NEO GENOMICS

866.776.5907, option 3

Neo Comprehensive™
Heme Cancers

SAMPLE CLIENT

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Patient Name: **Patient, Sample**
Patient DOB / Sex: **01/01/2050 / O**
Specimen Type: **Peripheral Blood**
Body Site: **Peripheral Blood**
Specimen ID:
MRN:

Ordering Physician(s): **Sample Doctor, M.D.**
Accession / CaseNo: **1234567/ NTP22-00000**
Collection Date: **03/24/2022 12:00:00 AM**
Received Date: **03/25/2022 12:00:00 PM PDT**
Report Date: **04/09/2022 12:00:00 PM EST**

Reason for Referral: **ACUTE MYELOBLASTIC LEUKEMIA, NOT HAVING ACHIEVED REMISSION**

Results Summary

5 Clinically Significant Variants Detected§	**CEBPA** N356_C357del; **STAG2** T875Cfs*19; **TET2** T646Nfs*35, C1271Lfs*29
RNA Fusions	**PML-RARA**
Copy Number Variations (CNVs)	**ASXL1** Loss

Interpretation

-CEBPA mutations have been associated with favorable risk status for both bi-allelic and single in-frame bZIP mutations in AML.

-TET2 mutations are commonly found in a diverse array of myeloid malignancies. TET2 mutations have been reported to be associated with an increased response to hypomethylating agents when the allele frequency is >10% and ASXL1 is not mutated.

-In AML cases STAG2 mutations are in the adverse risk category and are classified as 'AML, myelodysplasia-related' irrespective of any prior history of MDS (ELN 2022, WHO 2022).

-PML-RARA fusion, created as a consequence of the t(15;17)(q24;q21) translocation, is found in nearly all cases of and is a defining alteration for acute promyelocytic leukemia (APL, or AML subtype M3) [PMID:10233871]. PML-RARA fusion protein drives oncogenic transformation and promotes accumulation of immature promyelocytes in the bone marrow [PMID: 32182684]. APL with PML-RARA fusion is associated with a high rate (~90%) of complete remission due to sensitivity of leukemic cells to treatment with differentiating agents such as all trans-retinoic acid (ATRA) [PMID:23841729].

-ASXL1 is a tumor suppressor involved in epigenetic regulation of gene expression. Inactivating point mutations, truncations or deletions of ASXL1 are frequently observed in myeloid disorders, including approximately 45% of chronic myelomonocytic leukemia (CMML), 11% of acute myeloid leukemia(AML), 34% of primary myelofibrosis (PMF), 4% of polycythemia vera (PV) and essential thrombocythemia (ET), and 14% of myelodysplastic syndromes (MDS) [COSMIC Database, PMID: 30371878]. Loss of ASXL1 is generally associated with aggressive disease and poor clinical outcome [PMID: 22031865, 23018865]. In MDS, loss of ASXL1 is associated with reduced time to AML progression [PMID: 21576631].

§ See full list of genes tested in Biomarkers Evaluated section at end of report. See Profile Results Detail for Variants of Unknown Clinical Significance.

Therapeutic Implications					
Biomarker	**Tier**	**Therapies approved in this indication (LoE°)**	**Therapies approved in other indication (LoE°)**	**Possible Therapy Resistance (LoE°)**	**Potential Clinical Trials**
TET2 T646Nfs*35	2	None	None	None	None
TET2 C1271Lfs*29	2	None	None	None	None
CEBPA N356_C357del	2	None	None	None	None
STAG2 T875Cfs*19	2	None	Talazoparib (C), Olaparib (D), Niraparib (D), Rucaparib (D)	None	Yes, See Clinical Trials Section

°Level of Evidence (LoE) – See level of evidence table for additional information changes

Profile Results Detail

Molecular Testing Detail						
Gene name	**Amino Acid Change**	**Nucleotide Change**	**Consequence**	**Classification**	**Mutant Allele Frequency (%)**	**Read Depth**
TET2	p.T646Nfs*35	NM_001127208.2: c.1936dup	Frameshift	Pathogenic	33.7	5627
	p.C1271Lfs*29	NM_001127208.2: c.3811dup	Frameshift	Pathogenic	34.0	6050
CEBPA	p.N356_C357del	NM_004364.4: c.1066_1071del	Inframe deletion	Pathogenic	28.9	4171
STAG2	p.T875Cfs*19	NM_001282418.2: c.2622_2623del	Frameshift	Pathogenic	73.1	3190

Fusion Genes	Classification	ISCN	Coordinates
PML-RARA	Pathogenic	t(15;17)(q24.1;q21.2)	PML 15:74023408 - RARA 17:40348315

Copy Number Variations (CNVs)	Consequence
ASXL1	Loss

Variants of Unknown Clinical Significance	Consequence	Variant Allele Frequency (%)
RTEL1 V1060M NM_016434.4:c.3178G>A	Missense	27.8

Detected Alterations

TET2 T646Nfs*35 - Biomarker Information	
Clinical Relevance	TET2-T646fs*35 is an inactivating mutation. TET2 is a tumor suppressor that functions to create modified nucleotide precursors to methylated DNA (10, 11, 12). There are currently no approved therapies that directly target TET2 mutations in cancer.
Drug Sensitivity	There are currently no approved therapies that directly target TET2 mutations in cancer. While some small studies in patients with various myeloid malignancies have associated TET2 mutations with modest increases in response rate to hypomethylating agents, these associations have not been correlated with improvements in progression-free or overall survival (13, 14, 15, 16). Additionally, the NCCN Guidelines for Myelodysplastic Syndromes (v.3.2021) state that molecular status should not preclude the use of, or influence the selection of, hypomethylating agents.
Molecular Function	This frameshift alteration is expected to effectively truncate the 2002-amino acid Tet2 protein prior to or within the 2-oxoglutarate-Fe(II)-dependent dioxygenase (2OGFeDO) catalytic domain and the substrate binding region (Interpro, UniProt). Truncations involving these highly conserved regions have been reported to disrupt Tet2 protein function, with amino acids 1129–1936 shown to be required for catalytic activity (17). In addition, this alteration is likely to elicit nonsense-mediated decay (34, 35, 36, 37). Therefore, this mutation is predicted to be inactivating.
Role in Disease	Tet2 deficiency, through inactivating mutation or reduced expression, has been correlated with decreased levels of 5-hydroxymethylcytosine (5hmC) and altered DNA methylation patterns in cancer samples (18, 19, 20, 21, 22). TET2 mutations have been associated with normal karyotype, older patient age, higher white blood cell counts, and lower platelet counts in studies of AML (4, 23, 5, 24).
Prevalence	TET2 mutations have been reported in 11% (893/7800) of Acute myelocytic leukemia (AML) samples analyzed in COSMIC (May 2020). TET2 mutations have been reported in 3.3-8.6% of Acute myelocytic leukemia (AML) samples (cBioPortal for Cancer Genomics, May 2020). TET2 mutations have been variably reported in 8-50% of AML cases, including 6-32% of cytogenetically normal AML (CN-AML) cases and 24-30% of secondary AML cases (25, 26, 27, 28, 5, 29, 4, 30, 7, 31, 32, 33, 24, 9).

TET2 C1271Lfs*29 - Biomarker Information	
Clinical Relevance	TET2-C1271fs*29 is an inactivating mutation. TET2 is a tumor suppressor that functions to create modified nucleotide precursors to methylated DNA (10, 11, 12). There are currently no approved therapies that directly target TET2 mutations in cancer.
Drug Sensitivity	There are currently no approved therapies that directly target TET2 mutations in cancer. While some small studies in patients with various myeloid malignancies have associated TET2 mutations with modest increases in response rate to hypomethylating agents, these associations have not been correlated with improvements in progression-free or overall survival (13, 14, 15, 16). Additionally, the NCCN Guidelines for Myelodysplastic Syndromes (v.3.2021) state that molecular status should not preclude the use of, or influence the selection of, hypomethylating agents.
Molecular Function	This frameshift alteration is expected to effectively truncate the 2002-amino acid Tet2 protein prior to or within the 2-oxoglutarate-Fe(II)-dependent dioxygenase (2OGFeDO) catalytic domain and the substrate binding region (Interpro, UniProt). Truncations involving these highly conserved regions have been reported to disrupt Tet2 protein function, with amino acids 1129–1936 shown to be required for catalytic activity (17). Therefore, this mutation is predicted to be inactivating.
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CEBPA N356_C357del - Biomarker Information	
Clinical Relevance	CEBPA-N356_C357del is predicted to be an inactivating mutation. CEBPA encodes the transcription factor C/EBPalpha, which has been reported to function as a tumor suppressor in several types of cancer (45, 46, 47, 48). There are currently no therapies directed toward CEBPA inactivating mutation or loss.
Drug Sensitivity	There are currently no therapies directed toward CEBPA inactivating mutation or loss. Loss of C/EBPalpha protein may result in decreased inhibition of Cdk2 and Cdk4; however, additional studies are needed to determine if Cdk2/4 inhibition would be relevant in the context of CEBPA inactivating alterations (49).
Molecular Function	CEBPA N356_C357del is an inframe deletion that occurs in the basic-leucine zipper (bZIP) domain of the C/EBPalpha protein (UniProt) (39). Inframe insertions and deletions in the C-terminal bZIP domain, including N356_C357del, have been commonly reported in acute myeloid leukemia (AML) patients (50, 39, 51, 52, 53). Additionally, mutations that disrupt the bZIP domain of C/EBPalpha have been reported to result in a loss of DNA-binding, reduced transactivation activity, and the development of myeloid leukemia in preclinical animal models (50, 54, 55, 56). Therefore, although CEBPA N356_C357del has not been functionally characterized, it may also result in a loss of protein function (51).
Role in Disease	Decreased expression of C/EBPalpha has been reported to be involved in the pathogenesis of several types of cancer (45, 46, 47, 57, 48). Germline CEBPA mutations have also been associated with a predisposition to AML development and frequently involve an acquired somatic mutation in the second allele (58, 59, 60).
Prevalence	CEBPA mutations have been reported in 9.3% (1352/14569) of Acute myelocytic leukemia (AML) samples analyzed in COSMIC (May 2020). CEBPA mutations have been reported in 0.0-6.6% of Acute myelocytic leukemia (AML) samples (cBioPortal for Cancer Genomics, May 2020). Literature studies have reported CEBPA mutations in 7-15% of analyzed AML samples, including studies citing single or monoallelic mutation in 3-6% of cases and double or biallelic mutations in 4-15% of cases (61, 40, 39, 62, 41).

STAG2 T875Cfs*19 - Biomarker Information	
Clinical Relevance	STAG2-T875fs*19 is an inactivating mutation. Inactivation of STAG2, which encodes SA-2, may result in chromosomal instability (109, 110). While there are currently no therapies that specifically target the loss of SA-2, STAG2 alterations may predict sensitivity to DNA-damaging drugs, including platinum chemotherapy and poly(ADP-ribose) polymerase (PARP) inhibitors (111, 112, 113).
Drug Sensitivity	At present, there are no therapies that directly address the loss of SA-2. However, STAG2 inactivation has been reported to sensitize cancer cells to ionizing radiation and platinum-based therapies as well as to PARP inhibitors (111, 112, 113). PARP inhibitors have been investigated both alone and in combination therapeutic strategies in several cancer types in clinical studies and are currently under investigation in clinical trials (114, 115).
Possible Therapy Resistance	In one study of 140 AML or high-risk MDS patients treated with decitabine with or without ibrutinib, STAG2 mutation was associated with lower rates of complete remission/complete remission with incomplete hematologic recovery (CR/CRi) after three cycles of decitabine; STAG2 mutation was not significantly associated with overall survival (116). In another study of 250 AML or high-risk MDS patients treated with azacitidine with or without vorinostat, STAG2 mutation was associated with lower rate of complete response in univariate, but not multivariable analysis (117).
Molecular Function	This frameshift alteration is expected to effectively truncate the 1231 amino acid SA-2 protein, resulting in the loss of a portion of the protein that may include the LXXLL motifs and glutamine-rich region (UniProt) (118). Truncating STAG2 mutations, including those that occur in the C-terminal portion of the protein, have been reported to result in reduced SA-2 expression and sister chromatid cohesion (119). In addition, truncating alterations up to R1205* have been reported several times as somatic variants in COSMIC (Jan 2021) and the NCCN Guidelines (v.2.2021) state that STAG2 nonsense, frameshift, and splice site mutations are likely to indicate clonal hematopoiesis in myelodysplastic syndrome (MDS) patients and are associated with a poor prognosis. In addition, this alteration is likely to elicit nonsense-mediated decay (34, 35, 36, 37). This alteration is therefore predicted to be inactivating.
Role in Disease	STAG2 deletion and inactivating mutations have been reported in several types of cancer and inactivating STAG2 alterations have been reported to cause chromosomal instability (109, 110). STAG2 mutations have been reported to be associated with secondary AML as compared with primary AML (72, 90). An additional preclinical study reported that loss of cohesion complex genes, including STAG2, in mouse bone marrow cells resulted in altered hematopoiesis and development of a myeloproliferative neoplasm (120).

STAG2 T875Cfs*19 - Biomarker Information

Prevalence	STAG2 mutations have been reported in 3.8% (189/4973) of Acute myelocytic leukemia (AML) samples analyzed in COSMIC (May 2020). STAG2 mutations have been reported in 0.0-3.0% of Acute myelocytic leukemia (AML) samples (cBioPortal for Cancer Genomics, May 2020). Literature studies have reported STAG2 mutation in 1-20% of AML cases, with increased frequency of STAG2 mutations reported in secondary AML cases, as compared with primary AML cases (108, 72, 90, 121, 122). One study has reported STAG2 mutations in 16.5% (14/85) of cases of AML with partial tandem duplication of MLL (MLL-PTD AML) (123).

STAG2 T875Cfs*19 - Clinical Evidence from Completed Clinical Trials

Phase 1

A Phase 1 study of veliparib plus topotecan and carboplatin in patients with acute leukemia, aggressive MPN, and CMML reported an overall response rate of 33% (33/99), including 14 complete responses, 11 complete responses with incomplete count recovery, and eight partial responses, as well as a median duration of response lasting 7.5 months (124). A Phase 1 study in 49 elderly patients with relapsed or refractory ALL or AML, including 47 patients with AML, treated with veliparib in combination with temozolomide reported an overall response rate of 33%, with eight patients achieving complete remission and two remaining in complete remission at three years. Median overall survival was five months for all patients and 19.9 months for those with a complete remission (125, 126).

Pre-Clinical

Talazoparib has been reported to selectively inhibit proliferation of STAG2-mutant AML cells, as compared with STAG2 wild-type cells, in vitro and in a xenograft model (127). Olaparib has been reported to inhibit survival of AML cell lines as well as in 92.3% (13/14) of primary AML samples analyzed in one study (128). Treatment with talazoparib alone, or in combination with azacitidine, in a FLT3-ITD xenograft model of AML has been reported to decrease leukemia burden, peripheral blood blast counts, and spleen weights as compared with control treatment (129). A preclinical study in an AML and an ALL cell line reported increased efficacy of rucaparib in combination with 5-fluorouracil (5FU) as compared with either monotherapy; the combination also increased survival in xenotransplantation models of AML and ALL using patient-derived blasts, although rucaparib alone had no effect (130).

Open & Recruiting Clinical Trials

Gene	Trial ID	Title	Targets	Phase	Locations
TET2	None	None	None	None	None
TET2	None	None	None	None	None
CEBPA	None	None	None	None	None
STAG2	NCT03974217	Talazoparib for Cohesin-Mutated AML and MDS With Excess Blasts	PARP	Phase 1	Boston, MA
STAG2	NCT04207190	Talazoparib and Gemtuzumab Ozogamicin for the Treatment of CD33 Positive Relapsed or Refractory Acute Myeloid Leukemia	CD33, PARP	Phase 1/ Phase 2	Buffalo, NY
STAG2	NCT03907969	A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers.	DNA-PK, PARP	Phase 1/ Phase 2	Houston, TX; London, United Kingdom; Newcastle upon Tyne, United Kingdom; New Haven, CT

Gene	Trial ID	Title	Targets	Phase	Locations
STAG2	NCT03878524	Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) PRIME Trial	ABL1, ALK, AR, AXL, BCL2, BRAF, BTK, CD274, CDK4, CDK6, COX-2, CSF1R, CTLA4, EGFR, EPHA2, EPHA3, ERBB2, ERBB3, ERBB4, FGFR1, FGFR2, FGFR3, FGFR4, FLT1, FLT3, FLT4, HDAC, HDAC1, HDAC2, IDH2, JAK1, JAK2, KDR, KIT, MEK, MET, MTOR, NTRK1, NTRK2, NTRK3, PARP, PDCD1, PDGFRA, PDGFRB, PI3K, PIK3CD, proteasome, RAF1, RARA, RET, ROS1, SMO, SRC, TEK, VEGFA, VEGFR1, VEGFR3, YES1	Phase 1	Portland, OR

NOTE: Although we make every attempt to ensure that the information provided is as accurate as possible, please note that the information provided in this report has been obtained through public domains that are updated constantly and should be researched by the physician or research professionals. NOT ALL TRIALS ARE INCLUDED. Please go to www.clinicaltrials.gov to perform a detailed search of available clinical trials as the trials provided in this report are not meant to be a complete list.

Test Description & Methodology

Test Description

The Neo Comprehensive - Heme Cancers test is a next-generation sequencing (NGS) assay using dual DNA- and RNA- sequencing from total nucleic acid (TNA) to detect both DNA and RNA alterations relevant to the spectrum of hematologic malignant disorders in one assay. The assay detects mutations such as single nucleotide variants (SNV) and short insertions/deletions (indels) in 302 genes and copy number variations (CNV) in 23 genes by DNA sequencing. Gene rearrangements generating fusion RNA transcripts in 184 frequently rearranged genes are detected by RNA-sequencing. Test reports include summary interpretation of all results to help guide treatment decisions.

Clinical Significance

The Neo Comprehensive - Heme Cancers test is a DNA + RNA panel that detects known mutations, CNVs and RNA fusions associated with most forms of hematologic malignancies from myeloid or lymphoid lineages, including but not limited to: acute myeloid leukemia (AML), myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and different types of lymphoma. Testing using this panel can provide key diagnostic information, including critical molecular determinations affecting therapeutic approaches, can aid in risk stratification and predicting prognosis, and can also be used in clinical research.

Methodology

Total Nucleic Acid (TNA) is isolated from peripheral blood, bone marrow or Formalin Fixed Paraffin Embedded (FFPE) tissue. Testing is performed by Next Generation Sequencing (NGS) using a custom amplicon-based targeted panel for simultaneous sequencing of DNA and RNA. DNA sequencing of all the exons for the listed genes is performed. An additional 10 nucleotides at the 5ô and 3ê nds of each coding exon are also sequenced to detect important splicing abnormalities. This assay detects SNVs and Indels <40 bp. Copy Number Variants (CNV) are detected as full gene gains (n≥3) or losses (n≤1). In general, the NGS method has a typical sensitivity of 3% for detecting common specific clinically actionable mutations and 5% for other mutations. RNA fusions for the listed genes with known and novel fusion partners are detected. Gene fusions are detected through in house bioinformatic analysis and interpreted in conjunction with known fusions in reference databases and literature. JAK3 exon 13, containing p.A572 and p.A573, has a limit of detection of 11%. The following regions are not included in the panel as they are not sufficiently covered with high quality sequence reads: ASXL1 exon 1 (AA 1-19), FLT3 (exon 1: AA 1-15), NOTCH1 exon 1 (AA1-21), NPM1 (exon 1: AA 1-19), TP53 (exon 4: AA 72-93). For a full list of low-coverage regions, please contact Client Services. Various factors including quantity and quality of nucleic acid, sample preparation, and sample age can affect assay performance.

Biomarkers Evaluated (by molecular analysis unless otherwise noted)

- **SNV/Indel Alterations (302):** ABL1, ABL2, AKT1, AKT2, AKT3, ALK, ANKRD26, APC, ARAF, ARHGEF1, ARID1A, ARID1B, ARID2, ASXL1, ASXL2, ATG2B, ATM, ATP2A2, ATRX, AXL, B2M, BAP1, BCL2, BCL2L11, BCL6, BCOR, BCORL1, BCR, BIRC3, BLM, BRAF, BRCA1, BRCA2, BRINP3, BRIP1, BTK, C17orf97, CALR, CARD11, CBFB, CBL, CBLB, CBLC, CCND1, CCND2, CCND3, CD274, CD33, CD79A, CD79B, CDC25C, CDK2, CDK4, CDK6, CDKN1B, CDKN2A, CDKN2B, CEBPA, CHEK2, CIC, CIITA, CREBBP, CRLF2, CSF1R, CSF3R, CTC1, CTCF, CTNNB1, CUX1, CXCR4, CYLD, DAXX, DCK, DDX3X, DDX41, DIS3, DKC1, DNMT1, DNMT3A, EBF1, EED, EGFR, EGLN1, EGR1, ELANE, EP300, EPCAM, EPHA2, EPHA7, EPOR, ERBB2, ERBB3, ERCC4, ETNK1, ETV6, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, FOXO1, FUBP1, G6PC3, GAB2, GATA1, GATA2, GATA3, GFI1, GNA12, GNA13, GNAI2, GNAQ, GNAS, GNB1, GSKIP, H1-4, HAX1, HIF1A, HNRNPK, HRAS, ID3, IDH1, IDH2, IGF1R, IKBKB, IKZF1, IKZF3, IL7R, IRAK4, IRF4, ITPKB, JAK1, JAK2, JAK3, KDM6A, KDR, KEAP1, KIT, KLF2, KLHL6, KMT2A, KMT2C, KMT2D, KRAS, LUC7L2, MALT1, MAP2K1, MAP3K1, MAP3K14, MAPK1, MCL1, MDM2, MDM4, MED12, MEF2B, MET, MLH1, MPL, MSH2, MSH6, MTOR, MYC, MYCN, MYD88, NBN, NCAPH, NF1, NFKBIE, NHP2, NOP10, NOTCH1, NOTCH2, NOTCH3, NPM1, NRAS, NSD1, NT5C2, NTRK1, NTRK2, NTRK3, NUP214, NUP98, P2RY8, PALB2, PAX5, PDCD1LG2, PDGFRA, PDGFRB, PHF6, PIGA, PIK3CA, PIK3CD, PIK3R1, PIM1, PLCG1, PLCG2, PML, PMS2, POT1, PPM1D, PRDM1, PRPF40B, PRPF6, PRPF8, PRPS1, PTCH1, PTEN, PTPN11, PTPRC, RAC1, RAD21, RAD51C, RAD51D, RB1, RBBP6, REL, RHEB, RHOA, RICTOR, RIPK1, RIT1, RPL11, RPL35A, RPL5, RPN1, RPS10, RPS15, RPS17, RPS26, RPS7, RTEL1, RUNX1, S1PR2, SAMD9, SAMD9L, SAMHD1, SBDS, SETBP1, SETD2, SF1, SF3A1, SF3B1, SGK1, SH2B3, SLX4, SMAD4, SMARCB1, SMC1A, SMC3, SMO, SOCS1, SPEN, SRP72, SRSF2, STAG2, STAT3, STAT5B, STAT6, STK11, SUZ12, TBL1XR1, TCF3, TENT5C, TERC, TERT, TET2, TET3, THPO, TINF2, TLR2, TNFAIP3, TNFRSF14, TP53, TP63, TRAF2, TRAF3, TSC1, TSC2, U2AF1, U2AF2, UBR5, VHL, WAS, WRAP53, WT1, XPO1, ZFHX4, ZMYM3, ZRSR2.

- **Copy Number Variants (CNV) (23):** ABL1, ASXL1, BRAF, CBL, CD274, CDKN1B, CDKN2A, DNMT1, EPOR, EZH2, FLT3, IKZF1, JAK2, KMT2A, KRAS, MYC, PAX5, RAD21, REL, STAG2, TNFRSF14, TP53, XPO1

- **RNA Fusions (184):** ABI1, ABL1, ABL2, ACTN4, ADAMTS17, AFDN, AFF1, AFF3, AGGF1, ALK, ARHGAP26, ARHGEF12, ATF7IP, ATIC, ATP2A1, ATP5MG, BCL11B, BCL2, BCL6, BCR, BIN2, BIRC3, CALR, CAPRIN1, KNL1, CBFB, CBL, CCDC6, CCDC88C, CCND1, CCND2, CCND3, CDK6, CEP85L, CHD1, CHIC2, CIITA, CNTRL, COL1A1, CPSF6, CREBBP, CRLF2, CSF1R, CXCR4, DEK, DTD1, DUSP22, EBF1, EIF4A1, ELL, EML1, EP300, EPOR, EPS15, ERC1, ERG, ERVK3, ETV6, FGFR1, CEP43, FGFR1OP2, FIP1L1, FLT3, FNBP1, FOXO4, FOXP1, FRYL, FUS, GAS7, GIT2, GLIS2, GOLGA4, GPHN, HIP1, HLF, HNRNPA2B1, IKZF1, IKZF2, IKZF3, JAK2, KANK1, KAT6A, KLF2, KMT2A, LAIR1, LMNA, LRRFIP1, MALT1, MAML2, MAP4, MECOM, MEF2D, MRTFA, MLF1, MLLT1, MLLT10, MLLT11, MLLT3, MLLT6, MYB, MYC, MYH11, MYO18A, MYO1F, NDE1, NF1, NFKB2, NIN, NOTCH1, NOTCH2, NPM1, NRIP1, NTRK1, NTRK2, NTRK3, NUP214, NUP98, P2RY8, PAG1, PAX5, PBX1, PCM1, PDCD1LG2, PDE4DIP, PDGFRA, PDGFRB, PICALM, PLAG1, PML, PRDM16, PRDM9, PRKG2, PTK2B, PVT1, RABEP1, RARA, RBM15, RBM6, RCSD1, ROS1, RPN1, RUNX1, RUNX1T1, SART3, SEMA6A, SEPTIN2, SEPTIN3, SEPTIN5, SEPTIN6, SEPTIN9, SET, SETD2, SNX2, SPECC1, SPTBN1, SQSTM1, SSBP2, STIL, SYNRG, TACC1, TAL1, TBL1XR1, TCF3, TERF2, TET1, TFG, TLX1, TLX3, TP53BP1, TP63, TPM3, TPR, TRIM24, TRIP11, TYK2, UBE2R2, WDR48, ZBTB16, ZCCHC7, ZEB2, ZMIZ1, ZMYM2, ZNF384, ZNF703.

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Definitions of Levels of Evidence

Tier 1: Variants of Strong Clinical Significance

Level A	**Predictive of response:** Therapy is FDA-approved in this disease, based on the presence of this biomarker. **Predictive of resistance:** Biomarker is included in professional guidelines as providing resistance to therapy. **Diagnostic:** Biomarker is included in professional guidelines as pathognomonic (required for diagnosis; characteristic of a particular disease). **Prognostic:** Biomarker is included in professional guidelines for clinical decision-making; specifically, the molecular criteria is included in an accepted, clinically relevant prognostic scoring system.
Level B	**Predictive of response:** Strong evidence (well-powered studies, consensus from experts) that biomarker predicts sensitivity to therapy. **Predictive of resistance:** Well-powered studies with expert consensus or smaller studies repeatedly confirmed or reproduced by different groups that variant predicts resistance to therapy. **Diagnostic:** Well-powered studies with expert consensus or repeatedly reported in smaller studies with consistent results or reproduced by different groups indicating diagnostic relevance. These markers may be mentioned in professional guidelines, but are suggestive of, rather than conclusive for, a specific diagnosis. **Prognostic:** Well-powered studies with expert consensus or smaller studies repeatedly with consistent results or reproduced by different groups indicating prognostic relevance.
Level B/C	**Predictive of response:** Consensus from experts, but lacking well-powered studies that biomarker predicts sensitivity to therapy.

Tier 2: Variants of Potential Clinical Significance

Level C	**Predictive of response:** Therapy is FDA-approved for a different disease, based on the presence of this biomarker; or, criteria for a clinical trial. **Predictive of resistance:** Preclinical data strongly suggests resistance; reported in clinical cases. **Diagnostic:** Small studies, diagnostic for a group of related cancers or variants that are supportive of a diagnosis along with other genomic variants. **Prognostic:** Multiple small studies providing prognostic relevance.
Level C/D	**Predictive of response:** Case reports or small case series including exceptional responders that indicate sensitivity to therapy. Not applicable for drug resistance, prognostic, or diagnostic levels of evidence.
Level D	**Predictive of response:** Plausible sensitivity to therapy based on preclinical studies, which do not need to be disease specific. **Predictive of resistance:** Limited preclinical data suggesting resistance; no clinical reports. **Diagnostic:** Small studies or a few case reports support this variant alone or in combination with other biomarkers as assisting diagnosis of this disease. **Prognostic:** Small studies or a few case reports support this variant alone or in combination with other biomarkers as assisting with prognostic assessment in this disease.
Level E	**Predictive of response:** Poor evidence that biomarker predicts sensitivity to an approved therapy. Not applicable for drug resistance, prognostic, or diagnostic levels of evidence.

Tier 3: Variants of Uncertain Clinical Significance

Tier 4: Benign or Likely Benign Variants

Electronic Signature

Sample Doctor, M.D., Pathologist

The Technical Component Processing, Analysis and Professional Component of this test was completed at NeoGenomics California, 31 Columbia, Aliso Viejo, CA / 92656 / 866-776-5907 / CLIA #05D1021650 / Medical Director(s): Vladislav Chizhevsky, M.D..
The performance characteristics of this test have been determined by the performing laboratory. 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.
Images that may be included within this report are representative of the patient but not all testing in its entirety and should not be used to render a result.