How to classify risk based on clinical and molecular modeling: integrating molecular markers in the risk assessment of myelodysplastic syndrome

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Myelodysplastic syndrome (MDS), also known as "myelodysplastic neoplasm," is a heterogeneous group of clonal myeloid neoplasms that typically affects older adults. The clinical phenotype, symptoms, and complications relate to the depth of cytopenia and progression to acute myeloid leukemia (AML). The diagnosis of MDS relies on morphologic criteria, such as evidence of dysplasia, disordered maturation, and increasing blast counts, which separate the disease into histologic subtypes with different probabilities for progression to AML. The treatment of MDS is often risk-adapted depending on the prognostic profile of each patient's disease. There has been a coevolution of diagnostic and prognostic systems for MDS developed over the past 40 years, both of which have now incorporated molecular markers. The new International Prognostic Scoring System-Molecular (IPSS-M) improves partitioning of patients compared to prior versions with resultant upgrading of 34% of patients into higher-risk groups due to the presence of mutations. The new IPSS-M also more accurately distinguishes intermediate-risk patients separating them into two tiers. The two new diagnostic classifications include MDS defined by mutations in *SF3B1* and *TP53*, though there are differences in diagnostic criteria. Future efforts to refine MDS prognostication could investigate the interface between MDS and clonal cytopenia of undetermined significance, expand access to genomic testing, obtain results in a less invasive manner, and develop treatment-response predictors and dynamic risk models.

LEARNING OBJECTIVES

- Compare the foundational risk-assessment models on which the IPSS-M builds
- Examine the clinical implications of the IPSS-M and new disease subclassification systems
- Describe future avenues for improving MDS risk stratification, prognostication, and patient outcomes

Introduction

Myelodysplastic syndrome, also known as myelodysplastic neoplasm (both abbreviated MDS), is a clonal myeloid neoplasm that typically affects older adults with the main symptoms and complications related to the depth of cytopenia and progression to acute myeloid leukemia (AML). There are both lower-risk and higher-risk MDS, with the higher-risk group being more likely to transform into AML. Treatment of MDS is often risk-adapted and relies on the prognostic profile of the disease. While there are several treatment options, the only curative therapy is allogeneic hematopoietic stem-cell transplantation (HSCT).

Similar to most cancers, the diagnosis, prognosis, and treatment of MDS have long been intertwined facets of disease management. The pathologic criteria for MDS captures the morphologic evidence of dysplasia, disordered maturation, and increasing blast counts separating the disease into low- and high-grade subtypes. The available genetic data are extensive, permitting a deeper understanding of the disease and enabling integrated risk-assessment models. Coupling the pathological and clinical features with genomic data, today's prognostic models are more individualized.[1] When treatments can vary from supportive care to hematopoiesis stimulating agents and to lower

intensity therapies, including immunosuppressive or immunomodulatory agents, and higher intensity therapies, including hypomethylating agents (HMA), induction chemotherapy, and HSCT, as well as newer targeted agents (in clinical trials), a uniform description and assignment of prognosis becomes increasingly important. In 2022, the clinical management of patients with MDS was transformed whereby genomic data became fully integrated into international prognostic and diagnostic standards—the International Prognostic Scoring System-Molecular (IPSS-M),[2] the World Health Organization (WHO) Classification of Haematolymphoid Tumours (WHO 5th ed.),[3] and the International Consensus Classification (ICC) of hematologic malignancies.[4] The historical context and the clinical implications of the IPSS-M and new disease classifications will be discussed, as well as unmet needs in MDS risk assessment.

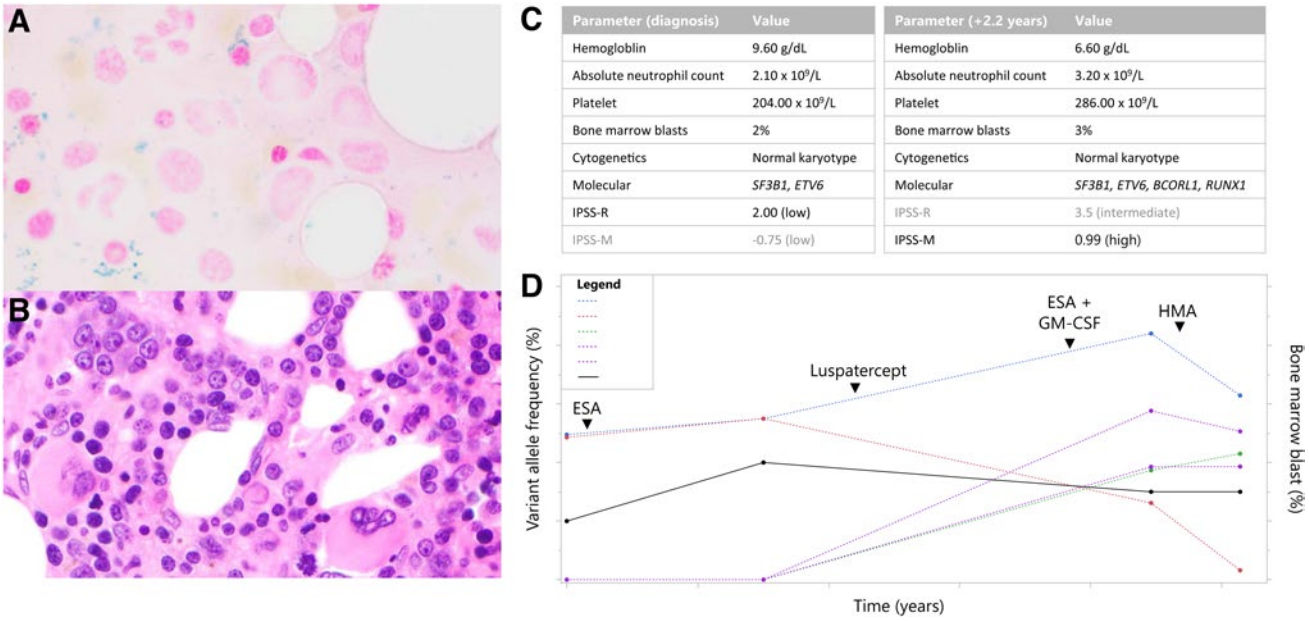
CLINICAL CASE

A 66-year-old woman presented in 2020 with abnormal blood counts, including a white blood cell count of 4.2×10^9/L, absolute neutrophil count (ANC) of 2.10×10^9/L, hemoglobin of 8.9 g/dL, mean corpuscular volume of 111.00 fL, platelet count of 204.00×10^9/L, and serum erythropoietin level of <200 mIU/mL (Figure 1). A bone marrow biopsy showed 2% blasts, erythroid and megakaryocytic dysplasia, and 30% ring sideroblasts. Cytogenetic studies revealed a normal karyotype. Next-generation sequencing (NGS) demonstrated two mutations (*ETV6*, 24% variant allele frequency [VAF]; *SF3B1*, 25% VAF). Based on the 2016 WHO revised 4th edition, a diagnosis of MDS with ring sideroblasts and multilineage dysplasia (MDS-RS-MLD) was rendered. Based on the 2012 revised IPSS (IPSS-R), this profile resulted in a score of 2, which corresponded to lower-risk MDS with a median overall survival (OS) of 9 years.

Continued refinement of MDS risk assessment

From the original French-American-British[5] subclassification of MDS (1982) and the Bournemouth[6] risk-assessment model (1985), there has long been a coevolution of diagnostic and prognostic systems for MDS (Figure 2A). As our understanding of the biology of MDS has improved,[7-9] so has the precision around which diagnostic and prognostic categories are assigned, leading to ever-increasing disease subtypes and risk groups. Since approximately 90% of patients with MDS have a driver mutation compared to 41% with a cytogenetic alteration,[2] somatic mutation testing is particularly informative. Similar to the impact that cytogenetic studies had on risk stratification of MDS in the 1990s, molecular studies have now changed the way patients diagnosed with MDS are managed. The new IPSS-M improves the accuracy of MDS prognosis by building on the foundational knowledge from prior MDS risk models.

Since the 1980, there have been 19 selected studies that propose a new risk-assessment model, modify, and/or validate a prior model for MDS prognosis. Factors that have been



Parameter (diagnosis)	Value
Hemoglobin	9.60 g/dL
Absolute neutrophil count	2.10 x 10^9/L
Platelet	204.00 x 10^9/L
Bone marrow blasts	2%
Cytogenetics	Normal karyotype
Molecular	*SF3B1, ETV6*
IPSS-R	2.00 (low)
IPSS-M	-0.75 (low)

Parameter (+2.2 years)	Value
Hemoglobin	6.60 g/dL
Absolute neutrophil count	3.20 x 10^9/L
Platelet	286.00 x 10^9/L
Bone marrow blasts	3%
Cytogenetics	Normal karyotype
Molecular	*SF3B1, ETV6, BCORL1, RUNX1*
IPSS-R	3.5 (intermediate)
IPSS-M	0.99 (high)

Figure 1. Clinical case findings at diagnosis and follow-up. (A) Diagnostic bone marrow iron stain (100×) showing abundant ring sideroblasts and multilineage dysplasia leading to a diagnosis of MDS with multilineage dysplasia and ring sideroblasts (MDS-MLD-RS). (B) Bone marrow biopsy (40×) 2.6 years after diagnosis obtained after initiation of azacytidine showing persistent multilineage dysplasia, erythroid hyperplasia, and new fibrosis (grade 1–2). (C) Clinical and laboratory parameters at diagnosis when the IPSS-M was not in use and at 2.2 years when the IPSS-M was in use upgrading the risk category to high, based on molecular findings. (D) Clinical course as illustrated by the bone marrow blast count, mutation profile obtained at each of the bone marrow biopsies (time 0, 0.8, 2.2, and 2.6 years), and new therapies initiated. ESA, erythropoiesis-stimulating agent; GM-CSF, granulocyte-macrophage colony-stimulating factor; HMA, hypomethylating agent.

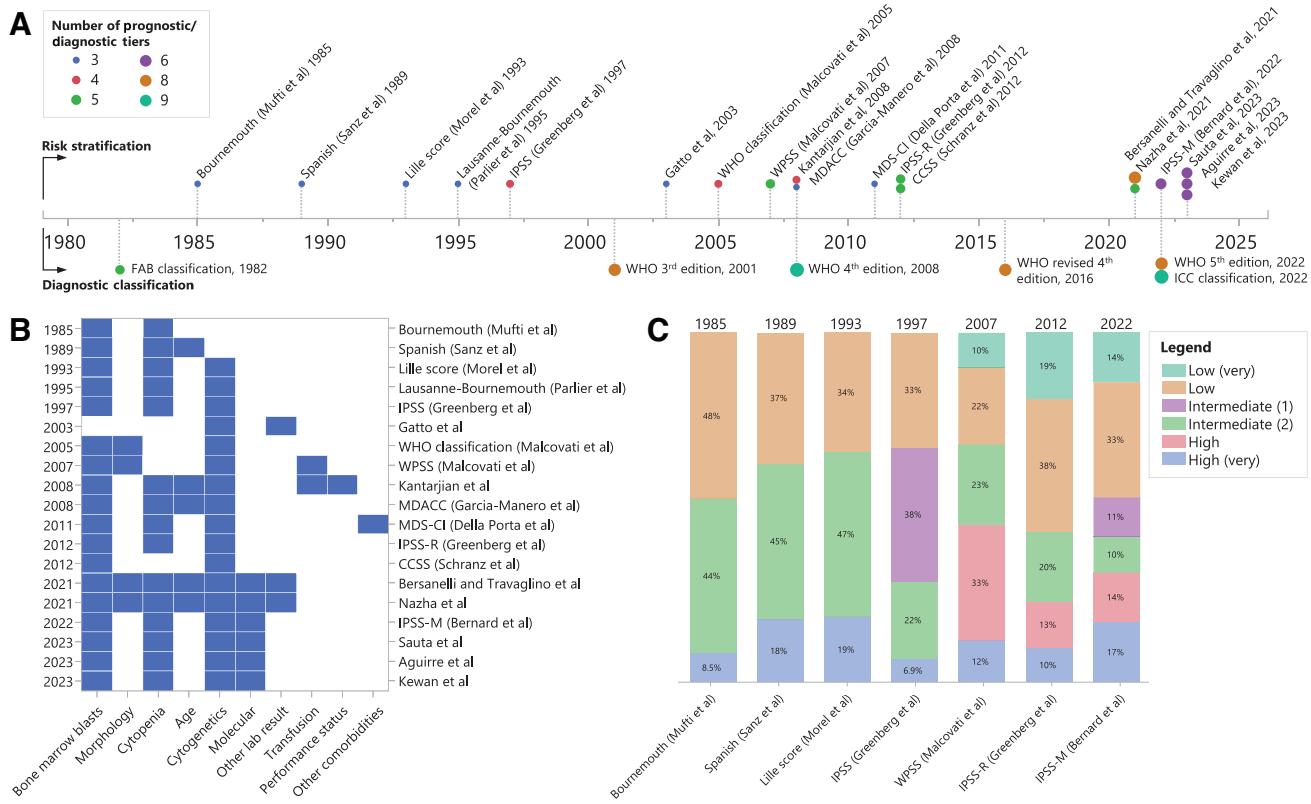


Figure 2. Historical perspective of MDS prognostic models and diagnostic subclassifications. (A) Risk stratification studies and MDS subclassifications from 1982 to present. Colored dots represent number of prognostic or diagnostic tiers used. (B) Select risk stratification studies showing different clinical, pathologic, and laboratory parameters deemed most prognostic. The other lab result is beta-2 microglobulin (Gatto et al[24]), neutrophils, ferritin, LDH (Bersanelli et al[25]), and absolute lymphocyte/neutrophil/monocyte counts (Nazha et al[26]). (C) Select prognostic models and the separation of patients into risk groups. When a single intermediate-risk group is used, this is arbitrarily set as "Intermediate (2)." When a single high-risk group is used, this is arbitrarily set as "High (very)."

consistently identified as prognostic include bone marrow blast count (18/19, 95%),[2,6,10-23] cytogenetic abnormalities (17/19, 89%),[2,11-24] and degree of cytopenia (15/19, 79%)[2,6,10-13,16-19,21-23,25,26] with molecular profiling becoming important in recent years (Figure 2B).[2,21-23,25,26] Interestingly, the MDS subtype, which often correlates with prognosis,[6,13] has only been incorporated into four prognostic models.[14,15,25,26] This may be related to the fact that the degree of dysplasia, while important for diagnosis, is not always externally consistent or prognostic. Over time, the number of risk stratifications has increased from 3 to 6 (Figure 2C), with the largest group being the low-risk group in the IPSS-M. Compared to prior systems, the proportion of low-risk and very-low-risk groups represents the largest fraction, the intermediate-risk group (low and high) remains relatively constant, and the very-high-risk group has increased modestly in the IPSS-M. The new categories improve the prediction of prognosis when comparing survival, hazard ratios (HR), and Harrell's concordance-indices (c-index).

Clinical implications of evolving prognostic and diagnostic systems

The introduction of any new risk-assessment model will lead to a reassortment of patients. The IPSS-R uses cytogenetics risk groups, bone marrow blast count, hemoglobin, platelet count, and ANC to assign points for each categorical variable, with the sum corresponding to five risk groups. The IPSS-M, though not the first to incorporate molecular markers,[25,26] is the first to formulate an integrated model on a continuous scale that can be directly compared to the IPSS-R. The IPSS-M uses the IPSS-R cytogenetics risk groups, bone marrow blast count, hemoglobin, platelet count (capped at 250×10^9/L), and the presence/absence of mutations in 31 genes (16 main genes and 15 additional genes) without ANC to assign points on a continuum that corresponds to six risk groups. Although more driver mutations correlate with inferior survival, as previously demonstrated,[7,25,26] the total number of mutations was not as informative as individual mutations. Despite the importance of gene mutations, the IPSS-M can accommodate missing data. Data for 15 genes (all of the main genes except *KRAS*) will maintain 70-80% accuracy, but fewer than 10 genes is not advisable.[21]

Given the weight that adverse cytogenetics and high blast counts provide, the additional molecular markers have a limited ability to reduce an already high-risk score, but they have a high likelihood of upgrading scores. If the same patients were scored using the IPSS-R and IPSS-M, 31-69% (54% overall) of the categorizations remain unchanged (Figure 3A), whereas 34%

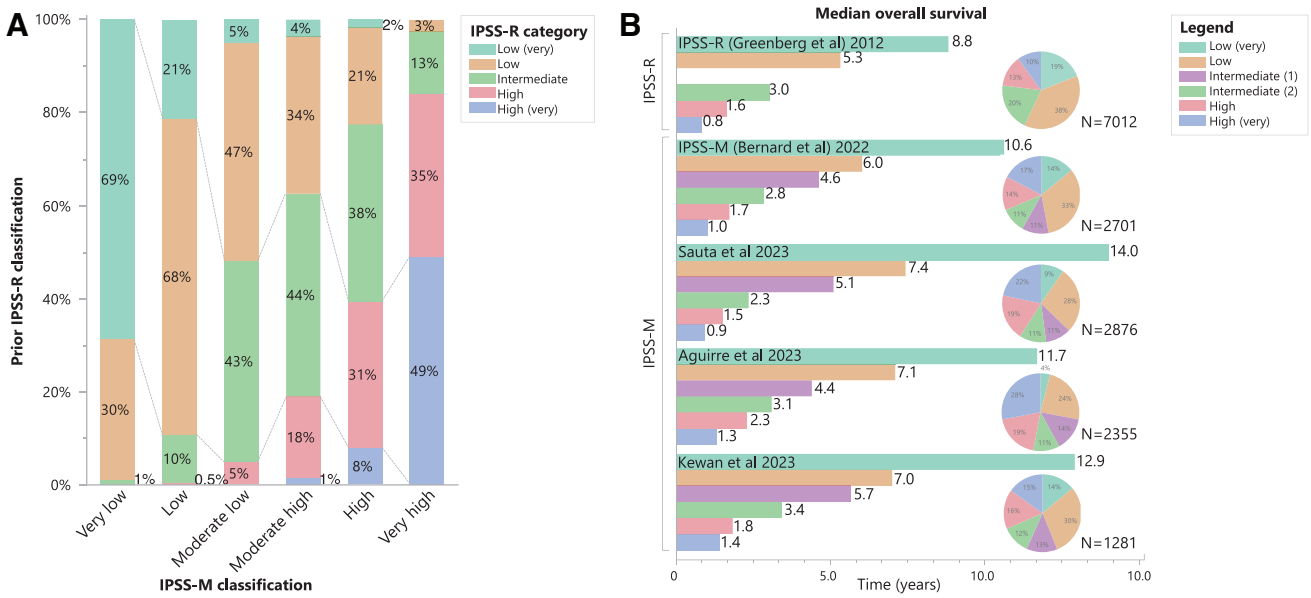


Figure 3. Clinical implications of changing risk stratifications using IPSS-M. (A) IPSS-M risk groups and the equivalent risk group using the prior IPSS-R criteria. Dashed lines outline unchanged risk classes based on either model. Adapted from Bernard et al.[2] (B) Comparison of median overall survival based on IPSS-R and IPSS-M in the indicated studies. Pie charts show groupings of patients into the different IPSS-M risk categories.

of the patients would be upgraded and 12% would be downgraded.[2] With the exception of IPSS-M very-low-risk patients, the majority of the reassignments using IPSS-M represent upgrades. For instance, 52% and 37% of the moderate-low and moderate-high, respectively, IPSS-M patients were previously lower risk. Similarly, 61% and 51% of the high and very-high IPSS-M patients had a lower IPSS-R assignment. This trend for upgrading the risk group according to IPSS-M has been confirmed by multiple studies.[21-23]

To determine whether the IPSS-M model translates into more distinct outcomes, median OS can be compared (Figure 3B).[2,19,21-23] Acknowledging that the study populations are different, the OS of the high-risk and very-high-risk patients are comparable. The most notable change is seen when a two-tiered intermediate group is introduced. Whereas a single IPSS-R intermediate group has a median OS of 3 years, the two-tiered IPSS-M intermediate groups now show survival differences ranging from 1.3-2.8 years. The importance of separating the intermediate group is additionally supported by the calculated HRs (IPSS-R intermediate 2 vs IPSS-M moderate-low 1.5 and IPSS-M moderate-high 2.5).[2] Another difference of the IPSS-M is the OS in the very-low-risk and low-risk groups. Whereas the IPSS-R very-low risk group shows a 3.5-

Table 1. Median survival comparison using IPSS-R and IPSS-M in the same cohort of MDS patients

Risk	IPSS	n (%)	Overall survival			Time to AML in 25%		
			Median (years)	95% CI (lower)	95% CI (upper)	Median (years)	95% CI (lower)	95% CI (upper)
Very low	R	293 (10.2)	12.9	12.9	NR	NR	NR	NR
	M	275 (9.6)	NR	10.5	NR	11.4	11.4	NR
Low	R	806 (28.0)	7.3	6.2	8.5	11.4	9.3	NR
	M	797 (27.7)	7.4	6.2	9.6	12.5	10.3	NR
Intermediate	R	610 (21.2)	3.5	3.2	4.8	4.3	3.7	6.2
Moderate Low	M	306 (10.6)	4.8	3.6	5.7	5.1	4.1	NR
Moderate High	M	319 (11.1)	2.3	1.9	3.2	2.7	1.9	4.7
High	R	595 (20.7)	1.6	1.3	1.8	2.5	1.9	3.3
	M	555 (19.3)	1.4	1.3	1.7	2.2	1.7	3.3
Very high	R	572 (19.9)	0.8	0.7	0.8	1.4	1.2	1.8
	M	624 (21.7)	0.8	0.8	1.0	1.7	1.2	2.0

M, IPSS-M; R, IPSS-R; NR, not reached.
Adapted from Sauta et al.[21]

year improvement in OS when compared to the low-risk group, the IPSS-M very-low-risk group gains 4.6-6.6 years over the low-risk group. If the IPSS-R and IPSS-M strata are compared within the same population, the main improvement is again demonstrated in the two-tiered intermediate group (Table 1).[21] With all these changes, the IPSS-M improves the c-index by 5 percentage points.[2,21-23,27] As an extension of improved risk stratification, there is the possibility of improving the selection of risk-adapted therapies. The IPSS-M has been shown to be a superior predictor of post-HSCT outcomes than the IPSS-R,[21] which may be related to high-risk mutational profiles, such as bi-allelic *TP53*.[2,28] With regard to HMA in higher-risk patients, the IPSS-M risk groups do not appear to correlate with the probably of overall response,[21] though bi-allelic *TP53* mutations continue to be a strong predictor of worse outcomes when receiving HMA or lenalidomide.[2]

As the prognostic models are now including somatic mutations, so are the diagnostic classifications. Since 1982, there have been six iterations of classification systems beginning with 5 to 8-9 present-day MDS subtypes (Figure 2A). While genetically defined entities are well-known in AML, until 2022, the only genetically defined MDS was MDS associated with isolated del(5q), which was first introduced in 2001. In 2022, the WHO 5th edition and ICC classifications both introduced two MDS subtypes defined by gene mutations (Table 2). Both systems now accept mutations in certain genes as evidence of AML with myelodysplasia-related changes, whereas this was only previously afforded to specific chromosomal abnormalities. The WHO has also recognized a set of genes mutated in clonal cytopenia of undetermined significance (CCUS), while the ICC also recognizes *UBA1*-mutated "VEXAS" syndrome as a related clonal cytopenia.

With regard to genetically defined MDS entities, both systems now recognize *SF3B1*[8,29] and *TP53*[2,28,30] mutations as specific disease subtypes. While the mutation requirements are subtly different, the main distinction between the diagnostic criteria is morphologic evidence of dysplasia. The WHO maintains dysplasia (10% of cells in at least one lineage) as a diagnostic criterion, but the ICC does not as long as the genomic profile is appropriate. While most patients will have a concordant diagnosis by either system, occasionally these differences may lead to a diagnosis of CCUS in one instance and a diagnosis of MDS in another, particularly for *SF3B1*-mutated cases with low blast counts. It is still unknown at this time whether patients diagnosed with CCUS in this context should be managed as presumptive MDS. It is also unknown if future disease classification systems will continue to uphold the requirement for morphologic dysplasia and if new mutation-defined subtypes will emerge.

Future opportunities for improving prognosis of MDS

Despite more comprehensive and accurate prognostication provided by the IPSS-M, there are still challenges. The IPSS-M is not designed to be used dynamically, though other models have been shown to be useful for repeat assessment.[15,26,31] The predictive power of the IPSS-M to guide the selection of therapies outside of HSCT and in patients without multiple *TP53* mutations remains unknown. The treatment implications for patients in IPSS-M-upgraded risk groups, previously lower-risk MDS according to IPSS-R, continues to be an open question. The response rates achieved in different IPSS-M risk groups when treated with higher-intensity therapies, such as HMA, and novel therapies will no doubt be an area of active investigation in the coming years. Complementary to these challenges, future avenues for improving MDS risk-modeling follow three main themes.

Clonal hematopoiesis was first reported 10 years ago[32,33] and is now recognized as a risk factor for developing hematologic malignancies,[34] particularly in the context of cytopenias.[35,36] CCUS is a recognized entity in both the WHO 5th edition and ICC classification systems, and some patients with CCUS may benefit from treatments for MDS.[37] It is known that idiopathic (non-clonal) cytopenia, even if accompanied by dysplasia, has a much lower risk of progression to MDS[35,36] and should not be diagnosed or treated as MDS. It is yet unknown if genetically defined MDS entities should be classified as CCUS in the absence of dysplasia. Continued efforts should be made to identify patients with high-risk CCUS that may progress imminently to MDS.[36] A related consideration is that future prognostic models may have to contend with differences in diagnostic criteria for CCUS and MDS, which may affect enrollment in prospective studies and outcomes studies related to the risk of progression to MDS/AML and the risk of cardiovascular disease. The clinical implications of differing diagnostic criteria would also be important areas of investigation, as well as efforts to harmonize the diagnostic classifications, especially as pertains to MDS and CCUS.

Another area of potential improvement in MDS prognostication is to increase testing of highly prognostic and predictive molecular targets and more routinely obtain these results from peripheral blood. While the availability of molecular diagnostics has improved, resource-limited settings are often excluded due to access and financial toxicity. Even when NGS is available, a subset of the markers is rarely tested. The diagnostic field should strive to improve the detection of markers that are difficult to identify by routine NGS, such as MLL (*KMT2A*)-PTD and *TP53* copy-neutral loss-of-heterozygosity. Germline predisposition to myeloid neoplasms is increasingly being recognized as an important aspect of clinical outcome. As paired-normal sequencing studies and dedicated germline predisposition testing become more accessible, this should enhance recognition of patients and families carrying germline risk mutations and enable ongoing research related to the screening and management of these individuals. While conventional cytogenetic studies are rarely informative in peripheral blood, whole genome sequencing[38] and targeted NGS[39] are both high yield. These types of peripheral blood studies could provide a genomic karyotype and mutational profile without the need for a bone marrow biopsy and may be useful in the initial evaluation of cytopenia and for treatment monitoring.

The last area for improvement involves dynamic risk-assessment models and treatment response predictors. Studies that profile risk parameters over time, including failure to respond to certain lines of therapy or the emergence of new clonal abnormalities, would be very useful. With regard to treatment response predictors, measurable residual disease (MRD) indicators have long been used in lymphoblastic leukemia to guide therapies. However, MRD markers for MDS are problematic to develop since most mutations are found in the entire myeloid compartment. One way to circumvent this may be monitoring blast-specific genomic abnormalities in plasma cell-free DNA,[40] which is enriched for DNA from cells with rapid

Table 2. **Diagnostic and prognostic significance of gene mutations**

Gene	IPSS-M main gene	IPSS-M residual gene	MDS defining (ICC)*	MDS subtype		AML with MRC		WHO 5th key mutations		Total categories
				ICC	WHO 5th	ICC	WHO 5th	CCUS	Other mutations	
SF3B1	■		■	■	■	■	■	■		7
TP53	■		■	■	■	■	■	■		
ASXL1	■					■	■	■		4
BCOR		■				■	■	■		
EZH2	■					■	■		■	
SRSF2	■					■	■	■		
STAG2		■				■	■		■	
U2AF1						■	■	■		
RUNX1						■		■		3
ZRSR2						■	■		■	
BCORL1		■						■		2
CBL	■							■		
CEBPA		■							■	
DNMT3A	■							■		
ETV6	■								■	
GATA2		■							■	
GNB1		■						■		
IDH1		■						■		
IDH2	■							■		
KRAS	■							■		
NRAS	■							■		
PHF6		■							■	
PPM1D		■						■		
PTPN11		■						■		
SETBP1		■							■	
WT1		■							■	
BRAF									■	1
BRCC3								■		
CALR									■	
CREBBP									■	
CSF1R									■	
CSF3R									■	
CTCF								■		
CUX1									■	
ETNK1		■								
FLT3	■									
GNAS								■		
JAK2								■		
JAK3									■	
KDM6A									■	
KIT									■	
KMT2A									■	

Table 2. Diagnostic and prognostic significance of gene mutations (*Continued*)

Gene	IPSS-M main gene	IPSS-M residual gene	MDS defining (ICC)*	MDS subtype		AML with MRC		WHO 5th key mutations		Total categories
				ICC	WHO 5th	ICC	WHO 5th	CCUS	Other mutations	
MLL (KMT2A)-PTD										
MPL										
MYD88										
NF1										
NOTCH1										
NPM1										
PIGA										
PRPF40B										
PRPF8										
PTEN										
RAD21										
SF1										
SF3A1										
SMC1A										
SMC3										
STAT3										
TET2										
U2AF2										
ZBTB33										

Genes are ranked from highest diagnostic and prognostic relevance to lowest with the number of categories implicated.

*Based on the ICC classification, a diagnosis of MDS with *SF3B1* may be made if the *SF3B1* mutation is present at ≥10% VAF, even if there is no known/appreciable dysplasia. A diagnosis of MDS with mutated *TP53* may be made without known/appreciable dysplasia if blasts are less than 10% and one of the following is true: two or more *TP53* mutations are each at ≥10% VAF, one *TP53* mutation is at ≥50% VAF, or one *TP53* mutation is ≥10% VAF combined with either chromosome 17p deletion/copy-neutral loss-of-heterozygosity or a complex karyotype. A diagnosis of MDS/AML with mutated *TP53* may be made without known/appreciable dysplasia if blasts are 10–19% and there is one *TP53* mutation ≥10% VAF. The presence f del(5q), –7 or del(7q), or a complex karyotype will also be sufficient to render a diagnosis of MDS without known/appreciable dysplasia. The presence of these mutations or cytogenetic abnormalities without evidence of dysplasia will not be sufficient for a diagnosis of MDS based on the WHO 5th classification.

MRC, myelodysplasia-related changes.

turnover. Future studies could also evaluate sensitizing and resistant molecular profiles to disease-modifying therapies and identify markers of treatment failure.

CLINICAL CASE (continued)

Since the patient was symptomatic to her anemia, an erythropoiesis-stimulating agent was started. The response waned after 18 months, and the patient became transfusion-dependent, despite interval treatment with luspatercept (Figure 1). A bone marrow biopsy performed in 2022 showed similar findings to the prior marrow 2 years before, but NGS revealed the emergence of new mutations—a *BCORL1* mutation (19% VAF) and two *RUNX1* mutations (29% and 20% VAF). In accordance with the new diagnostic classifications, the pathologic diagnosis was changed from MDS-RS-MLD to MDS with mutated *SF3B1* (ICC classification), and MDS with low blasts and *SF3B1* mutation (WHO 5th classification). Although neither the IPSS-R or IPSS-M are dynamic in nature, the patient's disease profile in 2022 would be associated with intermediate-risk MDS (IPSS-R, median OS 3 years) and higher-risk MDS (IPSS-M, median OS 2 years). The absence of treatment response and the evidence of clonal progression raised the possibility of off-label lenalidomide, Imetelstat in the setting of a clinical trial, and higher-intensity therapies. Ultimately, an HMA was initiated with plans for curative intent therapy with a future HSCT based on shared decision-making and the goals of the patient.

Conclusions

Enormous strides have been made over the last 40 years in the diagnosis, prognosis, and treatment of patients with MDS. Risk-assessment models, especially those arising from international collaborations, have been able to guide more consistent patient therapies and more informed clinical trials. These prognostic models are now more comprehensive than ever before incorporating somatic mutations. Despite these advances, there are still avenues for refining the approaches to risk assessment of

MDS. The clinical and scientific community will no doubt partner together in these future endeavors to improve patient outcomes.

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Conflict-of-interest disclosure

Rena R. Xian: no competing financial interests to declare.

Off-label drug use

Rena R. Xian declares no off-label drug use.

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