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Real-world diagnostic testing patterns for assessment of ring sideroblasts and *SF3B1* mutations in patients with newly diagnosed lower-risk myelodysplastic syndromes

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Abstract

Introduction: The presence of ring sideroblasts (RS) and mutation of the *SF3B1* gene are diagnostic of lower-risk (LR) myelodysplastic syndromes (MDS) and are correlated with favorable outcomes. However, information on testing and reporting in community-based clinical settings is scarce. This study from the Connect® MDS/

AML Disease Registry aimed to compare the frequency of RS and *SF3B1* reporting for patients with LR-MDS, before and after publication of the 2016 World Health Organization (WHO) MDS classification criteria.

Methods: Ring sideroblasts assessment and molecular testing data were collected from patients with LR-MDS at enrollment in the Registry. Patients enrolled between December 2013 and the data cutoff of March 2020 were included in this analysis.

Results: Among 489 patients with LR-MDS, 434 (88.8%) underwent RS assessment; 190 were assessed prior to the 2016 WHO guidelines (Cohort A), and 244 after (Cohort B). In Cohort A, 87 (45.8%) patients had RS identified; 29 (33.3%) patients had RS < 15%, none of whom underwent molecular testing for *SF3B1*. In Cohort B, 96 (39.3%) patients had RS identified; 31 (32.3%) patients had < 15% RS, with 13 undergoing molecular testing of which 10 were assessed for *SF3B1*.

Conclusions: In the Connect® MDS/AML Registry, only 32% of patients with <15% RS underwent *SF3B1* testing after the publication of the WHO 2016 classification criteria. There was no change in RS assessment frequency before and after publication, despite the potential impact on diagnostic subtyping and therapy selection, suggesting an unmet need for education to increase testing rates for *SF3B1* mutations.

KEYWORDS

diagnosis, Myelodysplastic syndromes, Registry, ring sideroblasts, SF3B1

1 | INTRODUCTION

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of myeloid neoplasms characterized by ineffective erythropoiesis, cytopenias, and possible progression to acute myeloid leukemia (AML).[1] Approximately 30%-35% of MDS patients have ring sideroblasts (RS), erythroblasts in the bone marrow that accumulate a minimum of five iron granules and cover at least one-third of the perinuclear region.[2,3] The presence of RS has been associated with somatic mutation of the gene coding for splicing factor 3B subunit 1 (*SF3B1*) with a concordance of up to 90%.[4] Patients with concomitant RS and mutation in *SF3B1* have shown improved overall survival (OS) and lower cumulative incidence of disease progression versus those with wild-type *SF3B1*.[4,5] The MDS with RS subtype was recognized in the World Health Organization (WHO) criteria for MDS published in 2016, with MDS-RS defined as the presence of ≥15% RS in the bone marrow or ≥5% RS when *SF3B1* is mutated.[6,7] This is in contrast to the previous WHO criteria published in 2008 before the discovery of recurrent *SF3B1* mutations in MDS, where the presence of RS in ≥15% of bone marrow erythroid precursors was diagnostic of refractory anemia with RS.[8] It is currently unknown if the updated definition of MDS-RS has led to significant changes in clinical practice regarding RS and *SF3B1* testing. Therefore, we conducted an analysis of pathology reports of patients diagnosed with lower-risk (LR) MDS enrolled in the Connect® MDS/AML Disease Registry,[8] to determine whether the frequency of RS and *SF3B1* mutational status assessments has increased as publication of the revised WHO criteria.

The Connect® MDS/AML Disease Registry (NCT01688011) is a large, multicenter, US, prospective observational cohort study of patients with newly diagnosed AML (aged ≥ 55 years) or newly diagnosed MDS (aged ≥ 18 years), initiated on December 12, 2013.[9] Recruitment is ongoing and will continue until approximately 2,100 patients with MDS or AML have been enrolled at 150-200 US sites. The study is noninterventional; all medical care is performed in accordance with standard clinical practice at each site. The Registry was approved by a central institutional review board (IRB; Advarra Review IRB, Seattle, WA, USA) or the local IRB at each site.

Eligible patients are aged ≥18 years and newly diagnosed with MDS according to the 2008 WHO criteria within 60 days of enrollment to the Registry.[8] Local diagnosis is confirmed by independent central review of all diagnostic test reports, including bone marrow aspirates and biopsies, flow cytometry, cytogenetics, molecular genetic testing, and laboratory results. Sites report data through an electronic case report form in an electronic data capture system at baseline and every 3 months, for up to 8 years or until study termination, patient withdrawal, or death.

Baseline patient characteristics and diagnostic testing patterns were collected for patients with LR-MDS at time of enrollment in the Registry. This analysis includes patients enrolled between December 12, 2013, and the data cutoff of March 9, 2020. LR-MDS patients were confirmed to have International Prognostic Scoring System (IPSS) Low- or Intermediate-1-risk status. Patients were divided into two groups based on their date of enrollment: those enrolled on or before December 1, 2016 (cohort A), and those enrolled after December 1, 2016 (cohort B)—roughly 6 months after publication of the revised WHO criteria for the diagnosis and classification of myeloid neoplasms including MDS.[6]

Ring sideroblasts assessment, RS status, and molecular testing data were collected from clinical diagnostic reports. RS status was reported either as a percentage or as an interval (or range of values) if the report provided a quantitative value. Reports containing qualitative values were correlated to an agreed convention for independent central review. Demographics and clinical characteristics were summarized using descriptive statistics. Differences in testing rates at enrollment were assessed using a chi-square test, with $P < .05$ considered statistically significant. All statistical analyses were conducted using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

As of March 9, 2020, 489 patients with LR-MDS were enrolled in the Registry from 134 sites: 20 (14.9%) academic (AC) and 114 (85.1%) community/government (CO/GOV) sites. A total of 216 patients were enrolled on or before December 1, 2016 (into cohort A), and 273 patients were enrolled after December 1, 2016 (into cohort B) (Table 1).

Patients in cohort A were older than those in cohort B (77 vs 74 years; $P = .0208$), and less likely to have overall comorbidity grade of 0 (13.1% vs 25.0%; $P = .0291$). There was also a significant difference in geographic location of patients in cohorts A and B ($P = .01$) (Table 1).

Patients in cohort B were less likely to have fluorescence in situ hybridization (FISH) testing performed ($P < .001$) and more likely to undergo molecular testing ($P < .001$) than patients in cohort A (Table 2).

TABLE 1 Baseline characteristics for patients with LR-MDS in the Connect® MDS/AML Disease Registry

Baseline characteristic[a]	All LR-MDS patients (N = 489)	Cohort A (patients enrolled before December 1, 2016) (n = 216)	Cohort B (patients enrolled after December 1, 2016) (n = 273)	*P* value
Age, median (range), years	75 (22-95)	77 (38-95)	74 (22-94)	.0208[b]
Sex, n (%)	n = 489	n = 216	n = 273	NS
Male	323 (66.1)	145 (67.1)	178 (65.2)	
Female	165 (33.7)	70 (32.4)	95 (34.8)	
Other[c]	1 (0.2)	1 (0.5)	0 (0)	
Race,[d] n (%)	n = 489	n = 216	n = 273	NS
White	438 (89.6)	194 (89.8)	244 (89.4)	
Black	21 (4.3)	11 (5.1)	10 (3.7)	
Other	6 (1.2)	3 (1.4)	3 (1.1)	
Not specified	25 (5.1)	9 (4.2)	16 (5.9)	
Geographic region, n (%)	n = 488	n = 216	n = 272	.01
Northeast	71 (14.5)	42 (19.4)	29 (10.7)	
Midwest	182 (37.3)	84 (38.9)	98 (36.0)	
South	162 (33.2)	58 (26.9)	104 (38.2)	
West	73 (15.0)	32 (14.8)	41 (15.1)	
Institution type, n (%)	n = 489	n = 216	n = 273	NS
Academic	54 (11.0)	26 (12.0)	28 (10.3)	
Community/ government	435 (89.0)	190 (88.0)	245 (89.7)	
IPSS risk classification, n (%)	n = 488	n = 216	n = 272	NS
Low	200 (41.0)	95 (44.0)	105 (38.6)	
Intermediate-1	288 (59.0)	121 (56.0)	167 (61.4)	
ECOG status, n (%)	n = 422	n = 182	n = 240	NS
0-1	344 (81.5)	154 (84.6)	190 (79.2)	
≥2	78 (18.5)	28 (15.4)	50 (20.8)	
Overall comorbidity grade, n (%)	n = 407	n = 175	n = 232	.0291[e]
0	81 (19.9)	23 (13.1)	58 (25.0)	
1	127 (31.2)	59 (33.7)	68 (29.3)	
2	104 (25.6)	47 (26.9)	57 (24.6)	
3	95 (23.3)	46 (26.3)	49 (21.1)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; LR-MDS, lower-risk myelodysplastic syndromes; NS, not significant.

[a]Rounding of numbers may cause totals to be < or >100%.

[b]Median 2-sample test, 2-sided Pr > | Z |. If not indicated by footnote, numbers in the table are chi-square *P* value.

[c]Patient identified as transgender.

[d]Patients were able to select multiple categories.

[e]*P* value for having comorbidity grade of 0 vs ≥1.

As of March 9, 2020, 434 patients (88.8%) with LR-MDS had an RS assessment via an iron stain of a suitable bone marrow aspirate or touch preparation smear. RS assessment rates were similar between cohort A and cohort B (190/216 [88.0%] and 244/274 [89.4%], respectively). RS were identified in 183 patients (42.2%) who were assessed: 87/190 patients (45.8%) in cohort A and 96/244 patients (39.3%) in cohort B (Figure 1).

Of the 87 patients with RS in cohort A, RS were reported as a percentage for 34 patients (39.1%) and as an interval for 48 patients (55.2%). While 29 patients (33.3%) had <15% RS, only 1 underwent molecular testing, and *SF3B1* was not assessed (Figure 1A).

Of the 96 patients with RS in cohort B, RS were reported as a percentage for 40 patients (41.7%) and as an interval for 54 patients (56.3%). Of 31 patients (32.3%) with <15% RS, only 13 underwent molecular testing, and only 10 were assessed for an *SF3B1* mutation (Figure 1B).

Overall, the testing rates for *SF3B1* increased for patients enrolled on or before December 1, 2016 (cohort A) compared with patients enrolled after December 1, 2016 (cohort B) from 6.0% to 23.8%. An increase in testing rates was seen for patients enrolled at CO/GOV sites (5.3% to 22.8%) and AC sites (11.5% to 32.1%).

Within the Connect® MDS/AML Disease Registry, the frequency of RS assessment in patients with LR-MDS remained unchanged at least 6 months after the publication of the 2016 WHO criteria. Just under 90% of patients underwent assessment for RS with just over 40% having RS present in the bone marrow. Despite this high number of patients presenting with RS, few received *SF3B1* testing after the publication of the updated WHO criteria, accounting for only one-third of patients with <15% RS.

The Association for Molecular Pathology Working Group for chronic myeloid neoplasms recommends obtaining molecular information on *SF3B1*.[10] In a study by Mian et al,[11] mutation of *SF3B1* was significantly associated with improved OS ($P < .003$) and improved progression-free survival ($P < .02$).

Molecular testing of *SF3B1* and other RNA splicing genes (eg, *SRSF2*, *U2AF1*, *and ZRSR2*) has also been used to improve diagnostic accuracy of MDS and could be incorporated into the initial screening in combination with Revised IPSS risk assessment. An analysis of 67 cases of MDS with high-resolution melting analysis showed the presence of *SF3B1* mutations in nine patients. These patients had higher platelet counts and lower blast percentages compared with patients with wild-type *SF3B1*. Moreover, absence of a mutation in *SF3B1* in patients with >5% RS was associated with poorer prognosis compared with those patients harboring a mutation in *SF3B1*.[12] RS and *SF3B1* mutation status in patients with LR-MDS may also serve as clinically actionable biomarkers to guide treatment decisions. The novel erythroid maturation agent, luspatercept, has been approved for treatment of anemia in patients with LR-MDS and RS and reduces the need for red blood cell transfusions.[13]

Despite this evidence and the current testing recommendations, our analysis of molecular testing for patients with LR-MDS did not show apparent changes in the frequency of *SF3B1* testing. Furthermore, only one-third of patients meeting the requirement for *SF3B1* testing (with < 15% RS) in the post WHO 2016 setting were actually tested. This may reflect a delay in the uptake of new next-generation sequencing technologies, particularly within community practice where accessibility may be a factor. It may be interesting to see how *SF3B1* testing patterns change as next-generation sequencing becomes more widely available. Due to the way in which data are collected in the Registry, information on the reason for not performing *SF3B1* testing was not captured, but there is clear room for improvement. Therefore, further research is warranted to understand why *SF3B1* testing rates remain low and to inform the development of potential educational activities

TABLE 2 Cytogenetic and molecular analyses conducted for patients with LR-MDS in the Connect® MDS/AML Disease Registry

Assessment, n (%)	All LR-MDS patients (N = 489)	Cohort A (patients enrolled before December 1, 2016) (n = 216)	Cohort B (patients enrolled after December 1, 2016) (n = 273)	*P* value*
FISH analysis performed				
Yes	320 (65.4)	160 (74.1)	160 (58.6)	<.001
No	169 (34.6)	56 (25.9)	113 (41.4)	
Flow cytometry analysis performed				
Yes	462 (94.5)	200 (92.6)	262 (96.0)	NS
No	27 (5.5)	16 (7.4)	11 (4.0)	
Molecular analysis performed				
Yes	133 (27.2)	33 (15.3)	100 (36.6)	<.001
No	356 (72.8)	183 (84.7)	173 (63.4)	
Normal cytogenetic test	n = 475	n = 209	n = 266	NS
Yes	272 (57.3)	118 (56.5)	154 (57.9)	
No	202 (42.5)	91 (43.5)	111 (41.7)	

Abbreviations: FISH, fluorescence in situ hybridization; LR-MDS, lower-risk myelodysplastic syndromes; NS, not significant.

*All values are chi-square *P* value.

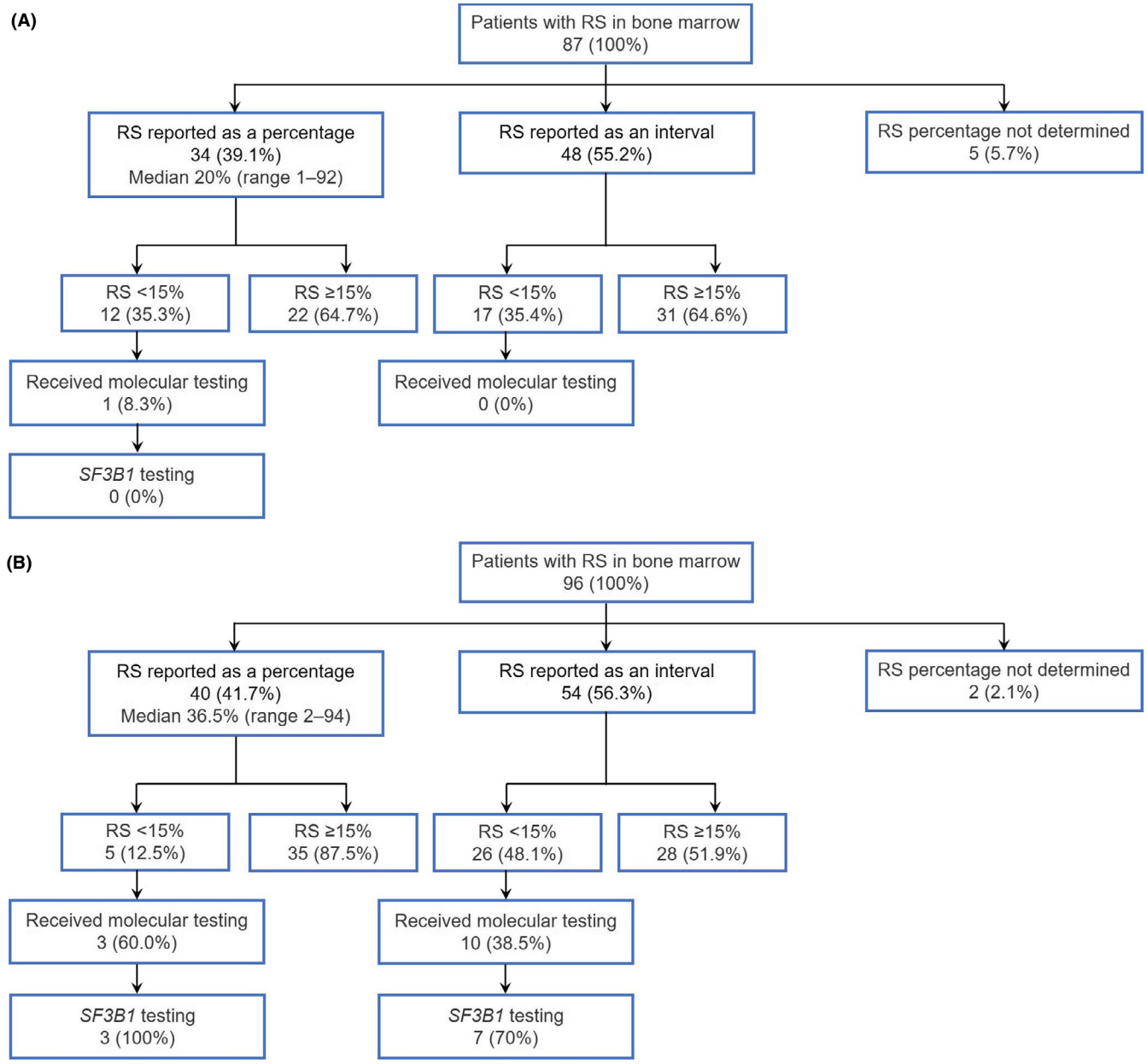

FIGURE 1 RS assessment for patients enrolled in the Connect® MDS/AML Disease Registry (A) on or before December 1, 2016, and (B) after December 1, 2016. Abbreviation: RS, ring sideroblasts [Colour figure can be viewed at wileyonlinelibrary.com]

to increase awareness of the importance of RS and *SF3B1* testing in LR-MDS. Recently, the International Working Group for the Prognosis of Myelodysplastic Syndromes proposed the introduction of a separate subtype of MDS, characterized by the presence of an *SF3B1* mutation alongside cytopenia, morphological dysplasia, bone marrow blasts <5%, and peripheral blood blasts <1%.[14] The adoption of this new subtype could lead to further demand for *SF3B1* testing; therefore, identification of any current barriers to the uptake of *SF3B1* testing is important.

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CONFLICT OF INTEREST

MA has served on an advisory board for Bristol Myers Squibb; and has participated in speaker panels for AbbVie, Bristol Myers Squibb, Gilead, Seattle Genetrix, and Takeda. CRC is a steering committee member for the Connect® MDS/AML Disease Registry for Celgene, a Bristol-Myers Squibb Company. HPE has participated in speakers bureau for Agios, Bristol Myers Squibb, Jazz Pharmaceuticals, Incyte, and Novartis; has provided consultancy to AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, Daiichi Sankyo, Glycomimetics, ImmunoGen, Incyte, Jazz, MacroGenics, Novartis, Pfizer, and Seattle Genetics; has received research funding from AbbVie, Daiichi Sankyo, ImmunoGen, and Macrogenics; has served on a data safety and monitoring committee for Glycomimetics; and has served on an independent review committee for Covance. KF has served on an advisory board for Bristol Myers Squibb. DLG has provided consultancy to AbbVie; and has served on advisory boards for Astellas and Bristol Myers Squibb. RSK has participated in speakers bureau for Alexion, Jazz Pharmaceuticals, and Novartis; and has provided consultancy to Agios, Bristol Myers Squibb, Daiichi Sankyo, Inc, Incyte, Janssen, and Pfizer. SEK has provided consultancy to Agios and Bristol Myers Squibb. DAP has served on advisory boards for AbbVie, Agios, Bristol Myers Squibb, Daiichi Sankyo, Forty Seven, and Pfizer; provided consultancy to AbbVie, Agios, Bristol Myers Squibb, and Takeda; and has served on a data safety and monitoring committee for Glycomimetics. DAR has received research funding and provided consultancy to Allergan, Amgen, Bristol Myers Squibb, and Takeda. GJR has provided consultancy and has served on an advisory board or safety data monitoring committee for AbbVie, Actinum, Agios, Amphivena, Argenx, Astex, Astellas, Bayer, Bristol Myers Squibb, Celltrion, Daiichi Sankyo, Eisai, Janssen, Jazz Pharmaceuticals, Novartis, MEI Pharma, Orsenix, Otsuka, Pfizer, Roche/Genentech, Sandoz, Takeda, and Trovgene; and has received research funding from Cellectis. MRS has received patents and royalties from Boehringer Ingelheim; has served on advisory boards for Bristol Myers Squibb and Selvita; has served on advisory boards and has received research funding from Incyte, Takeda, and TG Therapeutics; has served on an advisory board, has provided consultancy, and holds equity in Karyopharm; and has received research funding from Sunesis. BLS has participated in speakers bureau for Agios; has participated in speakers bureau and provided consultancy to Alexion and Bristol Myers Squibb; has participated in speakers bureau and has served on an advisory board for Incyte; and has received research funding from Novartis. MAS has served on advisory boards for Bristol Myers Squibb, Millennium Pharmaceuticals, and Syros. DPS has received research funding from Aprea Therapeutics; holds equity in Arrowhead Pharmaceuticals; has provided consultancy to Astex Pharmaceuticals, Onconova Therapeutics, Pfizer, Stemline Therapeutics, and Summer Road; and has received research funding from H3 Bioscience. MAT has served on advisory boards for AbbVie, Adaptive, Bristol Myers Squibb, Doximity, GlaxoSmithKline, Syapse Precision Medicine, Takeda, and VIA Oncology (Elsevier ClinicaPath); and has received research funding from AbbVie, Bristol Myers Squibb, CRAB CTC, Denovo, Hoosier Research Network, Lilly, LynxBio, Strata Oncology, Takeda, and TG Therapeutics. EDF is an employee of Bristol Myers Squibb. PK, CUL, MN, and ASS are employees of and hold equity in Bristol Myers Squibb. TIG has provided consultancy to and is a member of the steering committee member for the Connect® MDS/AML Disease Registry for Celgene, a Bristol-Myers Squibb Company. JLP, GG-M, and JPM have no conflict of interests to disclose.

AUTHOR CONTRIBUTIONS

All authors directed the development, critically reviewed, and approved the submitted version of this manuscript and are fully responsible for all content and editorial decisions.

DATA AVAILABILITY STATEMENT

BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html

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