DISCOVERY LIFE SCIENCES
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Discovery Life Sciences
800 Hudson Way, Suite 1700
Huntsville AL 35806

Test Performed: HAD Illumina AML

Report Date
Status -

Patient

DLS Patient ID XXXXXXX
Date of Birth XX XX, 19XX
Age XX
Sex Gender
Ethnicity _____
Race _____
Diagnosis Leukemia, Acute Myeloid (AML)

Specimen

Specimen Collection
Date of Procedure Oct XX, 20XX
Primary Harvest Site Bone marrow

Result: Positive

23
Clinically Significant Variants

Variants Without Associated Therapies

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
ASXL1 c.1751dupG p.G585fs*12 g.31022441_31022442insG	4.33% (of 5725 reads)	loss	**Tier 1A**	Pathogenic
ASXL1 c.1751delG p.G584fs*58 g.31022442delG	5.08% (of 5828 reads)	loss	**Tier 1A**	Pathogenic
ASXL1 c.2015_2016insC p.Q672fs*41 g.31022713_31022714insC	10.0% (of 2104 reads)	loss	**Tier 1A**	Pathogenic
ASXL1 c.2020delG p.A674fs*9 g.31022716delG	9.07% (of 2127 reads)	loss	**Tier 1A**	Likely Pathogenic
ASXL1 c.3944delG p.G1315fs*74 g.31024637delG	1.42% (of 3885 reads)	loss	**Tier 1A**	Likely Pathogenic
ASXL1 c.4411_4412insG p.K1471fs*? g.31025109_31025110insG	3.36% (of 2737 reads)	loss	**Tier 1A**	Likely Pathogenic

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
ASXL1 c.4414_4415insG p.L1472fs*? g.31025112_31025113insG	3.22% (of 2734 reads)	loss	**Tier 1A**	Likely Pathogenic
ASXL1 c.4417delT p.C1473fs*7 g.31025115delT	2.99% (of 2743 reads)	loss	**Tier 1A**	Likely Pathogenic
TP53 c.1158delG p.T387fs*? g.7572951delC	2.03% (of 1181 reads)	loss	**Tier 1A**	Likely Pathogenic
TP53 c.1146delA p.K382fs*? g.7572963delT	2.85% (of 1156 reads)	loss	**Tier 1A**	Pathogenic
TP53 c.1083delG p.S362fs*8 g.7573944delC	2.19% (of 1372 reads)	loss	**Tier 1A**	Pathogenic
BCOR c.3679delA p.R1227fs*33 g.39922927delT	2.27% (of 618 reads)	loss	**Tier 2C**	Likely Pathogenic
BCOR c.3182delA p.K1061fs*52 g.39930282delT	1.65% (of 2056 reads)	loss	**Tier 2C**	Likely Pathogenic
SF3B1 c.2359delA p.I787fs*3 g.198266477delT	1.73% (of 1502 reads)	loss	**Tier 2C**	Likely Pathogenic
STAG2 c.1400delT p.F467fs*3 g.123191805delT	1.27% (of 10472 reads)	loss	**Tier 2C**	Likely Pathogenic
STAG2 c.2534-2A>C g.123210180A>C	4.58% (of 2465 reads)	loss	**Tier 2C**	Likely Pathogenic

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
TET2 c.1842delG p.L615fs*24 g.106156936delG	1.31% (of 12705 reads)	loss	**Tier 2C**	Likely Pathogenic
TET2 c.3353delA p.N1118fs*19 g.106158447delA	1.64% (of 4693 reads)	loss	**Tier 2C**	Likely Pathogenic
ZRSR2 c.289A>T p.K97* g.15821896A>T	3.42% (of 1023 reads)	loss	**Tier 2C**	Likely Pathogenic
BCORL1 c.1491delC p.E498fs*15 g.129148235delC	1.71% (of 2748 reads)	loss	**Tier 3**	Likely Pathogenic
BCORL1 c.5042delC p.P1681fs*20 g.129190011delC	1.82% (of 3465 reads)	loss	**Tier 3**	Pathogenic
CUX1 c.1322delC p.P441fs*27 g.101839974delC	2.91% (of 1307 reads)	loss	**Tier 3**	Likely Pathogenic
NOTCH1 c.4732_4734delGTG p.V1578del g.139399409_139399411delCAC	1.5% (of 3858 reads)	loss	**Tier 3**	Pathogenic

Individual Variant Interpretations

Gene ***ASXL1***
Exon 12
Nucleotide NM_001363734.1:
g.31022441_31022442insG
c.1751dupG
Amino Acid p.G585fs*12
Function loss
Allelic Fraction 4.33% (of 5725 reads)
Classification **Tier 1A**
Assessment Pathogenic

Interpretation
ASXL1 encodes Asxl1, a member of the Asxl family of proteins involved in recruitment of epigenetic and transcriptional regulators at genomic loci. Asxl1 interacts directly with Bap-1 and several hormone receptors, and is involved in the recruitment of the PRC2 repressive complex [30]. Asxl1 may be found as a member of various transcriptional complexes, and its function has been shown to be context-dependent; Asxl1 may activate oncogenes or repress tumor suppressor expression [30]. Truncating mutations in ASXL1 are frequent in hematologic malignancies and in colorectal cancer cell lines with microsatellite instability [13, 74, 30]. ASXL1 inactivating alterations have been associated with clonal hematopoiesis and have been shown to lead to hematopoietic dysplasia in preclinical animal models [22, 1, 69, 24, 38, 46].

Gene	***ASXL1***
Exon	12
Nucleotide	NM_001363734.1: g.31022442delG c.1751delG
Amino Acid	p.G584fs*58
Function	loss
Allelic Fraction	5.08% (of 5828 reads)
Classification	**Tier 1A**
Assessment	**Pathogenic**

Interpretation
ASXL1 encodes Asxl1, a member of the Asxl family of proteins involved in recruitment of epigenetic and transcriptional regulators at genomic loci. Asxl1 interacts directly with Bap-1 and several hormone receptors, and is involved in the recruitment of the PRC2 repressive complex [30]. Asxl1 may be found as a member of various transcriptional complexes, and its function has been shown to be context-dependent; Asxl1 may activate oncogenes or repress tumor suppressor expression [30]. Truncating mutations in ASXL1 are frequent in hematologic malignancies and in colorectal cancer cell lines with microsatellite instability [13, 74, 30]. ASXL1 inactivating alterations have been associated with clonal hematopoiesis and have been shown to lead to hematopoietic dysplasia in preclinical animal models [22, 1, 69, 24, 38, 46].

Gene	***ASXL1***
Exon	12
Nucleotide	NM_001363734.1: g.31022713_31022714insC c.2015_2016insC
Amino Acid	p.Q672fs*41
Function	loss
Allelic Fraction	10.0% (of 2104 reads)
Classification	**Tier 1A**
Assessment	**Pathogenic**

Interpretation
ASXL1 encodes Asxl1, a member of the Asxl family of proteins involved in recruitment of epigenetic and transcriptional regulators at genomic loci. Asxl1 interacts directly with Bap-1 and several hormone receptors, and is involved in the recruitment of the PRC2 repressive complex [30]. Asxl1 may be found as a member of various transcriptional complexes, and its function has been shown to be context-dependent; Asxl1 may activate oncogenes or repress tumor suppressor expression [30]. Truncating mutations in ASXL1 are frequent in hematologic malignancies and in colorectal cancer cell lines with microsatellite instability [13, 74, 30]. ASXL1 inactivating alterations have been associated with clonal hematopoiesis and have been shown to lead to hematopoietic dysplasia in preclinical animal models [22, 1, 69, 24, 38, 46].

Gene	***ASXL1***
Exon	12
Nucleotide	NM_001363734.1: g.31022716delG c.2020delG
Amino Acid	p.A674fs*9
Function	loss
Allelic Fraction	9.07% (of 2127 reads)
Classification	**Tier 1A**
Assessment	**Likely Pathogenic**

Interpretation
ASXL1 encodes Asxl1, a member of the Asxl family of proteins involved in recruitment of epigenetic and transcriptional regulators at genomic loci. Asxl1 interacts directly with Bap-1 and several hormone receptors, and is involved in the recruitment of the PRC2 repressive complex [30]. Asxl1 may be found as a member of various transcriptional complexes, and its function has been shown to be context-dependent; Asxl1 may activate oncogenes or repress tumor suppressor expression [30]. Truncating mutations in ASXL1 are frequent in hematologic malignancies and in colorectal cancer cell lines with microsatellite instability [13, 74, 30]. ASXL1 inactivating alterations have been associated with clonal hematopoiesis and have been shown to lead to hematopoietic dysplasia in preclinical animal models [22, 1, 69, 24, 38, 46].

Gene	***ASXL1***
Exon	12
Nucleotide	NM_001363734.1: g.31024637delG c.3944delG
Amino Acid	p.G1315fs*74
Function	loss
Allelic Fraction	1.42% (of 3885 reads)
Classification	**Tier 1A**
Assessment	**Likely Pathogenic**

Interpretation
ASXL1 encodes Asxl1, a member of the Asxl family of proteins involved in recruitment of epigenetic and transcriptional regulators at genomic loci. Asxl1 interacts directly with Bap-1 and several hormone receptors, and is involved in the recruitment of the PRC2 repressive complex [30]. Asxl1 may be found as a member of various transcriptional complexes, and its function has been shown to be context-dependent; Asxl1 may activate oncogenes or repress tumor suppressor expression [30]. Truncating mutations in ASXL1 are frequent in hematologic malignancies and in colorectal cancer cell lines with microsatellite instability [13, 74, 30]. ASXL1

	inactivating alterations have been associated with clonal hematopoiesis and have been shown to lead to hematopoietic dysplasia in preclinical animal models [22, 1, 69, 24, 38, 46].
Gene ***ASXL1*** Exon 12 Nucleotide NM_001363734.1: g.31025109_31025110insG c.4411_4412insG Amino Acid p.K1471fs*? Function loss Allelic Fraction 3.36% (of 2737 reads) Classification **Tier 1A** Assessment **Likely Pathogenic**	**Interpretation** ASXL1 encodes Asxl1, a member of the Asxl family of proteins involved in recruitment of epigenetic and transcriptional regulators at genomic loci. Asxl1 interacts directly with Bap-1 and several hormone receptors, and is involved in the recruitment of the PRC2 repressive complex [30]. Asxl1 may be found as a member of various transcriptional complexes, and its function has been shown to be context-dependent; Asxl1 may activate oncogenes or repress tumor suppressor expression [30]. Truncating mutations in ASXL1 are frequent in hematologic malignancies and in colorectal cancer cell lines with microsatellite instability [13, 74, 30]. ASXL1 inactivating alterations have been associated with clonal hematopoiesis and have been shown to lead to hematopoietic dysplasia in preclinical animal models [22, 1, 69, 24, 38, 46].
Gene ***ASXL1*** Exon 12 Nucleotide NM_001363734.1: g.31025112_31025113insG c.4414_4415insG Amino Acid p.L1472fs*? Function loss Allelic Fraction 3.22% (of 2734 reads) Classification **Tier 1A** Assessment **Likely Pathogenic**	**Interpretation** ASXL1 encodes Asxl1, a member of the Asxl family of proteins involved in recruitment of epigenetic and transcriptional regulators at genomic loci. Asxl1 interacts directly with Bap-1 and several hormone receptors, and is involved in the recruitment of the PRC2 repressive complex [30]. Asxl1 may be found as a member of various transcriptional complexes, and its function has been shown to be context-dependent; Asxl1 may activate oncogenes or repress tumor suppressor expression [30]. Truncating mutations in ASXL1 are frequent in hematologic malignancies and in colorectal cancer cell lines with microsatellite instability [13, 74, 30]. ASXL1 inactivating alterations have been associated with clonal hematopoiesis and have been shown to lead to hematopoietic dysplasia in preclinical animal models [22, 1, 69, 24, 38, 46].
Gene ***ASXL1*** Exon 12 Nucleotide NM_001363734.1: g.31025115delT c.4417delT Amino Acid p.C1473fs*7 Function loss Allelic Fraction 2.99% (of 2743 reads) Classification **Tier 1A** Assessment **Likely Pathogenic**	**Interpretation** ASXL1 encodes Asxl1, a member of the Asxl family of proteins involved in recruitment of epigenetic and transcriptional regulators at genomic loci. Asxl1 interacts directly with Bap-1 and several hormone receptors, and is involved in the recruitment of the PRC2 repressive complex [30]. Asxl1 may be found as a member of various transcriptional complexes, and its function has been shown to be context-dependent; Asxl1 may activate oncogenes or repress tumor suppressor expression [30]. Truncating mutations in ASXL1 are frequent in hematologic malignancies and in colorectal cancer cell lines with microsatellite instability [13, 74, 30]. ASXL1 inactivating alterations have been associated with clonal hematopoiesis and have been shown to lead to hematopoietic dysplasia in preclinical animal models [22, 1, 69, 24, 38, 46].
Gene ***TP53*** Exon 11 Nucleotide NM_000546.6: g.7572951delC c.1158delG Amino Acid p.T387fs*? Function loss Allelic Fraction 2.03% (of 1181 reads)	**Interpretation** The TP53 gene encodes the tumor suppressor p53, a protein that is involved in the DNA damage cell cycle checkpoint and causes cell cycle arrest when it senses DNA damage. p53 can also activate DNA repair genes, or induce apoptosis in the presence of DNA damage. It has been called the cellular gatekeeper [40]. Loss of p53 is common in aggressive advanced cancers [5]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple

Classification **Tier 1A** Assessment **Likely Pathogenic**	tumors in early adulthood, including breast cancer, brain tumors, and leukemias [60, 47, 64]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects [36, 29, 72, 55, 20].
Gene ***TP53*** Exon 11 Nucleotide NM_000546.6: g.7572963delT c.1146delA Amino Acid p.K382fs*? Function loss Allelic Fraction 2.85% (of 1156 reads) Classification **Tier 1A** Assessment **Pathogenic**	**Interpretation** The TP53 gene encodes the tumor suppressor p53, a protein that is involved in the DNA damage cell cycle checkpoint and causes cell cycle arrest when it senses DNA damage. p53 can also activate DNA repair genes, or induce apoptosis in the presence of DNA damage. It has been called the cellular gatekeeper [40]. Loss of p53 is common in aggressive advanced cancers [5]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias [60, 47, 64]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects [36, 29, 72, 55, 20].
Gene ***TP53*** Exon 10 Nucleotide NM_000546.6: g.7573944delC c.1083delG Amino Acid p.S362fs*8 Function loss Allelic Fraction 2.19% (of 1372 reads) Classification **Tier 1A** Assessment **Pathogenic**	**Interpretation** The TP53 gene encodes the tumor suppressor p53, a protein that is involved in the DNA damage cell cycle checkpoint and causes cell cycle arrest when it senses DNA damage. p53 can also activate DNA repair genes, or induce apoptosis in the presence of DNA damage. It has been called the cellular gatekeeper [40]. Loss of p53 is common in aggressive advanced cancers [5]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias [60, 47, 64]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects [36, 29, 72, 55, 20].
Gene ***BCOR*** Exon 8 Nucleotide NM_017745.6: g.39922927delT c.3679delA Amino Acid p.R1227fs*33 Function loss Allelic Fraction 2.27% (of 618 reads) Classification **Tier 2C** Assessment **Likely Pathogenic**	**Interpretation** BCOR encodes a transcriptional repressor, BCoR or BCL-6 interacting corepressor, that interacts with both class I and class II histone deacetylases (HDACs) and represses the transcription of several genes, likely via epigenetic chromatin modifications [21, 14, 27, 8]. Preclinical studies have reported BCoR to play a role in stem cell homeostasis and differentiation [67, 11]. Germline BCOR mutations lead to oculofaciocardiodental (OFCD) syndrome, which is characterized by cataracts, facial anomalies, cleft palate, cardiac septal defects, and Lenz microphthalmia [53, 54]. The majority of BCOR mutations have been predicted to be inactivating, indicating BCoR may act as a tumor suppressor [57, 9, 66, 44].
Gene ***BCOR*** Exon 6 Nucleotide NM_017745.6: g.39930282delT	**Interpretation** BCOR encodes a transcriptional repressor, BCoR or BCL-6 interacting corepressor, that interacts with both class I and class II histone deacetylases (HDACs) and represses the transcription of several genes,

c.3182delA Amino Acid p.K1061fs*52 Function loss Allelic Fraction 1.65% (of 2056 reads) Classification **Tier 2C** Assessment **Likely Pathogenic**	likely via epigenetic chromatin modifications [21, 14, 27, 8]. Preclinical studies have reported BCoR to play a role in stem cell homeostasis and differentiation [67, 11]. Germline BCOR mutations lead to oculofaciocardiodental (OFCD) syndrome, which is characterized by cataracts, facial anomalies, cleft palate, cardiac septal defects, and Lenz microphthalmia [53, 54]. The majority of BCOR mutations have been predicted to be inactivating, indicating BCoR may act as a tumor suppressor [57, 9, 66, 44].
Gene ***SF3B1*** Exon 16 Nucleotide NM_012433.4: g.198266477delT c.2359delA Amino Acid p.I787fs*3 Function loss Allelic Fraction 1.73% (of 1502 reads) Classification **Tier 2C** Assessment **Likely Pathogenic**	**Interpretation** SF3B1 encodes Splicing factor 3B subunit 1 (SF3b155), a protein that forms a part of multiple snRNP complexes [73, 15, 68, 17]. SF3b155 has been reported to regulate mRNA splicing and nuclear export; SF3B1 mutations may result in altered splicing and expression of hundreds of cancer-associated genes [10, 4, 43].
Gene ***STAG2*** Exon 14 Nucleotide NM_006603.5: g.123191805delT c.1400delT Amino Acid p.F467fs*3 Function loss Allelic Fraction 1.27% (of 10472 reads) Classification **Tier 2C** Assessment **Likely Pathogenic**	**Interpretation** STAG2 is located at Xq25 and encodes the cohesin subunit SA-2; SA-2 is one of four core components of cohesin, a complex responsible for maintaining chromatid organization during mitosis to ensure proper chromosome segregation with each cell division [65, 51, 6, 7]. Germline micro duplication of the genetic region encompassing STAG2 has been reported in patients with cohesinopathy [78, 39]. STAG2 deletion and inactivating mutations have been reported in several types of cancer and inactivating STAG2 alterations have been reported to cause chromosomal instability [63, 33].
Gene ***STAG2*** Exon 25 Nucleotide NM_006603.5: g.123210180A>C c.2534-2A>C Amino Acid Function loss Allelic Fraction 4.58% (of 2465 reads) Classification **Tier 2C** Assessment **Likely Pathogenic**	**Interpretation** STAG2 is located at Xq25 and encodes the cohesin subunit SA-2; SA-2 is one of four core components of cohesin, a complex responsible for maintaining chromatid organization during mitosis to ensure proper chromosome segregation with each cell division [65, 51, 6, 7]. Germline micro duplication of the genetic region encompassing STAG2 has been reported in patients with cohesinopathy [78, 39]. STAG2 deletion and inactivating mutations have been reported in several types of cancer and inactivating STAG2 alterations have been reported to cause chromosomal instability [63, 33].
Gene ***TET2*** Exon 3 Nucleotide NM_001127208.3: g.106156936delG c.1842delG Amino Acid p.L615fs*24 Function loss Allelic Fraction 1.31% (of 12705 reads) Classification **Tier 2C** Assessment **Likely Pathogenic**	**Interpretation** The TET2 gene encodes Tet2, a methylcytosine dioxygenase that converts methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), a crucial component in the DNA methylation process [23, 18]. It is a tumor suppressor gene that is widely expressed in hematopoietic cells and plays a role in the progression of myeloid neoplasms [25]. 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 [35, 42, 77, 28, 50].
Gene ***TET2***	**Interpretation**

Exon	3
Nucleotide	NM_001127208.3: g.106158447delA c.3353delA
Amino Acid	p.N1118fs*19
Function	loss
Allelic Fraction	1.64% (of 4693 reads)
Classification	**Tier 2C**
Assessment	**Likely Pathogenic**

The TET2 gene encodes Tet2, a methylcytosine dioxygenase that converts methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), a crucial component in the DNA methylation process [23, 18]. It is a tumor suppressor gene that is widely expressed in hematopoietic cells and plays a role in the progression of myeloid neoplasms [25]. 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 [35, 42, 77, 28, 50].

Gene	***ZRSR2***
Exon	4
Nucleotide	NM_005089.4: g.15821896A>T c.289A>T
Amino Acid	p.K97*
Function	loss
Allelic Fraction	3.42% (of 1023 reads)
Classification	**Tier 2C**
Assessment	**Likely Pathogenic**

Interpretation
ZRSR2 encodes U2 small nuclear ribonucleoprotein auxiliary factor 35 kDa subunit-related protein 2 (U2AF1-RS2, also known as Urp), which is involved in spliceosome assembly and the splicing of both U2- and U12-type introns [62]. Mutations in ZRSR2 have not been widely reported in cancer, but have been found most frequently in hematological malignancies, including T-cell acute lymphoblastic leukemia, myelodysplastic syndromes, and acute myeloid leukemia [79, 76, 45, 52, 26].

Gene	***BCORL1***
Exon	4
Nucleotide	NM_021946.5: g.129148235delC c.1491delC
Amino Acid	p.E498fs*15
Function	loss
Allelic Fraction	1.71% (of 2748 reads)
Classification	**Tier 3**
Assessment	**Likely Pathogenic**

Interpretation
BCORL1 encodes a BCoR homologue, BCoRL1, a transcriptional repressor that interacts with class II histone deacetylases (HDACs) [56]. The majority of BCORL1 mutations have been predicted to be inactivating, indicating BCoRL1 may act as a tumor suppressor [41, 9, 70].

Gene	***BCORL1***
Exon	13
Nucleotide	NM_021946.5: g.129190011delC c.5042delC
Amino Acid	p.P1681fs*20
Function	loss
Allelic Fraction	1.82% (of 3465 reads)
Classification	**Tier 3**
Assessment	**Pathogenic**

Interpretation
BCORL1 encodes a BCoR homologue, BCoRL1, a transcriptional repressor that interacts with class II histone deacetylases (HDACs) [56]. The majority of BCORL1 mutations have been predicted to be inactivating, indicating BCoRL1 may act as a tumor suppressor [41, 9, 70].

Gene	***CUX1***
Exon	15
Nucleotide	NM_001202543.2: g.101839974delC c.1322delC
Amino Acid	p.P441fs*27
Function	loss
Allelic Fraction	2.91% (of 1307 reads)
Classification	**Tier 3**
Assessment	**Likely Pathogenic**

Interpretation
CUX1 encodes multiple isoforms of the CUT-like homeobox 1 (Cux1) protein, including Cux1 p200, Cux1 p110, and Cux1 p75; the former mediates transcriptional repression and DNA repair, while the latter two can play a role in either transcriptional activation or repression [49, 16, 2, 32]. Cux1 has been reported to function as both a haploinsufficient tumor suppressor and as an oncogene, with the former associated with tumor initiation and the latter associated with tumor progression [12, 75, 58]. Cux1 activation has been reported to enhance cell cycle progression and increase migration and invasive phenotypes in cell models [59, 3, 19, 31]. However, selection for CUX1 deletion has been described as a driver of

	loss of heterozygosity in multiple cancer types, and inactivating CUX1 mutations have been reported in tumors [61, 48, 75].
Gene ***NOTCH1*** Exon 26 Nucleotide NM_017617.5: g.139399409_139399411delCAC c.4732_4734delGTG Amino Acid p.V1578del Function loss Allelic Fraction 1.5% (of 3858 reads) Classification **Tier 3** Assessment **Pathogenic**	**Interpretation** NOTCH1 encodes Notch1, a member of the Notch family of receptors, which contain an extracellular domain with several EGF-like repeats. Upon binding of membrane bound ligands, the Notch1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex regulating genes involved in cell fate determination, proliferation, and apoptosis [37]. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or oncogene [34, 71].

Genes Tested

ABL1, ASXL1, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CBLC, CDKN2A, CEBPA, CSF3R, CUX1, DNMT3A, ETV6, EZH2, FBXW7, FLT3, GATA1, GATA2, GNAS, HRAS, IDH1, IDH2, IKZF1, JAK2, JAK3, KDM6A, KIT, KMT2A, KRAS, MPL, MYD88, NOTCH1, NPM1, NRAS, PDGFRA, PHF6, PTEN, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SMC1A, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1, WT1, ZRSR2

Methods and Limitations

Nucleic acid processing, library construction, and sequencing methods for the custom QIAGEN MultiModal QIAseq assay are available upon request. Sequencing data was processed using the CLC Genomics Server bioinformatics platform, the Biomedical Genomics Analysis Server Plugin, and QIAGEN Clinical Insight Interpret.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (8.0.20210827), Ingenuity Knowledge Base (D-release), CADD (v1.6), NCBI Gene (2021-02-19), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2021-02-19), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2021-07-23 16:14:57.512), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (D-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2 (HumVar)), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 37), CentoMD (5.3), dbVar (2021_04), OMIM (May 07, 2021), gnomAD (2.1.1), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2021-04-26), DGV (2016-05-15), COSMIC (v92), HGMD (2021.2), OncoTree (oncotree_2019_03_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 154, GRCh38 154), SIFT4G (2016-02-23)

Disclaimer

The results provided in this report are for Research Use Only (RUO) and informational in nature. The information contained in this report cannot be used for paient treatment and/or prognostic decisions. No interpretations of genomic variants have been made by Discovery Life Sciences.

Clinical Significance of Variants Based on AMP / ASCO / CAP Guidelines*

Strong Significance	**Tier 1A**	• Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis • Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis

	Tier 1B	• Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies • Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential Significance	**Tier 2C**	• Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis • Biomarker is an inclusion criterion for an active clinical trial • Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	• Biomarker shows plausible response or resistance based on case or preclinical studies • Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain Significance	**Tier 3**	• Biomarker has uncertain clinical significance and not known to be likely benign or benign

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