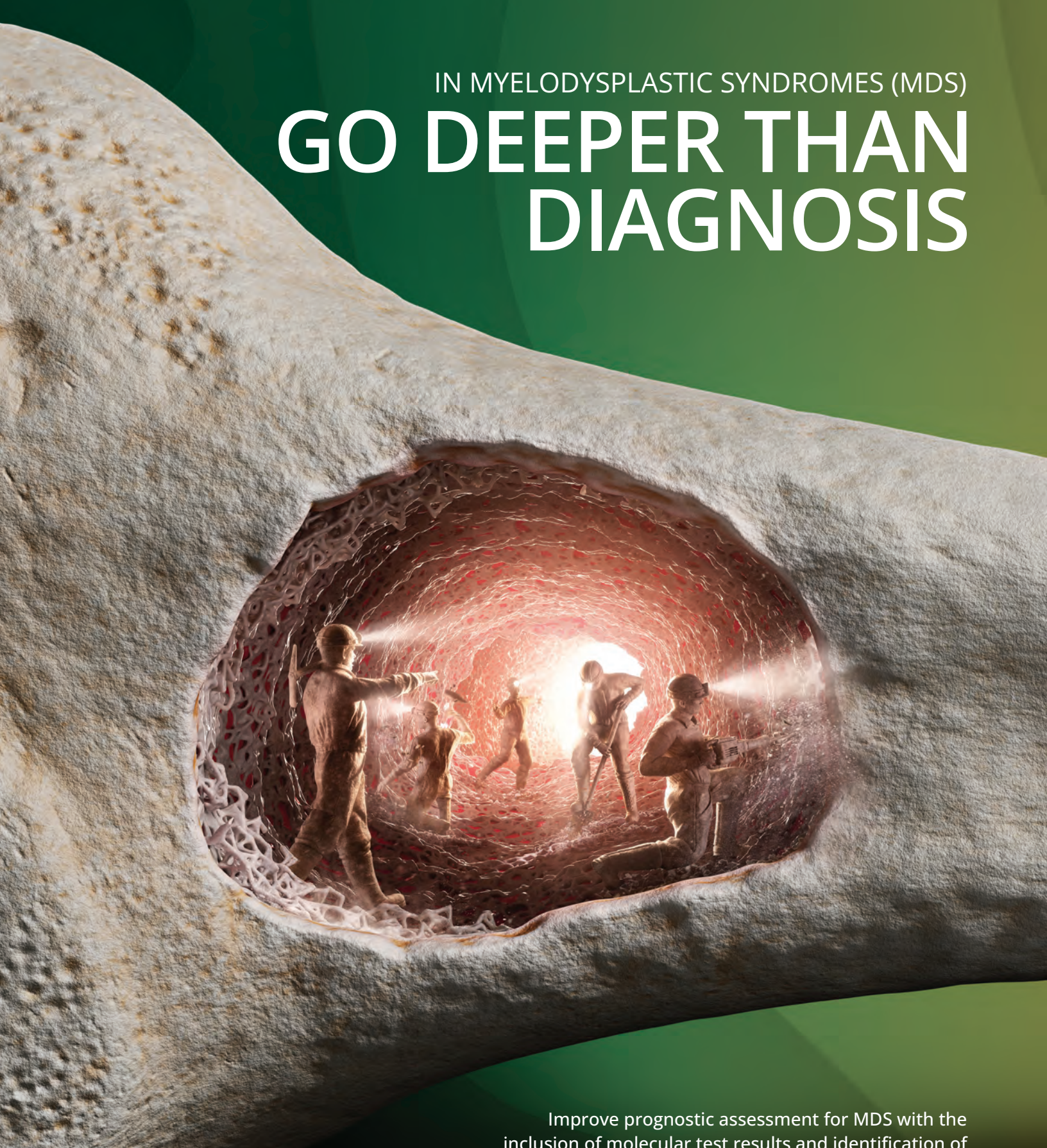
IN MYELODYSPLASTIC SYNDROMES (MDS)

GO DEEPER THAN DIAGNOSIS



Improve prognostic assessment for MDS with the inclusion of molecular test results and identification of key mutations, such as m*IDH1*, in your risk stratification.[1]

DEEPER THAN DIAGNOSIS

Test early. **Test again. Take action.**

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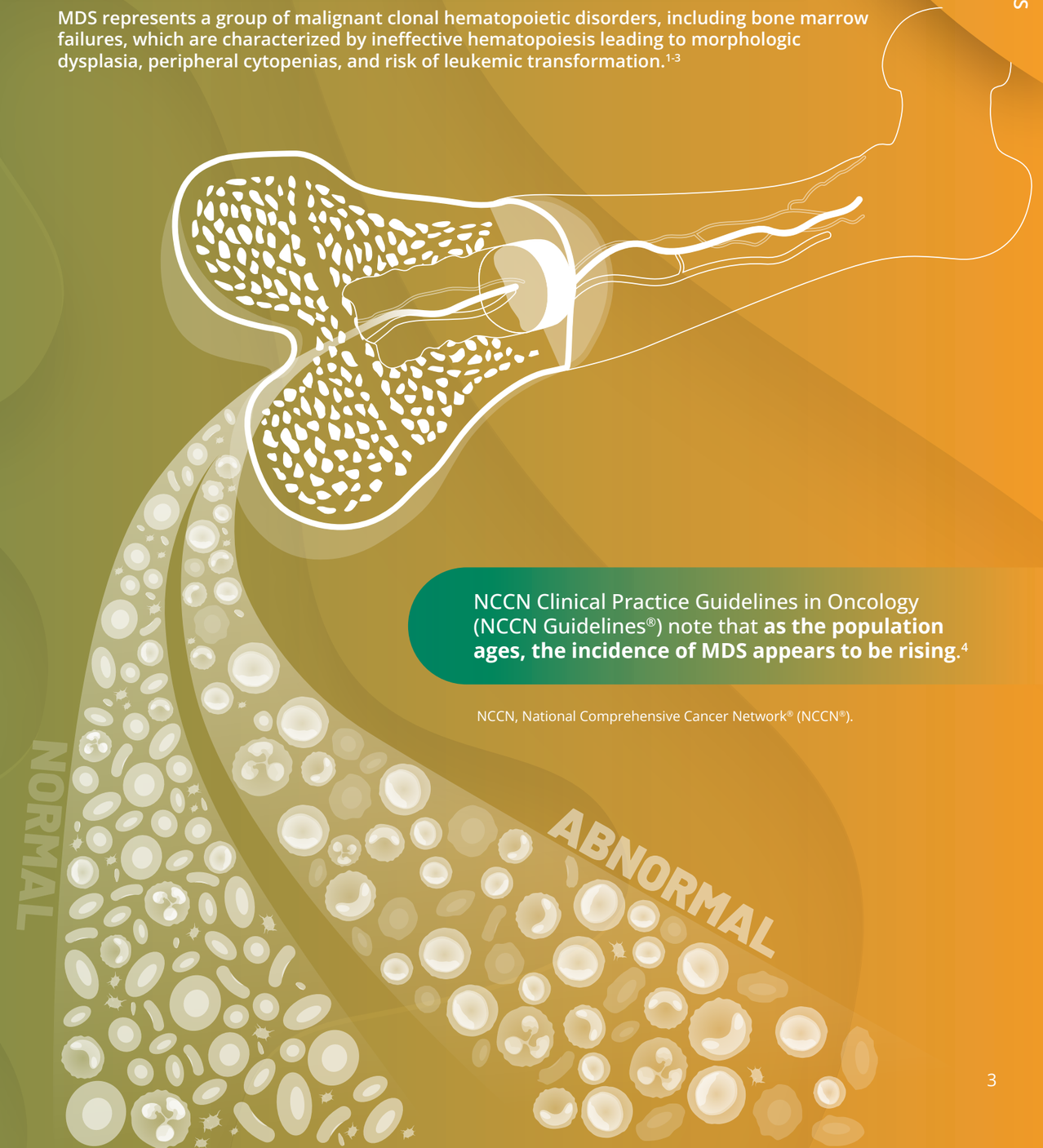
MDS: a group of rare blood disorders

MDS represents a group of malignant clonal hematopoietic disorders, including bone marrow failures, which are characterized by ineffective hematopoiesis leading to morphologic dysplasia, peripheral cytopenias, and risk of leukemic transformation.[1-3]



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) note that **as the population ages, the incidence of MDS appears to be rising**.[4]

NCCN, National Comprehensive Cancer Network® (NCCN®).

Epidemiology of MDS

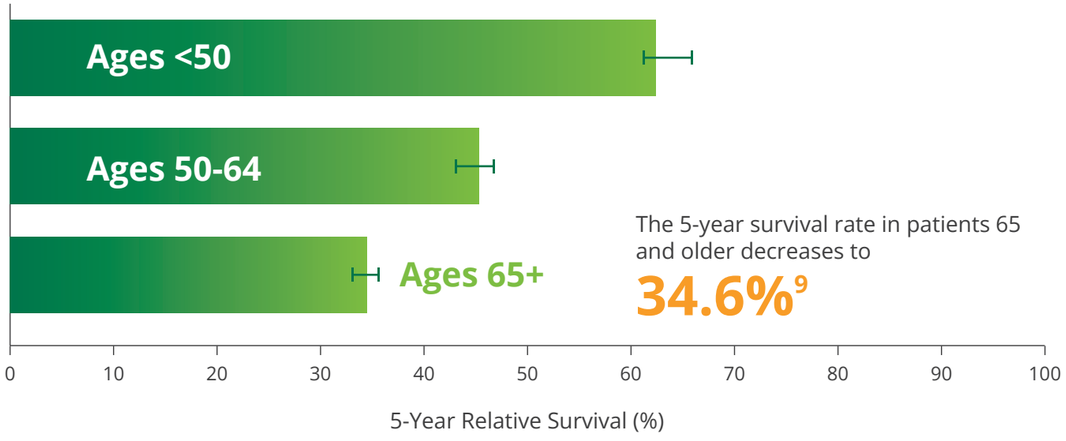
In the U.S., **20,000 people are diagnosed with MDS each year**.[5]

Approximately 4 in 100,000 people in the U.S. are diagnosed with MDS. Since 2009, the incidence rate has been decreasing over the years due to a variety of factors, which may be caused by underdiagnosis and underreporting.[6-8]

MDS is nearly
2X MORE LIKELY
in men than women[8]

The incidence of MDS is **~6-fold higher in patients who are 65 and older** (25 per 100,000), making them more vulnerable to the disease.[8]

In MDS, relative survival rates decrease with age[9]

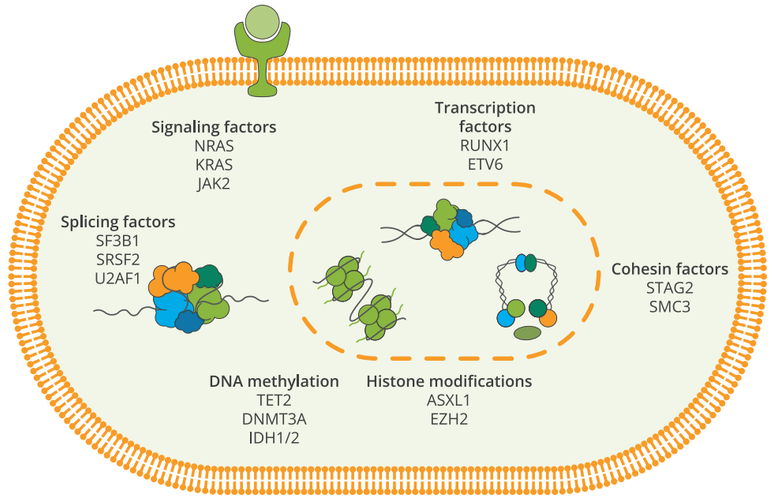


The 5-year survival rate in patients 65 and older decreases to
34.6%[9]

Evolving nature of molecular mutations

The presence of **mutations in MDS can be associated with a poorer prognosis**.[10] The molecular and cytogenetic evolution of MDS allows for the development of genetic diversity during disease progression with some mutations appearing in a predictive order, such as *DNMT3A*, *SF3B1*, and *TP53*. **Some mutations, such as *IDH1*, may appear in earlier or later phases of the disease.**

Important molecular mutations found in MDS[11]



Isocitrate dehydrogenase-1 (*IDH1*) mutations in MDS are associated with poor survival[12]

- **Approximately 4% of patients with MDS harbor *IDH1* mutations**, and the mutation rate may double in patients who experience disease progression
- **Mutated *IDH1*, or m*IDH1*, is associated with a high rate of leukemic transformation and poor event-free and overall survival rates**
  - Survival outcomes for m*IDH1* MDS patients are poor, with a 2-year survival rate of 14% (n=7) as compared with 52% (n=146) for those with wild-type *IDH1* MDS
  - The rate of transformation from m*IDH1* MDS to AML is high, with 67% of m*IDH1* MDS patients (4/7) experiencing leukemic transformation vs 28% of those with wild-type *IDH1* (41/145)

Molecular testing can play an important role in diagnosis and risk stratification of MDS patients.[13,14]

Identify risk factors, signs, and symptoms in MDS

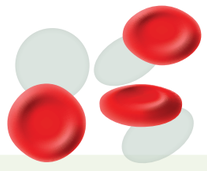
Identify key MDS risk factors[3,8]

- **Advanced age**
- **Sex**
  MDS is more common in men
- **Prior treatment** with chemotherapy
- **Genetic syndromes**
- **Familial MDS**
- **Environmental exposures**
  Exposure to radiation, benzene, and other chemical agents
- **Smoking**

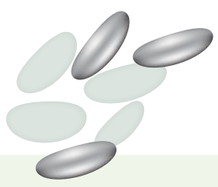
Recognize the signs and symptoms

MDS can be difficult to diagnose due to the dysplastic nature of the disease.[15] Certain disorders can resemble MDS because they also cause low blood counts or abnormal-appearing blood cells. Performing clinical tests can help you establish a firm diagnosis of MDS.

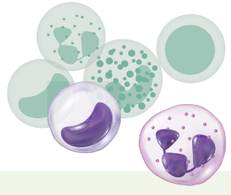
- Many patients are **asymptomatic and only diagnosed after incidental detection of cytopenias by their primary care physician during a routine blood test**[3]
- Patients may present with one cytopenia or several. **Anemia is the most common cytopenia** detected in MDS, affecting nearly all patients at some point during their disease course[2,16]



~90%
of MDS patients present with anemia[16]



~50%
of MDS patients present with neutropenia[17]



~40%
of MDS patients present with thrombocytopenia[3]

Importance of testing and retesting

Mutational testing should always be performed at diagnosis, but the molecular profile of patients can change over time.[14] **Retesting is recommended in[18]:**

- Patients who had a **lack of response to therapy**
- Patients who **relapsed after allogeneic stem cell transplant or therapy**
- Patients who show signs of **disease progression**

Testing methodologies—such as blood tests, bone marrow biopsy and aspiration, cytogenetic tests, molecular tests, and flow cytometry and immunocytochemistry—require adequate samples of peripheral blood and bone marrow (BM) at diagnosis **to build a comprehensive analysis of the patient's MDS status**.[19]

7

Rapid PCR tests can provide **results in under 7 days**.[20]
It is recommended to repeat molecular testing at the first sign of disease progression as new mutations may be revealed.[14,18]

MDS exists on a biological continuum with AML[21,22]

The 2022 WHO and ICC guidelines have evolved to de-emphasize morphologic features and fixed blast cutoffs, instead focusing heavily on molecular and genetic features when classifying MDS and AML.[23]

Updated classifications redefined the blast count cutoff in the absence of genetic abnormalities[21,22]

WHO 2022 guidance[21]	ICC 2022 guidance[22]
MDS-IB2[a]	MDS/AML[b]
10% to 19% blasts in the BM	10% to 19% blasts in the blood or BM

Certain genetic abnormalities determine a diagnosis of AML[21,22]

WHO 2022 guidance[21]	ICC 2022 guidance[22]
AML with defining genetic abnormalities	AML with recurrent genetic abnormalities
AML can be diagnosed in the presence of certain mutations and/or defined genetic abnormalities **irrespective of blast count**[c]	All entities defined by the presence of certain recurrent genetic abnormalities and other genetically related entities can be diagnosed as **AML if ≥10% blasts are present**[d]

[a]The WHO 2022 guidance for MDS-IB2 includes 5% to 19% blasts in the peripheral blood or Auer rods.[21]
[b]With the exception of AML-defining cytogenetics or mutations in *NPM1*, bZIP *CEBPA*, or *TP53*.[22]
[c]*RUNX1::RUNX1T1* fusion, *CBFB::MYH11* fusion, *DEK::NUP214* fusion, *RBM15::MRTFA* fusion, *BCR::ABL1* fusion, *KMT2A* rearrangement, *MECOM* rearrangement, *NUP98* rearrangement, *NPM1* mutation, *CEBPA* mutation, myelodysplasia-related genetic abnormalities, and other defined genetic alterations.[21]
[d]t(8;21) (q22;q22.1)/*RUNX1::RUNX1T1*), inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*, t(6;9)(p22.3;q34.1)/*DEK::NUP214*, t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*, other *KMT2A* rearrangements, inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2; MECOM(EVI1)*, other *MECOM* rearrangements, other rare recurring translocations, mutated *NPM1*, and in-frame bZIP *CEBPA* mutations.[22]
ICC, International Consensus Classification; MDS-IB2, MDS with increased blasts 2; WHO, World Health Organization.

Uncover patient risk of transformation to AML

	LR-MDS	HR-MDS
Median survival[8]:	3 to 10 years	Less than 3 years
Typically characterized as:	• Lower percentages of myeloblasts[8] • Fewer genetic variants associated with a better prognosis, such as *SF3B1*[8] • Less severe cytopenias[8]	• Higher percentage of myeloblasts[8] • Increased genetic variants associated with a worse prognosis, such as *IDH1, TP53*[8,12] • More severe cytopenias[8]
Risk of progression to AML[3]:	5-15%	40-50%

30%-40% of patients progress from MDS to AML[24]

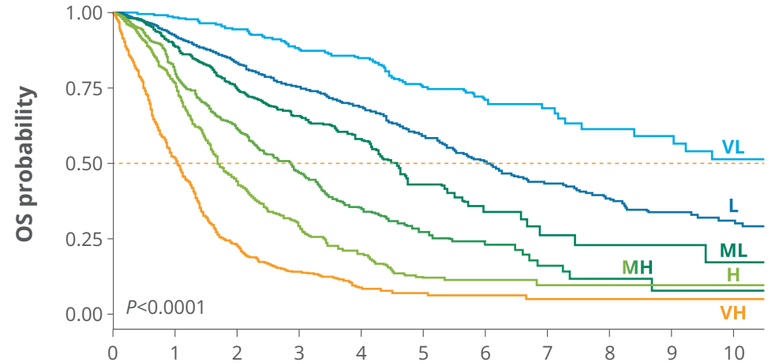
HR-MDS, high-risk MDS; LR-MDS, low-risk MDS.

Assess risk stratification with IPSS-M

The number of genetic mutations affects risk stratification of patients with MDS, in that a **higher number of DNA alterations is associated with worse outcomes**.[1] Over the past 10 years, the discovery of numerous mutated genes, and the impact of these genes on MDS survival, facilitated the need for an updated prognostic system in 2022: IPSS-M. Unlike IPSS-R, which was evaluated in 2012 and focuses on hematologic and cytogenetic features only, IPSS-M also considers molecular mutations to determine accurate risk stratification.[1,10,13]

The inclusion of clinical data, cytogenetics, and molecular data—including gene residuals such as *IDH1* mutations—are critical to stratify your MDS patient in the correct risk category.[1]

Reclassification to IPSS-M from IPSS-R impacts survival prognoses[1]



>50%
of patients reclassified to IPSS-M moderately high, high, or very high from the IPSS-R intermediate group[1,a]

Number at risk	Years										
Very Low	344	267	224	180	126	82	57	42	28	24	18
Low	852	640	496	382	270	176	112	83	57	40	31
Moderately Low	295	214	152	111	72	35	18	8	7	4	3
Moderately High	278	191	134	80	48	27	20	9	4	2	1
High	367	235	121	65	37	15	12	6	3	3	3
Very High	460	200	77	37	14	9	6	3	3	2	2

[a]Risk was encoded using the 5 categories for both IPSS-R and IPSS-M by merging the moderate low and moderate high categories for the intermediate group.[1] Please refer to the latest IPSS-M to assess the risk score of MDS based on the full guidance.

Test your patients for actionable mutations and use the calculator at mds-risk-model.com to determine their IPSS-M risk score.[1]

IPSS-M, International Prognostic Scoring System-Molecular; IPSS-R, International Prognostic Scoring System-Revised; OS, overall survival.

Assess treatment goals for your patients

Management of MDS is predominantly influenced by a patient's risk category, which can be assessed using the IPSS-M guidelines.[15]

	LR-MDS	HR-MDS
Goals for treatment[8]:	Reduce disease-related symptoms, lessen or eliminate the need for transfusions, and minimize morbidity associated with certain cytopenias	Delay transformation to AML, prolong survival, and improve quality of life through improvement of peripheral blood counts
Current treatment options[8]:	Supportive care agents, disease-modifying agents, clinical trials	Supportive care agents, disease-modifying agents, hematopoietic stem cell transplantation (HSCT), clinical trials

A **substantial proportion of patients with MDS lack effective treatment** for their cytopenias or for altering the natural history of disease. Clinical trials with novel therapeutic agents, along with supportive care, remain the hallmark of disease management.[18]

Treatment considerations for your patients

Supportive care agents

Promote the growth and maturation of specific HSPC lineages to address cytopenias.[25]

- **Erythropoiesis-stimulating agents (ESAs)**[25]
- **Erythroid-maturation agents (EMAs)** are an alternative consideration in patients who require red blood cell transfusion and are refractory or unlikely to respond to ESAs[26]
- **Granulocyte colony-stimulating factors (G-CSFs)**[25]
- **Thrombopoietin receptor agonists (TRAs)**[25]
- **Blood transfusions**[27]
- **Antibiotics and antifungals** to prevent or treat infections[28]

Disease-modifying agents

Target dysfunctional hematopoietic stem/progenitor cells (HSPCs) to reverse cytopenias and slow progression to AML.[25]

- **Hypomethylating agents (HMAs)**
- **Traditional chemotherapy agents**
- **Immunosuppressive therapy (IST)**

HSCT

HSCT is the only curative option for eligible patients with HR-MDS.[29]

Targeted therapies are available for the treatment of MDS

Targeted therapies work differently than chemotherapy because these agents work on specific types of cancer cells harboring a certain mutation and do less harm to normal cells.[30]

Participation in clinical trials

Various therapies are currently ongoing in previously untreated and R/R MDS, as well HR-MDS and LR-MDS aiming to fulfill the unmet clinical needs of the disease.[29]

Assess your patient's molecular profile at diagnosis and retest at first suspicion of clinical change.[13,14]

HSPC, hematopoietic stem progenitor cell; R/R, relapsed or refractory.

RETHINK
RISK STRATIFICATION IN MDS

- **Precise risk stratification of MDS requires the inclusion of molecular testing** per the latest IPSS-M guidelines[1]
- The IPSS-R guidelines do not evaluate gene mutations, resulting in inaccurate risk stratification and missed opportunities for potential precision therapy[1]

Test at the time of

Diagnosis[18]

First sign of disease progression[10]

Relapse[14,18]

Given that molecular profiles evolve over time, repeat genetic testing to help identify important mutations in MDS.[10,14]

Learn more about how you can help your patients with MDS at DeeperthanMDS.com

Test early. **Test again. Take action.**

Improve prognostic assessment for MDS with the inclusion of molecular test results and identification of key mutations, such as m*IDH1*, in your risk stratification.[1]

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