

Hematology Profile Plus

Patient Name: <input type="text"/> Date of Birth: <input type="text"/> Gender (M/F): <input type="text"/> Client: <input type="text"/> Case #: <input type="text"/> Body Site: <input type="text" value="Rt Iliac Crest"/>	Ordering Physician: <input type="text"/> Physician ID: <input type="text"/> Accession #: <input type="text"/> Specimen Type: <input type="text" value="BONE MARROW"/> Specimen ID: <input type="text"/>
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MRN: <input type="text"/> Collected Date: <input type="text"/> Time: <input type="text"/> Received Date: <input type="text"/> Time: <input type="text"/> Reported Date: <input type="text" value="05/05/2025"/> Time: <input type="text" value="09:16 AM"/>	Indication for Testing: <input type="text" value="C92.00 Acute myeloblastic leukemia, not having achieved remission"/>
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Detected Genomic Alterations				
FLT3-ITD (33bp ins)	WT1 (2 mutations)	t(5;11)(q35;p15) NSD1::NUP98 fusion mRNA	No detectable autosomal chromosomal structural gain or loss	B- and T-cell clonality : Not detected

Results Summary

- **-Mutations in FLT3-ITD and WT1 (2 mutations) genes**
 - **-t(5;11)(q35;p15) NSD1::NUP98 fusion mRNA**
 - **-No detectable autosomal chromosomal structural gain or loss**
 - **-EBV viral RNA: Not detected**
 - **-HPV viral RNA: Not detected**
 - **-TTV viral RNA: Not detected**
 - **-HLA Genotyping:**
 - HLA-A: A*02:844-A*23:01
 - HLA-B: B*07:02-B*14:02
 - HLA-C: C*07:02-C*08:02
 - **-B- and T-cell clonality : Not detected**
 - **-Increased HOXA9 mRNA**
 - **-Increased CD34 and CD117 mRNA**
- These findings are consistent with acute myeloid leukemia (AML).
- NUP98 fusion suggests response to menin inhibitors.
- See expression plots at the end of the report.**

Heterogeneity

There is a dominant abnormal clone with FLT3 and WT1 (p.Arg380feTer?) mutations. The WT1 (p.Pro372CysfsTer4) mutation is detected in a subclone.

Expression

Increased HOXA9 mRNA

Increased CD34 and CD117 mRNA

Diagnostic Implications

FLT3, WT1 (2 mutations)

These findings are consistent with acute myeloid leukemia (AML).

Therapeutic Implications

FLT3

FLT3 inhibitors

WT1

Sensitive to hypomethylating agents (Azacitidine)

Prognostic Implications

FLT3

Poor

WT1 (2 mutations)

Poor

Relevant Genes with NO Alteration

No evidence of mutation in NPM1, IDH1, or IDH2

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

- FLT3. This gene encodes a class III receptor tyrosine kinase that regulates hematopoiesis. This receptor is activated by binding of the fms-related tyrosine kinase 3 ligand to the extracellular domain, which induces homodimer formation in the plasma membrane leading to autophosphorylation of the receptor. The activated receptor kinase subsequently phosphorylates and activates multiple cytoplasmic effector molecules in pathways involved in apoptosis, proliferation, and differentiation of hematopoietic cells in bone marrow. Mutations that result in the constitutive activation of this receptor result in acute myeloid leukemia and acute lymphoblastic leukemia. [provided by RefSeq, Jan 2015]

- WT1. This gene encodes a transcription factor that contains four zinc-finger motifs at the C-terminus and a proline/glutamine-rich DNA-binding domain at the N-terminus. It has an essential role in the normal development of the urogenital system, and it is mutated in a small subset of patients with Wilms tumor. This gene exhibits complex tissue-specific and polymorphic imprinting pattern, with biallelic, and monoallelic expression from the maternal and paternal alleles in different tissues. Multiple transcript variants have been described. In several variants, there is evidence for the use of a non-AUG (CUG) translation initiation codon upstream of, and in-frame with the first AUG. Authors of PMID:7926762 also provide evidence that WT1 mRNA undergoes RNA editing in human and rat, and that this process is tissue-restricted and developmentally regulated. [provided by RefSeq, Mar 2015]

Drug Information

Gilteritinib

Gilteritinib is a potent selective inhibitor of both of the mutations, internal tandem duplication (ITD) and tyrosine kinase domain (TKD), of the FLT3 receptor.

Gilteritinib is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia with an FLT3 mutation detected by an FDA-approved test. Gilteritinib was FDA approved on November 28, 2018.

Midostaurin

Midostaurin (RYDAPT) is a kinase inhibitor indicated for the treatment of adult patients with: Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. It is also indicated for treatment of aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

Side effects: The most common adverse reactions (greater than or equal to 20%) were febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycemia, and upper respiratory tract infection.

DRUG INTERACTIONS Strong CYP3A4 Inhibitors: Strong CYP3A4 inhibitors may increase exposure to midostaurin and its active metabolites. Consider alternative therapies that do not strongly inhibit CYP3A4 or monitor for increased risk of adverse reactions. Strong CYP3A4 Inducers: Avoid concomitant use as strong CYP3A4 inducers decrease exposure to midostaurin and its active metabolites.

Vandetanib

Vandetanib is a potent and selective inhibitor of VEGFR (vascular endothelial growth factor receptor), EGFR (epidermal growth factor receptor) and RET (REarranged during Transfection) tyrosine kinases.

VEGFR- and EGFR-dependent signalling are both clinically validated pathways in cancer, including non-small-cell lung cancer (NSCLC). RET activity is important in some types of thyroid cancer, and early data with vandetanib in medullary thyroid cancer has led to orphan-drug designation by the regulatory authorities in the USA and EU.

Vandetanib is indicated for:

- Metastatic Medullary Thyroid Cancer
- Locally advanced Medullary thyroid cancer

On April 6, 2011, vandetanib was approved by the FDA to treat nonresectable, locally advanced, or metastatic medullary thyroid cancer in adult patients.

Azacitidine

Azacitidine is a pyrimidine analogue that inhibits DNA methyltransferase, impairing DNA methylation. It is also an antimetabolite of cytidine, incorporated primarily into RNA. Azacitidine has been used as an antineoplastic agent.

Azacitidine for injection is a nucleoside metabolic inhibitor indicated for the treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome (MDS) subtypes: Refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML).

Potential Clinical Trials

Trial URL	Status	Title	Disease	Drug	Sites
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https://clinicaltrials.gov/study/NCT05918692	Recruiting	A Phase 1, Open-label, Dose-escalation, and Dose-expansion Study of BMF-500, an Oral Covalent FLT3 Inhibitor, in Adults With Acute Leukemia	Acute Myeloid Leukemia	BMF-500	Fred Hutchinson Cancer Center, Seattle, Washington 98109 University of California, San Francisco, San Francisco, California 94143 University of California, Davis, Sacramento, California 95817
https://clinicaltrials.gov/study/NCT05520567	Recruiting	A Phase 1/2, Multicenter, Open-Label, Randomized Dose Ranging and Expansion Study of the Combination of Gilteritinib, Venetoclax and Azacitidine in Patients With Newly Diagnosed FLT3 Mutated Acute Myeloid Leukemia (AML) Not Eligible for Intensive Induction Chemotherapy	Acute Myeloid Leukemia	Gilteritinib, Venetoclax, Azacitidine	Oregon Health and Science University, Portland, Oregon 97239 UCLA Medical Center, Los Angeles, California 90095 City of Hope Nat'l Medical Center, Duarte, California 91010
https://clinicaltrials.gov/study/NCT05558124	Recruiting	A Phase 1/1b Dose Escalation and Expansion of CPX-351 in Combination With Gemtuzumab Ozogamicin in Newly Diagnosed Acute Myeloid Leukemia	Acute Myeloid Leukemia	Vyxeos, Gemtuzumab Ozogamicin	Moffitt Cancer Center, Tampa, Florida 33612

Detailed Results

Single Nucleotide Variant (SNV) and Insertions-Deletions (INDELS)								
Gene name	Hgvsnp	Hgvsc	Amino acids	Codons	Consequence	Allele frequency	Read depth	Predicted effect on protein
FLT3	NP_004110.2:p.Tyr597_Glu598insAspProLeuPheTyrValAspPheArgGluTyr	NM_004119.2:c.1793_1794insCCCTCTTCTACGTTGATTCAGAG AATATGA	E/DPLFYVDFR EYE	gaa/gaCCC CCTCTTCTA CGTTGATTT CAGAGAATA TGAA	inframe_insertion	40.39	614	0
WT1	NP_077744.3:p.Arg380feTer?	NM_024426.4:c.1138delCinsAA	R/X	C/AA	frameshift_variant	35.07	1557	0
WT1	NP_077744.3:p.Pro372CysfsTer4	NM_024426.4:c.1109_1110insAG	R/RX	cgt/cgAGt	frameshift_variant	0.96	1353	0

Methodology and Test Background

This is a next generation sequencing (NGS) test that analyzes DNA of 302 genes and RNA of >1600 genes for abnormalities that are reported in various types of hematologic neoplasms. The 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

- Maintenance Therapy in AML: What Is the Future Potential? Goulart H, Wei AH, Kadia TM. Am J Hematol. 2025 Mar;100 Suppl 2:38-49. doi: 10.1002/ajh.27583. PMID: 39960005.
- Contemporary Management of Acute Myeloid Leukemia: A Review. Venugopal S, Sekeres MA. JAMA Oncol. 2024 Oct 1;10(10):1417-1425. doi: 10.1001/jamaoncol.2024.2662. PMID: 39115831.
- CAR-T cell therapy in AML: recent progress and future perspectives. Saito S, Nakazawa Y. Int J Hematol. 2024 Oct;120(4):455-466. doi: 10.1007/s12185-024-03809-w. Epub 2024 Jul 4. PMID: 38963636.
- A review of FLT3 inhibitors in acute myeloid leukemia. Zhao JC, Agarwal S, Ahmad H, Amin K, Bewersdorf JP, Zeidan AM. Blood Rev. 2022 Mar;52:100905. doi: 10.1016/j.blre.2021.100905. Epub 2021 Nov 3. PMID: 34774343.

Electronic Signature

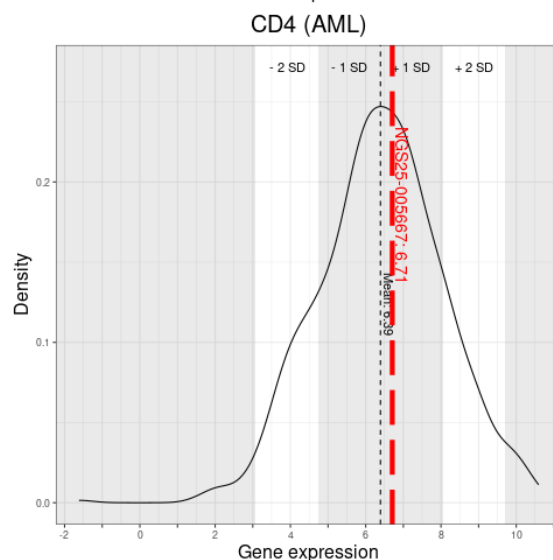
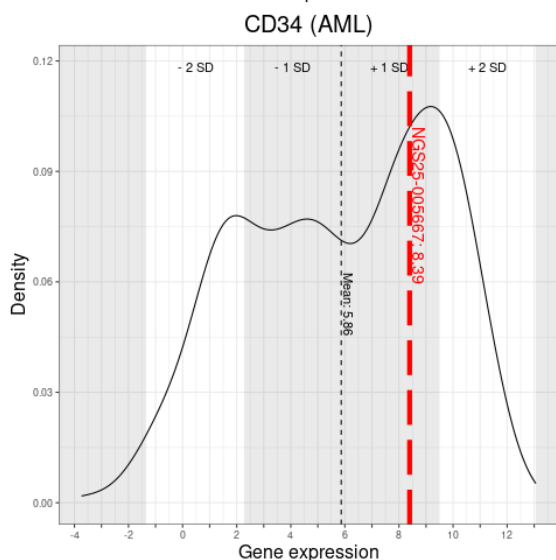
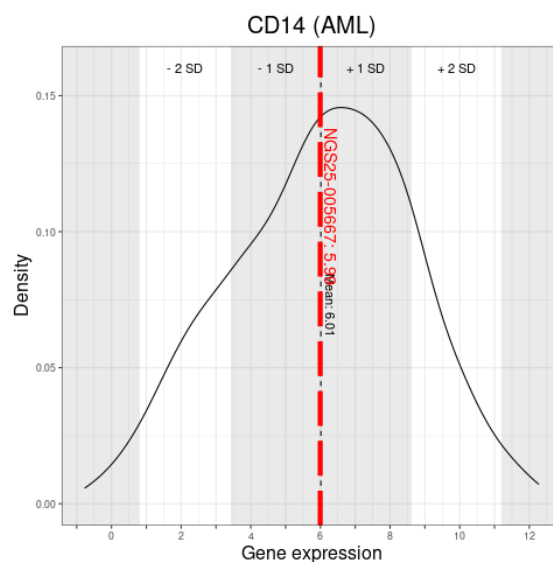
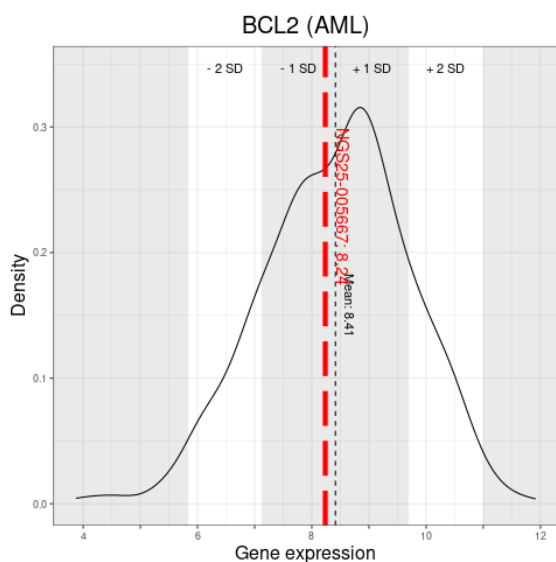
Maher Albitar, M.D.

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.

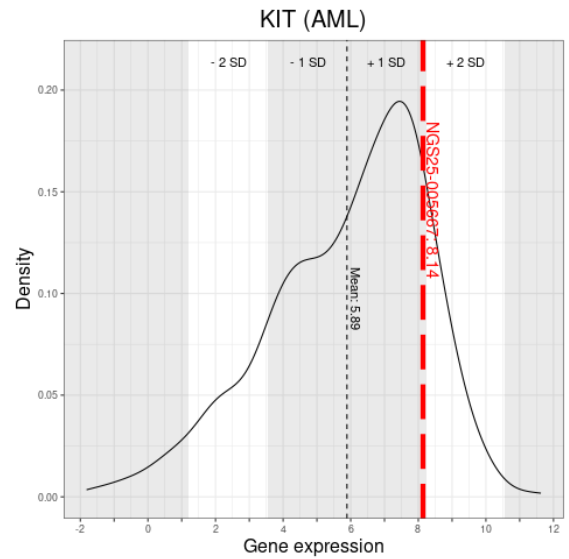
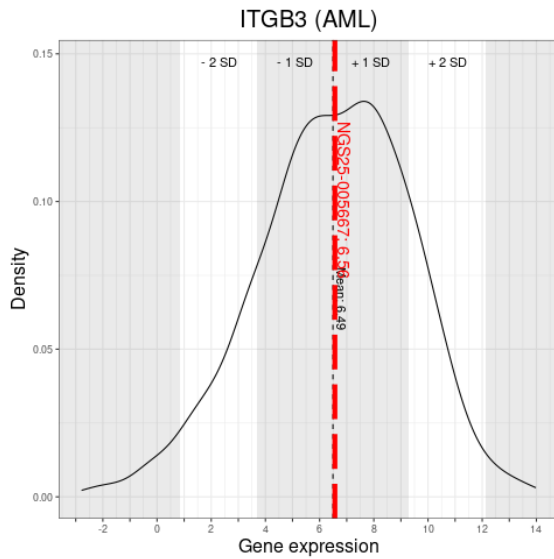
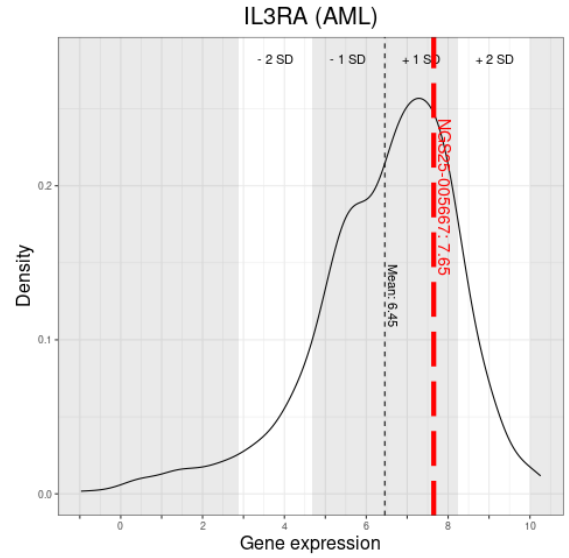
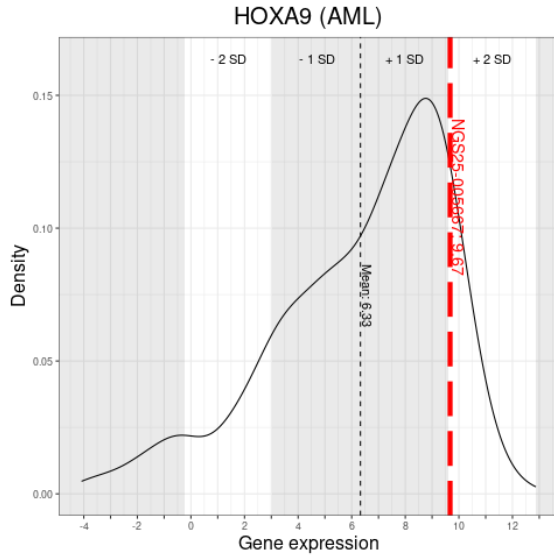
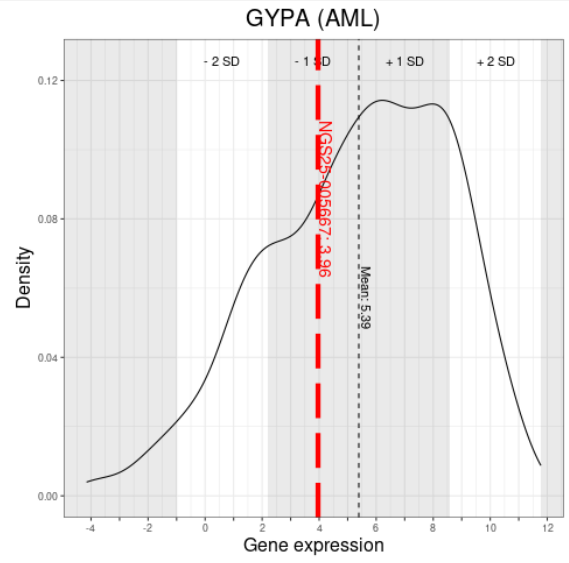
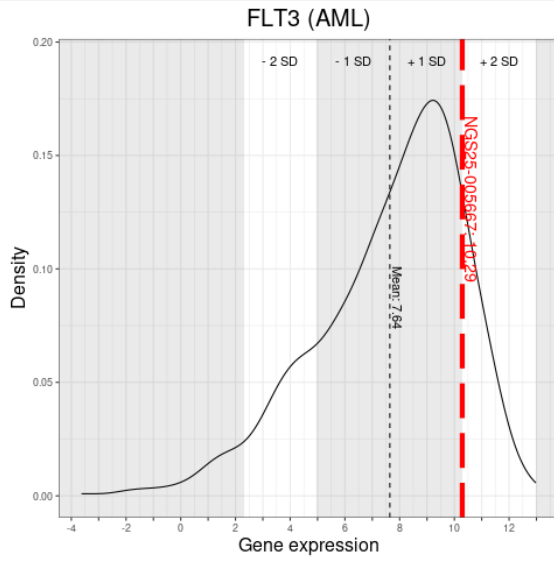
The test was developed and its performance characteristics have been determined by Genomic Testing Cooperative, LCA. This test has not been approved by the FDA. The FDA has determined such clearance or approval is not necessary. This laboratory is CLIA certified to perform high complexity clinical testing.

Additional Report Information

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



Additional Report Information