DIAGNOSTIC REPORT

agilus diagnostics

PATIENT NAME : ISHAMMA T M (MR000384802) **REF. DOCTOR :** ASHWIN V NAIR

CODE/NAME & ADDRESS : CA00008679 KIMS HOSPITAL P B NO: 1 ANAYARA P OTHIRUVANANTHAPURAM ANAYARA 695029 4712941400	ACCESSION NO : **4182YK008935** PATIENT ID : ISHAF2211444182 CLIENT PATIENT ID: L085863525	AGE/SEX : 81 Female DRAWN : 22/11/2025 20:21 RECEIVED : 22/11/2025 20:21 REPORTED : 27/11/2025 07:33

ONCOMINE MYELOID ASSAY GX V2 - 69 GENES (DNA+RNA)

Sample Attributes and QC:

Sample ID: 4182YK008935	**Tumor Cellularity:** NA	**Coverage:** 3345x
Sample Type: Bone Marrow	**DNA:** 21.4 ng/µl, **RNA**: 74.0 ng/µl	**Uniformity:** 99.54%

EXECUTIVE SUMMARY:		
• **Clinical Case Summary**	*This patient is a newly diagnosed case of AML.*	
• **Actionable Biomarkers & Therapy Implications**	● ***RUNX1***	• Oncogenic driver • Adverse prognosis
	○ ***ASXL1, BCOR, NRAS, SRSF2, STAG2***	• Prognostic
• **RNA based Sequencing**	No clinically significant gene rearrangements / fusions detected in the submitted sample	
• **Classification** • **WHO 2022** • **ICC 2022**	• **Acute Myeloid Leukemia, myelodysplasia related** • **Acute Myeloid Leukemia, myelodysplasia related**	

Quick Visual Format: Variant Actionability Legend

	Meaning	Description
●	**Targetable**	Variant linked to FDA/NCCN/ESMO-approved targeted therapy
●	**Resistance**	Variant confers resistance to specific therapies
○	**Prognostic Only**	Variant is not directly targetable but has prognostic/diagnostic relevance
●	**VUS**	Variant of Uncertain Significance (clinical significance not established)

PERFORMED AT :
Agilus Diagnostics Ltd
Reference Lab,2nd Floor, Plot No. 31,Urban Estate Electronic City,Sector-18,
Gurugram, 122015
Haryana, India
Tel : 9111591115. Fax : CIN - U74899PB1995PLC045956

ULR No. 666000016219917-0009

DIAGNOSTIC REPORT

agilus diagnostics

PATIENT NAME : ISHAMMA T M (MR000384802) **REF. DOCTOR :** ASHWIN V NAIR

CODE/NAME & ADDRESS : CA00008679 KIMS HOSPITAL P B NO: 1 ANAYARA P OTHIRUVANANTHAPURAM ANAYARA 695029 4712941400	ACCESSION NO : **4182YK008935** PATIENT ID : ISHAF2211444182 CLIENT PATIENT ID: L085863525	AGE/SEX : 81 Female DRAWN : 22/11/2025 20:21 RECEIVED : 22/11/2025 20:21 REPORTED : 27/11/2025 07:33

VARIANT DETAILS:

DETAILED DNA VARIANT TABLE (SNVs, InDels) (AMP/ASCO/CAP TIERED)

Gene	Nucleotide change	Amino acid change	Genomic Locus	Variant Allele Frequency (%)	MANE Select transcript	AMP/ASCO/CAP Tier
RUNX1	c.277_278insGAAACGGG (frameshift Insertion)	p.(Asp93GlyfsTer32)	chr21:36259213	4%	NM_001754.5	Tier I Variant of Strong Clinical Significance
ASXL1	c.4232G>A (Nonsense)	p.(Trp1411Ter)	chr20:31024747	28%	NM_015338.6	Tier I Variant of Strong Clinical Significance
BCOR	c.2428C>T (Nonsense)	p.(Arg810Ter)	chrX:39932171	17%	NM_001123385.2	Tier I Variant of Strong Clinical Significance
SRSF2	c.284C>A (Missense)	p.(Pro95His)	chr17:74732959	31%	NM_003016.4	Tier I Variant of Strong Clinical Significance
STAG2	c.3303_3304insT (frameshift Insertion)	p.(Met1102TyrfsTer34)	chrX:123224449	16%	NM_001042749.2	Tier I Variant of Strong Clinical Significance
NRAS	c.35G>A (Missense)	p.(Gly12Asp)	chr1:115258747	3%	NM_002524.5	Tier II Variant of Potential Clinical Significance

***Colour-code by tier:* Tier I (Red): Strong clinical significance; Tier II (Orange): Potential clinical significance; Tier III (Grey): VUS**

RNA SEQUENCING: GENE REARRANGEMENTS: NO FUSION DETECTED

PERFORMED AT :
Agilus Diagnostics Ltd
Reference Lab,2nd Floor, Plot No. 31,Urban Estate Electronic City,Sector-18,
Gurugram, 122015
Haryana, India
Tel : 9111591115. Fax : CIN - U74899PB1995PLC045956

ULR No. 666000016219917-0009

DIAGNOSTIC REPORT

agilus diagnostics

PATIENT NAME : ISHAMMA T M (MR000384802) **REF. DOCTOR :** ASHWIN V NAIR

CODE/NAME & ADDRESS : CA00008679 KIMS HOSPITAL P B NO: 1 ANAYARA P OTHIRUVANANTHAPURAM ANAYARA 695029 4712941400	ACCESSION NO : **4182YK008935** PATIENT ID : ISHAF2211444182 CLIENT PATIENT ID: L085863525	AGE/SEX : 81 Female DRAWN : 22/11/2025 20:21 RECEIVED : 22/11/2025 20:21 REPORTED : 27/11/2025 07:33

INTERPRETATION:

1. *RUNX1* p.(Asp93GlyfsTer32)

- **Type of mutation**: Frameshift truncating (loss-of-function) in the N-terminal region.
- **Functional effect**: *RUNX1* is a critical transcription factor for definitive hematopoiesis. Loss-of-function or dominant-negative effects impair differentiation and favor leukemic transformation.
- **Clinical significance**: According to WHO/ICC and ELN 2022, *RUNX1* defines or is strongly associated with AML with myelodysplasia-related gene mutation, which fall into an adverse-risk category. These are frequently secondary-type AMLs, often evolving from prior MDS/MPN, and are associated with resistance to standard induction and high relapse risk. *RUNX1* mutations can serve as specific leukemia-defining MRD markers. No direct *RUNX1*-targeted drug. The presence of *RUNX1* pushes the patient into adverse ELN risk , and supports early consideration of allogeneic HSCT in CR1 if medically feasible.
- **Classification**: Tier I – Variant of strong clinical significance

2. *ASXL1* p.(Trp1411Ter)

- **Type of mutation**: Nonsense SNV, introducing premature stop codon in C-terminal PHD domain of *ASXL1* leading to truncating loss-of-function.
- **Functional** effect: *ASXL1* is an epigenetic regulator (part of PRC2/*ASXL1*–BAP1 axis). Truncating variants lead to altered histone modification (H3K27me3, etc.), dysregulated myeloid differentiation, clonal hematopoiesis, and leukemogenesis.
- **Clinical significance**: It is recurrent in secondary AML, and therapy-related AML. It is associated with inferior OS, higher relapse, and resistance to intensive chemotherapy and/or HMA-based regimens, especially when co-occurring with *RUNX1*, SRSF2, or other secondary-type lesions. Considered a “secondary-type mutation”, and myelodysplasia related gene in WHO/ICC/ELN. It is not ideal as a sole MRD marker; persistence alone does not always equal morphologic relapse. No specific targeted drug against *ASXL1*. It helps classify as secondary-like / high-risk myeloid neoplasm, supporting consideration of allogeneic HSCT in fit patients and closer molecular follow-up.
- **Classification**: Tier I – Variant of strong clinical significance

PATIENT NAME : ISHAMMA T M (MR000384802) **REF. DOCTOR :** ASHWIN V NAIR

CODE/NAME & ADDRESS CA00008679 KIMS HOSPITAL P B NO: 1 ANAYARA P OTHIRUVANANTHAPURAM ANAYARA 695029 4712941400	ACCESSION NO : **4182YK008935** PATIENT ID : ISHAF2211444182 CLIENT PATIENT ID: L085863525	AGE/SEX : 81 Female DRAWN : 22/11/2025 20:21 RECEIVED : 22/11/2025 20:21 REPORTED : 27/11/2025 07:33

3. *BCOR* p.(Arg810Ter)

- **Type of mutation**: Nonsense SNV introducing premature stop codon, causing loss-of-function of *BCOR* (corepressor of *BCL6*, epigenetic regulator).
- **Function**: Loss of *BCOR* alters transcriptional repression and epigenetic control in hematopoietic stem/progenitor cells, favouring clonal expansion.
- **Clinical significance**: It is one of the defining entity in AML with myelodysplasia-related changes, and AML with "secondary-type" gene mutations (*BCOR, ASXL1, RUNX1*, etc.). It is frequently associated with adverse prognosis and secondary/therapy-related AML biology. Like *ASXL1*, BCOR is often an early, founding or co-founding clone, and useful as part of a composite MRD panel but persistence at low VAF may represent residual clonal hematopoiesis. No direct-targeted agent, strengthens classification into secondary-like / high-risk AML, and supports HSCT consideration and intensified surveillance.
- **Classification**: Tier I – Variant of strong clinical significance

4. *SRSF2* p.(Pro95His)

- **Type of mutation**: Canonical hotspot missense mutation at Pro95 in the RNA splicing factor *SRSF2*.
- **Functional** effect: Alters RNA-binding preference and global splicing (especially of genes regulating epigenetics and hematopoiesis). This promotes aberrant hematopoiesis and clonal dominance.
- **Clinical significance**: It has strong association with adverse prognosis, older age, and secondary evolution. Together with *ASXL1*, *BCOR*, *RUNX1* it supports classification as AML with myelodysplasia-related gene mutations / secondary-type AML. No specific *SRSF2* inhibitor in routine clinical use yet. Useful as part of a composite MRD panel, but persistence alone is not sufficient to call relapse. It confers high-risk phenotype, supporting HSCT consideration, HMA-based regimens in unfit patients, and close molecular follow-up.
- **Classification**: Tier I – Variant of strong clinical significance

5. *STAG2* p.(Met1102TyrfsTer34)

- **Type of mutation**: Frameshift insertion leading to premature stop codon, truncating loss-of-function of cohesin complex component *STAG2* (X-linked).

PATIENT NAME : ISHAMMA T M (MR000384802) **REF. DOCTOR :** ASHWIN V NAIR

CODE/NAME & ADDRESS CA00008679 KIMS HOSPITAL P B NO: 1 ANAYARA P OTHIRUVANANTHAPURAM ANAYARA 695029 4712941400	ACCESSION NO : **4182YK008935** PATIENT ID : ISHAF2211444182 CLIENT PATIENT ID: L085863525	AGE/SEX : 81 Female DRAWN : 22/11/2025 20:21 RECEIVED : 22/11/2025 20:21 REPORTED : 27/11/2025 07:33

- **Functional effect**: *STAG2* is part of cohesin, involved in chromatid cohesion, DNA repair, and 3D genome architecture. Truncating variants induce genomic instability and dysregulated gene expression.
- **Clinical significance**: It is consistent with myelodysplasia-related / adverse-risk disease. It often co-occurs with *ASXL1, SRSF2, RUNX1*, etc., in secondary-type myeloid neoplasms, and generally linked with adverse prognosis. It may be used as one MRD target but, like other secondary-type lesions, it can persist as background clone. No direct anti-*STAG2* therapy. Presence reinforces secondary-type, high-risk biology, and supports HSCT consideration and molecular surveillance.
- **Classification**: Tier I – Variant of strong clinical significance

6. *NRAS* p.(Gly12Asp)

- **Type of mutation**: Missense mutation at codon 12 (G12D) in *NRAS*, a classic RAS hotspot.
- **Functional effect**: Constitutive activation of *NRAS* (GTP-bound), leading to MAPK/ERK and PI3K/AKT pathway activation, enhancing proliferation and survival.
- **Clinical significance**: It is common in myeloid malignancies, and often a cooperating lesion rather than defining entity. Prognostic impact alone is modest and context-dependent; typically not independently favourable, may be neutral or slightly adverse depending on co-mutations. RAS mutations are unstable and can appear/disappear between diagnosis and relapse; not the most reliable sole MRD target. No approved *NRAS*-specific inhibitor. Downstream pathway blockade (MEK inhibitors) is under trial; not standard in routine AML practice.
- **Classification**: Tier II – Variant of potential clinical significance

INTEGRATED MOLECULAR SUMMARY

Targeted NGS of the bone marrow in this AML case demonstrates a complex secondary-type molecular profile with multiple cooperating lesions in epigenetic regulators, splicing/cohesin genes and a key hematopoietic transcription factor, together with a RAS pathway mutation. Truncating *ASXL1* p.Trp1411Ter and *BCOR* p.Arg810Ter support an antecedent myelodysplastic/secondary myeloid neoplasm with epigenetic deregulation. The presence of *RUNX1* truncating mutation defines an adverse-risk, myelodysplasia-related AML biology with impaired hematopoietic differentiation. Co-occurring

PATIENT NAME : ISHAMMA T M (MR000384802) **REF. DOCTOR :** ASHWIN V NAIR

CODE/NAME & ADDRESS : CA00008679 KIMS HOSPITAL P B NO: 1 ANAYARA P OTHIRUVANANTHAPURAM ANAYARA 695029 4712941400	ACCESSION NO : **4182YK008935** PATIENT ID : ISHAF2211444182 CLIENT PATIENT ID: L085863525	AGE/SEX : 81 Female DRAWN : 22/11/2025 20:21 RECEIVED : 22/11/2025 20:21 REPORTED : 27/11/2025 07:33

hotspot *SRSF2* p.Pro95His and truncating *STAG2* p.Met1102TyrfsTer34 further underline a myelodysplasia-related, secondary AML pattern through widespread aberrant RNA splicing and cohesin dysfunction. A subclonal *NRAS* p.Gly12Asp mutation provides additional proliferative drive via constitutive RAS–MAPK pathway activation.

Overall, this constellation of *ASXL1, BCOR, RUNX1, SRSF2, STAG2* and *NRAS* is characteristic of AML with myelodysplasia-related gene mutations / secondary-type AML, and corresponds to an adverse-risk molecular category, predicting higher resistance and relapse risk with conventional chemotherapy and supporting consideration of intensive therapy with allogeneic HSCT in first complete remission, where clinically appropriate, with *RUNX1* mutation serving as the preferred leukemia-specific markers for molecular MRD monitoring**.**

ASSAY INFORMATION AND METHODOLOGY

- **Test Description:** Oncomine Myeloid Assay is a comprehensive, targeted NGS assay which interrogates the below mentioned genes for all relevant DNA alterations and gene rearrangements associated with myeloid malignancies viz-a-vis acute myeloid leukemia(AML), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), MDS/MPN, in a single run.

- **Quality Metrics :** PASSED

- **Gene Analyzed :**

Hotspot genes (28)		Full genes (17)		Fusion driver genes (34)			Expression Genes (5)	Expression control genes (5)
ANKRD26	*KRAS*	*ASXL1*	*PRPF8*	*ABL1*	*HMGA2*	*NUP214*	*BAALC*	*EIF2B1*
ABL1	*MPL*	*BCOR*	*RB1*	*ABL2*	*JAK2*	*NUP98*	*MECOM*	*FBXW2*
BRAF	*MYD88*	*CALR*	*RUNX1*	*BCL2*	*KAT6A (MOZ)*	*PAX5*	*MYC*	*PSMB2*

DIAGNOSTIC REPORT

agilus diagnostics

PATIENT NAME : ISHAMMA T M (MR000384802) **REF. DOCTOR :** ASHWIN V NAIR

CODE/NAME & ADDRESS : CA00008679 KIMS HOSPITAL P B NO: 1 ANAYARA P OTHIRUVANANTHAPURAM ANAYARA 695029 4712941400	ACCESSION NO : **4182YK008935** PATIENT ID : ISHAF2211444182 CLIENT PATIENT ID: L085863525	AGE/SEX : 81 Female DRAWN : 22/11/2025 20:21 RECEIVED : 22/11/2025 20:21 REPORTED : 27/11/2025 07:33

CBL *CSF3R* *DDX41* *DNMT3A* *FLT3 (ITD + TKD)* *GATA2* *HRAS* *IDH1* *IDH2* *JAK2* *KIT*	*NPM1* *NRAS* *PPM1D* *PTPN11* *SMC1A* *SMC3* *SETBP1* *SF3B1* *SRSF2* *U2AF1* *WT1*	*CEBPA* *ETV6* *EZH2* *IKZF1* *NF1* *PHF6*	*SH2B3* *STAG2* *TET2* *TP53* *ZRSR2*	*BRAF* *CCND1* *CREBBP* *EGFR* *ETV6* *FGFR1* *FGFR2* *FUS*	*KAT6B* *KMT2A (includes PTD)* *MECOM* *MET* *MLLT10* *MRTFA (MKL1)* *MYBL1* *MYH11* *NTRK2* *NTRK3*	*PDGFRA* *PDGFRB* *RARA* *RUNX1* *TCF3* *TFE3* *ZNF384*	*SMC1A* *WT1*	*PUM1* *TRIM27*

- **Important Note -** The assay utilizes minimum 10ng of DNA & RNA at 1000X coverage provides an analytical sensitivity of more than equal to 5 percent for DNA based genetic alteration. Kindly note that variants <5% VAF, benign and likely benign variants are not being reported here.

End of Report*

Test performed & reviewed by
Haristuti Verma
Sr. Technical Supervisor

Shrinidhi Nathany

Dr.Shrinidhi Nathany
Consultant

Scan to View Details

Scan to View Report

PERFORMED AT :
Agilus Diagnostics Ltd
Reference Lab,2nd Floor, Plot No. 31,Urban Estate Electronic City,Sector-18,
Gurugram, 122015
Haryana, India
Tel : 9111591115. Fax : CIN - U74899PB1995PLC045956

ULR No. 666000016219917-0009