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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 bone marrow (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 labs, but the gold standard for MDS diagnosis 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 MDS diagnosis.

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 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.[3,6,7] Patients with MDS are classified using one of several scoring systems.[8-12] Most patients are assigned to the lower-risk (LR) or higher-risk (HR) 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 entity of MDS/MPN, and 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 for MDS

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 1a),[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 platelets count is low or if the platelets do not function normally.[15]

Other causes of anemia or other cytopenias must first be ruled out. 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 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 myeloproliferative neoplasms (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 1b.

Laboratory findings: Table 1c lists laboratory abnormalities that are typical, yet not specific for patients with MDS. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be elevated.[18] At least 90% of MDS patients will be anemic, and ~50% of them will have Hb less than 10g/dl.[10,14] The anemia is usually mildly macrocytic[1,3,8] with an increased red cell distribution width (RDW).[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] See Table 1c for 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, CMV, HIV and parvovirus B19 infections must be ruled out.

The peripheral blood (PB) smear is usually non-specific, but it might have findings consistent with disease. For example, the red blood cells (RBC) might have anisocytosis or poikylocytos,[8] and sometimes there may be nucleated RBCs. The WBC can have an increase in the number of immature myeloid cells ("left shift") with hypolobulation ("Pelger"-like cells) and hypogranulation. PB platelets might be distorted, clumped, big (megaplatelet), in addition to the 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 (see below).

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

Bone marrow examination – the gold standard for MDS diagnosis

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

BM aspirate: The BM aspirate (May-Grünwald-Giemsa stain) 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 the 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 ringed sideroblasts (RS).[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.

BM trephine biopsy: The 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 MDS diagnosis or prognosis.[3,8,21] BM biopsy might also identify fibrosis, which is found in the entity MDS with fibrosis, MDS-f (WHO).[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.

In summary, BM examination, especially the dysplastic features and blast percentage is mandatory for establishing an MDS diagnosis. Moreover, once diagnosed, these BM findings and especially the blast percentage further assist in categorizing and predicting the patient's prognosis according to the various classifications.[4,8,9,11] Finally, the blast

percentage also distinguishes between HR-MDS and acute leukemia, although the line between these two entities has most 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, BM evaluation of morphology and specific staining is still the gold standard for MDS diagnosis, there are several limitations with this diagnostic method. It is subjective, 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 bone marrow was sampled (sampling error). As such, additional data must be gathered from the BM examination, including flow cytometry, cytogenetics and genetics. In addition, there is increasing evidence that the peripheral blood can be used for MDS diagnosis (see "Novel approaches to diagnose MDS" 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 include over- or under-expression, gain or loss of expression, lineage infidelity, asynchronous expression of differentiation markers. The International and European LeukemiaNet Working Group focusing on standardisation of MFC in MDS (iMDSFlow) has published several recent 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) (see Table 2).[25,27,28] Analysis of the myelomonocytic lineage encompasses myeloid progenitors (MyPCs), neutrophils and monocytes. The percentage of MyPCs is one of the diagnostic parameters in the MFC assessment of BM and/or PB specimen.[29] An increase in MyPCs over 2% of total nucleated BM cells is commonly observed in MDS. A 3% cut-off level of MyPCs by MFC is critical 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 side scatter (SSC). Maturation from MyPCs towards segmented neutrophils can be tracked by expression levels of HLA-DR, CD117, CD13, CD11b and CD16, allowing to distinguish 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 instrumental 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 PNH 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 1.109/L monocytes.[33-35] This criterion may be affected by inflammatory conditions. In such cases, percentages of non-classical monocytes (CD14dimCD16+) 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 CD45neg-to-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] Evaluation of dyspoiesis in the megakaryocytic lineage by MFC is limited since megakaryoblasts are too large and too infrequent for reliable analysis.

The four-parameter diagnostic score also known as the Ogata score was designed for a simple MFC test for MDS.[42] This score consists of 4 parameters: neutrophil SSC (defined as a ratio to lymphocyte SSC, for internal reference), CD34+ MyPC percentage among all nucleated cells, CD34+ B-cell precursors percentage among all CD34+ cells and MyPC 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 MyPCs 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 of 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 multicentre study revealed that the aberrancies most informative for the diagnosis of MDS were: i) aberrant MyPCs percentage, aberrant expression levels of CD45, CD117, HLA-DR, CD13 and aberrant expression of CD5, CD7 and/or CD56 expression, ii) aberrant granulocyte percentage (as 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*:* Cytogenetics is performed with a combination of G-banding and FISH techniques. While it may not be required to establish MDS diagnosis, no diagnostic workup is complete without performing it[3,7,10] (Table 1d). 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 was 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 (CCUS),[11,12] but the principle is the same.

Genetics: Over the last decades, it has become clear that like other malignancies, genetic mutations are responsible for the development of the malignant clone(s) in MDS and these genetic signatures control the disease course (Table 1e).[46] We know today that 90% of MDS patients do harbor myeloid mutations,[3,47-50] with an average of 2-3 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, CML or CLL for example, introduction of genetics into clinical practice, both for diagnosis and prognosis[61] is still in its infancy. 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 (VAF) and the hotspot of the mutation appears to be important. The function of mutations as well as occurrence of co-mutations and gene-gene interaction is still not fully elucidated.

There are some situations where the genetic signature is very important in diagnosis. For example, SF3B1 defines MDS with ring sideroblasts. Also, mutations in NPM1 or FLT3 differentiate AML 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 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, GATA2[73]) may result in a clinical phenotype detected only at an adult age. For example, MDS with DDX41 is seen with a median age of around 65.[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 the pathogenesis and prognosis,[49,50,61] but in 2024 we are still in the beginning of this era, and the genetic profile, although routinely performed in many parts of the world, is still not a mandatory tool in the diagnostic workup. The cost of next generation sequencing (NGS) 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 wide application.

It should be noted that some mutations found in MDS already serve as targets for treatment and as a marker 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, refer to the review of Cazzola and Malcovati in this issue.[50]

Pre-MDS states:

Several pieces of evidence suggest that MDS develops over time[78] in 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 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 with clonal cytopenia of unknown significance (CCUS). ICUS is characterized by cytopenia without a known cause and not fulfilling minimal criteria to establish an MDS diagnosis.[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 MDS (and avoid BM 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” where 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: 1) modeling using readily accessible patient data, 2) automated morphology assessment of peripheral blood smears, and 3) genetic information taken from the peripheral blood.

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 lab data of 48 MDS patients to those of 63 non-MDS

controls, all having had a BM examination. A logistic regression (LoR) model was applied using 6 variables that were found to be relevant and influential: gender, age, hemoglobin (HB), mean red blood cell corpuscular volume (MCV), platelet (PLT), and white blood cell (WBC) counts.[84] This led to a formula that could be used for any individual suspected of MDS. The output was a score from 0 to 1. Subjects with a score ≥0.633 were classified as probable MDS (pMDS), and those with a score ≤0.288 were considered probably not MDS (pnMDS). 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 pMDS or pnMDS, and almost all the rest were classified as indeterminate.

We then improved the model using an expanded patient pool in collaboration with the European MDS (EUMDS) group, and used 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 6 variables were incorporated into the model.

In the third stage of the model, we continued with the GBM methodology, added 4 more variables (neutrophils, monocytes, glucose, and creatinine) 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 3 group classifications, pMDS, pnMDS, 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 (ROC) curve (AUC) of 0.96. Figure 2 shows that AUC curves and their improvement with each of the three stages of the model development: the LoR, the original GBM and the improved GBM models.

Figure 3 demonstrates the use of the model in individual patients with 3 examples. Patient data is entered for all 10 variables, and when the “calculate” button is pressed the GBM score is calculated. The blue line reflects the score: if GBM ≥ 0.82, then pMDS is predicted (panel A); GBM < 0.68, pnMDS (B). Anywhere in between these positions is considered indeterminate (C).

We recently validated the model using data from patients and controls who had not been included in the development of the model.[87] Also, external validation was

performed by the Düsseldorf group, using data from a different center, validating 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 peripheral blood in a collaboration between The Tel Aviv Sourasky Medical Center and Scopio labs. This method uses Full-Field Morphology (FFM) technology and performs analysis of blood smears at a significantly larger scale of 1000 fields of 100X view in a routine manner. This allows for high sensitivity, precision, and automated quantification of many cellular and sub-cellular 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 (GI) and distribution width (GIDW) were given. RBC measurements included the quantitative measurements of RBC size and contour changes (deformation), i.e. the percent of RBC that deviate from normal RBC shape. This FFM-based digital analysis of peripheral blood smears, has the potential to enable the detection and quantification of unique WBC and RBC morphologic alterations that are associated with MDS.[90] The technology has also been studied with BM aspirates.[91] and to detect peripheral blood CAR-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 diagnosis that is rapid, hopefully more accurate and objective, and for diagnosis through peripheral blood instead of bone marrow.

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 the Shlush team from the Weizmann Institute. Using single cell RNAseq on purified PB CD34+ hematopoietic stem and progenitor cells (HSPC) they were able to create maps of hematopoiesis, where every cells 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 can be identified.[95] Work is continuing along this line to fully characterize MDS states and to validate the use of this method clinically.

Other works have shown the high correlation between the BM and PB genetic profiles. Jansko-Gadermeir et al. demonstrated a concordance above 99% with NGS sample pairs in myeloid disease,[96] and Jumniensuk et at. 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 where there was a high VAF in the BM mutation.[98]

The authors of the IPSS-M,[61] who added genetics to prognosis, have developed a molecular taxonomy, an MDS classification system that divides patients into 18 distinct groups.[68] While IPSS-M and this extension of taxonomy are primarily for the purpose of prognostication, it 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.

Summary:

Today, in order establish the diagnosis of MDS, certain tests are mandatory, especially 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), peripheral blood abnormalities, presence of BM ringed

sideroblasts, characteristic flow cytometry and myeloid somatic mutations as well as other genetic assays are helpful and recommended but not critical for MDS diagnosis. 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 like diagnostic modeling, digital computational analysis and PB genetics, individually or in combination will become part of general practice in the diagnosis of MDS.

Table 1: Making the diagnosis of MDS

	Finding	Comments
1a: 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	
1b: Physical exam (suggestive)	Pallor	Associated with anemia
	Splenomegaly	In CMML
1c: Routine laboratory abnormalities[1,8,10,14,15,18-20]	Anemia	
	MCV elevation	
	RDW widening	
	Leukopenia	
	Neutropenia	
	Thrombocytopenia	
	Monocytosis	
	Elevated CRP/ESR	
	Normal chemistry	Unless comorbidity
1d: 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
	Ringed sideroblasts	In sideroblastic anemia
	Monocytosis	In CMML
	Cytogenetics	For diagnosis and prognosis
1e: Bone Marrow, recommended[3,7,13,24,42,48,61]	Flow cytometry	Helpful
	Genetics, somatic	Increasingly used
	Genetics, germline	Where familial disease is suspected

Table 2: Recommended antibodies by the ELN iMDS flow cytometry working group for flow cytometric analysis of bone marrow cells of various cell types in patients with cytopenia suspected of myeloid neoplasms (modified according to references: van de Loosdrecht et al.[22], Porwit et al.[25], 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

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Figure 1: Pictures from Haematologic Atlas of various BM cytologic abnormalities in MDS[99].

A. **Dyserythropoiesis**. Bone marrow smear. **Left**: A trinucleated erythroblast with distinctly separated nuclei of different sizes, an erythroblast containing a Howell-Holly body and an erythroblast with curiously lobulated nucleus. Late Erythroblasts show ill-defined borders. **Right**: A late erythroblast with budding nucleus and basophilic stippling.

B. **Dysgranulopoiesis**. Bone marrow smear. Two neutrophils with empty cytoplasm, one of which has a comb-shaped nucleus. Also present, erythoplasts with megaloblastoid changes, and blast cells.

C. **Dysmegakaryopoiesis**. Bone marrow smear. Large megakaryocytes with single large round or oval eccentric nucleus and granular cytoplasm. These is consistent with MDS with isolated del(5q).

D. **MDS with ring sideroblasts, single lineage dysplasia (MDS-RS-SLD)**. Bone marrow smear, high magnification, Perls' reaction. Several ring sideroblasts are evident.

E. **MDS with excess blasts type 2 (MDS-EB-2).** Bone marrow smear showing marked erythroid hypoplasia and granuloblastic hyperplasia with increased blasts cells. At top right, there is a mature neutrophil that is agranular with abnormal nuclear segmentation.

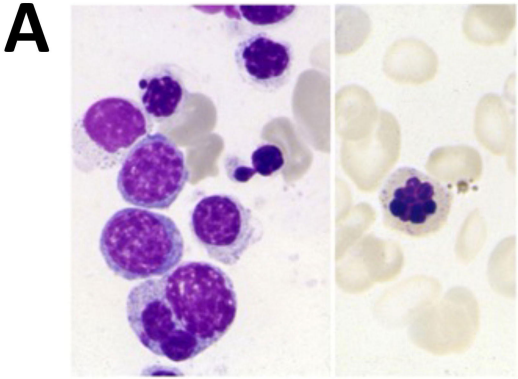
Figure 2: AUC curves for the non-invasive diagnostic MDS model. The three curves reflect three stages of the model: 1) the LoR model,[84] 2) the original GBM model, and 3) the improved GBM model. Note that the AUC improves progressively with each stage; AUC is 0.97 for the improved GBM model.[86]

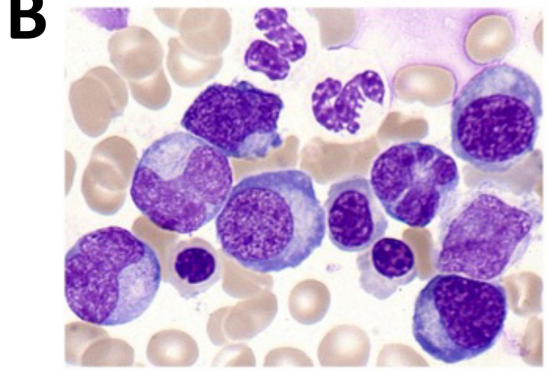
Figure 3: Three examples of the predictive model in practice (online app: https://shiny.york.ac.uk/mds). Values for a given patient's variables are entered into the appropriate spaces, and the "calculate" button is pressed. The blue line indicates the probability of the patient having MDS. **A.** Patient with pMDS, where the blue line is in the red region. **B.** Patient with pnMDS with the blue line in the green region. **C.** Patient with an indeterminate diagnosis (blue line in the lavender region). From Oster et al. 2021[86]

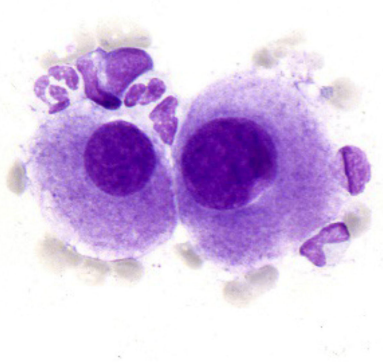
Figure 4: Diagnostic algorithms as of 2024. Both standard and investigational methods are presented.

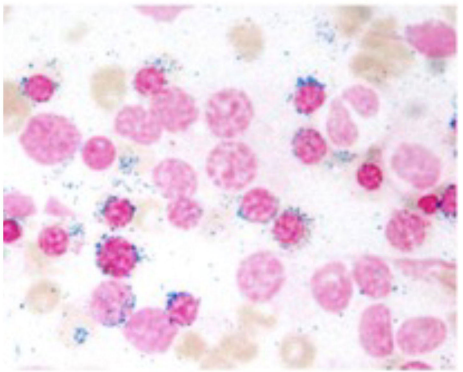
BM – Bone marrow, PB – peripheral blood.

*especially disease defining (e.g. SF3B1)









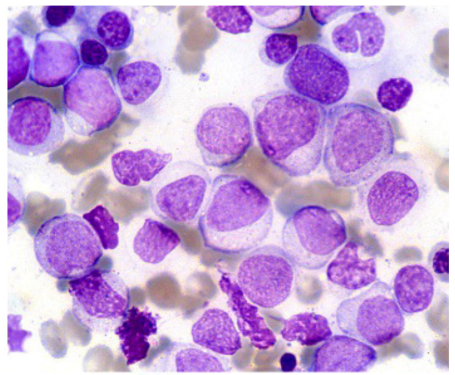
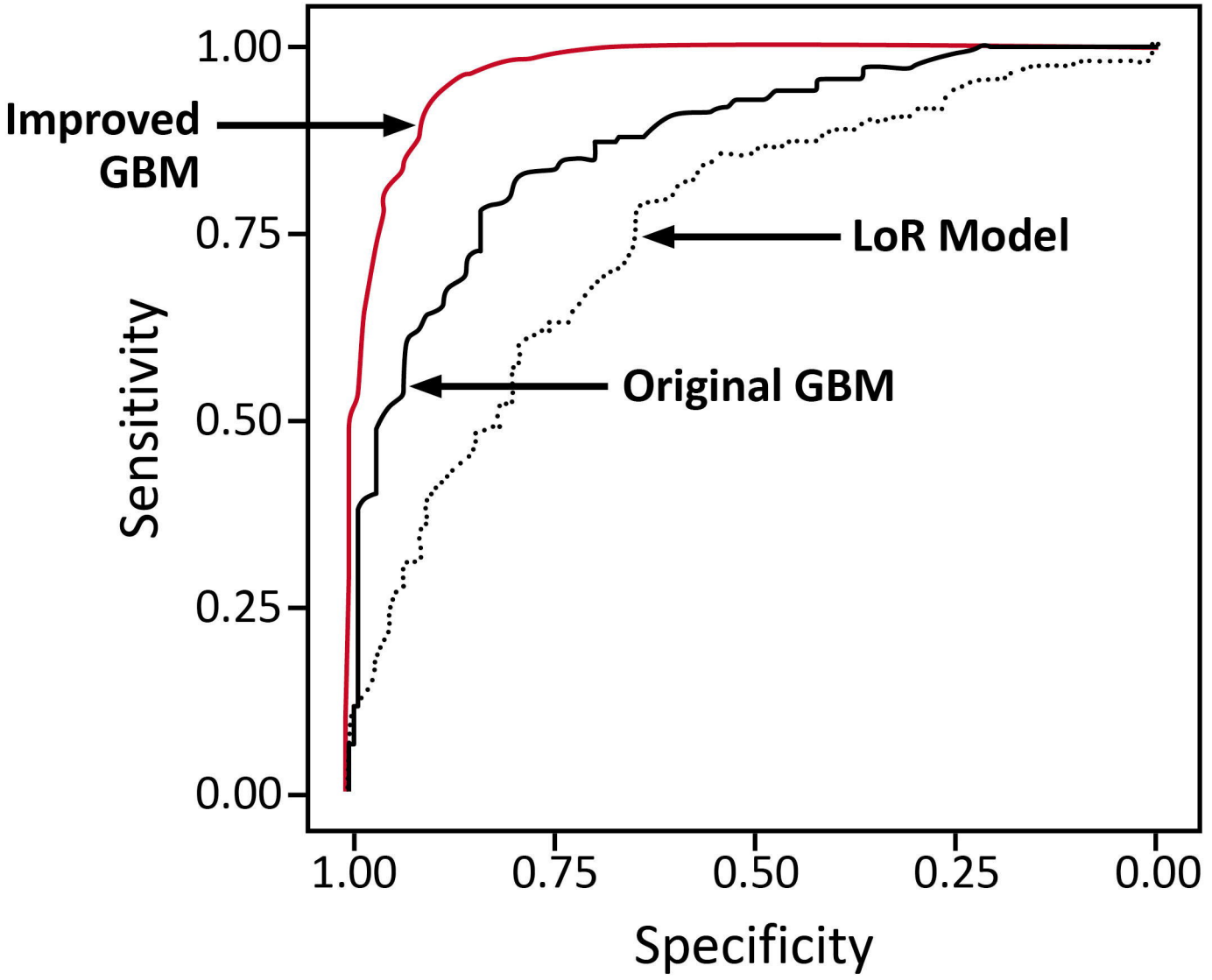


Figure 1



AUC = 0.97 (95% CI 0.96-0.98)

A

What is the age of the patient? (years)
75

Sex (M/F)
(•) Male
( ) Female

Haemoglobin count?
10.5

White blood count?
3.1

Platelet count?
125

Mean corpuscular volume?
101

Neutrophil count?
0.9

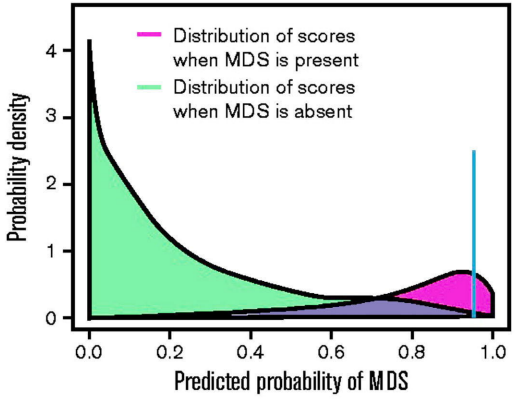
Monocyte count?
0.2

Blood glucose concentration?
100

Creatinine?
1.1

Calculate

Probably MDS (pMDS)



B

What is the age of the patient? (years)
70

Sex (M/F)
( ) Male
(•) Female

Haemoglobin count?
12

White blood count?
8

Platelet count?
220

Mean corpuscular volume?
80

Neutrophil count?
6

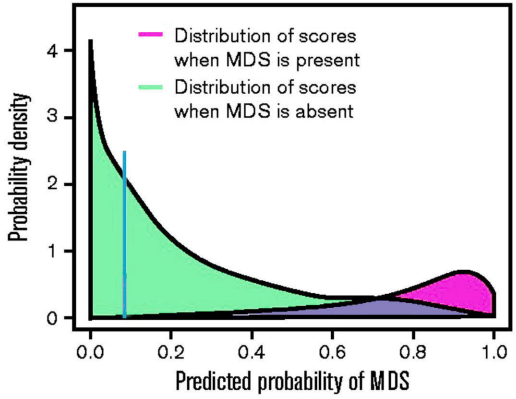
Monocyte count?
0.7

Blood glucose concentration?
120

Creatinine?
1.4

Calculate

Probably not MDS (pnMDS)



C

What is the age of the patient? (years)
80

Sex (M/F)
( ) Male
(•) Female

Haemoglobin count?
13

White blood count?
6

Platelet count?
120

Mean corpuscular volume?
100

Neutrophil count?
2

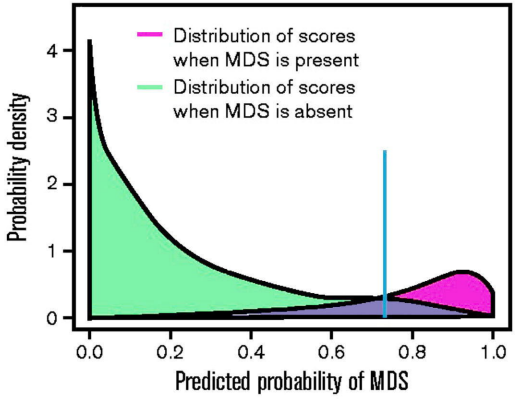
Monocyte count?
0.7

Blood glucose concentration?
100

Creatinine?
1.2

Calculate

Indeterminate



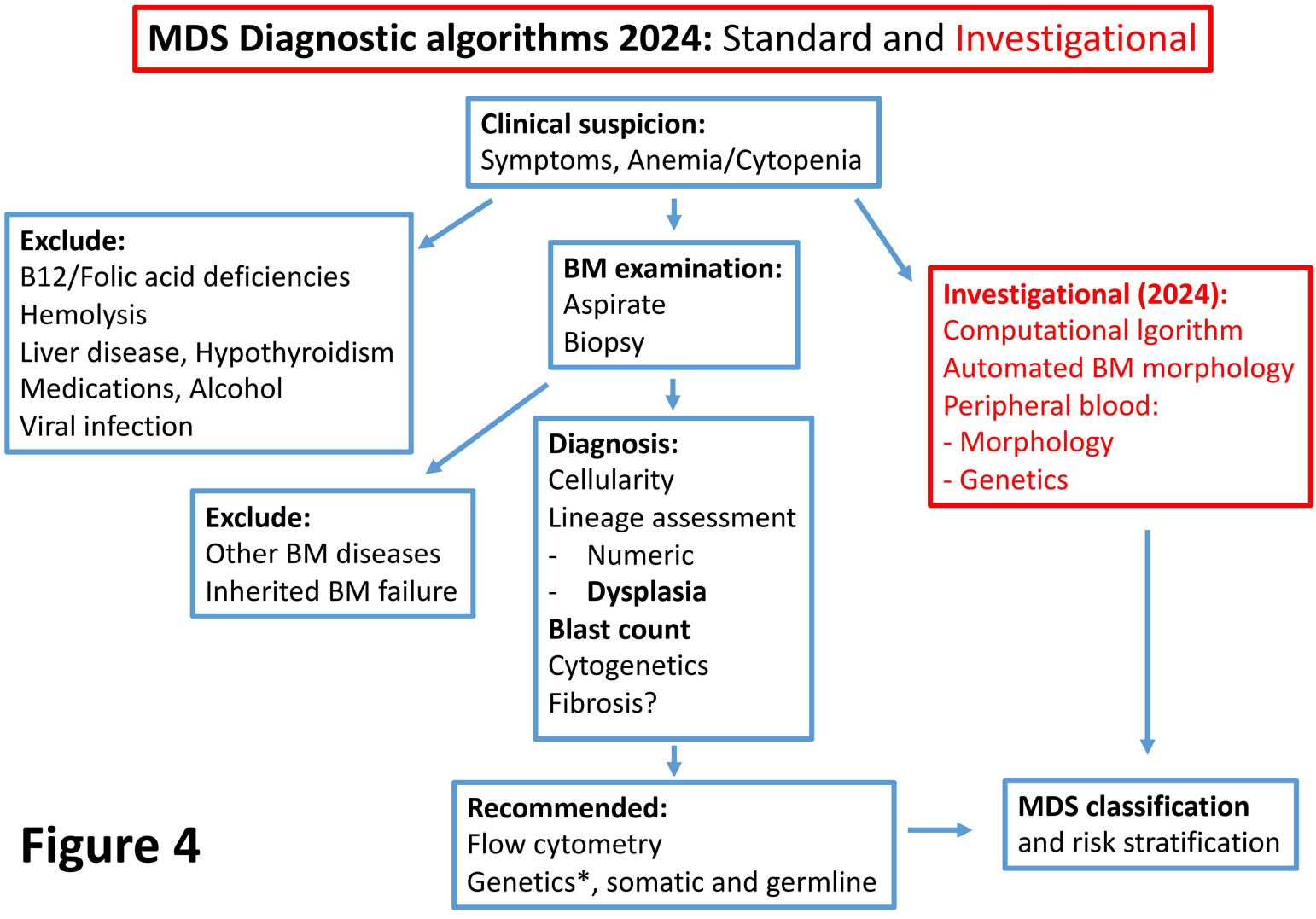

MDS Diagnostic algorithms 2024: Standard and Investigational
Clinical suspicion:
Symptoms, Anemia/Cytopenia
Exclude:
B12/Folic acid deficiencies
Hemolysis
Liver disease, Hypothyroidism
Medications, Alcohol
Viral infection
BM examination:
Aspirate
Biopsy
Investigational (2024):
Computational lgorithm
Automated BM morphology
Peripheral blood:
- Morphology
- Genetics
Exclude:
Other BM diseases
Inherited BM failure
Diagnosis:
Cellularity
Lineage assessment
- Numeric
- Dysplasia
Blast count
Cytogenetics
Fibrosis?
Recommended:
Flow cytometry
Genetics*, somatic and germline
MDS classification
and risk stratification

Figure 4