Myelodysplastic syndromes (MDS)

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Continuous research and targeted examinations of blood and bone marrow result in various diagnostic recommendations for patients with myelodysplastic syndrome (MDS).

Diagnostic recommendation

Method	Anticoagulant	Recommendation
Cytomorphology	EDTA	mandatory
Immunophenotyping	EDTA or Heparin	optional
Chromosome analysis	Heparin	mandatory
FISH	EDTA or Heparin	optional
Molecular genetics	EDTA or Heparin	optional

Definition and characteristics of myelodysplastic syndrome (MDS)

A myelodysplastic syndrome (MDS) is an acquired clonal bone marrow disease that occurs primarily in older age (mean age of onset 70 years) and with an age-related incidence of 4-50/100,000 per year. Starting from a pluripotent haematopoietic stem cell, it often causes anaemia, but also neutropenia and/or thrombocytopenia. Dysplasia signs can be recognized in at least one of the three hematopoietic cell lines and **leukemic transformations/transitions to acute myeloid leukemia are frequent.**

Classification of MDS

While the classification of myelodysplastic syndromes (MDS) used to be based exclusively on FAB via cytomorphology, the WHO has also included cytogenetics and clinical characteristics. In addition, molecular markers are being investigated with regard to their significance in MDS and are increasingly being implemented in routine. Below you will find the current classification of myelodysplastic syndromes (MDS) according to WHO 2017.

MDS WHO Classification 2017 (Swerdlow et al. 2017)

Myelodysplastic syndromes (MDS)
- MDS with single lineage dysplasia (MDS-SLD)
- MDS with ring sideroblasts (MDS-RS)
  - MDS-RS and single lineage dysplasia
  - MDS-RS and multilineage dysplasia
- MDS with multilineage dysplasia (MDS-MLD)
- MDS with excess blasts (MDS-EB)
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS-U)
- Childhood myelodysplastic syndrome

Diagnostic criteria for myelodysplastic syndrome
The morphological classification of myelodysplastic syndrome (MDS) is basically based on the percentage of blasts in bone marrow and peripheral blood, the form and degree of dysplasia and the percentage of ring sideroblasts in bone marrow (see Table 1).

Table 1: Diagnostic criteria for myelodysplastic syndrome

Entity name	Number of dysplastic lineages	Number of cytopenias[a]	Ring sideroblasts as percentage of marrow erythroid elements	Bone marrow (BM) and peripheral blood (PB) blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1-2	< 15% / < 5%[b]	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfils all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2-3	1-3	< 15% / < 5%[b]	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfils all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1-2	≥ 15% / ≥ 5%[b]	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfils all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 oder 3	1-3	≥ 15% / ≥5%[b]	BM < 5%, PB < 1%, no Auer rods	Any, unless fulfils all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM < 5%, PB < 1%, no Auer rods	del(5q) alone or with 1 additional abnormality, except loss of chromosome 7 oder del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	1-3	1-3	None or any	BM 5-9% or PB 2-4%, no Auer rods Auerstäbchen	any
MDS-EB-2	1-3	1-3	None or any	BM 10-19% or PB 5-19% or Auer rods	any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts[c]	1-3	1-3	None or any	BM < 5%, PB = 1%[c], no Auer rods	any
With single lineage dysplasia and pancytopenia	1	3	None or any	BM < 5%, PB < 1%, no Auer rods	any

[a] Cytopenia defined as haemoglobin concentration < 10 g/dl, platelet count < 100 x 10^9/l and absolute neutrophil count < 1.8 x 10^9/l.

[b] if *SF3B1* mutation is present.

[c] 1% PB blasts must be recorded on > 2 separate occasions.

[d] Cases with ≥ 15% ring sideroblasts by definition have significant erythroid dysplasia and are classified as MDS-RS-SLD

[e] see Table 2

Diagnostics of myelodysplastic syndrome (MDS)

Cytomorphology

Differentiation from other malignant diseases and reactive changes

The diagnosis of myelodysplastic syndrome (MDS) is made by cytomorphological examination of bone marrow and peripheral blood. The aim is to differentiate MDS from other clonal myeloid diseases such as acute myeloid leukemia, but also PNH, as well as from other benign and reactive changes that may be associated with dysplastic haematopoiesis.

Within the framework of cytomorphological diagnostics, at least 200 (according to the WHO classification even 500, although statistically this does not provide greater certainty) bone marrow cells and 20 megakaryocytes should be evaluated. Dysplasia signs should be detectable in at least 10% of the cells to be able to call the respective lineage dysplastic. So-called pseudo-Pelger neutrophils, ringsideroblasts, micromegakaryocytes and the number of blasts are of particular diagnostic importance. These morphological alterations correlate in part with the presence of clonal markers. Such a correlation of morphological and genetic markers is found, for example, in MDS with isolated 5q deletion ("5q-minus syndrome").

The differentiation between hypoplastic myelodysplastic syndrome (MDS) and aplastic anaemia is often difficult, since dysplastic signs in erythropoiesis can be found in both entities. PNH should also be included in the differential diagnosis. An early stage of refractory anaemia with single-line cytopenia is often difficult to diagnose and requires follow-up.

Immunophenotyping

Detection of aberrant antigen expression patterns of hematopoietic cells

Immunophenotyping can be used to detect aberrant antigen expression patterns typical of myelodysplastic syndrome (MDS). In patients with suspected or confirmed MDS, multiparametric flow cytometry can provide valuable information for diagnosis and prognosis. It is able to detect

aberrant antigen expression patterns on granulopoiesis, monocytopoiesis and erythropoiesis cells as well as on myeloid progenitor cells, which correlate with dysplasia (Westers et al. 2012).

With regard to granulopoiesis, granularity is assessed according to its position in the sideward scatter (SSC), and the expression of myeloid antigens such as CD11b, CD13 and CD16 is also recorded. In addition, myeloid progenitor cells are quantified and examined for the expression of lymphoid and mature cell markers. On the monocytes the expression of myelomonocytic markers such as CD4, CD13, CD14, CD33 and CD11b will be assessed. Furthermore, aberrant coexpression of the lymphoid antigens CD2 and CD56 will be assessed. An aberrant expression of CD71 can be detected on erythropoiesis cells.

Confirmation of diagnosis in case of unclear cytomorphological findings
A flow cytometric score can be determined from the results of the antigen expression patterns on the individual cell rows (Wells et al. 2003). Thus, immunophenotyping can support the diagnosis of myelodysplastic syndrome (MDS) especially in cases of cytomorphologically limited assessable bone marrow aspirates, in cases of ambiguous dysplasia and blasts or in cases with normal karyotype. Furthermore, the score results have a prognostic value, since patients with higher scores have a less favourable prognosis (Wells et al. 2003). The current guidelines of the "European LeukemiaNet" and the WHO 2017 recommend the implementation of immunophenotyping within the diagnostic algorithm for the suspected diagnosis of myelodysplastic syndrome (MDS) (Westers et al. 2012, Malcovati et al. 2013).

Chromosome analysis

Cytogenetics is of central importance in diagnostics of myelodysplastic syndrome (MDS). Since cells capable of division are required for chromosome analysis, chromosome analysis should be performed from bone marrow anticoagulated with heparin. If no bone marrow can be obtained, the analysis can be attempted from peripheral blood. In case of an aberrant karyotype, the clonality of the disease is confirmed first. Cytogenetic findings may also determine the entity. Thus, the diagnosis of 'MDS with isolated del(5q)' as well as 'MDS, unclassifiable, due to certain cytogenetic abnormalities' can only be made with the help of cytogenetics (see Table 1). The diagnosis of 'MDS with isolated del(5q)' is compatible with the presence of a cytogenetic abnormality other than deletion of 5q, but not monosomy 7 or deletion of 7q. MDS, unclassifiable, due to certain cytogenetic abnormalities' has persistent cytopenia but lacks morphological evidence of MDS such as significant dysplasia or increased blasts. According to the WHO classification, the chromosomal abnormalities listed in Table 2 are the decisive evidence for the presence of myelodysplastic syndrome (MDS) - with the exception of trisomy 8, loss of the Y chromosome and 20q deletion (Swerdlow et al. 2017). Furthermore, cytogenetics allows an assessment of the prognosis (see Figure 1 in the section 'Classification of MDS into 5 cytogenetic risk groups' and Prognosis.

Unbalanced rearrangements are the most frequent cytogenetic abnormalities
About 50% of all de novo MDS and about 80% of all therapy-associated MDS (t-MDS) show cytogenetic abnormalities. Predominantly there are unbalanced rearrangements which lead to the loss or gain of genetic material. Balanced rearrangements, such as translocations or inversions that lead to leukemia-specific fusion genes, are rare in myelodysplastic syndrome (MDS) (see Table 2). Common rearrangements include trisomy 8, monosomy 7 or 7q deletion, deletions in 5q and 20q and loss of the Y chromosome. In addition, there are a number of other abnormalities (see Table 2). More rarely, the following abnormalities occur: the(1;7)(q10;p10), trisomy 19, 1q gain, monosomy 1, 1p loss, trisomy 11, 16q deletion, 17p deletion and trisomy 21.

Table 2: Frequencies of chromosomal abnormalities in myelodysplastic syndrome (MDS) (Swerdlow et al. 2017)

	Frequency	
Chromosomal abnormality	**MDS (overall)**	**t-MDS**
Unbalanced		
Gain of chromosome 8[a]	10%	
Loss of chromosome 7 or del(7q)	10%	50%
del(5q)	10%	40%
del(20q)[a]	5-8%	
Loss of Y-chromosome[a]	5%	
Isochromosome 17q or t(17p)	3-5%	25-30%
Loss of chromosome 13 or del(13q)	3%	
del(11q)	3%	
del(12p) or t(12p)	3%	
del(9q)	1-2%	
idic(X)(q13)	1-2% (more frequent among women over 65)	
Balanced		
t(11;16)(q23.3;p13.3)		3%
t(3;21)(q26.2;q22.1)		2%
t(1;3)(p36.3;q21.2)	1%	
t(2;11)(p21;q23.3)	1%	
inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)	1%	
t(6;9)(p23;q34.1)	1%	

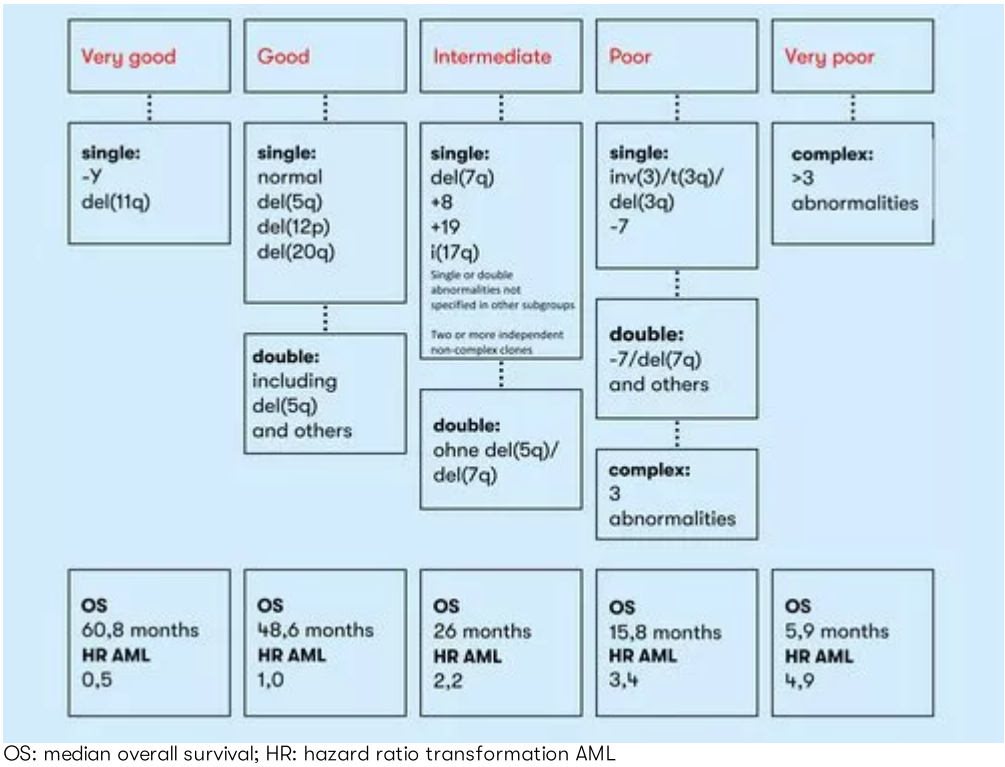
[a] as the sole cytogenetic abnormality in the absence of morphological criteria, gain of chromosome 8, del(20q) and loss of Y chromosome are not considered definitive evidence of MDS; in the setting of persistent cytopenia of undetermined origin, the other abnormalities shown in this table are considered presumptive evidence of MDS, even in the absence of definitive morphological features.

The frequency of chromosomal abnormalities varies in the different morphological WHO entities. Cytogenetic anomalies are found in about 25% of MDS-SLD, 30-40% of MDS-MLD, about 10% of MDS-RS and in 30-50% of MDS-EB.

In about 65% of all myelodysplastic syndromes (MDS) with aberrant karyotype single abnormalities are found, 15% show two alterations and about 20% show complex karyotypes with three or more chromosomal alterations. More often complex aberrant karyotypes are found in t-MDS. In about 20% of MDS with complex aberrant karyotypes *TP53* mutations are also found. Complex karyotypes are also associated with gene amplifications, e.g. the genes *KMT2A* or *CMYC*.

Classification of MDS into 5 cytogenetic risk groups
The typical chromosomal changes were first classified according to their prognostic relevance in 1997 in the so-called International Prognostic Scoring System (IPSS) (Greenberg et al. 1997). Based on this, Schanz et al. developed a new prognosis model in 2012 using data from 2,902 patients, which now allows the cytogenetic classification of 91% of patients into five risk groups. This cytogenetic scoring system was applied in the revision of IPSS in 7,012 patients (Greenberg et al. 2012) and is thus part of the new IPSS-R.

Figure 1: Cytogenetic risk groups for myelodysplastic syndrome (MDS) (according to Schanz et al. 2012) considered for the IPSS-R score



OS: median overall survival; HR: hazard ratio transformation AML

FISH

FISH can be used in MDS as a screening method with probes for the most common known genetic changes, if a chromosome analysis could not be performed successfully. Furthermore, results from classical chromosome analysis can be confirmed by FISH. In addition, FISH allows the quantification of the aberrant clone on native material and thus the monitoring of disease progression and therapy response. Since in some patients with myelodysplastic syndrome (MDS) the aberrant clone can only be detected in bone marrow, bone marrow is the ideal test material for FISH - as well as for chromosome analysis. FISH on smears or enriched cells of the peripheral blood is possible in principle, but the chromosomal abnormalities occurring in MDS can only be partially detected in peripheral blood.

Molecular genetics

In recent years, numerous gene mutations in myelodysplastic syndrome (MDS) have been discovered which are becoming increasingly important for the subclassification, risk assessment and characterisation of MDS (Haferlach et al. 2014, Papaemmanuil E et al. 2013). Another study showed that when all protein-coding genes are examined, including copy number variations, all patients show at least one genetic change (Makishima et al. 2017), which reflects a huge progress in the genetic characterization of patients with myelodysplastic syndrome (MDS).

Mutations often affect epigenetic regulation and transcription factors
There is an accumulation of mutations in genes involved in epigenetic regulation. These include: *TET2*, *ASXL1*, *IDH1/2*, *DNMT3A* and *EZH2*. In addition, transcription factors (*RUNX1*, *ETV6*, *WT1*) and splicing factors (*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*) are frequently mutated (Graubert et al. 2011, Yoshida et al. 2011, Papaemmanuil et al. 2013, Haferlach et al. 2014, Sperling et al. 2017). Table 3 lists the most important and most frequent mutations in detail. Often these gene mutations are not specific for MDS, but are also found in **acute myeloid leukemia (AML)** and partly in myeloproliferative neoplasms (MPN).

Table 3: Common gene mutations in MDS (i.e. found in at least 5% cases) (Swerdlow et al. 2017)

Gen	Pathway	Frequency	Prognostic impact
SF3B1[a]	RNA splicing	20-30%	Favourable
TET2[a]	DNA methylation	20-30%	See footnote[b]
ASXL1[a]	Histone modification	15-20%	Adverse
SRSF2[a]	RNA splicing	~15%	Adverse
DNMT3A[a]	DNA methylation	~10%	Adverse
RUNX1	Transkription factor	~10%	Adverse
U2AF1[a]	RNA splicing	5-10%	Adverse
TP53[a]	Tumor suppressor	5-10%	Adverse
EZH2	Histone modifikation	5-10%	Adverse
ZRSR2	RNA splicing	5-10%	See footnote[b]
STAG2	Cohesin complex	5-7%	Adverse
IDH1/2	DNA methylation	~5%	See footnote[b]
CBL[a]	Signalling	~5%	Adverse
NRAS	Transcription factor	~5%	Adverse
BCOR[a]	Transcription factor	~5%	Adverse

[a] These genes are also reported to be mutated in clonal haematopoietic cells in a subset of healthy individuals **(clonal haematopoiesis of indeterminate potential - CHIP)**.

[b] Either neutral prognostic impact or conflicting data.

In addition, a number of other gene mutations were found in MDS, which, however, occur very rarely (< 5%) and also overlap with other diseases and are therefore not discussed further here. These include *KMT2A*-PTD and *FLT3*-ITD as well as mutations in *ATM*, *BCORL1*, *CDKN2A*, *CEBPA*, *CUX1*, *ETV6*, *FLT3-TKD*, *GATA2*, *GNAS*, *KIT*, *KRAS*, *MPL*, *NPM1*, *NF1*, *PIGA*, *PHF6*, *PTPN11*, *PTEN*, *RB1*, *WT1* and others.

Prognostically relevant gene mutations
Prognostically relevant mutations have been described in several publications (Bejar et al. 2011 & 2015, Haferlach et al. 2014, Papaemmanuil et al. 2013) (see Table 4). A comprehensive study involving more than 3000 patients showed that mutations in *ASXL1*, *CBL*, *EZH2*, *RUNX1*, *TP53* and *U2AF1* have the strongest influence on shortened survival (Bejar et al. 2015). It is recommended that patients with mutated *ASXL1*, *CBL*, *EZH2*, *RUNX1*, *TP53* or *U2AF1* be placed in the next less favorable IPSS risk group.

Table 4: Prognostically relevant mutations in myelodysplastic syndrome (according to Bejar et al. 2015)

Mutation	Prognostic impact
ASXL1, *CBL*, *EZH2*, *RUNX1*, *TP53 U2AF1*	adverse
SF3B1 single	good

SF3B1 mutations, in contrast, are associated with a favourable prognosis (Papaemmanuil et al. 2011, Broseus et al. 2013, Bejar et al. 2015). In the current WHO classification 2017, an investigation of *SF3B1* is required for cases with ring sideroblasts (RS) between 5 and 14%, since a classification into the group of MDS-RS then already occurs from 5% RS and the presence of an *SF3B1* mutation.

Type 1 and type 2 mutations determine risk for s-AML progression:

A recent study showed an increase in mutation frequency over time and a higher mutation rate in high-risk MDS and secondary AML (Makishima et al. 2017). The study divided mutations in MDS patients into type 1 (*FLT3*, *PTPN11*, *WT1*, *IDH1*, *NPM1*, *IDH2* and *NRAS* mutations) and type 2 mutations (*TP53*, *GATA2*, *KRAS*, *RUNX1*, *STAG2*, *ASXL1*, *ZRSR2* and *TET2* mutations) (see Table 5). Type 1 mutations were associated with faster s-AML progression and shorter survival. Type 2 mutations were more common in high-risk MDS and had less impact on s-AML progression and survival than type 1 mutations.

Table 5: Influence of type 1 and type 2 mutations on the s-AML progression

Typ1 mutations	clinical impact
FLT3, *PTPN11*, *WT1*, *IDH1*, *NPM1*, *IDH2* and *NRAS*	• high, fast s-AML progression • shorter overall survival

Typ2 mutations	
TP53, *GATA2*, *KRAS*, *RUNX1*, *STAG2*, *ASXL1*, *ZRSR2* and *TET2*	• especially for high-risk MDS • less impact on s-AML progression and overall survival than type 1 mutations

Some of the gene mutations typically found in myeloid diseases have also been detected in recent years in individuals without known hematological disease (see **"Clonal hematopoiesis of indeterminate potential (CHIP)"**) or in patients with clonal cytopenia of undeterminate significance (see **"Clonal cytopenia of undetermined significance (CCUS)"**).

Overall, the question of the prognostic significance of somatic mutations is complex, since in addition to the type of mutation, the relevance of mutation load and various combinations of mutations must also be examined. Despite the comprehensive molecular genetic characterization (e.g. Papaemmanuil et al. 2013 and Haferlach et al. 2014), the significance of other mutations recurrent in MDS is therefore still a subject of research.

Prognosis of myelodysplastic syndrome (MDS)

For many years the "International Prognostic Scoring System" (IPSS), which was first published by Peter Greenberg in 1997 (Greenberg et al. 1997), was the main pillar of prognosis classification for patients with myelodysplastic syndrome (MDS). Prognostically relevant parameters are the proportion of bone marrow blast, the cytogenetic risk group and the number of relevant cytopenia. For an improved or more detailed risk stratification of patients with myelodysplastic syndrome (MDS) the IPSS was revised in 2012 (Revised-IPSS, "IPSS-R") (Greenberg et al. 2012, see Table 6). This should now be used.

The components used to determine the IPSS-R are the percentage of blasts in the bone marrow, the degree of cytopenia (Hb value as well as the number of platelets and neutrophils) and the cytogenetic risk group according to Schanz et al. 2012 (see Table 6 and Figure 1 in the section 'Classification of MDS into 5 cytogenetic risk groups'). The scoring points determined from this result in the classification of patients into five clinically relevant risk groups:

- "very low": ≤ 1.5
- "low": > 1.5-3
- "intermediate": > 3-4.5
- "high": > 4.5-6
- "very high": > 6

Table 6: Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome (Greenberg et al. 2012)

Prognostic variable	Scoring-Points						
	0	0,5	1,0	1,5	2,0	3,0	4,0
Cytogenetics	very good		good		intermediate	poor	very poor
BM-Blasts (%)	≤ 2		> 2- < 5		5-10	> 10	
Hemoglobin (g/dl)	≥ 10		8 - < 10	< 8			
Platelets (x 10^9/l)	≥ 100	50 - < 100	< 50				
ANC (x 10^9/l)	≥ 0,8	< 0,8					

The risk model is predictive both for the estimation of overall survival and for the transformation to secondary AML according to MDS (s-AML) (see Table 7). At the same time, it offers the possibility of age-adapted modification of the score. It thus enables the best possible risk stratification for patients with myelodysplastic syndrome (MDS) without taking into account previous findings in molecular genetics. Please note the different blast limits of the IPSS-R and the WHO 2017.

Table 7: IPSS-R prognostic risk category clinical outcomes (according to Greenberg et al. 2012)

IPSS-R risk group	very low	low	intermediate	high	very high
OS, all	8,8	5,3	3,0	1,6	0,8
HR AML	0,5	1,0	3,0	6,2	12,7

OS: median overall survival in years, HR: AML Hazard-Ratio transformation to AML

Recommendation for MDS

Peripheral blood diagnostics and cytomorphological bone marrow diagnostics in combination with cytogenetics represent the current gold standard in MDS diagnostics (Onkopedia Guideline MDS 2020). The European Leukemia Competence Network ("European LeukemiaNet" ELN, Malcovati et al. 2013) specifies in detail the methods summarised in Table 8.

Table 8: Diagnostic methods for myelodysplastic syndrome (MDS) according to ELN (2013)

Diagnostic tool	Diagnostic value	Priorität
Peripheral blood smear	• Evaluation of dysplasia in one or more cell lines • Enumeration of blasts	Mandatory
Bone marrow aspirate	• Evaluation of dysplasia in one or more hematopoietic cell lines • Enumeration of blasts • Enumeration of ring sideroblasts	Mandatory
Bone marrow biopsy	• Assessment of cellularity, $CD34^+$ cells, and fibrosis	Mandatory
Cytogenetic analysis	• Detektion of acquired clonal chromosomal abnormalities that can allow a conclusive diagnosis and also prognostic assessment	Mandatory
FISH	• Detection of targeted chromosomal abnormalities in interphase nuclei following repeated failure of standard G-banding	Recommended
Flow cytometry immunophenotyping	• Detection of abnormalities in erythroid, immature myeloid, maturing granulocytes, monocytes, immature and mature lymphoid compartments	Recommended
SNP array	• Detection of chromosomal defects at a high resolution in combination with metaphase cytogenetics	Suggested
Mutation analysis of candidate genes	• Detection of somatic mutations that can allow a conclusive diagnosis and also reliable prognostic evaluation	Suggested

Myelodysplastic syndrome (MDS) - Therapy

The therapy of a myelodysplastic syndrome (MDS) according to German guidelines depends amongs others on the risk group as well as the age and clinical condition of the patients (Onkopedia guideline MDS 2020). In addition to cytogenetics, which is included in risk stratification and therapy selection, the German guideline also classifies the molecular genetic analysis of the genes listed in Table 9 as clinically relevant.

Table 9: Clinically relevant molecular markers (according to Onkopedia guideline MDS 2020)

Function	Mutation
Splicing	*SF3B1*, *SRSF2*, *U2AF1*, *ZRSR2*
Methylation	*DNMT3A*, *TET2*
Methylation/Histone modification	*IDH1/2*
Histone modification	*ASXL1*, *EZH2*
Transkription factor	*RUNX1*, *TP53*, *BCOR*, *ETV6*
Signaling	*NRAS/KRAS*

The therapeutic breadth in low-risk MDS (IPSS-R score "very low", "low" and "intermediate") ranges from a watch-and-wait strategy (in the presence of asymptomatic cytopenia and absence of high-risk cytogenetics), through supportive therapies to the indication for allogeneic stem cell transplantation. The latter may be indicated in good clinical condition and in the presence of high-risk cytogenetics and/or pancytopenia. The group of patients with isolated del(5q) shows good response to the immunomodulator lenalidomide (Oncopedia Guideline MDS 2020).

In the group of high-risk MDS (IPSS-R score "high" and "very high") azacitidine, chemotherapy and allogeneic stem cell transplantation (allo-SZT) are the main pillars of therapy (Onkopedia Guideline MDS 2020).

Influence of genetic abnormalities on azacitidine therapy
In line with the effect of azacitidin as a DNA hypomethylating agent (HMA), there is evidence for a possible association between genetic abnormality and treatment response, especially in the case of mutations of epigenetic factors. In one study, azacitidin resistance was associated with *DNMT3A R882* mutations and mutations of the SKI domain of *SETBP1* (Falconi et al. 2019). In contrast, patients with *TET2* mutation (without concurrent *ASXL1* mutation) showed a particularly high sensitivity to HMAs (Itzykson et al. Leukemia 2011, Bejar et al. Blood 2014). However, in comparison of patients with mutated and wild type *TET2* there were no significant differences in overall survival and duration of response (Itzykson et al. Leukemia 2011, Bejar et al. Blood 2014).

Cytogenetic abnormalities may also influence the response to azacitidine. In one study, abnormal karyotypes were associated with a reduced response rate to azacitidine therapy and complex karyotypes with a shortened response time (Itzykson et al. Blood 2011, Kubasch & Platzbecker 2019). Patients with abnormalities of chromosome 7 had a survival advantage compared to conventional therapy by treatment with azacitidine (Raj et al. 2007, Rüter et al. 2007, Fenaux et al. 2009).

Gene mutations with potential influence on therapy decisions

***NPM1* mutations**
NPM1 mutations are extremely rare with an estimated mutation frequency of 2% in patients with myelodysplastic syndrome (MDS). Their presence should give rise to a thorough differential diagnosis, since they can also occur in the context of CMML. Due to the rarity it is unclear which therapy regimen is suitable for this patient group. The largest study to date includes a cohort of 31 patients with MDS and MDS/MPN neoplasias. In a comparison of the four therapeutic arms (HMA, HMA + allo-SZT, intensive chemotherapy, intensive chemotherapy + allo-SZT), intensive chemotherapy was superior to HMA treatment in terms of response rates and progression-free and overall survival. Patients on the HMA therapy arm also benefited significantly from allogeneic stem cell transplantation (Montalban-Bravo et al. 2019).

***TP53* mutations**
The mutation status of *TP53* plays a role in therapy planning in several ways.

While patients with isolated 5q deletion benefit from treatment with lenalidomide, *TP53* mutations against this genetic background are associated with a reduced response and an increased risk of progression (Jädersten et al. 2011). Therefore, a *TP53* mutation analysis should be performed before the administration of lenalidomide and the use of lenalidomide despite *TP53* mutation detection should only take place after thorough consideration and under close monitoring of clonal evolution (Onkopedia guideline MDS 2020).

According to the German guideline, an indication for an allogeneic stem cell transplantation should be considered also for younger low-risk patients, among others in the presence of prognostically unfavourable genetic markers such as *ASXL1* and *TP53* mutations (Onkopedia Guideline MDS 2020). The *TP53* mutation status should also be known for the choice of conditioning regimen, as patients with *TP53* mutation do not benefit from myeloablative conditioning (Lindsley et al. 2017). However, a *TP53* mutation retains its negative prognostic value with regard to overall survival even after allogeneic stem cell transplantation (Bejar et al. JCO 2014, Della Porta et al. 2016, Lindsley et al. 2017, Sperling et al. 2017). Further studies are needed to improve survival after transplantation in this patient group (Steensma et al. 2018).

References

You can find the corresponding references here:
https://www.mll.com/en/diagnostic-offer/myelodysplastic-syndrome-mds/myelodysplastic-syndromes-mds.html#references