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Guidelines for the Diagnosis and Prognosis of Adult Myelodysplastic Syndromes

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Guidelines for the Diagnosis and Evaluation of Prognosis of Adult Myelodysplastic Syndromes

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A British Society for Haematology Guideline

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Scope

This document represents an update of the British Society of Haematology guideline published in 2014 due to advances in understanding the biology and therapy of the myelodysplastic syndromes (MDS)[1]. The objective of these guidelines is to provide healthcare professionals with clear guidance on the diagnosis and evaluation of prognosis of adult patients with MDS. A separate BSH guideline covers the Management of Adult MDS which is published alongside this guideline. A separate good practice paper detailing the management of patients with chronic myelomonocytic leukaemia (CMML) will follow and is not considered in these guidelines.

Methodology

These guidelines were compiled according to the BSH process https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature Review Details

The guideline group was selected to be representative of UK medical experts and the manuscript was reviewed by the UK MDS Patient Support Group. Recommendations are based on a review of the literature using Medline/Pubmed searches. Search terms included: Myelodysplasia, MDS, myelodysplastic, refractory an(a)emia, refractory cytopenia, deletion 5q, del(5q), idiopathic cytopenia of

undetermined significance (ICUS), clonal cytopenia of undetermined significance (CCUS), clonal haematopoiesis of indeterminate potential (CHIP), diagnosis, diagnostic, investigation, cytogenetic, molecular, mutation, bone marrow, flow cytometry risk, prognosis.

Only English language publications from January 2012 to December 2020 were included in the literature search. Additional searches and subsection heading terms were conducted by members of the writing committee at the time of final submission to the British Journal of Haematology. Titles and/or abstracts of publications obtained from the database searches described were curated and manually reviewed by members of the writing committee.

Review of the Manuscript

Review of the manuscript was performed by the BSH Guidelines Committee Haemato-oncology Task Force, the BSH Guidelines Committee and the haemato-oncology sounding board of the BSH. It was also posted on the members section of the BSH website for comment. This guideline has also been reviewed by patient representatives from the MDS UK Patient Support Group (mdspatientsupport.org.uk). These organisations do not necessarily endorse the contents.

Introduction

The myelodysplastic syndromes (MDS) are a group of clonal bone marrow neoplasms characterised by ineffective haematopoiesis and manifested by morphological dysplasia in haematopoietic cells and by peripheral cytopenia(s)[2]. They have a variable predilection for the development of acute myeloid leukaemia (AML). The incidence of MDS in the UK is 3.72/100,000 population/year, it is predominantly a disease of the elderly (median age at diagnosis 75.7 years) and more common in men (approximately 2:1)[3].

Patients with suspected MDS should be assessed by a haematologist with a specialist interest in the disease. They should be referred for a second opinion to a regional or national centre when required by the clinician, or requested by the patient. All patients with a diagnosis of MDS must be discussed at a multi-disciplinary team meeting (MDT), which should include /s with experience of allogeneic stem cell transplantation. All patients diagnosed with MDS should be reported to the National Cancer Registry, via the MDT, and to MDS-specific registries if appropriate.

Diagnosis of MDS

Myelodysplastic syndrome is defined by a combination of cytopenias and morphological bone marrow dysplasia. Myelodysplastic syndromes should be considered in all patients with otherwise unexplained cytopenia(s). World Health Organisation (WHO) thresholds for cytopenias are haemoglobin <10 g/dl, absolute neutrophil count <1.8 x 10^9/l and platelets <100 x 10^9/l[2]. However, higher values (as defined by local laboratory ranges) do not exclude the diagnosis if definitive morphological and/or cytogenetic abnormalities are present. A diagnostic algorithm for suitable patients is outlined in Figure 1. Table 1 shows the minimum clinical

assessment and laboratory investigation of a patient with possible MDS. Selected patients may require further investigations (Table 2). Alternative causes of marrow dysplasia should also be considered.

In the context of persistent and otherwise unexplained cytopenias, a WHO-defined diagnosis of MDS requires either (i) morphological dysplasia (involving ≥10% of bone marrow cells in ≥1 lineage); (ii) increased myeloblasts (≥5%, but <20%); or (iii) evidence of clonality with a typical MDS-associated cytogenetic abnormality[2,4]. Dysplasia is not restricted to MDS patients and can occur following a toxic insult, in reactive conditions or secondary to haematinic deficiencies. Furthermore, dysplasia has been reported in healthy individuals[5,6].

Identifying MDS can therefore be challenging and caution is required when the diagnosis is based solely on morphology, particularly in borderline cases or those with unilineage dysplasia. Other causes of morphological dysplasia should be excluded and a period of observation followed by repeat sampling may be warranted. New technologies, in particular genomic testing, may help in challenging cases by providing additional markers of clonality. Although the presence of clonal markers should not be considered in isolation of other diagnostic modalities, there are strong associations between particular genetic lesions (for example mutations in *SF3B1* or isolated deletion of chromosome 5q) with WHO-defined MDS subtypes.

In patients with <10% marrow dysplasia and lacking a clonal abnormality, the term 'idiopathic cytopenia of undetermined significance' (ICUS) may be used where cytopenias are sustained (>6 months) and there is no other identifiable cause[7]. Such patients should be observed (with repeat investigation if necessary) for subsequent development of overt MDS.

Chronic myelomonocytic leukaemia (CMML) has been reclassified to the WHO subgroup of myelodysplastic/myeloproliferative neoplasms (MDS/MPN)[2] and is not considered further in this guideline.

In confirmed cases of MDS, family history and clinical features should be reviewed to identify those with germline predisposition, which may have implications for prognosis, genetic counselling and management.

Morphological Features

Both blood film and bone marrow examination by a haematologist or haemato-pathologist with experience in diagnosing MDS, looking for characteristic morphological features of dysplasia, are necessary for diagnosis, classification and prognostic evaluation of MDS.

Blood films should be assessed for dysplasia in erythroid, platelet and white cell lineages[2,8]. Bone marrow examination of May-Grünwald-Giemsa (or equivalent) stained smears should routinely comment on myeloid, megakaryocyte and erythroid maturation, and report dysplasia if present. Blast percentage should be enumerated. Optimal differential count should evaluate 500 or more nucleated cells, including 30 or more megakaryocytes.

Good quality smears and stains are essential for accurate diagnosis. Fresh specimens should be processed within 2 hours, where possible, and excess of EDTA should be strictly avoided. Stains should be well controlled and checked by examining non-MDS films.

Prussian Blue or Perls' stain should be performed on all marrow aspirates to assess iron stores and to quantitate ring sideroblasts. In the revised WHO classification[2], the

presence of an *SF3B1* mutation reduces the ring sideroblast percentage threshold required for a diagnosis of MDS with ring sideroblasts (MDS-RS) from 15% to 5%[2].

A trephine biopsy (decalcified, paraffin or plastic-embedded) should be taken from all patients and sectioned for analysis alongside the aspirate. Whilst dysplasia can be harder to assess, the histology of the trephine section provides supportive information for diagnosis, including architectural disruption (e.g., disruption of erythroid islands; abnormal localisation of immature precursors), cellularity and fibrosis (with reticulin staining). Trephine section histology is especially helpful for the diagnosis of hypocellular MDS and MDS/MPN overlap syndromes[9]. Patients with MDS/MPN overlap including CMML are now considered a distinct entity by the WHO where features of both MDS and MPN are present. This includes MDS/MPN-RS-T which may evolve from MDS-RS. Around 10–20% of patients with MDS have decreased marrow cellularity[10]. The WHO classification of myeloid neoplasm terms this hypoplastic MDS (h-MDS), although does not give it a distinct category[2]. Hypocellularity in MDS can present diagnostic difficulties with other bone marrow failure (BMF) syndromes especially aplastic anaemia. A study integrating cytohistological and genetic features in adult patients with hypocellular bone marrows has led to proposed criteria to define h-MDS[10]. This separates patients into two distinct groups, one with features highly consistent with myeloid neoplasm and one more consistent with a non-malignant BMF. The two groups have significantly different risk of blast progression and OS. Flow cytometry should be performed for paroxysmal nocturnal haemoglobinuria in patients with h-MDS.

Enumeration of blast percentage should be undertaken by morphological assessment of the bone marrow aspirate. This is considered the gold standard.

However, if the aspirate smear is suboptimal, then the bone marrow trephine section may be used to quantitate blasts using immunohistochemistry.

Flow Cytometry

There is no specific immunophenotypic finding diagnostic of MDS, and flow cytometry is therefore not mandatory. Aberrant flow cytometric profiles may support the diagnosis of MDS but should be interpreted with morphological and cytogenetic or molecular findings. Common findings are aberrant antigen expression on myeloid progenitors, maturing myeloid, monocytic and erythroid lineages, reduced numbers of B-cell progenitors[11], and increased CD34+ cells. Many cases also show lineage infidelity antigen expression. Flow cytometry can be useful to enumerate myeloid progenitor cells (CD34+ cells) which may in turn be a proxy for morphological blast percentage but these do not always correlate precisely, for example due to haemodilution of the aspirate or the progenitor cell phenotype lacking CD34 expression. Recommendations for standardisation of flow cytometric methodology, including consensus recommendations for cell sampling, handling and processing have been published[12–16]; validation is ongoing.

Cytogenetics

Chromosomal abnormalities evidencing a clonal disorder are detected by cytogenetic analyses in approximately 50% of MDS patients. Some recurrent abnormalities (most commonly, –5, del(5q), –7, del(7q), i(17q)) are considered MDS-defining in a cytopenic patient, even without morphological dysplasia (a comprehensive list is shown in Figure 1 and Table 3)[2,17]. G-banding or metaphase cytogenetic analysis should be performed on all suspected MDS cases to aid diagnosis, prognosis and inform management. When no abnormality is found in a

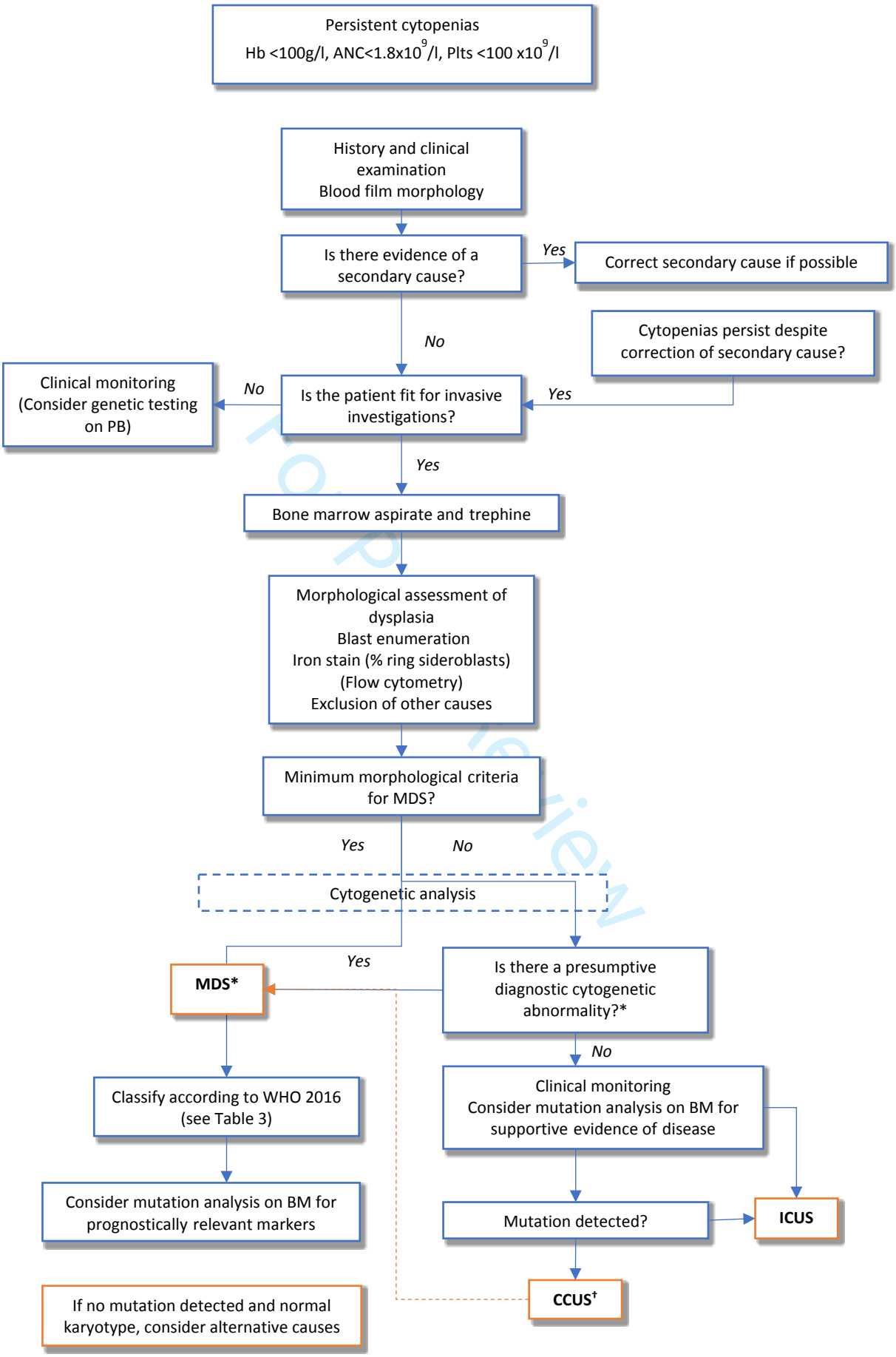
diagnostic sample, a minimum of 20 metaphases should be examined and reported using International System for Human Cytogenetic Nomenclature Recommendations[18]. Cytogenetic assessment is essential for international prognostic scoring systems[17]. Furthermore, specific cytogenetic abnormalities may provide a marker for assessing response to therapy and evaluating residual disease. Since both the type and number of karyotypic abnormalities may have prognostic significance, adherence to International Working Group on MDS Cytogenetics consensus guidelines in the enumeration of abnormalities is recommended[19].

In cases where G-banding analysis is not possible or fails, fluorescence in situ hybridisation (FISH) analysis of marrow aspirate or peripheral blood smears for selected common cytogenetic anomalies (e.g., –7, del(5q), +8) may be performed, to detect key abnormalities of prognostic significance or provide confirmation of clonality in borderline diagnostic cases.

Where available, single nucleotide polymorphisms array analysis (SNP-A) can provide a more precise, genome-wide analysis which is independent of metaphases[20–22]. Although not currently mandated in diagnostic work-up, this can provide useful additional information. In particular, where conventional cytogenetics fails SNP-A array can provide a full karyotype, and should be strongly considered in such cases. SNP-A may also detect karyotypic abnormalities in ~16–30% additional cases where they were not detected by metaphase cytogenetics (MC)[20–22]. Importantly, copy number abnormalities detected by SNP-A in cases where none were found by MC, are prognostic[23], thus prognostic equivalence can be reasonably assumed for larger structural abnormalities detected by this approach, and should be reported as such. This, however, cannot currently be assumed for smaller abnormalities below the detection resolution of conventional cytogenetics. SNP-A

reports should state clearly those lesions considered detectable by MC and which should (and should not) be considered when calculating the cytogenetic risk score for current prognostic systems (e.g., R-IPSS). Furthermore, SNP-A have limited capacity for detecting translocations which are confined to those with associated microdeletions or uni-parental disomy[24].

Figure 1 Myelodysplastic Syndrome Diagnostic Algorithm



Abbreviations: PB, peripheral blood; MDS, myelodysplastic syndrome; BM, bone marrow; ICUS,

idiopathic cytopenias of undetermined significance; CCUS, clonal cytopenias of undetermined significance

*Presumptive evidence of MDS (Schanz *et al*, 2012, Swerdlow *et al* 2017)[17,2] –7 or del(7q); –5 or del(5q); i(17q) t(17p) or del(17p); -13 or del(13q); del(11q); del(12p) or t(12p); del(9q); Idic(X)(q13); t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23.3); inv(3)(q21q26.2)/t(3;3)(q21;q23.3); t(6;9)(p23;q34.1)

†The following mutations in CCUS are strongly suggestive of a clinical outcome similar to MDS and/or the subsequent development of overt MDS: 1. Spliceosome mutations (*SRSF2, U2AF1, ZRSR2*); 2. co-mutation patterns involving *TET2, ASXL1* or *DNMT3A* along with any of *RUNX1, EZH2, CBL, BCOR, CUX1, TP53* or *IDH1/2* (Malcovati *et al*, 2017)[41].

Molecular Genetics

Next-generation sequencing (NGS) has identified recurrent gene mutations in DNA from haematopoietic cells of ~90% of MDS patients, some of which may have independent prognostic significance[25–27]. Molecular testing using targeted mutation panels is now widely available, increasingly affordable and should be considered in all patients (unless clearly not appropriate) for its potential to inform on diagnosis, prognosis and management. Sensitivity is highest on bone marrow, but can usefully be performed on peripheral blood in situations in which bone marrow biopsy is impractical or undesirable (provided that circulating myeloid cells are present). Patients should be counselled and at least verbal consent taken prior to genetic testing to explain the possible results including the implications of identifying a germline mutation.

Detection of certain MDS-associated mutations can be used to establish subtypes with prognostic relevance. For example, *SF3B1* mutations are found in >95% of MDS cases with ring sideroblasts, and are associated with a relatively favourable prognosis[28] compared with *SF3B1* wild-type MDS-RS cases[29]. Due to its characteristic features *SF3B1*-mutated MDS has been proposed by The International Working Group as a distinct MDS subtype, although this is not yet formally incorporated into the WHO classification[30]. *TP53* mutations in MDS with isolated del(5q) helps identify early clonal evolution and predict disease progression and

poorer prognosis in this generally favourable subgroup[31]. In MDS more broadly, combinations of mutation, deletion and/or loss of heterozygosity events, resulting in "double-hit" biallelic loss of *TP53*, are strongly associated with complex (typically monosomal) karyotype and exceptionally poor survival outcomes[32]. By contrast, patients with single-hit, monoallelic *TP53* mutations often lack associated chromosomal aneuploidies and display similar therapy response and outcomes to MDS patients without mutated *TP53*[32,33].

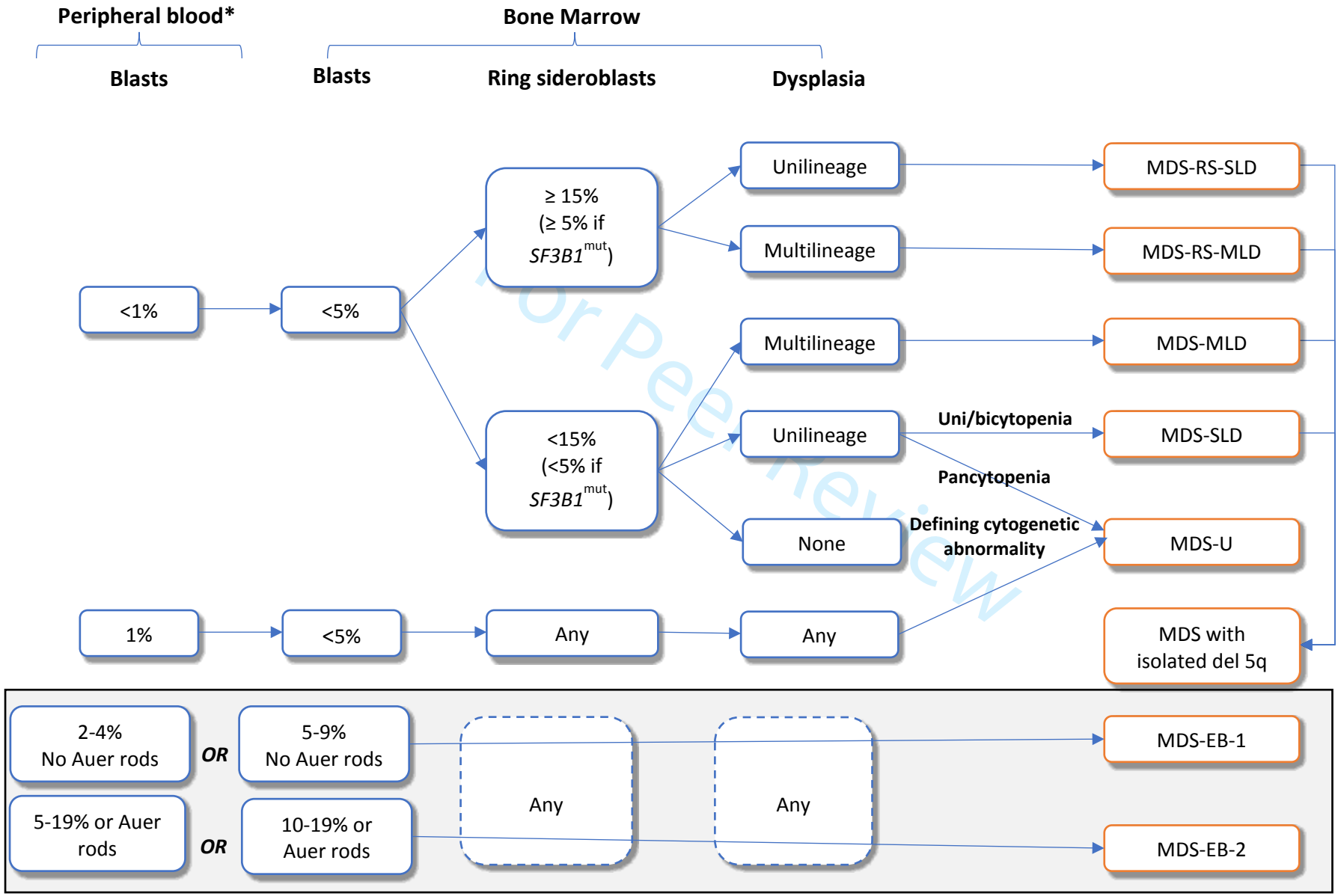
Mutations in genes such as *ASXL1, EZH2* and *RUNX1* confer adverse prognosis in univariate analysis but their prognostic significance in multivariate analysis has not yet been consistently reproduced in independent series[34,28]. Mutation status will likely inform prognosis in future models (e.g., International Prognostic Scoring System [IPSS]-Molecular; in development) and guide eligibility for clinical trials of emerging targeted therapies (e.g., *IDH1/IDH2* inhibitors; spliceosome inhibitors).

In view of potential challenges of morphological diagnosis of MDS, mutation analysis can provide objective evidence of clonal disease. However, somatic mutations can be identified in healthy individuals and detection of mutations alone is not considered diagnostic[2]. Notably, MDS patients tend to have a higher allele fraction and greater number of mutations than healthy, older individuals[35,36].

In an attempt to standardise testing, NHS England has created the NHS Genomic Medicine service, comprised of a national Genomic Laboratory Hub (GLH) network. A National Genomic Test Directory specifies genomic tests commissioned by the NHS in England and patients who are eligible for testing. Each GLH will provide cytogenetics and DNA sequencing with analysis and expert interpretation. Currently, those with suspected or confirmed MDS are eligible for a targeted NGS panel.

Classification of MDS

Classification of MDS remains largely based upon morphological examination[2]. The latest WHO revision has updated nomenclature and removed the focus on specific lineage of cytopenia (Table 3 and Figure 2)[2]. A WHO classification subtype should be recorded for every patient in the bone marrow report. In adult patients with at least 20% blasts the disease is classified as AML, although cases with 20–30% blasts were included in derivation of the IPSS. Myelodysplastic syndrome secondary to prior cytotoxic therapy is classified separately, under therapy-related myeloid neoplasms.



Abbreviations: MDS-EB, MDS with excess blasts; MDS-MLD, MDS with multilineage dysplasia; MDS-RS, MDS with ring sideroblasts; MDS-RS-

MLD, MDS with ring sideroblasts and multilineage dysplasia; MDS-RS-SLD, MDS with ring sideroblasts and single lineage dysplasia; MDS-SLD, MDS with single lineage dysplasia; MDS-U, unclassifiable MDS; mut, mutated ; SLD, single lineage dysplasia

*Peripheral blood monocytes must be <1x10^9/l. Therapy related neoplasms (T-MNs) remain as a distinct category in the WHO classification.

Clonal Haematopoiesis of Indeterminate Potential and Other Related Entities

Clonal haematopoiesis can be detected in the healthy population, typically with increasing age[37–40]. This is frequently characterised by acquisition of MDS-associated mutations, but without other clinico-pathological features of MDS. This has been termed “clonal haematopoiesis of indeterminate potential” (CHIP) or “age-related clonal haematopoiesis” (ARCH), and can be found in >10% of healthy individuals over 70 years of age[38]. The most commonly identified mutations are in genes involved in epigenetic regulation (*DNMT3A, TET2*, *ASXL1*). These are commonly mutations in single genes only, at low allele frequency (<10%). Risk of transformation to haematological malignancy is low (<1% per year). Annual monitoring of blood counts in individuals found to have CHIP may therefore be appropriate. Factors that might increase risk of progression to myeloid malignancy include higher variant allele frequency, presence of multiple CHIP mutations or particular high risk mutations (e.g., *TP53, IDH2*)[35].

A new nomenclature has emerged for conditions related to MDS but not fulfilling the formal diagnostic criteria (Table 4). These are increasingly used to describe observed states bearing isolated molecular, cytopenic or morphological features associated with MDS, and which might predispose to haematological malignancy. ICUS carries approximately 9% risk of developing myeloid malignancy at 10 years[41]. Evidence-based recommendations on monitoring cannot yet be made and decisions should be guided by the overall clinical picture and context; the possibility of non-MDS-related causes for the cytopenia should be reviewed during follow-up. By contrast, close monitoring of patients with CCUS is recommended, given emerging evidence that these patients carry a high — possibly universal — risk of progression to frank haematological malignancy[41].

MDS with Germline Predisposition

Beyond securing a diagnosis, identification of a germline condition underlying MDS can have important implications for treatment planning; for example, when selecting sibling donors for allogeneic stem cell transplantation. A 3-generational family history should be taken. Table 5 outlines individuals in whom the possibility of a myeloid neoplasm with germline predisposition should be considered.

Some germline mutations, such as those in *TP53, RUNX1* and *GATA2,* may also be detected by NGS platforms aimed at detecting somatic mutations. Germline variants may be suggested by a variant allele frequency around 50%, although can be the case too for dominant, deeply established somatic clones, so cannot alone be routinely taken as presumptive evidence.

Early contact with a centre having clinical experience of constitutional marrow failure syndromes and a clinical genetics department is indicated in cases of suspected germline conditions. Patients and family members should ideally be offered genetic counselling before genetic screening if there is a high clinical suspicion[42].

Recommendations:

- **Myelodysplastic Syndromes (MDS) should be suspected in patients with otherwise unexplained cytopenias(s) or macrocytosis (1A).**
- **The initial assessment of a patient with unexplained cytopenia(s) may not confirm a diagnosis of MDS. Further follow-up and reassessment may be necessary to reach a firm diagnosis (2 B,C).**
- **Initial assessment of a patient with suspected MDS should include a minimum set of investigations and the differential diagnosis of marrow dysplasia should be considered (1A).**

- **A detailed clinical and family history should identify potential cases of MDS with germline predisposition. In suspected cases early referral to clinical genetics is indicated.**
- **All cases of MDS should be classified according to the current WHO Classification (1A).**
- **Bone marrow cytogenetic analysis should be performed on all patients with suspected MDS having a bone marrow examination (1A).**
- **Where conventional karyotyping is not possible or fails, fluorescence in situ hybridisation (FISH) for selected abnormalities (e.g., –7, del(5q), +8) or alternatively SNP array analysis should be performed (2B).**
- **Mutational analysis is recommended where it might help clarify sub-classification of disease, identify prognostic mutations in the relevant setting or guide management decisions (1A).**
- **Mutational analysis should be considered in diagnostically difficult cases to either support or refute a diagnosis of MDS (2B).**
- **All cases of MDS should be reported to the National Cancer Registry and to MDS-specific registries if available.**
- **Patients with MDS should be reviewed by a haematologist with a specialist interest in MDS and referred for a second opinion if the patient or clinician so desires (2B).**

Prognosis of Myelodysplastic Syndromes

Since its publication in 1997, the IPSS has been an important tool for assessing the outcome of patients with untreated, primary adult MDS[43]. Additional prognostic variables have been identified, the most important of which are newer cytogenetic groupings (Table 6) that give more accurate prognostic information[17].

The Revised IPSS (IPSS-R) described the relative importance of defined clinical factors to prognosis by multivariate analysis of 7012 primary, adult MDS patients not treated with disease-modifying therapies. Using the same parameters as the IPSS (cytogenetic groups, marrow blast percentage and cytopenias), it provided extended categorization of cytogenetic subgroups, refinement of blast counts <5% and depth of cytopenias (Table 7)[44]. The IPSS-R stratifies into 5 risk categories and has improved the prognostic ability to determine survival and AML evolution in untreated adult patients with primary MDS (Table 8). A web-based tool to calculate the IPSS-R can be accessed via the UK MDS Forum website (www.ukmdsforum.org.uk).

In some head-to-head comparisons the IPSS-R has outperformed both the IPSS and WHO-based (WPSS) prognostic models, at least for some subgroups[45–47] and is currently the recommended scoring system for determining prognosis. However, as long as NICE approval for azacitidine is based on IPSS risk, that earlier model retains clinical utility in the UK.

Mutation data do not currently inform any prospectively validated prognostic scoring system in MDS. An IPSS-Molecular is currently under development.

Consideration should be given to a regular review of prognosis for individual MDS patients. For example, loss of response to erythropoiesis stimulating agents or lenalidomide is associated with a reduction in overall survival. By contrast, dynamic IPSS or IPSS-R data indicate that for lower-risk MDS, the longer the patient remains

low risk, the better the overall prognosis compared with the prognosis at diagnosis[48,49].

In lower-risk patients potentially eligible for allogeneic stem cell transplantation, consideration should be given to surveillance bone marrow testing. Although mathematical modelling of timing of transplantation was originally based on a move to transplant after AML transformation in lower-risk MDS, expert opinion would favour considering transplantation following identification of earlier signs of progression, such as increased bone marrow blast percentage, clonal evolution (cytogenetic/molecular), or increasing fibrosis in subtypes such as del(5q) MDS[50]. Such surveillance should be in liaison with the transplant centre.

Recommendations:

- **At diagnosis the prognosis for all patients should be calculated using IPSS-R & IPSS (1B).**
- **Dynamic review of prognosis should be performed, for example at loss of response to therapy (2C).**
- **Patients with low-risk MDS at diagnosis and who may be candidates for allogeneic transplantation should be monitored carefully for the development of higher risk features (2B).**

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Declaration of Interests

All authors and the UK MDS Patient Support Group have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request.

Review Process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/).

Disclaimer

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

Tables

Table 1: Minimum clinical assessment and laboratory investigation of a patient with possible MDS*

Assessment	Data Collected
History	Alcohol intake
	Prior exposure to chemotherapy/radiotherapy
	Family history of MDS/AML, thrombocytopenia, malignancy, or pulmonary/liver fibrosis
	Nutritional and environmental/occupational history considering exposure to benzenes and potential nutrient deficiencies or exposures e.g., copper, zinc, selenium, B6, lead exposure.
Examination	Dysmorphic features (suggesting congenital bone marrow failure)
	Active infection/bruising/bleeding
Blood Tests	Full blood count including differential white cell count
	Blood film analysis
	Haematinics – B12, folate, ferritin and iron studies
	Lactate Dehydrogenase
	Reticulocyte count
	Direct Coombs test
	Renal and liver function tests
Bone marrow aspirate and trephine section histology	Morphological assessment and quantification of blast population
	Iron stain of aspirate
	Cellularity assessment and reticulin stain of trephine biopsy
	Cytogenetic analysis – G-banding, FISH and/or SNP array
	Bone marrow immune-phenotyping with analysis of aberrant antigen expression and quantification of marrow blasts**
	Marrow mutational analysis/genomic studies**

Abbreviations: MDS, myelodysplastic syndromes; AML, acute myeloid leukaemia
*It is assumed that investigations have excluded alternative causes of macrocytic anaemia, sideroblastic change (if present) and cytopenias.
**Not mandatory in all cases, but can provide potentially useful diagnostic and prognostic information and should be considered for all patients.

Table 2: Further investigations indicated in selected patients

Assessments Indicated for Selected Patients
Erythropoietin level
Flow cytometric screen for paroxysmal nocturnal haemoglobinuria
Fanconi anaemia screen
Mutational analysis if constitutional causes suspected e.g., telomerase complex gene mutations
Tissue typing of patient and siblings if the patient is a candidate for stem cell transplantation
Full virology including HIV, Hepatitis B, C & E, CMV and parvovirus
Red blood cell phenotyping in patients requiring transfusion or stem cell transplant candidates
JAK2 gene mutational analysis in patients with features of myeloproliferation and/or thrombocytosis
Copper levels where nutritional deficiency suspected in association with dysplasia

Abbreviations: HIV, human immunodeficiency virus; CMV, Cytomegalovirus

Table 3: WHO Classification of Myelodysplastic Syndromes

Entity Name	Number of dysplastic lineages	Number of cytopenia[a]	Ring sideroblasts as percentage of marrow erythroid elements	Bone marrow and peripheral blood blasts	Cytogenetics by conventional karyotype analysis
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-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-RS					
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-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 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 or del(7q)

Entity Name	Number of dysplastic lineages	Number of cytopenia[a]	Ring sideroblasts as percentage of marrow erythroid elements	Bone marrow and peripheral blood blasts	Cytogenetics by conventional karyotype analysis
MDS-EB					
MDS-EB-1	1–3	1–3	None or any	BM 5-9% or PB 2-4%, BM <10% and PB <5%, No Auer rods	Any
MDS-EB-2	1–3	1–3	None or any	BM 10-19% or PB 5-19%, Or Auer rods BM and PB <20%	Any
MDS-U					
With 1% blood blasts	1–3	1–3	None or any	BM <5%, PB <1%, No Auer rods	Any
With SLD and pancytopenia	1	3	None or any	BM <5%, PB <1%, No Auer rods	Any
Based on defining cytogenetic abnormality	0	1–3	<15%[d]	BM <5%, PB <1%, No Auer rods	MDS-defining abnormality[e]

Abbreviations: BM, bone marrow; PB, peripheral blood; MDS-EB, MDS with excess blasts; MDS-MLD, MDS with multilineage dysplasia; MDS-RS, MDS with ring sideroblasts; MDS-RS-MLD, MDS with ring sideroblasts and multilineage dysplasia; MDS-RS-SLD, MDS with ring sideroblasts and single lineage dysplasia; MDS-SLD, MDS with single lineage dysplasia; MDS-U, unclassifiable MDS; SLD, single lineage dysplasia; WHO, World Health Organisation

[a] Cytopenias defined as haemoglobin concentration <10g/dl, platelet count <100x10^9/l and absolute neutrophil count <1.8x10^9/l, although MDS can present with mild anaemia or thrombocytopenia above these levels; PB monocytes must be <1x10^9/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 6.03, p. 104 (Swerdlow et al, 2017)[2] and Figure 1 in this manuscript.

Notes: Therapy-associated MDS and MDS/MPN should classify in the category “Therapy-associated Myeloid Neoplasms”. Reproduced, with the permission of the publisher (Swerdlow et al, 2017)[2].

Table 4: Definitions of Clonal Haematopoiesis and Related Conditions not Fulfilling the Diagnostic Criteria for Myelodysplastic Syndromes

Acronym	Full Name	Accepted Definition
CHIP/ARCH	Clonal haematopoiesis of indeterminate potential Age-related clonal haematopoiesis	Identification (≥2% variant allele frequency) of somatic mutations associated with myeloid malignancy in blood or bone marrow cells in individuals without diagnostic evidence of a haematological disorder.
ICUS	Idiopathic cytopenia of undetermined significance	Patients with ≥1 unexplained cytopenia but without features sufficient to diagnose MDS or another haematological disorder; typically used where CHIP/ARCH is not detected.
CCUS	Clonal cytopenia of undetermined significance	Patients with ≥1 unexplained cytopenia without features sufficient to diagnose MDS or another haematological disorder, but with associated clonal haematopoiesis.

Abbreviations: MDS, myelodysplastic syndromes
Note: Reproduced, with the permission of the publishers (Bejar R, 2017)[53].

Table 5: Individuals in Whom the Possibility of a Myeloid Neoplasm with Germline Predisposition Should Be Considered

Subjects in whom the possibility of a myeloid neoplasm with germline predisposition should be considered
Any patient presenting with MDS or AML, with any of the following:
A personal history of multiple cancers
Thrombocytopenia, bleeding propensity, or macrocytosis preceding the diagnosis of MDS/AML by several years
A first- or second-degree relative with a haematological neoplasm
A first- or second-degree relative with a solid tumour consistent with germline predisposition; i.e. sarcoma, early-onset breast cancer (at patient age <50 years), or brain tumours
Abnormal nails or skin pigmentation, oral leukoplakia, idiopathic pulmonary fibrosis, unexplained liver disease, lymphoedema, atypical infections, immune deficiencies, congenital limb anomalies, or short stature (in the patient or a first- or second-degree relative)
Any healthy potential haematopoietic stem cell donor who is planning to donate for a family member with a haematological malignancy with any of the conditions listed above or who fails to mobilise stem cells with standard protocols

Abbreviations: AML, acute myeloid leukaemia; MDS, myelodysplastic syndromes
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Table 6: IPSS-R Cytogenetic Prognostic Subgroups

Very Good	–Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double that include del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	–7, inv(3)/t(3q), double including –7/del(7q), complex: 3 abnormalities
Very Poor	Complex: >3 abnormalities

Abbreviations: IPSS-R, revised international prognostic scoring system
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Note: Unless indicated otherwise, these prognostic classifications of chromosomal aneuploidies apply only if they are in isolation.

Table 7: IPSS-R Prognostic Score Values

Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
Bone marrow blast %	≤2		>2–<5		5–10	>10	
Haemoglobin concentration (g/l)	≥100		80–<100	<80			
Platelet count (x 10^9/l)	≥100	50–<100	<50				
Neutrophil count (x 10^9/l)	≥0.8	<0.8					

Abbreviations: IPSS-R, revised international prognostic scoring system
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Table 8: IPSS-R Prognostic Risk Categories/Scores and Clinical Outcomes

Risk category	**Risk Score**	**Survival (median–years)**	**25% AML evolution (median–years)**
Very Low	≤1.5	8.8	Not Reached
Low	>1.5–3	5.3	10.8
Intermediate	>3–4.5	3.0	3.2
High	>4.5–6	1.6	1.4
Very High	>6	0.8	0.73

Abbreviations: AML, acute myeloid leukaemia; IPSS-R, revised international prognostic scoring system
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