Whole Genome Sequencing of Patients with Myelodysplastic Syndrome Uncovers Novel, Clinically Relevant Biomarkers Missed by Standard Of Care Methods

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Poster Number: MDS - 1210

Background

- Genomic analysis is essential for accurate diagnosis and risk stratification of myeloid malignancies.
- Whole genome sequencing (WGS) can capture a breadth of alterations, augmenting and potentially replacing current profiling.
- Traditional diagnostic techniques such as targeted next generation sequencing (NGS), chromosomal banding, FISH, and OGM (optical genome mapping) are standard of care (SOC) methods for diagnostic/prognostic workup for MDS patients.
- This study validated the molecular findings of the Tempus xH WGS assay against SOC diagnostic results from MDACC.

Methods

Bioinformatic Filtering & Inclusion Criteria

- **SNV/Indels**
- **Copy Number Alterations (CNAs):** ≥ 5 Mb in size.
- **Structural Variants (SVs):** Included if they overlapped orthogonal truth or represented recurrent myeloid fusions.
- **Cytogenetic Quality:** Minimum ≥ 10 metaphases required for SOC comparison and composite karyotype calls not included.

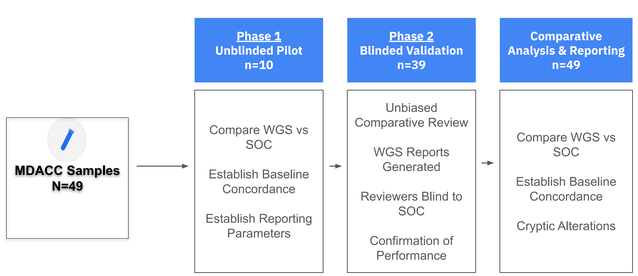


Figure 1: Study Design Workflow.

Results

a

Characteristic	MDS cohort n=49
Median age (range), years	71 (29-91)
Male sex, no. (%)	33 (67)
Median hemoglobin (range), g/L	92 (69-143)
Median platelet count (range), $\times 10^9$/L	123 (9-660)
Median white blood cell count (range), $\times 10^9$/L	3.6 (0.6-185)
Median abs. neutrophil count (range), $\times 10^9$/L	1.6 (0.15-112.3)
Median BM blast (range), %	4 (1-19)
WHO 2022, no. (%)	
MDS-5q	0
MDS-SF3B1	8 (16)
MDS-biTP53	7 (14)
MDS-LB	16 (33)
MDS-h	0
MDS-IB1	11 (22)
MDS-IB2	7 (14)
Cytogenetic risk, no. (%)	
Very Good	2 (4)
Good	17 (35)
Intermediate	11 (22)
Poor	8 (16)
Very Poor	11 (22)
IPSS-R, no. (%)	
Very Low	2 (4)
Low	10 (20)
Intermediate	16 (33)
High	11 (22)
Very high	10 (20)
IPSS-M, no. (%)	
Very low	0
Low	8 (16)
Moderate low	3 (6)
Moderate high	9 (18)
High	12 (24)
Very High	14 (29)

b

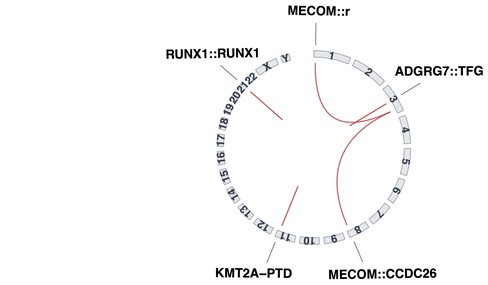
	WGS (+)	WGS (+)	WGS (-)
	SOC (+)	SOC (-)	SOC (+)
CNV	16	2	2
SNV	26	1	0
SV	6	0	1
Total	48	3	3

C

	WGS (+)	WGS (+)	WGS (-)
	SOC (+)	SOC (-)	SOC (+)
CNV	49	24	1
SNV	107	1	0
SV	3	5	1
Total	159	30	3

Figure 2: (a) Clinical and demographic characteristics of the patient population. **(b)** Concordance between WGS (Tempus) and SOC (MDACC) in the unblinded analysis set (n=10) demonstrating high sensitivity (≥ 94.1%). WGS identified 90% (16 of 18) of the CNVs detected by cytogenetics and 100% of the OGM calls among the 10 patients. One event missed by WGS was a derivative chromosome der(1;20)(q10;q10); the events occur over NGS masked centromere. We did observe copy changes in the arms of chr 1 and chr 20 indicating an event was captured. **(c)** Analyses for the remaining blinded analysis set (n=39) show similarly high sensitivity (≥ 98.9%). WGS identified 98% (49 of 50) of the CNVs detected by cytogenetics among the n=24 patients with unambiguous results identified by karyotyping.

a



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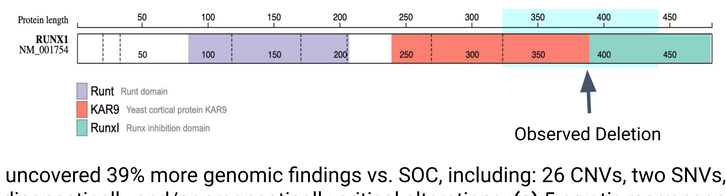

Figure 3: WGS uncovered 39% more genomic findings vs. SOC, including: 26 CNVs, two SNVs, and five SVs, including diagnostically and/or prognostically critical alterations: **(a)** 5 *cryptic* rearrangements identified on a Circos plot. **(b)** a focal RUNX1 deletion removing amino acids 323-448 (teal color) and the inhibitory domain associated with poor prognosis.

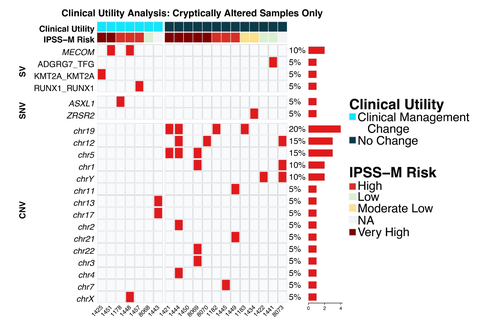

Figure 4: Retrospective utility of WGS findings: Waterfall plot combining phase 1 and 2 data, showing only additional WGS findings with indications where additional findings add utility (n=7, 14%). IPSS-M risk assessments were used to retrospectively evaluate utility, distinguishing between new WGS findings that influence patient management (left) and those with unknown clinical influence (right).

Conclusions

- **Superior Diagnostic Yield:** WGS demonstrates high concordance with SOC (NGS, OGM, and cytogenetics) while uncovering significant novel, actionable, and prognostic findings previously undetected.
- **Precision Clinical Impact:** By providing a comprehensive genomic landscape, WGS advances MDS biology and equips clinicians with the granular data needed for more informed, targeted treatment decisions.