Diagnosis of myelodysplastic syndromes: the classic and the novel

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Abstract

The myelodysplastic syndromes (MDS) are a heterogenous group of clonal bone marrow (BM) stem cell myeloid neoplasms, characterized by BM dysplasia, macrocytic anemia or cytopenia with a tendency for leukemic transformation. The suspicion of MDS is raised by a typical but not specific clinical picture and routine laboratory findings, but the gold standard for the diagnosis of MDS is still BM examination with the presence of uni-or multi-lineage dysplasia and blast percentage, together with exclusion of other reasons. Cytogenetics is also a part of the diagnostic process. Flow cytometry and genetics are helpful but are not always mandatory for the diagnosis of MDS. This review summarizes the current steps in the diagnostic approach for a patient suspected of having MDS. We also describe new concepts that use non-invasive diagnostic technologies, especially digital methods as well as peripheral blood genetics. The hope is that one day these will mature, be introduced into clinical practice, and perhaps in many cases even replace the invasive BM biopsy.

Introduction

The myelodysplastic syndromes (MDS) are a heterogenous group of clonal myeloid neoplasms originating in hematopoietic stem cells. They are characterized by ineffective hematopoiesis resulting in dysplasia in hematopoietic cells, and are associated with peripheral blood (PB) cytopenias, especially anemia, and a propensity to leukemic transformation.[1-5] The incidence of MDS increases with age and in the general population is approximately 5 cases per 100,000 people per year. The median age of onset is above the age of 70 years.[3,6,7] Patients with MDS are classified using one of several scoring systems.[8-12] Most patients are assigned to the lower-risk or higher-risk groups. While these classifications may assist in diagnosis, they mainly serve for prognostication and to direct management.

In this work, we focus on the diagnosis of MDS and emphasize some of the more modern modalities currently under study. The entities of MDS/myeloproliferative neoplasms (MPN), and chronic myelomonocytic leukemia (CMML) are beyond the scope of this paper.

As MDS encompasses a heterogeneous group of disorders, the diagnostic process is based on a combination of clinical and laboratory features and the exclusion of other diseases. As such, there is no single specific diagnostic test, and there are no definitive diagnostic criteria for MDS.

What may raise suspicion of myelodysplastic syndromes

MDS is suspected when there are appropriate clinical and laboratory findings, especially in the elderly. MDS symptoms are non-specific and range from none (asymptomatic) to weakness and fatigue. There may be cardiac complications, due to the common anemia (Table 1),[1,3,5,6,13,14] and a decreased neutrophil count might be associated with recurrent infections. Patients may have epistaxis, gingival bleeding or easy bruising if their platelet count is low or if the platelets do not function normally.[15]

Other causes of anemia or other cytopenias must be ruled out first. This requires taking a careful history to search for these etiologies. These may include nutritional deficiencies (folic acid and vitamin B12, especially in vegetarians), medications, alcohol and tobacco use, or viral infection. The

Table 1. Making the diagnosis of myelodysplastic syndromes.

Diagnostic element	Finding	Comments
History (suggestive)[1,3,6,13,14,16-18]	Weakness and fatigue	Associated with anemia
	Shortness of breath/angina	Associated with anemia
	Recurrent infections	Associated with neutropenia
	Bruising, bleeding	Associated with thrombocytopenia
	Family history of BM disease	
	History of chemo/radiation therapy	
Physical examination (suggestive)	Pallor	Associated with anemia
	Splenomegaly	In CMML
Routine laboratory tests[1,8,10,14,15,18-20]	Anemia	
	MCV elevation	
	RDW widening	
	Leukopenia	
	Neutropenia	
	Thrombocytopenia	
	Monocytosis	
	Elevated CRP/ESR	
	Normal chemistry	Unless comorbidity
Bone marrow, mandatory[3,7,8,10,11,16]	Cellularity (general) Hypo, hyper, normal	Typical, but not diagnostic
	Cell number in each lineage	Helpful, but not diagnostic
	Dysplasia in any line	Mandatory for diagnosis
	Blast percentage	For diagnosis and prognosis
	Ring sideroblasts	In sideroblastic anemia
	Monocytosis	In CMML
	Cytogenetics	For diagnosis and prognosis
Bone marrow, recommended[3,7,13,24,42,48,61]	Flow cytometry	Helpful
	Genetics, somatic	Increasingly used
	Genetics, germline	When familial disease is suspected

BM: bone marrow; CMML: chronic myelomonocytic leukemia; MCV: mean corpuscular volume; RDW: red cell distribution width; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

patient's history may reveal prior exposure to radiation or chemotherapy, or a familial predisposition to hematologic disease.[16,17]

A thorough history can help to rule out conditions such as paroxysmal nocturnal hemoglobinuria, aplastic anemia, and MPN that may mimic MDS clinically.[3,16,17]

Physical examination is usually non-specific and with no abnormal findings. For details, please see Table 1.

Laboratory findings

Table 1 lists the laboratory abnormalities that are typical, yet not specific for patients with MDS. C-reactive protein levels and erythrocyte sedimentation rate can be elevated.[18] At least 90% of MDS patients will be anemic, and ~50% of them will have a hemoglobin concentration of less than 10 g/dL.[10,14] The anemia is usually mildly macrocytic[1,3,8] with an increased red cell distribution width.[19,20] Reflecting the BM dysfunction that characterizes MDS, patients usually do not have an increased reticulocyte count, in contrast to patients with hemolytic anemia.[16] Table 1 lists other laboratory findings.

Serum chemistry is usually normal unless there is a comorbidity associated with anemia. Serum iron and iron saturation as well as serum ferritin can be elevated in the sideroblastic subtype. It is important to exclude nutritional deficiencies, especially folic acid and vitamin B12 deficiency, both of which can cause macrocytic anemia. Blood chemistries can also rule out underlying liver or kidney disease. Hepatitis B and C, cytomegalovirus, human immunodeficiency virus and parvovirus B19 infections must be ruled out.

The PB smear is usually non-specific, but it might show features consistent with disease. For example, the red blood cells (RBC) might have anisocytosis or poikylocytos,[8] and sometimes there may be nucleated RBC. The white blood cells may include an increased number of immature myeloid cells ("left shift") with hypolobulation ("Pelger"-like cells) and hypogranulation. PB platelets might be distorted, clumped, and big (megaplatelets), in addition to being present in low number. Persistent monocytosis suggests CMML,[8,16] on the assumption that other etiologies for monocytosis have been excluded. The PB smear

is especially helpful in that it may uncover a disease other than or in addition to MDS. For example, thrombocytosis or leukocytosis would suggest an MPN, or at least an overlap MDS/MPN syndrome.

Altogether, the combination of symptoms and laboratory findings along with the exclusion of other causes of anemia/cytopenia, raises the suspicion of MDS (Table 1), but other investigations are required in order to establish the diagnosis of MDS.

Bone marrow examination

The next step in the workup of an unexplained anemia (or cytopenia) is a BM examination, still the gold standard for the diagnosis of MDS (Table 1).

Bone marrow aspirate

A BM aspirate (stained with May-Grünwald-Giemsa) is essential to assess the morphology of individual cells.[3] The typical findings of MDS in the aspirate include dysplasia in any lineage as well as possible hyperplasia or hypoplasia. The cellularity, however, is best estimated with a biopsy. Blasts may have granules or Auer rods, and they are counted and reported as percentage of nucleated BM cells. The smears are also stained for iron (Prussian blue) to assess for the presence of ring sideroblasts.[8] The BM aspirate is also the substrate of special tests to exclude MDS and to establish the diagnosis of another hematologic disorder. Figure 1 provides pictures of BM abnormalities in MDS.

Bone marrow trephine biopsy

A BM biopsy is important for evaluating the BM cells in their milieu. This is where the cellularity can be assessed more accurately, although this parameter has not been found to be critical for either the diagnosis or prognosis or MDS.[3,8,21] BM biopsy might also identify fibrosis, which is found in the World Health Organization (WHO)-defined entity MDS with fibrosis (MDS-f).[11] BM biopsy is less reliable than the aspirate for evaluating the morphology of single cells or for assessing the blast count.[3,16] Importantly, BM histology may reveal metastatic disease from non-hematopoietic malignancies and granulomas suggestive of sarcoidosis or an infectious process.

Bone marrow studies as the gold standard for the diagnosis of myelodysplastic syndromes

In summary, BM examination, especially the dysplastic features and blast percentage is mandatory for establishing a diagnosis of MDS. Moreover, once diagnosed, the BM findings and especially the blast percentage further assist in categorizing and predicting the patient's prognosis ac-

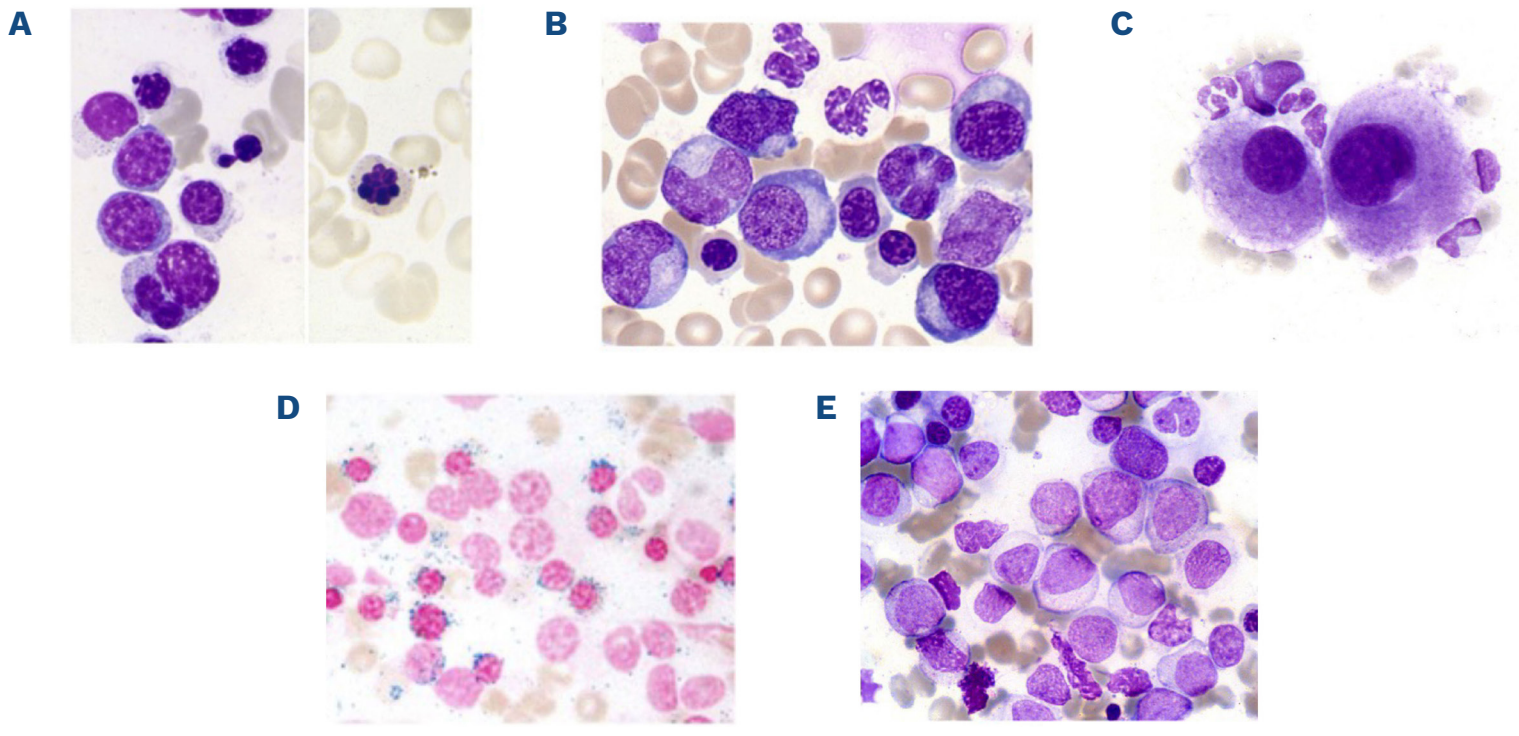

Figure 1. Pictures of various bone marrow cytologic abnormalities in myelodysplastic syndromes. (A) Dyserythropoiesis. Bone marrow smear. *Left*. A trinucleated erythroblast with distinctly separated nuclei of different sizes, an erythroblast containing a Howell-Jolly body and an erythroblast with a curiously lobulated nucleus. Late erythroblasts show ill-defined borders. *Right*. A late erythroblast with a budding nucleus and basophilic stippling. (B) Dysgranulopoiesis. Bone marrow smear. Two neutrophils with empty cytoplasm, one of which has a comb-shaped nucleus. Erythroblasts with megaloblastoid changes, and blast cells are also present. (C) Dysmegakaryopoiesis. Bone marrow smear. Large megakaryocytes with a single large round or oval eccentric nucleus and granular cytoplasm. These are consistent with myelodysplastic syndrome (MDS) with isolated del(5q). (D) MDS with ring sideroblasts, single lineage dysplasia. Bone marrow smear, high magnification, Perls' reaction. Several ring sideroblasts are evident. (E) MDS with excess blasts type 2. Bone marrow smear showing marked erythroid hypoplasia and granuloblastic hyperplasia with increased blasts cells. At the top right, there is a mature neutrophil that is agranular with abnormal nuclear segmentation. Figures reproduced, with permission, from the *Haematologica Atlas of Hematologic Cytology*.[99]

cording to the various classifications.[4,8,9,11] Finally, the blast percentage also distinguishes between higher-risk MDS and acute leukemia, although the dividing line between these two entities has recently been blurred because acute leukemia may be confirmed with blast counts from 10% to 30% depending on genetic signatures.[4,8,11,12]

While in the year 2024, evaluation of BM morphology and specific staining is still the gold standard for MDS diagnosis, there are several limitations to this diagnostic method. It is subjective, being dependent upon the person (hematologist/pathologist) who provides the interpretation. In addition, because the BM is not homogeneous throughout, the quality of the diagnosis depends on where the BM was sampled (sampling error). As such, additional data must be gathered from the BM examination, including those obtained by flow cytometry and cytogenetic and genetic studies. In addition, there is increasing evidence that the PB can be used for MDS diagnosis (see the section on "Novel approaches to diagnose myelodysplastic syndromes" below).

Multiparameter flow cytometry

Multiparameter flow cytometry (MFC) of BM may contribute to optimizing and refining the diagnosis and classification of myeloid neoplasms.[3,22-24] MFC enables the evaluation of differentiation antigen features that are different-from-normal with respect to an altered distribution of cell subsets or altered levels of antigen expression.[25] Aberrant antigen expression includes over- or under-expression, gain or loss of expression, lineage infidelity, and asynchronous expression of differentiation markers. The International and European LeukemiaNet Working Group focusing on standardization of MFC in MDS (iMDSFlow) has recently published several reviews and guidelines.[22,25,26]

The most important markers for the diagnosis of MDS are CD45, CD34, HLA-DR, CD117, CD13, CD33, CD10, CD11b, CD16, CD15, CD14, CD64, CD123, CD7, CD19, CD56 and CD71 next to light scatter properties i.e., forward scatter and side scatter (SSC) (Table 2).[25,27,28] Analysis of the myelomonocytic lineage encompasses myeloid progenitors, neutrophils and monocytes. The percentage of myeloid progenitors is one of the diagnostic parameters in the MFC assessment of BM and/or PB specimens.[29] An increase in myeloid progenitors over 2% of the total nucleated BM cells is commonly observed in MDS. A 3% level of myeloid progenitors, identified by MFC, is a critical cut-off above which most cases are MDS or MDS/MPN.[30] A key feature of granulocytic cells in MDS is hypogranulation, which is reflected by a decrease in SSC. Maturation from myeloid progenitor cells towards segmented neutrophils can be tracked by the levels of expression of HLA-DR, CD117, CD13, CD11b and CD16, allowing the distinction between aberrant and disturbed neutrophil differentiation. Neutrophils in MDS may aberrantly express markers such as CD14, CD56 and CD71. CD56 expression on neutrophils often coincides with that on monocytes. MFC analysis of the monocytic lineage in MDS and MDS/MPN can be useful since dyspoiesis in these cells may be difficult to identify by morphology. Combinations of antibodies to CD11b and HLA-DR, or CD14 or CD300e with CD36 and/or CD64 enable the discrimination of immature and mature stages of monocytic cells.[25,31] CD14 can be (partly) lost due to the existence of a paroxysmal nocturnal hemoglobinuria clone.[32] Aberrancies in monocytes may also concern a homogenously increased expression or loss of CD13 and the presence of CD2 and CD56. In CMML, a cut-off of ≥94% for the presence of PB classical monocytes, defined as $CD14^{+}CD16^{-}$ cells has been recognized as a diagnostic criterion for patients with more than $1x10^{9}$/L monocytes.[33-35] This criterion may be affected by inflammatory conditions. In such cases, percentages of non-classical monocytes ($CD14^{dim}CD16^{+}$) or $Slan^{+}$ monocytes below 2.5% and 1.7%, respectively, may still point to a diagnosis of CMML.[36] Monocyte subsets in BM often mirror those in the blood.[35] However, only results in blood are considered diagnostic. Erythroid cells are selected based on their $CD45^{neg/dim}$, low/medium SSC profile and absence of myeloid markers. Erythroid lineage aberrancies in MDS may be an increased number of nucleated erythroid cells, an abnormal proportion of erythroid differentiation stages and altered expression levels of CD36, CD71 and CD105.[37-39] An increased erythroid SSC was most frequently observed in MDS with ring sideroblasts.[40,41]

Table 2. Antibodies recommended by the International and European LeukemiaNet Myelodysplastic Syndrome Flow Cytometry Working Group for flow cytometric analysis of bone marrow cells of various cell types in patients with cytopenia suspected of having myeloid neoplasms (modified from van de Loosdrecht *et al.*,[22] Porwit *et al.*,[25] and van der Velden *et al.*[26]).

Cell subset	Backbone markers	Recommended markers	Optional
Myeloid progenitor cells	CD45, CD34, CD117, HLA-DR	CD13, CD33, CD10, CD11b, CD15, CD38, CD7, CD56	TdT, CD5, CD19, CD25, CD133
Lymphoid progenitor cells	CD45, CD34	HLA-DR, CD10, CD19	CD22
Granulocytic cells	CD45, CD117	HLA-DR, CD13, CD33, CD11b, CD16, CD10, CD15, CD14, CD64, CD56	CD34, CD5, CD7
Monocytic cells	CD45	HLA-DR, CD13, CD33, CD11b, CD14, CD34, CD36, CD64, CD16, CD56, CD117	CD2, MDC8 (Slan), CD300e
Erythroid cells	CD45, CD34, CD117	HLA-DR, CD36, CD71, CD105, CD13, CD33	CD235a

Evaluation of dyspoiesis in the megakaryocytic lineage by MFC is limited since megakaryoblasts are too large and too infrequent for reliable analysis.

A four-parameter diagnostic score also known as the Ogata score was designed for a simple MFC test for MDS.[42] This score consists of four parameters: neutrophil SSC (defined as a ratio to lymphocyte SSC, for internal reference), $CD34^+$ myeloid progenitor percentage among all nucleated cells, $CD34^+$ B-cell precursor percentage among all $CD34^+$ cells and myeloid progenitor CD45 expression as an inverse ratio to lymphocyte CD45 expression. Specificity and sensitivity were shown to be approximately 93% and 70%, respectively. The addition of CD7 and/or CD56 expression on myeloid progenitors and/or CD56 expression on monocytes may increase sensitivity while specificity remained similar. The integrated flow score (iFS) in which the Ogata score is combined with MFC aberrancies of immature and maturing myeloid cells and aberrancies of immature and maturing erythroid cells further improved the diagnostic utility for MDS.[43] This model categorizes three scores, i.e. A, B or C which respectively represent no MFC aberrancies, minimal MFC aberrancies not enough to consider MDS, and MFC aberrancies compatible with MDS. A study that compared several diagnostic MDS-MFC scores identified iFS as the most sensitive and specific diagnostic scoring model to date.[44] Finally, a recent iMDSFlow multicenter study revealed that the aberrancies most informative for the diagnosis of MDS were: (i) aberrant myeloid progenitor percentage, aberrant expression levels of CD45, CD117, HLA-DR, CD13 and aberrant expression of CD5, CD7 and/or CD56; (ii) aberrant granulocyte percentage (as a ratio to lymphocytes), lowered SSC, CD33 expression and CD13/CD16 pattern; (iii) aberrant monocyte percentage, SSC, CD13 and CD56 expression and HLA-DR/CD11b ratio; and (iv) erythroid cell aberrant CD71 expression. Three or more of these aberrancies were associated with the diagnosis of MDS.[30] Reporting MFC results in MDS should be done in an integrated diagnostic report. The iMDSFlow group provided an algorithm for the work-up of patients with cytopenia suggestive of myeloid neoplasms that is easy to implement in daily laboratory practice.[22] Addition of MFC results to cytomorphology in inconclusive cases, or if smears are of poor quality, can support a diagnosis of MDS or suggest thorough clinical follow-up.

Cytogenetics

Cytogenetic studies are performed with a combination of G-banding and fluorescence *in situ* hybridization techniques. While cytogenetic studies may not be required to establish a diagnosis of MDS, no diagnostic workup is complete without performing them[3,7,10] (Table 1). At least 20 cells in metaphase should be examined. Thus, applying cytogenetics with the typical chromosomal abnormalities assists in the diagnosis. Common cytogenetic findings in MDS are partial or complete deletion of chromosomes 5 and 7, and trisomy 8.[45] Cytogenetics is even more important in predicting prognosis.[9,10] In the WHO 2016 classification of MDS the use of cytogenetics is important for diagnosis especially where dysplasia is not seen at all, is less than 10% in all cell lineages, or is equivocal. Such patients were then regarded as MDS-unclassifiable.[4] In the current classification systems, this has been replaced by incorporation of clonal cytopenia of undetermined significance,[11,12] but the principle is the same.

Genetics

Over the last decades, it has become clear, as in other malignancies, that genetic mutations are responsible for the development of the malignant clone(s) in MDS and these genetic signatures control the disease course (Table 1).[46] We know today that 90% of MDS patients do harbor myeloid mutations,[3,47-50] with an average of two or three mutations per patient at MDS diagnosis. Mutations in many genes are seen in MDS, but seven genes are involved in at least 10% of MDS patients: *SF3B1*, *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, *RUNX1*, and *TP53*.[7,49-60] In contrast to other hematologic neoplasms, chronic myeloid leukemia or chronic lymphocytic leukemia for example, introduction of genetic studies into clinical practice, both for diagnostic and prognostic purposes,[61] is still in its infancy in MDS. Several tough hurdles still prevent broad genetic application.[7,48,49,62-65] We have learned that not all mutations are equal. There are driver mutations of greater clinical importance, and there are other mutations which are just passengers. The variant allele frequency and the hotspot of the mutation appear to be important. The function of mutations as well as the occurrence of co-mutations and gene-gene interactions are still not fully elucidated.

There are some situations in which the genetic signature is very important in diagnosis. For example, *SF3B1* defines MDS with ring sideroblasts. Also, mutations in *NPM1* or *FLT3* differentiate acute myeloid leukemia from MDS.[66,67] The recent work on MDS taxonomy might further characterize MDS subgroups and their correlation with specific genetic signatures.[68]

In most other situations, no mutations have yet been found to be unique to or diagnostic for MDS.[11,12,16] Moreover, these mutations have been found in healthy aging people too, and most of them will never develop a myeloid neoplasm, a phenomenon referred to as age-related clonal hematopoiesis (ARCH),[69,70] or clonal hematopoiesis of indeterminate potential (CHIP).[71,72] It should be noted that the genes commonly mutated in CHIP are *DNMT3A*, *TET2*, and *ASXL1*, while mutations in splicing genes (*SF3B1*, *SRSF2*, *U2AF1*) are less common in CHIP.

A relatively new area is the germline mutation in MDS. Until several years ago we looked at germline mutations as a pediatric problem. It is now understood that several such

mutations (e.g., *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, and *GATA2*[73]) may result in a clinical phenotype detected only at an adult age. For example, MDS with *DDX41* mutations is seen in patients with a median age of around 65 years.[74] The challenges we face now are how to detect these individuals, how to follow and manage them, and most importantly which family members to screen. We expect to have some of the answers within the next few years.

In summary, one cannot underestimate the role of genetics in diagnosis, as well as in pathogenesis and prognosis,[49,50,61] but in 2024 we are still at the beginning of this era, and the genetic profile, although routinely determined in many parts of the world, is still not a mandatory tool in the diagnostic workup. The cost of next-generation sequencing is progressively declining, but the test is still not accessible to all. This and the relative paucity of those with professional skills to perform this analysis further prevent its widespread application.

It should be noted that some mutations found in MDS already serve as targets for treatment and as markers of treatment response. Examples are APR-246 targeting mutant *TP53*,[75] the IDH1/2 inhibitors,[76] and luspatercept for patients with *SF3B1* mutations.[77]

For more details on genetics and MDS, the reader is referred to the review by Cazzola and Malcovati in this issue of *Haematologica*.[50]

Pre-myelodysplastic syndrome states

Several pieces of evidence suggest that MDS develops over time,[78] during which the malignant clone evolves before the clinical disease is diagnosed. The occurrence of myeloid mutations in healthy individuals with a higher tendency to evolve further into full-blown myeloid diseases, especially MDS, further supports this concept.[69,70] Like other hematologic neoplasms with pre-malignant states, such as multiple myeloma (monoclonal gammopathy of undetermined significance) and chronic lymphocytic leukemia (monoclonal B-cell lymphocytosis), pre-MDS states are recognized too. These entities include idiopathic cytopenia of undetermined/unknown significance (ICUS), and many of these patients end up being classified as having clonal cytopenia of unknown significance (CCUS). ICUS is characterized by cytopenia without a known cause and not fulfilling minimal criteria to establish a diagnosis of MDS.[79-81] In CCUS, a clonal myeloid mutation is observed, with some overlap with ARCH and CHIP,[71] however, it (still) cannot be defined as MDS. There may also be dysplasia without cytopenia (IDUS, idiopathic dysplasia of unknown significance),[79,82] and BM clonal changes without cytopenia.

It makes sense to diagnose these pre-MDS states. Although therapeutic interventions are currently unavailable, one can foresee that in the future, less invasive biological technologies will enter the clinic. It is likely that establishing the diagnosis of pre-MDS and risk stratification will require genetic studies, including identification of germline mutations. However, one cannot ignore the social, ethical, and financial considerations associated with this approach.

Novel approaches to diagnose myelodysplastic syndromes (and avoid bone marrow examination)

BM morphology is still the gold standard to diagnose MDS. Many still believe that the information obtained, including the morphological findings and the blast percentage cannot be replaced by any other method. However, there are some significant limitations. This examination is invasive and painful, and morphological evaluation is somewhat subjective with high inter-observer variation.[83] Sometimes the BM aspirate is a "dry tap" so only the biopsy can be evaluated, and at times a second attempt is required. For all of these reasons diagnostic methods that replace the BM evaluation without compromising diagnostic accuracy are a high priority. At this point in time, although emerging methods are promising, the technologies are still considered investigational. Here we examine three approaches: (i) modeling using readily accessible patient data; (ii) automated morphology assessment of PB smears; and (iii) genetic information taken from the PB.

Modeling

The first approach applies digital tools comparing numerous data collected from large numbers of patients to data obtained from healthy subjects. We first compared such clinical and laboratory data from 48 MDS patients to those from 63 non-MDS controls, all of whom had had a BM examination. A logistic regression model was applied using six variables that were found to be relevant and influential: gender, age, hemoglobin concentration, mean red blood cell corpuscular volume, platelet count, and white blood cell count.[84] This led to a formula that could be used for any individual suspected of having MDS. The output was a score from 0 to 1. Cases with a score ≥0.633 were classified as probable MDS and those with a score ≤0.288 were considered as probably not MDS. Any individuals falling between these two cutoff scores had an indeterminate status. Upon validation, we found that approximately 50% of the patients were classified correctly as either probable MDS or probably not MDS, and almost all the rest were classified as indeterminate.

We then improved the model using an expanded pool of patients in collaboration with the European MDS (EUMDS) group, and studied 178 MDS patients and 178 controls.[85] We also improved the methodology and used a gradient boosted model (GBM) instead of the logistic regression model. The same six variables were incorporated into the model.

In the third stage of the model, we continued with the GBM methodology, adding four more variables (neutrophil,

monocyte, glucose, and creatinine levels) and used a total of 501 MDS patients (again from the EUMDS registry) and 501 controls to build the model.[86]

We used the same three group classifications, probably MDS, probably not MDS, and indeterminate and found that we could predict or rule out MDS in over 80% of patients with unexplained anemia with an area under the receiver operator characteristics curve (AUC) of 0.96. Figure 2 shows that AUC curves and their improvement with each of the three stages of development of the model: the logistic regression, the original GBM and the improved GBM.

Figure 3 demonstrates the use of the model in individual patients with three examples. A patient's data are entered for all ten variables, and when the "calculate" button is pressed the GBM score is calculated. The blue line reflects the score: if the GBM score is ≥0.82, then a probable MDS is predicted (Figure 3A); with a GBM score <0.68 the case is probably not MDS (Figure 3B). The category for any scores between these is considered indeterminate (Figure 3C).

We recently validated the model using data from patients and controls who had not been included in the development of the model.[87] Furthermore, using data from a different center, the Düsseldorf group performed external validation, demonstrating that the model is especially useful in ruling out MDS.[88]

Automated morphology assessment

Another approach that is being examined is automated assessment of morphology in smears of PB in a collaboration between The Tel Aviv Sourasky Medical Center and Scopio laboratories. This method uses full-field morphology technology and analyzes blood smears at a significantly larger scale of 1,000 fields at 100X view in a routine manner. This allows for high sensitivity, precision, and automated quantification of many cellular and subcellular morphological parameters.[89]

In a study evaluating the method's ability to detect MDS, the following parameters were assessed: blast number, neutrophil cytoplasmic granulation, and RBC morphology. In addition, a quantitative granulation index and distribution width were given. RBC measurements included the quantitative measurements of RBC size and contour changes (deformation), i.e., the percent of RBC that deviates from normal RBC shape. This full-field morphology-based digital analysis of PB smears has the potential to enable the detection and quantification of unique morphological alterations of red and white blood cells that are associated with MDS.[90] The technology has also been studied with BM aspirates.[91] and to detect PB chimeric antigen receptor T transduced cells following engagement with target cells.[92]

Other methods include assessment of neutrophil morphology using interferometric phase microscopy and fluorescent flow cytometry to detect high-risk MDS.[93] Technology using computer vision to enable rapid and accurate quantitation of RBC morphology has been studied in thrombotic microangiopathy,[94] and could perhaps be broadened to assess other RBC abnormalities as seen in MDS.

These technologies allow for a diagnosis that is rapid, hopefully more accurate and objective, as well as a diagnosis from PB rather than from the BM.

Peripheral genetics

The third approach to obviate the BM examination in diagnosing MDS is based on the assumption that most relevant information, especially genetics, can be found in the PB. What is needed is an appropriate technique to identify it. One example is the work recently presented by Shlush's team from the Weizmann Institute. Using single-cell RNA sequencing on purified PB CD34$^+$ hematopoietic stem and progenitor cells they were able to create maps of hematopoiesis, in which every cell is characterized and placed in its location on the map, providing a robust method to identify cells with aberrant genetic makeup. In the case of MDS, patients with either MDS or pre-MDS states could be identified.[95] Work is continuing along this line to fully characterize MDS states and to validate the use of this method clinically.

Other work has shown the strong correlation between the BM and PB genetic profiles. Jansko-Gadermeir *et al*. demonstrated a concordance above 99% with sample pairs analyzed by next-generation sequencing in myeloid disease,[96] and Jumniensuk *et al*. demonstrated concordance of 99% in myeloid neoplasms, and 87% in lymphoid neoplasms.[97] Using data from the National MDS Study, DeZern *et al*. found a good correlation between BM and PB genetics when the

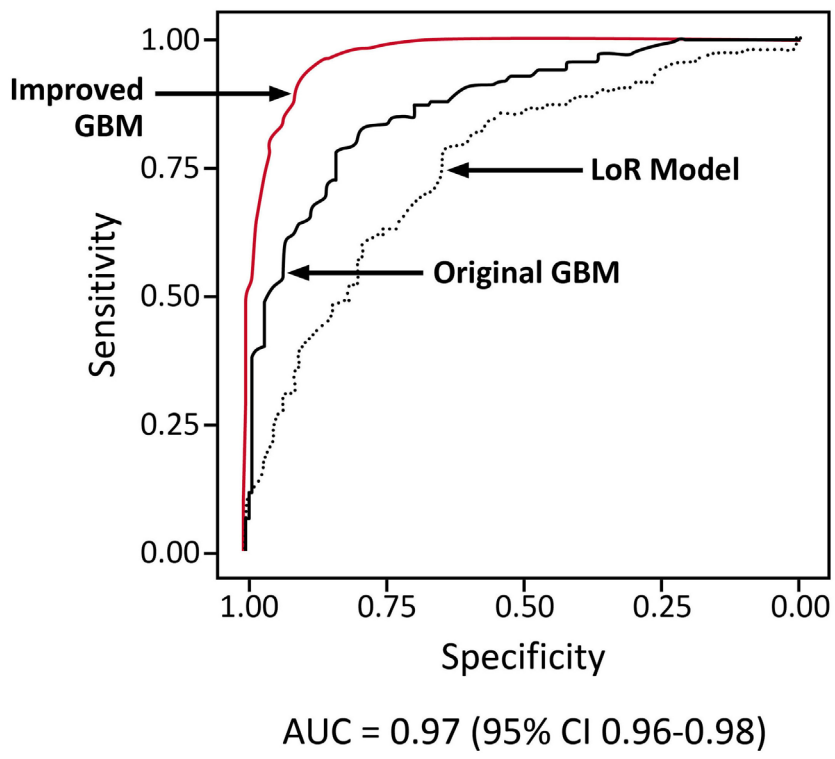

Figure 2. Areas under the curves for the non-invasive model for the diagnosis of myelodysplastic syndrome. The three curves reflect three stages of the development of the model: (i) the logistic regression model,[84] (ii) the original gradient boosted model (GBM), and (iii) the improved GBM. Note that the area under the curve (AUC) improves progressively with each stage; the AUC for the improved GBM is 0.97.[86] LoR: logistic regression; 95% CI: 95% confidence interval.

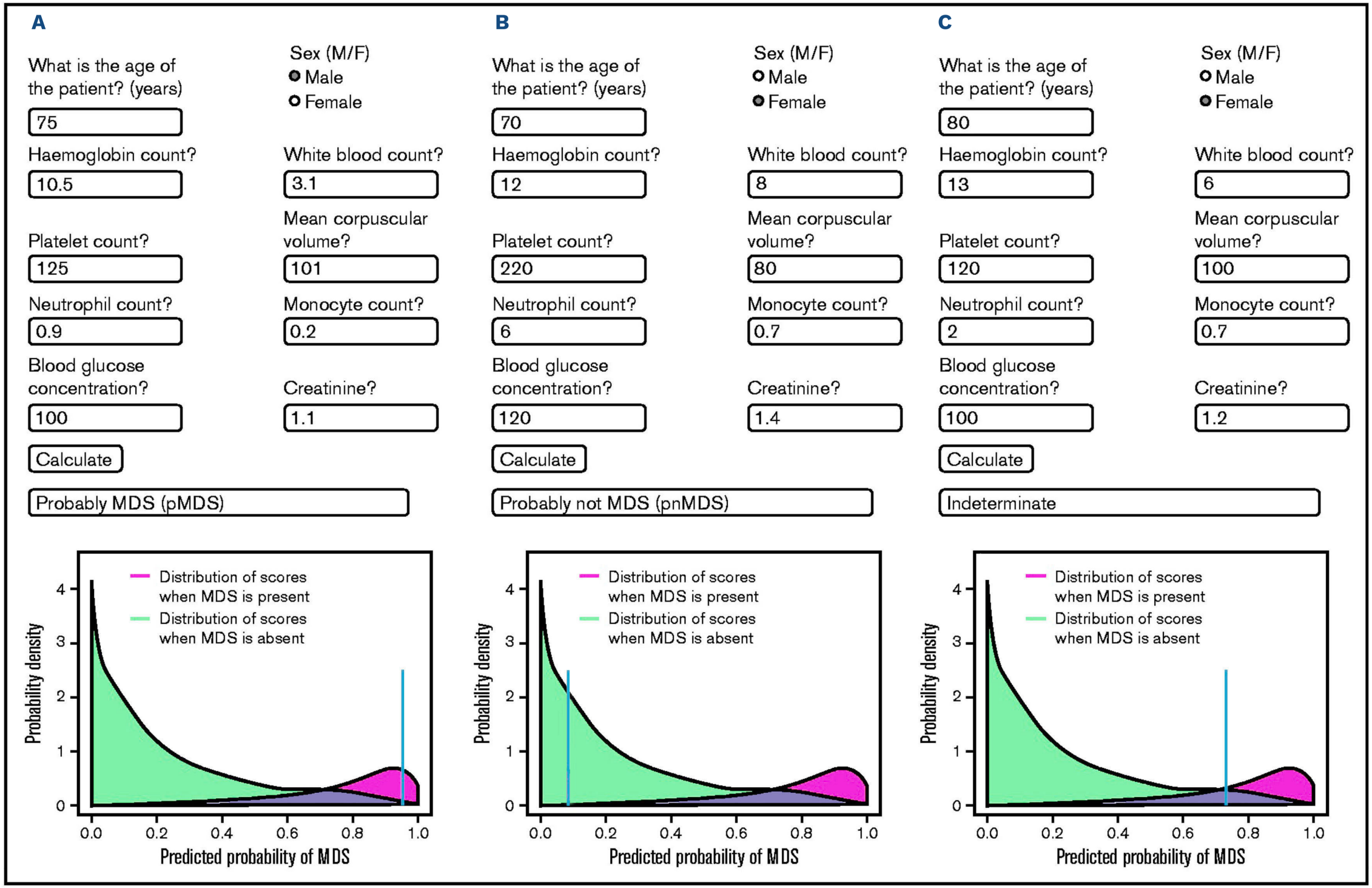

Figure 3. Three examples of the predictive model in practice. The app is online at: *https://shiny.york.ac.uk/mds*. Values for a given patient's variables are entered into the appropriate spaces, and the "calculate" button is pressed. The blue line indicates the probability of the patient having a myelodysplastic syndrome (MDS). (A) A patient with a probable MDS, with the blue line within the red region. (B) A patient who probably does not have MDS, with the blue line within the green region. (C) A patient with an indeterminate diagnosis (blue line within the lavender region). From Oster *et al*. 2021.[86]

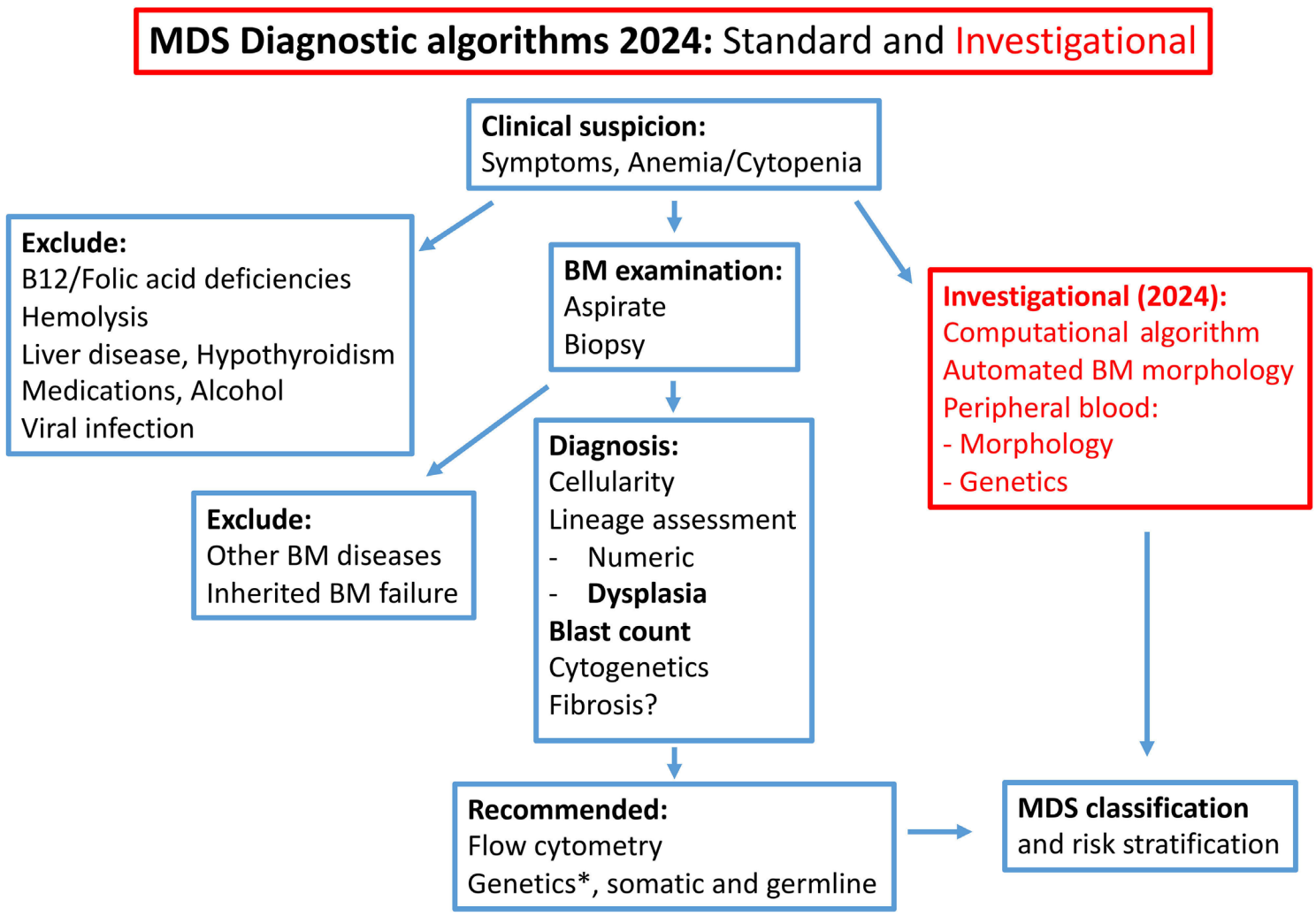

Figure 4. Diagnostic algorithm for myelodysplastic syndromes as of 2024, including both standard and investigational methods.
*Especially disease-defining mutations (e.g., *SF3B1*). BM: bone marrow; MDS: myelodysplastic syndrome.

variant allele frequency of the BM mutation was high.[98]
The authors of the Molecular International Prognostic Scoring System (IPSS-M),[61] who added genetic information to prognostic features, have developed a molecular taxonomy, an MDS classification system that divides patients into 18 distinct groups.[68] While the IPSS-M and this extension of taxonomy are primarily for the purpose of prognostication, they may turn out to be a useful tool as part of the diagnosis. Moreover, because much of the genetic information is becoming more accessible from the PB, it stands to reason that this method could be an important part of the diagnosis of MDS.
All of these approaches are still investigational and are not the standard for MDS diagnosis. However, it is likely that such non-invasive methods will reduce and perhaps obviate the need for BM evaluations in many patients.

Conclusion

At present, certain tests are mandatory in order to establish the diagnosis of MDS, the foremost being the BM examination (aspirate and/or biopsy), which determines whether there is dysplasia in one or more cellular lineage. It is also important for the enumeration of blasts, as well as exclusion of other reasons for anemia/cytopenia. Cytogenetics is also an essential part of the diagnostic process. A suspicious clinical picture, macrocytic anemia (or cytopenia), PB abnormalities, presence of BM ring sideroblasts, characteristic flow cytometry and myeloid somatic mutations as well as other genetic assays are helpful and recommended but not critical for the diagnosis of MDS. Figure 4 summarizes the steps necessary (and recommended) for making the diagnosis of MDS, and also summarizes experimental modalities. It is very likely that in the near future, non-invasive techniques, such as diagnostic modeling, digital computational analysis and PB genetics, individually or in combination, will become part of general practice in the diagnosis of MDS.

Disclosures
No conflicts of interest to disclose.

Contributions
HSO and MM collected information and wrote most of the sections of the manuscript. AAvdL summarized information and wrote the section on flow cytometry.

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