Institute, Atlanta, Georgia 30322 The Center for Cancer and Blood Disorders (CCBD), Bethesda, Maryland 20817 Community Health Network, Indianapolis, Indiana 46227

https://clinicaltrials.gov/study/NCT06698003	Recruiting	A Phase 2 Study for Screening and Prevention of Adult T-cell Leukemia/Lymphoma With Mogamulizumab in High-Risk Carriers of HTLV-1	T-Cell Lymphoma	Mogamulizumab	Memorial Sloan Kettering Monmouth (All protocol activities), Middletown, New Jersey 07748 Memorial Sloan Kettering at Basking Ridge (All protocol activities), Basking Ridge, New Jersey 07920 Memorial Sloan Kettering Cancer Center (All Protocol Activities), New York, New York 10065
https://clinicaltrials.gov/study/NCT06692452	Recruiting	A Phase II Study of Tazemetostat in Combination With CHOP for Previously Untreated T Cell Lymphoma	T-Cell Lymphoma	Tazemetostat, Doxorubicin, Vincristine, Prednisone, Cytoxan, Carmustine, Etoposide, Cytarabine, Melphalan	Dana-Farber Cancer Institute, Boston, Massachusetts 02115 Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215 Brigham and Women's Hospital, Boston, Massachusetts 02215
https://clinicaltrials.gov/study/NCT04301076	Recruiting	A Phase 1 Study of Lenalidomide in Combination With EPOCH Chemotherapy for HTLV-Associated Adult T-Cell Leukemia-Lymphoma (ATLL)	T-Cell Lymphoma	Biospecimen Collection, Bone Marrow Biopsy, Computed Tomography, Cyclophosphamide, Doxorubicin Hydrochloride, Etoposide, Lenalidomide, Positron Emission Tomography, Prednisone, Vincristine Sulfate	Emory University Hospital Midtown, Atlanta, Georgia 30308 Emory University Hospital/Winship Cancer Institute, Atlanta, Georgia 30322 VCU Massey Comprehensive Cancer Center, Richmond, Virginia 23298

Detailed Results

Single Nucleotide Variant (SNV) and Insertions-Deletions (INDELS)

Gene name	Hgvsp	Hgvsc	Amino acids	Codons	Consequence	Allele frequency	Read depth	Predicted effect on protein
CDKN1B	NP_004055.1:p.Glu105Ter	NM_004064.3:c.313G>T	E/*	Gag/Tag	stop_gained	45.37	1567	0
TP53	NP_000537.3:p.Arg273His	NM_000546.5:c.818G>A	R/H	cGt/cAt	missense_variant	21.17	1346	tolerated
PLCG1	NP_002651.2:p.Asp342Asn	NM_002660.2:c.1024G>A	D/N	Gac/Aac	missense_variant	12.72	1596	deleterious
CEBPA	NP_004355.2:p.Tyr147Ter	NM_004364.3:c.441C>G	Y/*	taC/taG	stop_gained	11.74	1201	0
MTOR	NP_004949.1:p.Gln45Ter	NM_004958.3:c.133C>T	Q/*	Cag/Tag	stop_gained	11.49	1279	0
GRIN2A	NP_000824.1:p.Phe1158Val	NM_000833.3:c.3472T>G	F/V	Ttc/Gtc	missense_variant	11.33	1174	tolerated

NOTCH1	NP_060087.3:p.Gly1301Glu	NM_017617.3:c.3902G>A	G/E	gGg/gAg	"missense_variant,splice_region_variant"	9.72	2911	deleterious
EP300	NP_001420.2:p.Phe1353ProfsTer9	NM_001429.3:c.4056_4063del	FPY/X	tcCTTTCCATac/tcac	frameshift_variant	9.25	1286	0
KMT2C	NP_733751.2:p.Gly972Arg	NM_170606.2:c.2914G>A	G/R	Gga/Aga	missense_variant	8.11	715	deleterious
NOTCH1	NP_060087.3:p.Ser2432Arg	NM_017617.3:c.7296C>G	S/R	agC/agG	missense_variant	7.93	2421	tolerated
GATA3	NP_001002295.1:p.Ser67ProfsTer225	NM_001002295.1:c.199_233del	NSVRATVQRYPP/X	aACTCGGTCAGGGCCACGGTGCAGAGGTACCCTCCG/a	frameshift_variant	7.34	2601	0
NOTCH1	NP_060087.3:p.Ser2439Arg	NM_017617.3:c.7317C>G	S/R	agC/agG	missense_variant	7.14	2214	tolerated
KMT2C	NP_733751.2:p.Asp341Val	NM_170606.2:c.1022A>T	D/V	gAt/gTt	missense_variant	3.66	410	deleterious
PLCG1	NP_002651.2:p.Phe691Ile	NM_002660.2:c.2071T>A	F/I	Ttc/Atc	missense_variant	2.6	1271	deleterious
PLCG1	NP_002651.2:p.Arg707Gln	NM_002660.2:c.2120G>A	R/Q	cGg/cAg	"missense_variant,splice_region_variant"	1.46	1028	deleterious
KMT2C	NP_733751.2:p.Ser773Pro	NM_170606.2:c.2317T>C	S/P	Tca/Cca	missense_variant	1.13	705	deleterious
CCR4 (RNA)	NP_005499.1:p.Tyr347Ter	NM_005508.4:c.1041C>A	Y/*	taC/taA	stop_gained	22.59	1098	0
TFPT (RNA)	NP_037474.1:p.Arg201Ter	NM_013342.3:c.601C>T	R/*	Cga/Tga	stop_gained	13.1	145	0

Methodology and Test Background

This is a next generation sequencing (NGS) test that involves separate analysis of DNA and RNA panels for abnormalities that are reported in various types of hematologic neoplasms. The DNA panel is composed of 302 genes and the RNA panel is composed of >1600 genes. The DNA and RNA components of this assay were developed, validated, and set up as separate workflows, with independent extraction, library preparation, sequencing, and analysis pipelines. The NGS assay also detects several viruses that are important in oncology, including EBV, HPV and TTV. TTV (torque teno virus) was first discovered in a patient with non-A-E hepatitis and is now regarded as a part of the human virome. In general, TTV does not cause pathology in immunocompetent individuals. TTV is considered as a marker of immune competence in patients with immunological impairment and inflammatory disorders. High TTV load is associated with increased risk of infection. In patients with organ transplant, low TTV load is associated with an increased risk of rejection.

Nucleic acid is isolated from fresh cells, peripheral blood cells, bone marrow, body fluid, or paraffin-embedded tissue. For optimal results, neoplastic cells should be >30% of the analyzed cells. For fresh bone marrow specimens with the clinical indication of myeloma, enrichment for CD138-positive cells may be performed using immunomagnetic positive selection and both the CD138-positive and CD138-negative cell fractions extracted for NGS testing and the findings integrated within the final report. Testing is performed using massive parallel sequencing of the coding DNA of the listed genes. This includes sequencing of all the exons as well as approximately 50 nucleotides at the 5' and 3' ends of each coding exon to detect splice site abnormalities. The TERT promoter region, including the hotspots at -124 and -146 bp, is also covered. Our DNA sequencing method has a sensitivity of 1% for detecting single nucleotide variants (SNVs) and small (<60 bp) insertions/ deletions (indels). Significant gene amplification and deletion (copy number variants) are also reported. In addition, fragment length analysis is performed for CALR, FLT3, and NPM1 to enhance the detection of large indels and has a sensitivity of 2%-5% for detecting CALR, FLT3-ITD, and NPM1 indels in wildtype background. For cases with indication of acute myeloid leukemia, preliminary FLT3-ITD results based on fragment

analysis will be reported. Targeted RNA NGS is performed by hybrid capture and duplicates are excluded for levels measurements. The Universal Human Reference (UHR) RNA is used as control. All detected fusion transcripts are reported. While the major focus of the RNA analysis is the detection of fusion mRNA, mutations in the expressed RNA of the analyzed genes, B- and T-cell clonality, HLA class I genotyping, and Epstein-Barr virus (EBV), human papillomavirus (HPV) and torque teno virus (TTV) viral RNA are also analyzed and reported. In cases of suspected chronic lymphocytic leukemia (CLL), IgVH mutation rate will also be reported. The sensitivity of this assay for detecting fusion mRNA is between 5% and 10%. This test specifically detects translocations that lead to the expression of fusion RNA. Translocations that lead to deregulation of expression can be addressed by this test if compared to the proper normal expression control. Since the clinical relevance of the RNA expression level of most of the genes is not well-characterized at this time, only a small subset of the genes may be described based on the suspected disease, including but not limited to MYC, BCL2, CD274, CD19, CD22, CD34, and CD138. CRLF2 mRNA levels are reported in acute lymphoblastic leukemia. CD274 (PD-L1) mRNA levels are reported when they are significantly elevated. Performance of the assay may vary dependent on the quantity and quality of nucleic acid, sample preparation, and sample age. Decalcified specimens have not been validated. Decalcification with strong acids is not recommended and may lead to poor nucleic acid quality and suboptimal results.

Based on our validation study, the following exonic regions of the genes listed below are not covered appropriately <100 X coverage and sequencing by NGS may not be reliable in these regions. The poor coverage is primarily due to the inherent difficulty in obtaining adequate sequencing coverage in regions with high GC content. No well-characterized hotspots are present in these regions. RAD51 NM_133487 chr15:40994004-40994124, BRCA1 NM_007300 chr17:41231351-41231416, FUBP1 NM_003902 chr1:78435609-78435699, CBLB NM_170662 chr3:105420938-105421303, TERT NM_198253 chr5:1295183-1295250, ARID1B NM_017519 chr6:157098715-157100605, CUX1 NM_001202543 chr7:101740644-101740781, KMT2C NM_170606 chr7:151891314-151891346 and 151935792-151935911, GALNT12 NM_024642 chr9:101569952-101570351, ATM NM_000051 chr11:108164040-108164204, CDK17 NM_001170464 chr12:96679880-96679926, RB1 NM_000321 chr13:48954189-48954220, SETBP1 NM_015559 chr18:42643044-42643692, KMT2B NM_014727 chr19:36208921-36209283, AR NM_000044 chrX:66764889-66766604, STAG2 NM_001042749 chrX:123200025-123200112.

The table below may contain a partial list of the tested DNA genes. For a complete list, please go to: https://genomictestingcooperative.com/genomic-tests/gtc-hematology-profile-plus/ *(click the DNA tab)*

The table below contains a partial list of the tested RNA genes (Fusions/Expression). For a complete list, please go to: https://genomictestingcooperative.com/genomic-tests/gtc-hematology-profile-plus/ *(click the RNA tab)*

Tested genes

Genes Tested for Abnormalities in Coding Sequence												
ABL1	B2M	CCNE1	CUX1	ETNK1	GALNT12	IL7R	MCL1	NFE2L2	PIM1	RB1	SMO	TRAF3
ABRAXAS1	BAP1	CD274	CXCR4	ETV6	GATA1	INHBA	MDM2	NFKBIA	PLCG1	RET	SOCS1	TSC1
ACVR1B	BARD1	CD79A	CYLD	EXO1	GATA2	IRF4	MDM4	NKX2-1	PMS1	RHEB	SOX2	TSC2
AKT1	BCL2	CD79B	DAXX	EZH2	GATA3	JAK1	MED12	NOTCH1	PMS2	RHOA	SOX9	TSHR
AKT2	BCL2L1	CDC73	DDR2	FANCA	GEN1	JAK2	MEF2B	NOTCH2	POLD1	RIT1	SPOP	U2AF1
AKT3	BCL6	CDH1	DDX41	FANCC	GNA11	JAK3	MEN1	NOTCH3	POLE	RNF43	SRC	U2AF2
ALK	BCOR	CDK12	DICER1	FANCD2	GNAQ	KAT6A	MET	NPM1	POT1	ROS1	SRSF2	UBA1
AMER1	BCORL1	CDK4	DNM2	FANCE	GNAS	KDM5C	MITF	NRAS	PPM1D	RUNX1	STAG2	VHL
ANKRD26	BCR	CDK6	DNMT3A	FANCF	GNB1	KDM6A	MLH1	NSD1	PPP2R1A	SAMD9	STAT3	WT1
APC	BIRC3	CDKN1B	DOT1L	FANCG	GREM1	KDR	MPL	NSD2 (WHSC1)	PRDM1	SAMD9L	STAT5B	XPO1
AR	BLM	CDKN2A	EED	FAS	GRIN2A	KEAP1	MRE11	NTHL1	PRKAR1A	SDHA	STK11	XRCC2
ARAF	BMPR1A	CDKN2B	EGFR	FBXW7	H3-3A (H3F3A)	KIT	MSH2	NTRK1	PRKDC	SDHAF2	SUFU	XRCC3
ARID1A	BRAF	CDKN2C	EGLN1	FGF4	H3C2 (HIST1H3B)	KMT2A	MSH3	NTRK2	PRPF8	SDHB	SUZ12	ZNF217
ARID1B	BRCA1	CEBPA	ELANE	FGF6	HGF	KMT2B	MSH6	NTRK3	PRSS1	SDHC	TAL1	ZRSR2

ARID2	BRCA2	CHEK1	EP300	FGFR1	HNF1A	KMT2C	MTOR	PAK3	PTCH1	SDHD	TCF3	-
ASXL1	BRIP1	CHEK2	EPAS1	FGFR2	HOXB13	KMT2D	MUTYH	PALB2	PTEN	SETBP1	TENT5C (FAM46C)	-
ATM	BTK	CIC	EPCAM	FGFR3	HRAS	KRAS	MYC	PAX5	PTPN11	SETD2	TERC	-
ATR	CALR	CREBBP	EPHA3	FGFR4	HSP90AA1	LRP1B	MYCL	PBRM1	RAC1	SF3B1	TERT	-
ATRX	CARD11	CRLF2	EPHA5	FH	ID3	MAP2K1	MYCN	PDGFRA	RAD21	SMAD2	TET2	-
AURKA	CBL	CSF1R	ERBB2	FLCN	IDH1	MAP2K2	MYD88	PDGFRB	RAD50	SMAD4	TGFBR2	-
AURKB	CBLB	CSF3R	ERBB3	FLT3	IDH2	MAP2K4	NBN	PHF6	RAD51	SMARCA4	TMEM127	-
AURKC	CBLC	CTCF	ERBB4	FLT4	IGF1R	MAP3K1	NF1	PIK3CA	RAD51C	SMARCB1	TNFAIP3	-
AXIN1	CCND1	CTNNA1	ERG	FOXL2	IKZF1	MAP3K14	NF2	PIK3R1	RAD51D	SMC1A	TNFRSF14	-
AXIN2	CCND3	CTNNB1	ESR1	FUBP1	IKZF3	MAPK1	NFE2	PIK3R2	RAF1	SMC3	TP53	-

RNA Fusions/Expression

Fusion/Expression																
ABL1	BCL2	CCND1	CREBBP	EGFR	ETV4	FGFR2	FOXO1	IKZF3	MAP3K1	MYH9	NTRK3	PAX5	PDGFRB	PTK2B	ROS1	TAL1
ABL2	BCL6	CD274 (PD-L1)	CRLF2	EPOR	ETV5	FGFR3	FUS	JAK2	MECOM	NOTCH1	NUP214	PBX1	PICALM	RARA	RUNX1	TCF3
AKT3	BRAF	CBL	CSF1R	ERG	ETV6	FIP1L1	GLI1	KMT2A	MRTFA	NTRK1	NUP98	PCM1	PIGA	RET	RUNX1T1	TFG
ALK	CBFB	CIC	DUSP22	ETV1	FGFR1	FLT3	HLF	LYN	MYC	NTRK2	P2RY8	PDGFRA	PML	RHOA	STAT6	TYK2

Reference

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3. T cell lymphoma: time to make discoveries and advance treatment. Ishitsuka K. Int J Hematol. 2023 Apr;117(4):473-474. doi: 10.1007/s12185-023-03573-3. Epub 2023 Mar 14. PMID: 36918503.

4. Hepatosplenic T-cell lymphoma: treatment challenges. Bron D, De Leval L, Michiels S, Wittnebel S; EuroBloodNet for rare diseases. Curr Opin Oncol. 2021 Sep 1;33(5):406-411. doi: 10.1097/CCO.0000000000000775. PMID: 34409955.

Electronic Signature

Maher Albitar, M.D.

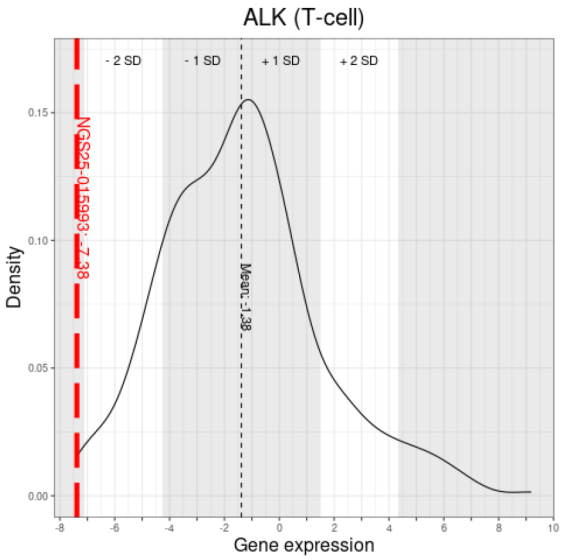
The test (sample processing, sequencing and data generation) was performed at Genomic Testing Cooperative, LCA, 25371 Commercentre Drive Lake Forest, CA 92630. Medical Director Maher Albitar, M.D. Analysis of the data was performed by Genomic Testing Cooperative, LCA, 25371 Commercentre Drive, Lake Forest, CA 92630. Medical Director: Maher Albitar, M.D. (CLIA #: 05D2111917 CAP #: 9441574). The signing pathologist is fully responsible for the accuracy and interpretation of results and the release of this report.

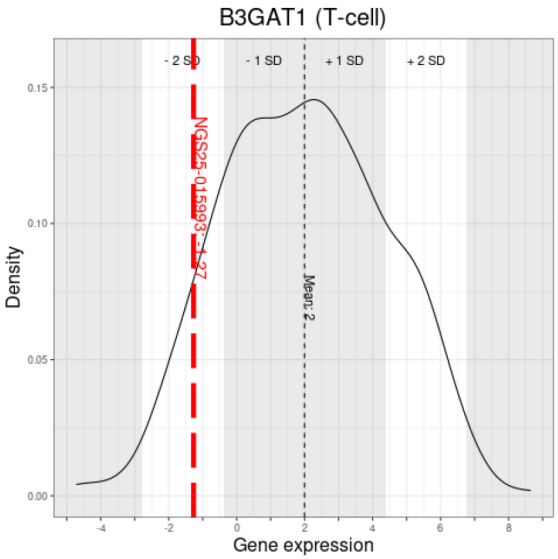
The test was developed and its performance characteristics have been determined by Genomic Testing Cooperative, LCA. This test has not been approved by the FDA. The FDA has determined such clearance or approval is not necessary. This laboratory is CLIA certified to perform high complexity clinical testing.

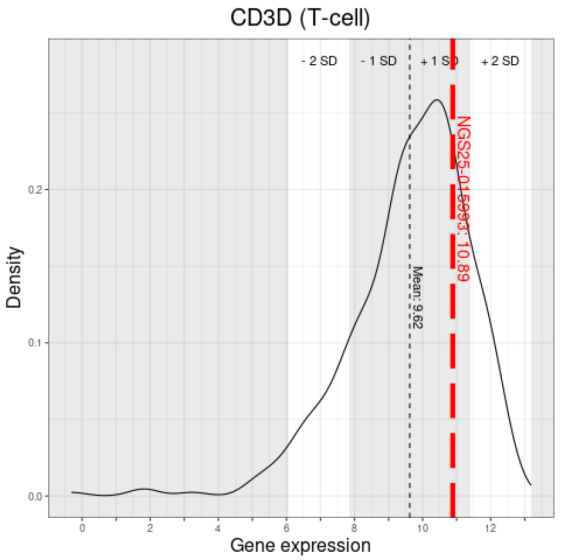
Additional Report Information

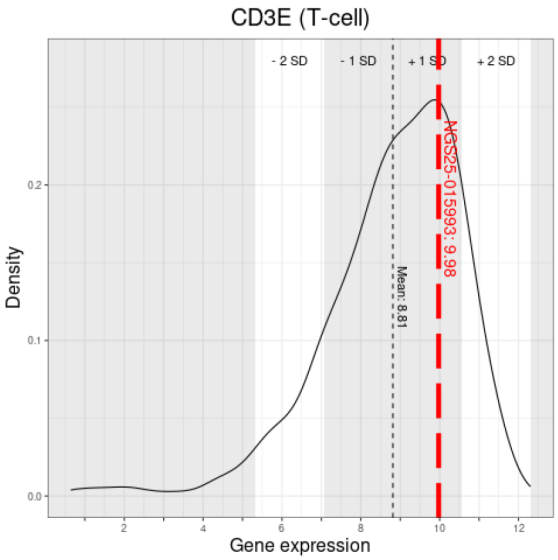
RNA Expression Plots

These plots represent the distribution of the expression in log2 transformed TPM (transcript per million) for each gene across GTC's history for the specified disease. The mean for each distribution is denoted by the black dotted line, while the alternating shaded areas depict the standard deviation. The expression for the current patient is marked by the red dotted line.





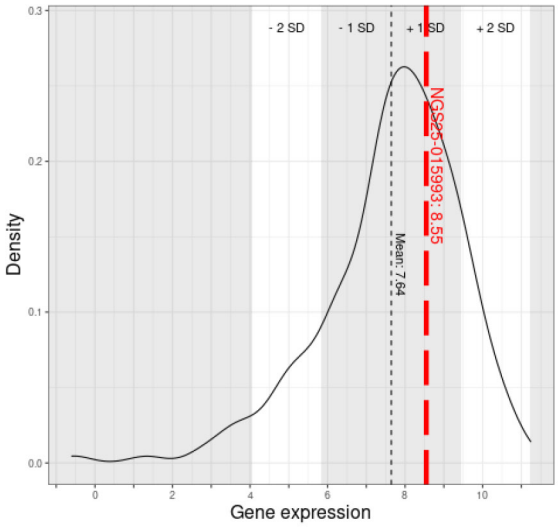




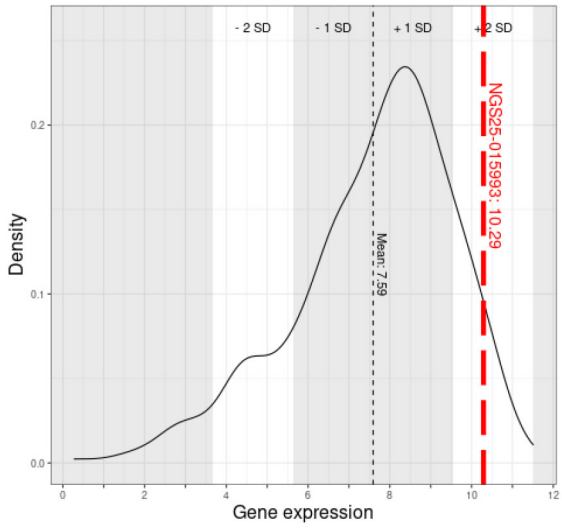
Additional Report Information

RNA Expression Plots

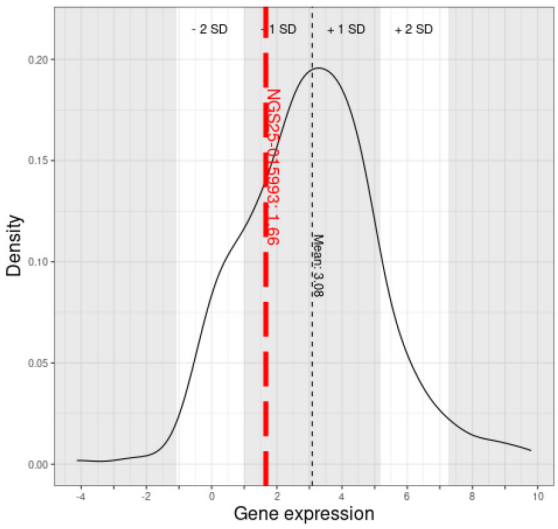
CD3G (T-cell)



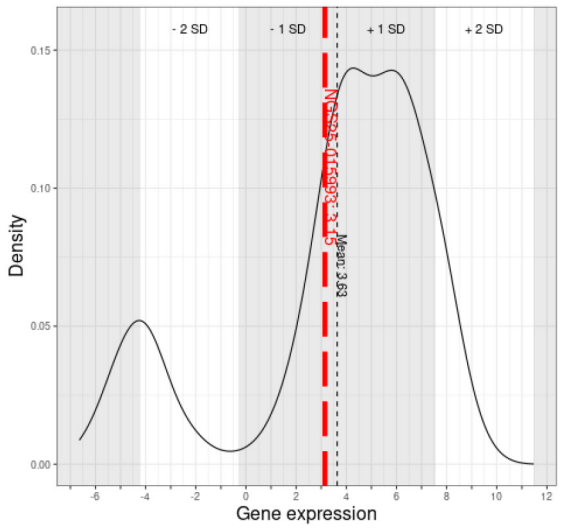
GATA3 (T-cell)



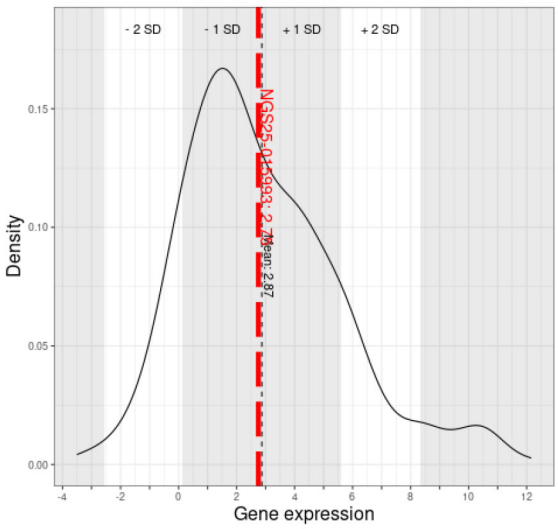
NCAM1 (T-cell)



TBX21 (T-cell)



TNFRSF8 (T-cell)



Additional Report Information

Chromosomal Abnormality Graph