LABORATORY REPORT

Reg. No	:	**30300200033**	Reg. Date	:	03-Mar-2023 10:58
Name	:	**MANOREMA SHARMA**	Collected on	:	03-Mar-2023 10:58
Sex/Age	:	**Female / 65 Years**	Approved Date	:	07-Mar-2023 18:22
Ref. By	:		Tele. No	:	9833253102
Location	:	LILAC INSIGHTS PVT. LTD. @ MUMBAI	Dispatch At	:	

Please find detailed report of NGS Oncomine Myeloid GX V2 Assay(DNA only) in the following pages.

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Neeraj Arora

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Patient Details

Patient Name	**MANOREMA SHARMA**	**Sample Id/LabID**	**30300200033**
Gender	Female	**Sample Type**	Bone Marrow
DOB/AGE	65 Yrs	**Date of Sample Collection**	03-Mar-2023
Ref.By	LILAC INSIGHTS PVT. LTD.	**Date of Receipt**	03-Mar-2023
		Date of Report	07-Mar-2023

NGS Oncomine Myeloid GX V2 Assay (Only DNA)

Clinical Details:

? AML(Acute Myeloid Leukemia)

RESULT

POSITIVE:

- Clinically relevant Pathogenic mutations Identified.

Variants Identified:

Table-1

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NRAS	p.(G12D)	c.35G>A	COSM564	chr1:115258747	18.83%	NM_002524.5	missense
IDH2	p.(R140Q)	c.419G>A	COSM41590	chr15:90631934	44.12%	NM_002168.4	missense
SRSF2	p.(P95_R102del)	c.284_307delCCCCGGACTCACACCACAGCCGCC	COSM146289	chr17:74732935	54.37%	NM_003016.4	nonframeshift Deletion

Note: As per 2022 ELN risk classification , AML with Mutated SRSF2 will fall under adverse prognosis category.(PMID:35797463)

Variant Description

NRAS:c.35G>A:p.Gly12Asp: Pathogenic: The p.Gly12Asp variant (also known as c.35G>A), was detected in NRAS gene on chromosome 1 at position 115258747 with variant allele frequency of 18.82% (represented by 276 reads). This heterozygous mutation is having a total depth of 1466X. It is located at exon 2 of NM_002524.5 transcript and was found to change amino acid, Glycine to Aspartic acid at codon 12. It leads to Gain-of-Function. It is a hotspot variant. It is represented by rs121913237 in dbSNP database and COSM564 in Cosmic database. It is interpreted as pathogenic according to ClinVar database [VCV000039648], associated with range of disease condition including Acute myeloid leukemia[PMID: 16434492,19075190]. It is one of the most common somatic mutation type in myeloid neoplasm [PMID: 34155503]. It is predicted as pathogenic by MutationTaster2, and SIFT, which is an in-silico DNA variant effect prediction tool. It was found in the population frequency database like gnomAD exome and ExAC at global minor allele frequency of 0.0007953% and 0.0008237% respectively.

Its alternative form p.Gly12Cys, p.Gly12Arg, p.Gly12Val, p.Gly12Ser and p.Gly12Ala are classified as pathogenic by Clinvar.

IDH2:c.419G>A:p.Arg140Gln: Pathogenic: The p.Arg140Gln variant (also known as c.419G>A), was detected in IDH2 gene on chromosome 15 at position 90631934 with variant allele frequency of 44.12% (represented by 882 reads). This heterozygous mutation is having a total depth of 1999X. It is located at exon 4 of NM_002168.4 transcript and was found to change amino acid, Arginine to Glutamine at codon 140. It leads to Gain-of-Function. It is a hotspot variant. It is represented by rs121913502 in dbSNP and COSM41590 in Cosmic database. It is interpreted as pathogenic according to ClinVar database [VCV000014716], association with Acute myeloid leukemia [PMID: 2381590, 22397365, 24606448]. IDH2 R140Q is one of the common somatic mutation type in myeloid neoplasm [PMID: 34155503]. It is predicted as deleterious by SIFT, polyphen2 and MutationTaster2 which is an in-silico DNA variant effect prediction tool. It was found in the population frequency database like gnomAD exome and ExAC having global minor allele frequency of 0.0032% and 0.0099% respectively.

SRSF2:c.284_307delCCCCGGACTCACACCACAGCCGCC: p.Pro95_Arg102del: Pathogenic: The p.Pro95_Arg102del variant (also known as c.284_307delCCCCGGACTCACACCACAGCCGCC), was detected in SRSF2 gene on chromosome 17 at position 74732935 with variant allele frequency of 54.36% (represented by 417 reads). This heterozygous mutation is having a total depth of 767X. It is located at exon 1 of NM_003016.4 transcript and was found to change amino acid, Proline to Arginine at codon 95. This non-frame shift deletion was found to delete 8 amino acids starting from codon 95 to 102, leading to Gain-of-function. It is a hotspot variant. It is represented by rs766200080 in dbSNP and COSM146289 in Cosmic database. The position of this variant is conserved across species. It is one of the most common somatic mutation type in myeloid neoplasm [PMID: 34155503]. It is predicted as deleterious by MutationTaster2 which is an in-silico DNA variant effect prediction tool. It was found in the population frequency database like gnomAD exome and ExAC at global minor allele frequency of 0.0004293 % and 0.001958 % respectively.

Note: Variants with variant allele frequency at nearly 50% or 100% should be considered Germline mutation. However, to rule out germ line mutations, repeat analysis using peripheral blood/saliva sample is recommended.

Comments:

These findings should be correlated with other clinical and laboratory tests like CBC, Bone marrow aspirate, biopsy, flowcytometry for a definite conclusive interpretation.

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*IDH2 R140Q* isocitrate dehydrogenase (NADP(+)) 2 Allele Frequency: 44.12% Transcript: NM_002168.4	**enasidenib** [1] azacitidine decitabine venetoclax + chemotherapy	None	12
IIC	*NRAS G12D* NRAS proto-oncogene, GTPase Allele Frequency: 18.83% Transcript: NM_002524.5	None	None	4
IIC	*SRSF2 P95_R102del* serine and arginine rich splicing factor 2 Allele Frequency: 54.37% Transcript: NM_003016.4	None	None	3

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO

Biomarker Descriptions

IDH2 (isocitrate dehydrogenase (NADP(+)) 2)

Background: The IDH1 and IDH2 genes encode homologous isocitrate dehydrogenase enzymes that catalyze the conversion of isocitrate to α-ketoglutarate (α-KG)[1]. The IDH1 gene encodes the NADP+ dependent cytoplasmic isocitrate dehydrogenase enzyme; IDH2 encodes the mitochondrial isoform.

Alterations and prevalence: Recurrent somatic mutations in IDH1 and IDH2 are mutually exclusive and observed in several malignancies including glioma, chondrosarcoma, intrahepatic cholangiocarcinoma, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS)[2]. Recurrent IDH2 variants include predominately R140Q and R172K plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity[3]. Although wild-type enzymatic activity is ablated, recurrent IDH2 variants catalyze the conversion of α-KG to D-2-hydroxyglutarate, an oncometabolite with diverse effects on cellular metabolism, epigenetic regulation, redox states, and DNA repair[1,4]. Recurrent IDH2 mutations are present in 10-20% of patients with AML and 5% of patients with MDS[5,6,7].

Potential relevance: Enasidenib[8] is FDA approved (2017) for the treatment of AML patients with IDH2 R140G/L/Q/W and R172G/K/M/S/W mutations. In AML, acquired resistance to enasidenib has been associated with the emergence of Q316E or I319M mutations[9]. IDH2 R172 and R140Q variants are associated with poor prognosis in MDS but have been shown to confer improved prognosis in lower grade gliomas[10,11,12]. Additionally, IDH2 mutations are associated with inferior overall survival in polycythemia vera (PV) and essential thrombocythemia (ET) as well as inferior leukemia-free survival in primary myelofibrosis (PMF)[13].

NRAS (NRAS proto-oncogene, GTPase)

Background: The NRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[14,15,16].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. NRAS mutations are particularly common in melanomas (up to 25%) and are observed at frequencies of 5-10% in acute myeloid leukemia, colorectal, and thyroid cancers[17,18]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[17,19]. Mutations at A59, K117, and A146 have also been observed but are less frequent[20,21].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[22] and panitumumab[23], are contraindicated for treatment of colorectal cancer patients with NRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[21]. The FDA has granted fast track designation to the pan-RAF inhibitor, KIN-2787[24], for the treatment of NRAS mutation positive metastatic or unresectable melanoma. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome[10] as well as melanoma[25]. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively[26].

SRSF2 (serine and arginine rich splicing factor 2)

Background: The SRFS2 gene encodes the serine/arginine (SR)-rich splicing factor 2, a member of the SR-rich family of pre-mRNA splicing factors which make up part of the spliceosome. SRFS2 contains an RNA recognition motif (RRM) that recognizes and binds exonic splicing enhancers (ESE) in a sequence-specific manner[27]. SR proteins are essential regulators of alternative RNA splicing due to their ability to bind RNA and interact with other splicing factors. These proteins can influence the exclusion of cassette exons, a form of alternative splicing also known as exon skipping, which allows for the production of different protein isoforms[27,28]. SRSF2 is the target of somatic missense mutations and in-frame deletions in hematological malignancies, particularly myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), and myeloproliferative neoplasms (MPN)[29,30,31]. Such mutations in SRSF2 result in a differential gain of function which influences cassette exon exclusion, thereby supporting an oncogenic role in cancer[32].

Alterations and prevalence: Mutations in SRSF2 are observed in approximately 10% of MDS cases and 30-40% of CMML[30,33,34]. Missense mutations at P95 are most recurrent, which leads to an amino acid change from proline to histidine (H), leucine (L), or arginine (R)[34]. Specifically, the P95H substitution alters SRSF2 affinity for ESEs and drives preferential recognition of cassette exons containing C- versus G-rich ESEs[31,32]. Although less prevalent, recurrent in-frame deletions (P95H_R102del) are observed in primary myelofibrosis (PMF)[35]. This mutation results in the deletion of 8 amino acids which has been shown to exhibit greater variation of splicing events relative to the P95 missense mutation alone[36].

Biomarker Descriptions (continued)

Potential relevance: In CMML, SRSF2 mutations are often enriched and can be used to support diagnosis[10,37]. SRSF2 mutations confer poor prognosis in MDS and systemic mastocytosis (SM) and are associated with decreased overall survival (OS)[10,38,39]. In MPN, SRSF2 mutations are considered high-risk mutations and are independently associated with inferior OS as well as leukemia-free survival[13,40]. Additionally, SRSF2 mutations are predictive of leukemic transformation in patients with PMF[13].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

IDH2 R140Q

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
enasidenib	●	●	✖	●	✖
azacitidine	✖	●	✖	✖	✖
decitabine	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖
enasidenib, chemotherapy	✖	✖	✖	✖	● (III)
enasidenib, chemotherapy, venetoclax	✖	✖	✖	✖	● (II)
olaparib	✖	✖	✖	✖	● (II)
BI-836858 + chemotherapy	✖	✖	✖	✖	● (I/II)
enasidenib, venetoclax	✖	✖	✖	✖	● (I/II)
venetoclax, ivosidenib, enasidenib, chemotherapy	✖	✖	✖	✖	● (I/II)
cobimetinib, enasidenib	✖	✖	✖	✖	● (I)
HMPL-306	✖	✖	✖	✖	● (I)
LY-3410738	✖	✖	✖	✖	● (I)
SH-1573	✖	✖	✖	✖	● (I)
TQB-3455	✖	✖	✖	✖	● (I)

NRAS G12D

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trametinib, venetoclax, chemotherapy	✖	✖	✖	✖	● (II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

NRAS G12D (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AZD-0364	✖	✖	✖	✖	● (I)
cobimetinib, enasidenib	✖	✖	✖	✖	● (I)
JZP-815	✖	✖	✖	✖	● (I)

SRSF2 P95_R102del

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
E7820	✖	✖	✖	✖	● (II)
nonengraftment donor lymphocyte infusion	✖	✖	✖	✖	● (I/II)
venetoclax, chemotherapy	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Methodology

Nucleic acid (DNA/RNA) was extracted from whole blood EDTA sample, using standard Qiagen nucleic acid isolation kits. Automated library preparation and sequencing run was perfomed using Oncomine myeloid assay GX v2 on Genexus platform as per user manual. Generated data was analyzed using on board analysis software with default filter chain. Default filter chain is optimized for reporting detected variants with the Oncomine™ Myeloid Assay GX.This filter chain provides results for INDELs and SNV variant types, and minor allele frequencies between 0.0 and 1.0E-6 based on 5000Exomes and ExAC annotation source databases that have homopolymer lengths less than or equal to 7 and allele frequencies between 0.05 and 1.0.

Run QC statistics: Sample is sequenced at Average base coverage depth of 3,483. The Target base coverage at 500X is 99.86%.

Variant Classification

- **Pathogenic**: The pathogenic variant are the one which is believed to account for the symptoms. It increases an individual's susceptibility or predisposition to a certain disease or disorder. This mutation is always included in results section of report.
- **Likely Pathogenic**: The likely pathogenic variant are the one which most likely have harmful effect but, there is insufficient evidence that a variant is the definite cause for symptoms. This mutation is always included in results section of report
- **Variant of Uncertain Significance**: The Variant of Uncertain Significance (VUS) are the one which have limited and/or conflicting evidence regarding pathogenicity. Its exact effect on gene function is not known. With more information available over time, a VUS may be reclassified as likely pathogenic or likely benign. This mutation is always included in results section of report.
- **Likely benign**: The likely benign variants are the one which are most likely not associated with disease risk. However, additional evidence is needed to confirm this assertion. This mutation is not included in report
- **Benign**: The benign variants are the one which are represented by alteration in gene compare to wild-type allele but it is not associated with disease risk. This mutation is not included in report.

Evidence-based variant Categorization

Tier I	Variants with strong clinical significance	Level A evidence	FDA-approved therapy included in professional guidelines
		Level B evidence	Well-powered studies with consensus from leaders in the field
Tier II	Variants with potential clinical significance	Level C evidence	FDA-approved therapies for different tumor types or investigational therapies. Multiple small published studies with some consensus
		Level D evidence	Preclinical trials or few case reports without consensus.
Tier III	Variants of unknown clinical significance		Not observed at significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases. No convincing published evidence of cancer association

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, BRAF, CBL, CSF3R, DNMT3A, FLT3, GATA2, HRAS, IDH1, IDH2, JAK2, KIT, KRAS, MPL, MYD88, NPM1, NRAS, PTPN11, SETBP1, SF3B1, SRSF2, U2AF1, WT1, ANKRD26, DDX41, SMC1A, PPM1D, SMC3

Genes Assayed with Full Exon Coverage

ASXL1, BCOR, CALR, CEBPA, ETV6, EZH2, IKZF1, NF1, PHF6, PRPF8, RB1, RUNX1, SH2B3, STAG2, TET2, TP53, ZRSR2

Limitations and Disclaimer

1. This test was developed and its performance characteristics determined by Unipath Specialty Laboratory Ltd, Ahmedabad. It has not been cleared or approved by the US Food and Drug Administration and NABL.
2. This NGS test used does not allow definitive differentiation between germline and somatic variants. However, variants with variant allele frequency at nearly 50% or 100% should be considered Germline mutation. To rule out germ line mutations, repeat analysis using peripheral blood/saliva sample is recommended.
3. Certain genes may not be covered completely, and few mutations may not be detected in the presence of pseudogenes or in repetitive or homologous regions.
4. False negative results may be due to sampling issues, errors in sample handling, mislabeling, transportation issues, technical limitations of the assay and mutations frequency below the limit of detection of the assay, i.e., 5% for SNVs and 10% for short indels. It is also possible some complex insertion/deletion variants may not be identified.
5. Sanger confirmation of reported mutations is available on request with additional charges.
6. This test is not intended to detect minimal residual disease.
7. Results of this test need be interpreted within the context of clinical findings and other relevant clinical and laboratory data and should not be used alone.

Report Signed by:

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References

1. Molenaar et al. Wild-type and mutated IDH1/2 enzymes and therapy responses. Oncogene. 2018 Apr;37(15):1949-1960. PMID: 29367755
2. Yan et al. IDH1 and IDH2 mutations in gliomas. N. Engl. J. Med. 2009 Feb 19;360(8):765-73. PMID: 19228619
3. Dang et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009 Dec 10;462(7274):739-44. PMID: 19935646
4. Ward et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell. 2010 Mar 16;17(3):225-34. PMID: 20171147
5. Paschka et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J. Clin. Oncol. 2010 Aug 1;28(22):3636-43. PMID: 20567020
6. Chou et al. The prognostic impact and stability of Isocitrate dehydrogenase 2 mutation in adult patients with acute myeloid leukemia. Leukemia. 2011 Feb;25(2):246-53. PMID: 21079611
7. Marcucci et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J. Clin. Oncol. 2010 May 10;28(14):2348-55. PMID: 20368543
8. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209606s004lbl.pdf
9. Intlekofer et al. Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. Nature. 2018 Jul;559(7712):125-129. PMID: 29950729
10. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]
11. Cancer Genome Atlas Research Network. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med. 2015 Jun 25;372(26):2481-98. doi: 10.1056/NEJMoa1402121. Epub 2015 Jun 10. PMID: 26061751
12. Houillier et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology. 2010 Oct 26;75(17):1560-6. PMID: 20975057
13. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 3.2022]
14. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. Nat. Rev. Cancer. 2011 Oct 13;11(11):761-74. PMID: 21993244
15. Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
16. Scott et al. Therapeutic Approaches to RAS Mutation. Cancer J. 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.0000000000000187. PMID: 27341593
17. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
18. Janku et al. PIK3CA mutations frequently coexist with RAS and BRAF mutations in patients with advanced cancers. PLoS ONE. 2011;6(7):e22769. PMID: 21829508
19. Ohashi et al. Characteristics of lung cancers harboring NRAS mutations. Clin. Cancer Res. 2013 May 1;19(9):2584-91. PMID: 23515407
20. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
21. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J. Clin. Oncol. 2016 Jan 10;34(2):179-85. PMID: 26438111
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125147s210lbl.pdf
24. https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food
25. Johnson et al. Treatment of NRAS-Mutant Melanoma. Curr Treat Options Oncol. 2015 Apr;16(4):15. doi: 10.1007/s11864-015-0330-z. PMID: 25796376
26. Dummer et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017 Apr;18(4):435-445. PMID: 28284557
27. Liang et al. SRSF2 mutations drive oncogenesis by activating a global program of aberrant alternative splicing in hematopoietic cells. Leukemia. 2018 Dec;32(12):2659-2671. PMID: 29858584

References (continued)

28. Cui et al. Comparative Analysis and Classification of Cassette Exons and Constitutive Exons. Biomed Res Int. 2017;2017:7323508. doi: 10.1155/2017/7323508. Epub 2017 Dec 4. PMID: 29349080
29. Meggendorfer et al. The mutational landscape of 18 investigated genes clearly separates four subtypes of myelodysplastic/ myeloproliferative neoplasms. Haematologica. 2018 May;103(5):e192-e195. PMID: 29700173
30. Arbab et al. Prognostic significance of SRSF2 mutations in myelodysplastic syndromes and chronic myelomonocytic leukemia: a meta-analysis. Hematology. 2018 Dec;23(10):778-784. PMID: 29757120
31. Kim et al. SRSF2 Mutations Contribute to Myelodysplasia by Mutant-Specific Effects on Exon Recognition. Cancer Cell. 2015 May 11;27(5):617-30. PMID: 25965569
32. Zhang et al. Disease-associated mutation in SRSF2 misregulates splicing by altering RNA-binding affinities. Proc. Natl. Acad. Sci. U.S.A. 2015 Aug 25;112(34):E4726-34. PMID: 26261309
33. Ethan et al. AACR Project GENIE: Powering Precision Medicine through an International Consortium. Cancer Discov. 2017 Aug;7(8):818-831. PMID: 28572459
34. Thol et al. Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. Blood. 2012 Apr 12;119(15):3578-84. PMID: 22389253
35. Lasho et al. SRSF2 mutations in primary myelofibrosis: significant clustering with IDH mutations and independent association with inferior overall and leukemia-free survival. Blood. 2012 Nov 15;120(20):4168-71. PMID: 22968464
36. Komeno et al. SRSF2 Is Essential for Hematopoiesis, and Its Myelodysplastic Syndrome-Related Mutations Dysregulate Alternative Pre-mRNA Splicing. Mol. Cell. Biol. 2015 Sep 1;35(17):3071-82. PMID: 26124281
37. Arber et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. PMID: 27069254
38. NCCN Guidelines® - NCCN-Systemic Mastocytosis [Version 1.2020]
39. Jawhar et al. Splenomegaly, elevated alkaline phosphatase and mutations in the SRSF2/ASXL1/RUNX1 gene panel are strong adverse prognostic markers in patients with systemic mastocytosis. Leukemia. 2016 Dec;30(12):2342-2350. PMID: 27416984
40. Vannucchi et al. Mutations and prognosis in primary myelofibrosis. Leukemia. 2013 Sep;27(9):1861-9. PMID: 23619563