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Case ID **XB-1064**	Patient sex **Female**	Diagnosis **Chronic lymphocytic leukemia**	Tumor purity not specified	Ordering physician **Dr. Niklaus Marti**
Patient MRN **MRN1234567**	Patient DOB **04/08/1957**	Sample type **Blood**	Sample collection date **10/01/2020**	Ordering institution **Universitätsklinik Liestal**
Patient name not specified	Patient ethnicity not specified	Sample site **Blood**	Sample receipt date **10/03/2020**	Ordering institution ID **OID123**

Report summary

4 clinically significant variants & combinations 0 relevant therapies
0 other biomarkers

variant **SF3B1** p.K700E | variant **NOTCH1** p.P2514fs | variant **NPM1** p.W288fs | variant **CTNNB1** p.D32Y

variant
SF3B1 p.K700E VAF **36%** RD **67** Tier I-A

SF3B1 mutations are associated with worse or intermediate prognosis in CLL (WHO, NCCN, ESMO). These mutations may be present in CHIP (WHO).

no approved therapies

variant
NOTCH1 p.P2514fs VAF **28%** RD **25** Tier I-B

In a phase III trial, the addition of rituximab to FC chemotherapy showed no benefit in patients with CLL harboring NOTCH1 P2514Rfs*4. NOTCH1 P2514Rfs*4 was associated with poor overall survival, progression-free survival, and treatment risk in clinical studies of CLL patients.

no approved therapies

variant
NPM1 p.W288fs VAF **27%** RD **1,590** Tier II-C

NPM1 mutations are associated with with a favorable prognosis in cytogenetically normal acute myeloid leukemia (AML), (NCCN), (ESMO), (ELN), (WHO, 2016). Multiple clinical studies have reported that NPM1 mutation is associated with favorable prognosis in AML lacking FLT3 internal tandem duplication or other FLT3 mutation. NPM1 mutation is an important diagnostic marker in AML (NCCN), (WHO), and testing is strongly recommended for certain patients with suspected or confirmed AML (CAP-ASH) to confirm molecular subtype. Clinical studies have reported that patients with AML harboring NPM1 mutations are sensitive to kinase, BCL-2, and proteasome inhibitors. Primary and cultured AML cells expressing NPM1 W288fs*12 were sensitive to an investigational NPM1 inhibitor alone or in combination with chemotherapy. Patients with acute myeloid leukemia harboring NPM1 mutations match partial inclusion criteria for clinical trials, such as trials SYK and DNMT inhibitors.

no approved therapies

variant

CTNNB1 p.D32Y VAF **50%** RD **1,746** Tier II-D

Activating mutations in CTNNB1 result in increased β-catenin-dependent transcription. Small molecule β-catenin inhibitors are under clinical investigation in hematologic cancers, including one drug that has demonstrated safety and preliminary efficacy in a phase I trial in AML.

no approved therapies

End of findings section

SF3B1 p.K700E missense variant

Tier I-A

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
SF3B1 hotspot mutation	Gain of function	Chr:2 Pos:197402110 Change:T>C	c.2098A>G p.Lys700Glu	ENST00000335508.10

Gene clinical summary
Alterations in SF3B1 are found in cancers, including hematological cancers, melanoma, breast cancer, and pancreatic cancer (PMID: 25510282). Hotspot missense mutations in the HEAT regions alter SF3B1 interactions with other spliceosomal proteins or transcriptional complexes to change splicing patterns. However, the functional impact of this on oncogenesis is not yet understood (PMID: 26842708). There are currently no approved targeted therapies, but spliceosomal inhibitors are under preclinical and clinical investigation in SF3B1-mutated cancers (PMID: 25424858) (NCT03614728).

Variant group clinical summary
SF3B1 mutations were associated with worse or intermediate prognosis in chronic lymphocytic leukemia (CLL) (WHO, NCCN, ESMO) (PMID: 24943832)(PMID: 26200345)(PMID: 26466571). SF3B1 mutations may be present in clonal hematopoiesis of indeterminate potential (CHIP) (WHO) (PMID: 25931582).

Gene biological summary
SF3B1 is an essential component of the major U2-dependent and minor U12-dependent spliceosomes, with additional functions in regulation of apoptosis, cell cycle, and Hox gene regulation (PMID: 25510282). Important domains in SF3B1 include the tandem HEAT repeat regions (residues 529-1201) and the PPP1R8 binding domain (resides 223-491). (PMID: 26842708) (UniProt.org).

Variant functional summary
SF3B1 K700E lies within the HEAT repeat 1 region of the SF3B1 protein (UniProt.org). This mutation confers a gain of function to the SF3B1 protein as indicated by aberrant mRNA splicing of SF3B1 target genes in cell culture and knock-in animal models (PMID: 26565915)(PMID: 27818134).

Variant group functional summary
SF3B1 hotspot mutations are missense mutations in codons E622, Y623, R625, N626, H662, T663, K666, I704, G740, G742, and D781, and SF3B1 K700E, which lie within the HEAT repeats of the splicing factor SF3B1 (UniProt.org). These mutation are predicted to confer a gain of function to the SF3B1 protein as indicated by aberrant mRNA splicing of SF3B1 target genes in cell culture and knock-in animal models (PMID: 26565915)(PMID: 27818134).

NOTCH1 p.P2514fs frameshift variant

Tier I-B

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
NOTCH1 activating mutati… NOTCH1 inactivating mut… NOTCH1 truncating mutati…	Gain of function (predicted)	Chr:9 Pos:136496196 Change:CAG>C	c.7541_7542delCT p.Pro2514fs	ENST00000277541.6

Gene clinical summary
Alterations in NOTCH1 are found in cancers, including hematologic, breast, prostate, colorectal, head and neck, and lung cancer. NOTCH1 activation leading to oncogenic signaling results from gene amplifications, activating mutations in the extracellular heterodimerization domain, or truncating mutations within the NOTCH1 PEST domain (PMID: 21948802)(PMID: 15472075). Inactivating mutations in NOTCH1 result in a nonfunctional protein and subsequent upregulation of oncogenic pathways including WNT (PMID: 21798897). There are currently no approved therapies targeting NOTCH1; however, drugs targeting the NOTCH pathway including direct NOTCH1 inhibitors and γ-secretase inhibitors are under clinical development (PMID: 29726923)(PMID: 26341688).

Variant clinical summary
In a phase III clinical trial, the addition of the CD20 antibody rituximab to fludarabine and cyclophosphamide chemotherapy did not increase clinical or MRD response and gave no improvement in PFS or OS in chronic lymphocytic leukemia patients with NOTCH1 mutations, 61/62 of whom harbored P2514Rfs*4. (PMID: 24652989).

In additional clinical studies of chronic lymphocytic leukemia patients, NOTCH1 P2541fs*4 was significantly associated with poor overall survival in two studies (PMID: 24217197)(PMID: 23167503) and significantly associated with increased treatment risk and decreased progression-free survival in one study (PMID: 24579978).

Variant group clinical summary
In multiple clinical studies, NOTCH1 mutations were associated with worse prognosis in chronic lymphocytic leukemia (CLL) (PMID: 26200345)(PMID: 21670202)(PMID: 22077063)(PMID: 23086750)(PMID: 23243274)(PMID: 23295735).

In a phase III clinical trial of patients with CLL, NOTCH1 mutations (n=62) were not associated with clinical benefit on fludarabine, cyclophosphamide, and rituximab therapy (PMID: 24652989). In a phase II trial, patients with CLL harboring NOTCH1 mutations treated with alemtuzumab (n=13) demonstrated improved progression-free survival, but not overall survival, compared to NOTCH1 wild-type CLL (n=84) (PMID: 23821658).

Gene biological summary
NOTCH1 is a member of the NOTCH family of transmembrane receptors. NOTCH1 plays a key role in cellular development by regulating cell fate lineage decisions. Upon ligand binding, the NOTCH1 receptor is cleaved by γ-secretase, thereby releasing the active signaling fragment from the NOTCH intracellular domain, which translocates to the nucleus (PMID: 28969930). Important domains in NOTCH1 include the EGF-like domains (residues 20-1426), the extracellular heterodimerization domains (residues 1571-1618 and 1674-1722), the ankryin repeat domains (residues 1928-2122), and the PEST domain (residues 2311-2555)(UniProt.org)(PMID: 15472075).

Variant functional summary
NOTCH1 P2514fs results in a change in the amino acid sequence of the NOTCH1 protein beginning at aa 2514 of 2555, likely resulting in premature truncation of the functional protein (UniProt.org). This mutation expressed with L1600P demonstrates constitutive NOTCH signaling in culture (PMID: 17646409), but has not been characterized individually and therefore, its effect on NOTCH1 protein function unknown.

Variant group functional summary

NOTCH1 activating mutations confers a gain of function to the NOTCH1 protein as demonstrated by biochemical, in vitro, or in vivo assays. Truncating mutations within the C-terminal PEST domain result in a loss of negative regulation (PMID: 26341688), and mutations within the extracellular heterodimerization domain result in ligand-independent activation of NOTCH1 signaling (PMID: 19778842).

NOTCH1 inactivating mutations result in a loss of function of the NOTCH1 protein, which has been verified via biochemical, in vitro, or in vivo assays. Additionally, this group includes variants that are predicted to have a loss of function due to a truncation leading to the disruption or deletion of key functional domains (PMID: 21798897)(PMID: 21948802).

NPM1 p.W288fs frameshift variant

Tier II-C

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
NPM1 inactivating mutation NPM1 truncating mutation	Loss of function	Chr:5 Pos:171410540 Change:T>TCTGC	c.863_864insCCTG p.Trp288fs	ENST00000296930.9

Gene clinical summary
Alterations in NPM1 are found in cancers, including hematologic cancer. Frameshift mutations in the C-terminal region generate a protein lacking the nucleolar localization signal but with a novel nuclear export signal, which results in a mislocalized cytoplasmic protein. Loss of functional NPM1 may result in myeloproliferation, transformation and cancer development (PMID: 28111462). There are currently no targeted therapies approved for use in NPM1-mutated cancers, but NPM1 inhibitors and degraders and indirect are under preclinical investigation (PMID: 26828965).

Variant clinical summary
NPM1 mutations are associated with with a favorable prognosis in cytogenetically normal acute myeloid leukemia (AML), (NCCN), (ESMO), (ELN), (WHO, 2016), (PMID: 23970018), (PMID: 27895058). Additionally, multiple clinical studies have reported that NPM1 mutation is associated with favorable prognosis in AML lacking FLT3 internal tandem duplication or other FLT3 mutation (PMID: 26676635), (PMID: 16109776), (PMID: 24573385), (PMID: 25713434).

NPM1 mutation is an important diagnostic marker in AML (NCCN), (WHO), and testing is strongly recommended for certain patients with suspected or confirmed AML (CAP-ASH) to confirm molecular subtype.

Clinical studies have reported response to a kinase inhibitor (PMID: 27406088), BCL-2 inhibitor, (Blood 2018; 132 (suppl, abstr 283), and proteasome inhibitor (PMID: 26634271) in AML patients harboring NPM1 mutations. In a preclinical study, primary and cultured AML cells expressing NPM1 W288fs*12 were sensitive to the investigational NPM1 inhibitor NSC348884 alone or in combination with all-trans retinoic acid (ATRA) (PMID: 21719597).

Patients with acute myeloid leukemia harboring NPM1 mutations match partial inclusion criteria for clinical trials, such as trials with SYK and DNMT inhibitors (NCT02450877) (NCT03013998).

Variant group clinical summary
NPM1 mutations are associated with with a favorable prognosis in cytogenetically normal acute myeloid leukemia (AML), (NCCN, ESMO, ELN, WHO), (PMID: 23970018), (PMID: 27895058). Additionally, multiple clinical studies have reported that NPM1 mutation is associated with favorable prognosis in AML lacking FLT3 internal tandem duplication or other FLT3 mutations (PMID: 26676635), (PMID: 16109776), (PMID: 24573385), (PMID: 25713434).

NPM1 mutation is an important diagnostic marker in AML (NCCN, WHO), and testing is strongly recommended for certain patients with suspected or confirmed AML to confirm molecular subtype (CAP-ASH) and to guide therapy selection (NCCN).

Clinical studies have reported response to a kinase inhibitor (PMID: 27406088), BCL-2 inhibitor, (Blood 2018; 132 (suppl, abstr 283), and proteasome inhibitor (PMID: 26634271) in AML patients harboring NPM1 mutations.

Patients with acute myeloid leukemia harboring NPM1 mutations match inclusion criteria for clinical trials, such as trials with SYK and DNMT inhibitors (NCT02450877), (NCT03013998).

Gene biological summary
NPM1 (nucleophosmin) is a phosphoprotein with numerous cellular functions that normally shuttles between the cytoplasm and the nucleolus. In the nucleolus, NPM1 functions in ribosome biogenesis, genome stability, stress response, and cell cycle control via protection of the tumor suppressor ARF (PMID: 23436734). Important domains in NPM1 include two nuclear export signals (residues 42-49 and 94-102), two nuclear localization signals (residues 152-157 and 191-197), and the C-terminal domain which includes a nucleolar localization signal (residues 243-294) (Uniprot.org) (PMID: 23436734).

Variant functional summary
NPM1 W288Cfs*12 is a hotspot mutation that results from a 4 bp-duplication causing a frameshift at aa 288 of 294, followed by 12 amino acids creating a novel nuclear export sequence (PMID: 16501600), (PMID: 15659725). This mutation confers a loss of function as demonstrated by mislocalization of the NPM1 protein (PMID: 15659725).

Variant group functional summary
NPM1 inactivating mutation indicates that variants in this group result in a loss of function of the NPM1 protein, which has been verified via biochemical, in vitro, or in vivo assays. Additionally, this group includes variants that are predicted to have a loss of function due to a truncation leading to the disruption or deletion of key functional domains (PMID: 15659725), (PMID: 16076867), (PMID: 15659725), (PMID: 17535915).

NPM1 truncating mutation indicates any nonsense or frameshift mutation resulting in a premature termination codon. This class of NPM1 mutation frequently occurs within the last exon (exon 12) resulting the loss or disruption of the nucleolar localization and mislocalization of the NPM1 protein to the cytoplasm (PMID: 15659725), (PMID: 16076867), (PMID: 15659725).

CTNNB1 p.D32Y missense variant

Tier II-D

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
CTNNB1 activating mutati…	Gain of function	Chr:3 Pos:41224606 Change:G>T	c.94G>T p.Asp32Tyr	ENST00000349496.9

Gene clinical summary
Alterations in CTNNB1 are found in cancers, including colorectal, breast, uterine cancer (PMID: 28731148). Activating missense mutations and small deletions in the N-terminal domain (PMID: 28927523) result in WNT-independent activation of the WNT/β-catenin signaling pathway and constitutive activation of genes promoting cell growth and division. Emerging drugs under preclinical and clinical investigation inhibit β-catenin protein-protein interactions. WNT signaling inhibitors are currently in clinical trials and drugs targeting the nuclear β-catenin complex and downstream pathways are under preclinical investigation (PMID: 28731148).

Variant group clinical summary
Activating mutations in CTNNB1 result in increased β-catenin-dependent transcription. Small molecule β-catenin inhibitors are under clinical investigation in hematologic cancers (PMID: 28474989)(PMID: 28731148)(NCT01398462), and one such drug has demonstrated safety and preliminary efficacy in a phase I trial in acute myeloid leukemia (J Clin Oncol (Meeting Abstracts) 2015 33: 7044)).

Gene biological summary
CTNNB1 or β-catenin, is a component of cadherin-based adherens junctions and a transcriptional co-activator in the WNT/β-catenin signaling pathway (PMID: 28731148). Activation of WNT signaling results in translocation of cellular β-catenin to the nucleus and activation of genes regulating cell proliferation, migration, differentiation and survival (PMID: 28752891). Important domains in CTNNB1 include the N-terminal domain (residues 1-151), the C-terminal domain (residues 664-781), and a central armadillo repeat domain (residues 151-664) (PMID: 28927523).

Variant functional summary
CTNNB1 D32Y lies within the ubiquitination recognition motif of the β-catenin protein (PMID: 15064718). CTNNB1 D32Y confers a gain of function to the β-catenin protein as demonstrated by decreased ubiquitination and increased β-catenin-dependent transcription (PMID: 15064718), (PMID: 10987273).

Variant group functional summary
CTNNB1 activating mutations result in a gain of function in the β-catenin protein, leading to increased β-catenin-dependent transcription (PMID: 28731148).

Variants of Unknown Significance

The variants listed here are not sufficiently characterized in the current literature and variant databases, and are therefore, currently, of uncertain or unknown clinical significance. They are reported here for future reference in the event they become clinically significant in light of additional supporting evidence.

NOTCH3 p.A1802fs

✓ Electronically Signed by Anoop Grewal | **Dr. Martin Gerber** Lab Director | *10/06/2020*

Appendix

Clinical Disclaimer

Interpretation of the test results is limited by the information that is currently available at the time. Treatment decisions are the responsibility of the physician. Results of this test must always be interpreted within the clinical context, such as the patient's conditions, patient and family history, physical examinations, information from other diagnostic tests and patient preferences.
The Inov Heme Panel was developed and its performance characteristics determined by Inov Labs.

Genomic Regions Tested

We sequence all coding exons for each given transcript, plus approximately 10 basepairs of flanking non-coding DNA in each intron-exon junction. Unless specifically indicated, test results contain no information about other regions of the gene, such as regulatory domains or deep intronic regions.
The genes on the panel: ABL1, ASXL1, ATM, BCL11B, BCOR, BCORL1, BRAF, BRCC3, CALR, CBL, CBLB, CD79B, VRBPS, CNOT3, CREBBP, CRLF2, CSF1R, CSF3R, CTCF, CTNNB1, CUX1, CXCR4, DNMT3A, DNMT3B, EED, EGFR, EP300, ETV6, EZH2, FANCL, FBXW7, FLT3, GATA1, GATA2, GATA3, GNAS, GNB1, IDH1, IDH2, IKZF1, IKZF2, IKZF3, IL7R, JAK1, JAK2, JAK3, KIT, KRAS, LUC7L2, MAPK2K1, MDM2, MEF2B, MPL, MYD88, NOTCH1, NOTCH2, NOTCH3, NPM1, NRAS, NT5C2, PAX5, PDGFRA, PDS5B, PHF6, PIGA, PIM3, PRPF40B, PRPF8, PTEN, PTPN11, RAD21, RET, RIT1, RPL10, RUNX1, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, TET2, TLR2, TP53, U2AF1, U2AF2, WT1, XPO1, ZRSR2.
LIMIT OF DETECTION: 5 percent variant allele fraction for single nucleotide variants (SNVs), small to medium sized multi-nucleotide variants (MNV) (less than 50bp).

Methodology

Genomic DNA is isolated from plasma and then enriched for the targeted regions of the tested genes. The variant status of the targeted genes is determined by massively parallel sequencing (next generation sequencing). The GRCh38 reference sequence is used as a reference for identifying genetic variants.

Limitations

This test will not detect variants in areas outside the targeted genomic regions or below the assay's limit of detection. This test evaluates for variants in hematological samples only. It cannot distinguish between somatic and germline variants.
For variants of potential germline origin, germline testing may be warranted. Consider seeking genetic counseling prior to such testing. In some cases, variants may not be identified due to technical limitations, especially when in the presence of known pseudogenes, homologous regions or regions of low mappability. Larger insertions or deletions (>50 basepairs) may not be detected.

NAVIFY® Mutation Profiler disclaimer

The information available in this report is obtained from third party sources (such as biomedical literature, medical guidelines, and publicly available data such as drug labels and clinical trials) and is subject to change over time based on future findings (including scientific and medical research).

NAVIFY® Mutation Profiler is not able to differentiate between germline and somatic variants. In general, variant interpretations are provided assuming the variants are of somatic origin.

3rd party attributions

A portion of the somatic gene variant annotations and related content have been provided by The Jackson Laboratory Clinical Knowledgebase (JAX-CKB™)

Clinical trial matching based on reported biomarkers are provided by MolecularMatch.

Tier definitions

Tier I-A: Approved therapy. Included in professional guidelines.

Tier I-B: Well-powered studies with consensus from experts in the field.

Tier II-C: Approved therapies for different tumor types or investigational therapies. Multiple small published studies with some consensus. Inclusion criteria for clinical trials.

Tier II-D: Limited clinical or preclinical studies.

Tier III (VUS): Variants of Unknown Clinical Significance.

Tier IV: Benign or likely benign variants (not included in the report, except for other biomarkers).

Software and content version numbers

NAVIFY® Mutation Profiler Version 2.0.0.7b4557e, Release date: 09/30/2020

NAVIFY® Therapy Matcher Version 2.0.0.7b4557e, Release date: 09/30/2020

Roche content Version 2.29.0, Release date: 08/18/2020

CIViC Version 01-july-2020, Release date: 07/01/2020

ClinVAR Version 20200727, Release date: 07/27/2020

COSMIC Version v91.r1, Release date: 04/07/2020

dbNSFP Version 4.0, Release date: 05/03/2019

gnomAD Version 2.1.1-VnV, Release date: 10/16/2019

TCGA Version 24.0.r2, Release date: 05/07/2020

Mitelman Version 15-apr-2020, Release date: 04/15/2020

dbVar Version 2020-06-07, Release date: 06/07/2020

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