CORRESPONDENCE

MYELODYSPLASTIC NEOPLASM

Finding consistency in classifications of myeloid neoplasms: a perspective on behalf of the International Workshop for Myelodysplastic Syndromes

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TO THE EDITOR:

Myelodysplastic syndromes (MDS) include a heterogenous group of clonal hematopoietic neoplasms characterized by dysplastic morphologic changes in one or more hematopoietic lineages in the bone marrow and/or peripheral blood, various degrees of cytopenias and a risk of progression to acute myeloid leukemia (AML) [1]. The World Health Organization (WHO) classification of Hematolymphoid Tumors has been used widely for pathological reporting, clinical decision-making, clinical trial eligibility, drug labels, and disease registry reporting across the world. With advances in diagnostic techniques such as molecular testing, and the increased understanding of the close link between the genetic landscape of MDS, disease biology, and phenotype, a revised classification incorporating these disease aspects was published in 2022 as part of the 5th edition of the WHO classification of diseases [1–4].

Concurrently, an International Consensus Classification (ICC) of myeloid neoplasms and acute leukemia, which also incorporates clinical, histopathologic and molecular data for myeloid and lymphoid malignancies, including MDS, was published in 2022 [5].

In this commentary, we compare and contrast specific aspects of the WHO 2022 and ICC classification, highlight their implications and concerns for routine clinical care and in clinical research in MDS, and provide potential solutions to overcome these challenges (Table 1). The International Consortium for MDS (icMDS); a panel of international experts with a focus on preclinical and clinical MDS research including basic scientists, medical oncologist/hematologists, and pathologists convened in the 1st international workshop on MDS, which was held in Miami, FL in June 2022. This manuscript was drafted by a core group with iterative review by all authors.

ABANDONING THE ARBITRARY 20% BLAST THRESHOLD—MDS/AML AS A NOVEL DISEASE ENTITY IN ICC BUT NOT WHO 2022

While there is a strong consensus for many of the definitions proposed by the ICC and WHO 2022, for example, the requirement of ≥10% dysplasia in at least one lineage, there are several important and consequential differences (Table 2) [3, 5]. One notable and clinically relevant difference between both proposals is the creation of a novel entity of "MDS/AML" in the ICC, which is applied to patients with 10–19% blasts in the peripheral blood and/or bone marrow in the absence of AML-defining recurrent genetic abnormalities [5]. The creation of this novel category by the ICC is supported by a growing body of evidence showing that the prognosis of patients with oligoblastic (20–30% blasts) AML and patients with the WHO category of MDS-increased blast 2 (which is eliminated from the ICC) is comparable [5–7]. The lack of survival difference for patients with 10–19% vs. >20% blasts in the original International Prognostic Scoring System (IPSS) and its Revised version (IPSS-R) lends some support to this change as well [8, 9]. However, the recently published molecular IPSS (IPSS-M) demonstrates that blast count differences within the MDS/AML overlap range retain a clinically relevant prognostic impact [10]. This suggests that a bone marrow blast count cut-off of 20% may remain relevant and blast percentage could be considered as a continuum rather than a specific cut-off, which is the goal of the MDS/AML definition. We, however, agree with abandoning these arbitrary thresholds in specific AML-defining molecular subgroups in line with both classifications [3, 5].

This continuum of disease presentations is also reflected by patients with higher-risk MDS and oligoblastic AML being occasionally enrolled in the same clinical trials and the off-label use of therapeutic regimens approved for AML such as azacitidine/venetoclax or liposomal cytarabine/daunorubicin for the treatment of MDS patients [11–13]. While the novel MDS/AML overlap category could formalize the enrolment of patients to either MDS or AML trials, it is critical to emphasize that treatment decisions should involve a multidimensional assessment of the patient's clinical history, symptom burden, suitability for treatment and the cytogenetic and molecular characteristics of the disease. As such, additional stratification within large, phase 3 studies may be needed to appropriately assess these nuanced differences. Based on consideration of these factors, some patients may be more suited for "MDS-type" and others for "AML-type" therapy. For example, given that the median age of MDS patients is nearly a decade older than that of AML patients at diagnosis, differences in bone marrow reserve and a patient's ability to tolerate various treatment intensities need to be carefully considered as demonstrated by the recent azacitidine + venetoclax trials [13–15].

The novel MDS/AML disease entity could also have important implications from a health system and payer perspective as the use of novel therapies approved in AML could be adopted for patients with MDS/AML as well. Although the WHO 2022 continues to distinguish MDS and AML based on a 20% blast threshold, the definition of MDS with increased blasts (MDS-IB2) is essentially equivalent to the MDS/AML definition in ICC [3, 5].

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Table 1. Comparison of MDS subtype definitions in WHO 2016, WHO 2022, and ICC classification of MDS.

WHO 2016 [1]	WHO 2022 [3]	ICC [5]
MDS with single lineage dysplasia (MDS-SLD)	Not included MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (MDS, NOS-SLD)
MDS with multi-lineage dysplasia (MDS-MLD)	MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with multi-lineage dysplasia (MDS, NOS-MLD)
MDS with ring sideroblasts • With single lineage dysplasia (MDS-RS-SLD) • With multi-lineage dysplasia (MDS-RS-MLD)	MDS with low blasts and mutated *SF3B1* or MDS with ring sideroblasts (if ≥ 15% RS and *SF3B1* wild-type)	MDS with mutated *SF3B1*
MDS with isolated del(5q)	MDS with low blasts and isolated 5q deletion (MDS-5q)	MDS with del(5q)
MDS unclassifiable	Not included	Not included
Not included	Not included	MDS, not otherwise specified without dysplasia (e.g., monosomy 7/del(7q))[a]
MDS excess blasts-1 (MDS-EB1; 5–9% bone marrow blasts)	MDS with increased blasts-1 (MDS-IB1; 5–9% bone marrow and/or 2–4% peripheral blood blasts)	MDS excess blasts (5–9% bone marrow and/or 2–9% peripheral blood blasts)
MDS excess blasts-2 (MDS-EB2; 10–19% bone marrow or peripheral blood blasts or Auer rods)	MDS with increased blasts-2 (MDS-IB2; 10–19% bone marrow or 5–19% peripheral blood blasts or Auer rods)	MDS/AML (10–19% bone marrow or peripheral blood blasts)
AML-defining genetics[b]	AML-defining genetics independent of bone marrow and peripheral blood blast count	AML-defining genetics with ≥10% bone marrow and peripheral blood blasts
AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)
Not included	MDS with biallelic *TP53* inactivation (Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH)	MDS with mutated *TP53* (Multi-hit *TP53* mutation, or *TP53* mutation (VAF > 10%) and loss of 17p) and MDS/AML with mutated *TP53* (Any somatic TP53 mutation (VAF > 10%)
Not included	MDS, hypoplastic (MDS-h)	Not included
Not included	MDS with fibrosis (MDS-f)	Not included
Not included	Clonal hematopoiesis (CHIP, CCUS)[c]	Pre-malignant clonal cytopenias and CCUS[c]

[a]This would have been classified as MDS-unclassifiable (MDS-U) in the WHO 2016 classification.
[b]AML-defining genetic abnormalities: Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML::RARA*; APL with other *RARA* rearrangements; AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*; AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*; AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*; AML with other *KMT2A* rearrangements; AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214*; AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2; MECOM(EVI1)*; AML with other *MECOM* rearrangements; AML with other rare recurring translocations; AML with mutated *NPM1*; AML with in-frame bZIP *CEBPA* mutations (ICC only); AML with *RBM15::MRTFA* fusion (WHO only); AML with *NUP98*-rearrangement (WHO only).
[c]cytopenias are defined as follows: hemoglobin <13 g/dL in males and <12 g/dL in females for anemia, absolute neutrophil count $<1.8 \times 10^9$/L for leukopenia, and platelets $<150 \times 10^9$/L for thrombocytopenia.

The WHO classification discussed the pros and cons of merging MDS-IB2 with AML and adopting a 10% blast cut-off to create the MDS/AML category, but ultimately it was decided to retain the term MDS-IB2 arguing that lowering the blast cut-off to 10% would replace one arbitrary cut-off with another, and may introduce the risk of overtreatment in some patients and potentially excess toxicity [3]. That said, the counter-argument is that the definition MDS/AML does not mandate that the patient must receive AML-type therapy, merely that they are able to, if deemed appropriate by their physician. In fact, the WHO 2022 definition explicitly notes that MDS-IB2 can be considered as an AML-equivalent and that treatment decisions as well as clinical trial enrollment should be individualized based on patient and disease characteristics [3].

While MDS-IB2 can be regarded as AML-equivalent or AML-in evolution for therapeutic considerations and from a clinical trial design perspective when appropriate, it is important to note that most of the data supporting the MDS/AML category were derived from patients treated with intensive chemotherapy or HMA monotherapy alone [6]. These criteria remain to be prospectively evaluated whether this assertion still holds true in an era of novel combination therapies. To this end, the recent trial of APR-246 in combination with azacitidine showed an overall response rate (ORR) of 62% and 33% in MDS and AML patients, respectively [16]. Additionally, the CR rates were numerically higher in the MDS patients (47% vs 17%)[16]. Here, differences in ORR and CR rate could be related to differences in the response criteria used for AML vs MDS rather than in biology of response to novel agents (see below for additional discussion regarding differences in response criteria) [16]. Similar results have been reported for the combination of the anti-CD47 antibody magrolimab + azacitidine in higher-risk MDS and oligoblastic AML [12]. Therefore, if patients are enrolled on the basis of MDS/AML to AML trials, investigators should consider stratifying outcomes for patients with 10–19% and ≥20% blasts, until sufficient information is available regarding the long-term clinical outcome with new drugs.

One potential difference between MDS and AML that transcends an arbitrary blast cut-off is the relative disease stability in MDS compared to most cases of frank AML. In contrast to most AML patients, MDS patients can present with relatively stable blood counts for 2–4 months, which was also a component of the International Working Group for Prognosis in MDS classification

Table 2. Comparison of key components included in ICC and WHO 2022 definitions of MDS.

	ICC [5]	WHO 2022 [3]	Potential benefits	Potential disadvantages
MDS/AML overlap category for patients with 10–19% bone marrow or peripheral blood blasts	Included	Not included; patients should be classified as MDS-IB2	- more flexibility for trial enrollment and clinical practice - May better reflect natural history of HR-MDS and oligoblastic AML	- additional prospective validation needed - thresholds remain arbitrary - decrease cross-trial comparison if discrepant criteria (e.g., should MDS IWG or AML ELN response criteria be applied)
Dysplasia and ring sideroblasts as diagnostic criteria	≥10% dysplasia required for diagnosis; distinction between single- and multilineage dysplasia maintained; select molecular features enable diagnosis without dysplasia (e.g., monosomy 7). Ring sideroblasts no longer impact diagnosis.	≥10% dysplasia required for diagnosis; no distinction between single- and multi-lineage dysplasia. Ring sideroblasts still used for diagnosis of MDS cases lacking SF3B1 mutation or with unknown SF3B1 status.	- less emphasis on dysplasia reduces interobserver variability - highlights importance of genetic features	- De-emphasis of morphology and increased reliance on genetic features present a challenge for areas with limited access to NGS testing.
MDS with fibrosis and hypoplastic MDS	Not included	Included as MDS-f and MDS-h	- could enable targeted research due to standardized definitions	
Molecular characteristics as disease-defining features	Addition of biallelic *TP53* mutations, SF3B1 mutation, and various AML-defining genetic alterations	Addition of biallelic *TP53* mutations, SF3B1 mutation, and various AML-defining genetic alterations; name change to myelodysplastic neoplasms	- more reproducible than histopathologic criteria - incorporates more individualized prognostic features into diagnosis, with better alignment with prognostic models (e.g., IPSS-M) and more potential to impact treatment decisions. - emphasis that MDS is clonal and neoplastic	- NGS studies not universally available (e.g., *TP53* LOH) and costly - standardization of assays required - prospective validation needed if used for treatment decisions
Addition of premalignant clonal hematopoiesis (CHIP, CCUS)	Formalized definition of CCUS and CHIP provided	Formalized definition of CCUS and CHIP provided	- standardization of definitions for clinical use and trials - could become foundation for inclusion in ICD codes (reimbursement, outcomes research)	- NGS studies not universally available and costly - standardization of assays required - prospective validation needed if used for treatment decisions

for the IPSS and IPSS-R [8, 9]. This issue is important in demonstrating biologic differences between MDS and AML, which is also reflected in the differing therapeutic responses in these entities. Such differences point to the transitional nature of MDS with its important features for discerning the evolutionary potential of relatively indolent to aggressive stages of myeloid diseases. Thus, blood count stability could be informative in influencing management for patients across the spectrum of MDS-IB2, MDS/AML and oligoblastic AML.

Solving the issue of harmonizing trial eligibility criteria, however, begets a problem with response criteria, the selection of which (i.e., MDS criteria or AML criteria) is likely to be heterogeneous between investigators and study sponsors. Whether AML or MDS response criteria (i.e., monitoring measurable residual disease [MRD] or hematologic improvement) should be applied to these patients is unclear, but standardization is necessary: Application of AML (ELN 2017 and ELN 2022) and MDS response criteria (IWG 2006/2018 criteria) can lead to substantially different results, as demonstrated by a prospective study of CPX-351 in MDS patients treated with liposomal cytarabine/daunorubicin [11, 17–19]. Furthermore, the revised ELN 2022 AML response criteria introduce a novel response category of CR with partial hematologic recovery (CRh) and how it applies in this context warrants further studies [19]. Limited retrospective data suggest that CRh is also associated with improved OS in MDS patients treated with HMA [20].

An additional challenge is the emphasis on an assessment of MRD by flow cytometry or molecular methods in AML response criteria, which is substantially more challenging to standardize, interpret and implement in MDS [19, 21]. If clinical trial enrolment and response assessment harmonization is accomplished, the separation of MDS-IB2 and MDS/AML is hopefully primarily semantic with limited implications on patient care. This could also reduce inappropriate enrolment of MDS patients in non-specific AML clinical trials or AML patients in MDS trials but would require a collaborative approach with mutual agreements on the principles of goals and classifications.

MOVING TOWARDS A GENETIC DEFINITION OF MYELOID NEOPLASMS

While MDS subtypes had been defined in the past primarily based on morphology and only a few select genetic features (e.g., del(5q) and *SF3B1* mutations) [1], the implications of molecular disease characteristics have been increasingly appreciated [22, 23]. *TP53* mutations particularly have been associated with a poor prognosis in patients with either AML or MDS, with multiple studies showing that *TP53* mutation status supersedes other disease features such as blast percentage or other cytogenetic abnormalities [4, 24, 25]. The negative prognostic impact of *TP53* mutations in MDS appears to be primarily driven by multi-hit *TP53* alterations [4, 25–27]. "Multi-hit" (ICC) or bi-allelic (WHO) *TP53* loss can be a function of several scenarios including the presence of multiple mutations (presumably affecting both alleles), one mutation and deletion of the other *TP53* locus on chromosome 17p (often in the context of a complex karyotype) or one mutation combined with copy neutral loss-of-heterozygosity (cn-LOH). Unfortunately, assessment of cn-LOH is not routinely performed in most clinical laboratories at this time; although we anticipate that the new guidelines including ELN 2022 and both classification schemes recognizing the prognostic importance of cn-LOH will lead to efforts to more widely adopt *TP53* cn-LOH testing in clinical laboratories [3, 5, 19]. Notably, the majority of *TP53* mutant MDS (as high as 90% in higher risk MDS/AML) fall into high molecular risk categories (i.e., multi-hit, variant allele fraction [VAF] >40%, and/or complex karyotype). In accordance with this, two recent studies showed similar outcomes of such patients across MDS-EB and AML without further stratification of outcomes based on allelic status or VAF

[24, 25]. This serves as a call to action for additional studies validating surrogates of *TP53* mutation with cn-LOH, such as a high *TP53* mutation burden (inferred by VAF) in specific clinical settings.

Additional differences between the ICC and WHO 2022 exist in the definition of AML-defining or recurrent genetic abnormalities either independent of blast count (WHO 2022) or subject to a ≥ 10% blast threshold (ICC) [3, 5]. These recommendations emphasize the importance of delivering potentially curative treatment with intensive chemotherapy +/− allogeneic hematopoietic cell transplant in this setting. While many of these genetic abnormalities are rare, patients with *NPM1* mutations represent a key subgroup that will be better recognized as a clear AML entity in both of the revised classifications [3, 5]. How these changes are adopted in routine clinical practice remains to be seen, as patients with *NPM1* mutations without increased bone marrow or peripheral blood blast counts could be eligible for either intensive induction chemotherapy or azacitidine/venetoclax. Although prospective data is lacking to prove that earlier treatment will translate into more favorable outcomes, compared to treatment at the time of clinically manifest AML with ≥20% blasts, both classifications increase awareness of this patient population and their enrolment into AML clinical trials.

However, to move towards a molecular definition of both MDS and AML it is essential to ensure prompt access to standardized molecular testing results, especially in resource-limited and community-based treatment settings. If not readily available, immunohistochemical studies for select molecular abnormalities such as p53 and NPM1 have shown acceptable sensitivity and specificity and can serve as an alternative in resource-limited settings [28–30]. As treatment decisions are increasingly being made based on these results with the approval of targeted therapies, adequate and timely access to these results may allow for an increasingly individualized care of MDS and AML patients. With the majority of MDS patients receiving HMA being treated in the community setting and variations in using next-generation sequencing results for treatment decision-making [31, 32], efforts to standardize practice patterns and increase access to molecular testing globally will be increasingly important to fully adopt any new genetically-based classification into real-world practice.

BLURRY BORDERS—CLONAL CYTOPENIAS, HYPOPLASTIC MDS AND MDS WITH FIBROSIS

The implications of clonal hematopoiesis including an increased risk for development of myeloid neoplasms as well as cardiovascular events, chronic obstructive pulmonary disease, and all-cause mortality have been increasingly appreciated over the last decade [2, 33–36]. Both the ICC and the WHO 2022 define clonal hematopoiesis (CH) as the presence of a somatic mutation (VAF ≥ 2%) or cytogenetic abnormalities associated with a myeloid neoplasm in a patient not meeting the criteria for a myeloid neoplasm [3, 5]. In the absence of morphologic dysplasia in the bone marrow, patients with CH and cytopenias would now be formally diagnosed with clonal cytopenia of undetermined significance (CCUS) [3, 5]. Applying identical thresholds for the definition of cytopenias and the degree of dysplasia (<10%) is an important step forward that could facilitate the conduct of clinical trials in patients with CCUS aiming to prevent or at least delay the progression to a manifest myeloid neoplasm. The formal inclusion of CCUS in the WHO 2022 could support the inclusion of a more specific code in future iterations of the ICD and enable claims-based research and higher quality epidemiologic data. Additional studies on the natural history of CCUS considering variations including type, number of alterations/mutations, clone size (VAF), clonal evolution in the context of selection pressure, association with inflammatory processes or solid tumors and treatment thereof are also needed [37–41]. With the growing body of evidence demonstrating an association of CHIP and CCUS with cardiovascular, cerebrovascular, and pulmonary diseases as well as other aging-related diseases, the inclusion of CHIP and CCUS as clearly defined disease entities in the WHO 2022 and ICC definition will certainly have implications beyond the field of myeloid malignancies [33, 36, 42]. For example, such a standardized definition of CHIP and CCUS can enable prospective, intervention studies to modify the risk of e.g., cardiovascular events in patients with CHIP or patients with therapy-related or pre-existing CHIP or CCUS undergoing chemotherapy [40, 43].

In contrast to the ICC definition, the WHO 2022 added hypoplastic MDS (MDS-h) and MDS with fibrosis (MDS-f) as novel disease entities[3]. These cases have long presented diagnostic and management challenges, as the distinction from aplastic anemia and primary myelofibrosis, respectively, can be sometimes challenging (albeit, molecular testing offered some additional diagnostic tools) [44–47]. It remains to be seen how useful defining these new WHO MDS entities will be in clinical practice although carefully defined hypoplastic MDS has been shown to have a higher likelihood of response to immunosuppressive therapy [48]. Similarly, how to best distinguish MDS-f from the MDS/MPN overlap diseases remains to be seen [3, 49].

IMPLICATIONS FOR REGULATORY AND ADMINISTRATIVE ASPECTS OF MDS

Formal and standardized classifications are the foundation for epidemiologic assessments, outcomes research, health care administration (e.g., reimbursement), and drug approval. While the introduction of the MDS/AML category in ICC might foster clinical trial enrolment and accelerate drug development in MDS and AML, this reclassification does not solve the current considerations for off-label use of AML therapies such as azacitidine/venetoclax in MDS [5]. How are insurance providers and national health systems around the world going to respond to requests for the use of such therapies in MDS patients that would now be re-classified as MDS/AML? It will also require additional discussions with regulatory agencies such as the US Food and Drug Administration, the European Medicines Agency, and other regulatory agencies to harmonize how these new classification schemes will be adopted into clinical trial designs, which may be used to support future drug approvals.

As mentioned previously, ICD codes are the foundation of cancer registries such as the SEER program in the United States and the European Network of Cancer Registries. Population level studies have yielded important information on the epidemiology of MDS as well as practice patterns and outcomes in patients treated outside of the controlled clinical trial setting [50–52]. As only a minority of patients with MDS are being treated in a clinical trial and various differences in terms of baseline patient characteristics exist, such population-based studies are essential [52, 53]. However, such population-based studies are limited by the absence of granular information as exemplified by the fact that the majority of patients with MDS included in the SEER-Medicare database are coded as MDS, not otherwise specified (MDS-NOS) [54]. Additionally, using the term "refractory anemia with excess blasts" in disease registries and epidemiologic and population-based outcome studies as a surrogate for higher-risk MDS has limitations as well [51]. The elimination of the MDS-U from both the ICC and WHO 2022 offers the opportunity for more specific disease classification in disease registries but the various differences in definitions could further hamper research efforts if not reconciled.

FUTURE DIRECTIONS

While it could be viewed as a concerning development to have two separate and divergent classifications for a comparatively rare

disorder such as MDS, we acknowledge that this does bring thoughtful divergent opinions to the forefront and provides an impetus to enhance international consistency in standards of clinical care and in clinical trial design for MDS and ultimately help move the field forward. One example is the use of two different terms for MDS, with the WHO adopting the new term "myelodysplastic neoplasms" to emphasize the neoplastic nature of MDS while maintaining the abbreviation of MDS, while the ICC maintains the term "myelodysplastic syndromes". Although we recognize that highlighting the neoplastic and clonal nature of MDS is important, we anticipate that this difference in MDS nomenclature may pose several challenges affecting routine clinical care, clinical trial design, conduct, and interpretation, and regulatory aspects of therapies, disease registries (e.g., Surveillance, Epidemiology, and End Results [SEER]), and health system administration such as medical billing codes (e.g., ICD codes) and drug reimbursement [3]. Of even greater importance, the potential for discordant opinions regarding diagnosis between one physician and another poses the risk of increasing patient confusion and anxiety.

While many definitions proposed by the ICC and WHO 2022 are concordant [3, 5], several key differences as outlined above exist and could impact the design and outcome of clinical trials, patient care, and drug development and regulatory approval in MDS. There is agreement among the community of MDS providers to remain vigilant and ensure that differences in disease classification are accounted for in clinical trial design, enrolment, and reporting of outcomes. As the evidence supporting the different classifications continues to evolve and acknowledging that the primary principles guiding both the WHO 2022 and the ICC classification are molecular and clinicopathologic disease characteristics, it remains unclear which definitions capture disease biology best. However, these differences will hopefully spawn research efforts to refine definitions with the next revision of the classification system. Genetically defined disease entities and the suggested MDS/AML category, particularly, will require additional validation. Finally, it will be important to assess the implications of each classification system on other key aspects of MDS management such as risk stratification tools incorporating molecular data as well as efforts aiming to redefine response criteria in MDS [10, 23, 55]. We remain hopeful that these competing and divergent classifications schemes will eventually be harmonized to achieve one uniform consensus for MDS classification that will be adopted in the near future. Until such a consensus definition is achieved, this serves as a call-to-action to minimize any unintended, negative impact on patient care and to continue with collaborative research efforts to improve patient outcomes.

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AUTHOR CONTRIBUTIONS

AMZ and JPB wrote the initial draft of the manuscript and contributed equally to this study. AMZ, JPB, RB, MAS, DPS, UP, SL, AHW, and VS were involved with the conception and design of the study. All authors were involved in writing, reviewing, and editing the manuscript and approved the final version for submission.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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