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Special Report

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

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The classification of myeloid neoplasms and acute leukemias was last updated in 2016 within a collaboration between the World Health Organization (WHO), the Society for Hematopathology, and the European Association for Haematopathology. This collaboration was primarily based on input from a clinical advisory committees (CACs) composed of pathologists, hematologists, oncologists, geneticists, and bioinformaticians from around the world. The recent advances in our understanding of the biology of hematologic malignancies, the experience with the use of the 2016 WHO classification in clinical practice, and the results of clinical trials have indicated the need for further revising and updating the classification. As a continuation of this CAC-based process, the authors, a group with expertise in the clinical, pathologic, and genetic aspects of these disorders, developed the International Consensus Classification (ICC) of myeloid neoplasms and acute leukemias. Using a multiparameter approach, the main objective of the consensus process was the definition of real disease entities, including the introduction of new entities and refined criteria for existing diagnostic categories, based on accumulated data. The ICC is aimed at facilitating diagnosis and prognostication of these neoplasms, improving treatment of affected patients, and allowing the design of innovative clinical trials.

Introduction

The third, fourth and revised fourth editions of the World Health Organization (WHO) Classification of the Tumors of Hematopoietic and Lymphoid Tissues[1-3] were collaborations between the WHO, the Society for Hematopathology (SH), and the European Association for Haematopathology (EAHP) based on input from clinical advisory committees (CACs) composed of numerous pathologists, hematologists, oncologists, and geneticists. The outcome of those CACs were published in peer-reviewed journals and ultimately resulted in the "blue book" monographs.[4-8] As described in more detail elsewhere[9] and the commentary in this issue, the fifth edition blue book series as planned by the International Agency for Research on Cancer (IARC) lacked oversight of SH and EAHP and did not follow a CAC process. Ultimately, a CAC endorsed by SH and EAHP, separate from the WHO, was held to update the prior classification. Because it was a revision of the prior fourth edition, the revised fourth edition WHO classification, published in 2016, was tasked to not be a major overhaul of disease categories but simply as an update based on new knowledge. Major advances in the understanding of myeloid neoplasms and acute leukemia have occurred since the original fourth edition publication in 2008, and a more significant change to disease classification is now warranted. This new classification represents a major revision of the prior classifications and includes many authors of the prior WHO editions but is no longer affiliated with the WHO. This report summarizes the new International Consensus Classification (ICC) with a focus on myeloid neoplasms and acute leukemia (Table 1). A separately published report will summarize the ICC of lymphoid neoplasms which together constitute the International Consensus Classification of Myeloid and Lymphoid Neoplasms.

Myeloproliferative neoplasms

The major categories of myeloproliferative neoplasms (MPN)[3] remain unchanged in the ICC; however, continuous integration of new molecular data and improved understanding of morphology have sharpened the proposed diagnostic criteria.[10,11]

In chronic myeloid leukemia (CML), progression to advanced phases[12-14] (Table 2) is a consequence of continued *BCR::ABL1* activity, induced proliferation of leukemic cells, and further genetic instability and DNA damage.[15] This invariably leads to clonal evolution and acquisitions of mutations both inside and outside the *BCR::ABL1* kinase domain and additional chromosomal abnormalities (ACAs). Therefore, the presence of major route ACAs at diagnosis or the acquisition of major route ACAs on treatment are considered as the hallmark of CML in accelerated phase (CML-AP),[14,16] although most ACAs were defined prior to the use of tyrosine kinase inhibitor therapy. A bone marrow (BM) trephine biopsy is indicated for patients who meet any of the criteria for CML-AP or blast phase (CML-BP) and for patients who have a clinical history suggestive of disease progression (eg, progressive splenomegaly). Importantly, an increase in BM reticulin fibers at the time of diagnosis is correlated with a decreased major molecular response rate in the first year of tyrosine kinase inhibitor therapy.[17] The ICC has maintained a blast percentage threshold of 10% to 19% and at least 20% in the blood or BM to establish the diagnosis of AP and BP, respectively. Increasing numbers of lymphoblasts (>5%) in

Table 1. Major ICC categories of myeloid neoplasms and acute leukemias

MPNs
Chronic myeloid leukemia
Polycythemia vera
Essential thrombocythemia
Primary myelofibrosis
Early/prefibrotic primary myelofibrosis
Overt primary myelofibrosis
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia, not otherwise specified
MPN, unclassifiable
Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions
Myeloid/lymphoid neoplasm with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasm with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasm with *FGFR1* rearrangement
Myeloid/lymphoid neoplasm with *JAK2* rearrangement
Myeloid/lymphoid neoplasm with *FLT3* rearrangement
Myeloid/lymphoid neoplasm with *ETV6::ABL1*
Mastocytosis
Myelodysplastic/myeloproliferative neoplasms
Chronic myelomonocytic leukemia
Clonal cytopenia with monocytosis of undetermined significance
Clonal monocytosis of undetermined significance
Atypical chronic myeloid leukemia
Myelodysplastic/myeloproliferative neoplasm with thrombocytosis and *SF3B1* mutation
Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, not otherwise specified
Myelodysplastic/myeloproliferative neoplasm, not otherwise specified
Premalignant clonal cytopenias and myelodysplastic syndromes
Clonal cytopenia of undetermined significance
Myelodysplastic syndrome with mutated *SF3B1*
Myelodysplastic syndrome with del(5q)
Myelodysplastic syndrome with mutated *TP53*
Myelodysplastic syndrome, not otherwise specified (MDS, NOS)
MDS, NOS without dysplasia
MDS, NOS with single lineage dysplasia
MDS, NOS with multilineage dysplasia
Myelodysplastic syndrome with excess blasts
Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)
MDS/AML with mutated *TP53*
MDS/AML with myelodysplasia-related gene mutations
MDS/AML with myelodysplasia-related cytogenetic abnormalities
MDS/AML, not otherwise specified

Table 1. (continued)

Pediatric and/or germline mutation-associated disorders
Juvenile myelomonocytic leukemia
Juvenile myelomonocytic leukemia-like neoplasms
Noonan syndrome-associated myeloproliferative disorder
Refractory cytopenia of childhood
Hematologic neoplasms with germline predisposition
Acute myeloid leukemias (Tables 25 and 26)
Myeloid proliferations associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemia of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR::ABL1*
MPAL, with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma (Tables 27 and 28; supplemental Table 6)
T-lymphoblastic leukemia/lymphoma (Table 27; supplemental Table 6)

peripheral blood (PB) or BM may indicate impending lymphoid BP and thus should prompt further laboratory and genetic studies.[18] Of note, other classification and risk stratification systems that include the International Blood and Marrow Transplant Registry,[19] M. D. Anderson Cancer Center,[20] and the European LeukemiaNet[21] have defined a higher blast threshold of more than 30% for BP and are frequently used as eligibility criteria in clinical trials.[12,21]

The classical *BCR::ABL1*-negative MPN subtypes include polycythemia vera (PV) (Table 3), essential thrombocythemia (ET) (Table 4), and primary myelofibrosis (PMF) (Table 5). The principal objective in the classification of these cases is to reduce diagnostic uncertainty especially in initial/early disease stages presenting with elevated platelet counts and to optimize clinical management of patients.[10] The integration of molecular findings with BM morphology and blood counts remains the cornerstone of diagnosis. Importantly, morphologic diagnosis should not only focus on megakaryocytic atypia but has to consider characteristic patterns of other features like age-related cellularity, changes in erythropoiesis, and neutrophil granulopoiesis in context with the grade of BM fibrosis.[22] Following the 2016 revision of the WHO classification, an increasing number of investigators were able to validate the diagnostic accuracy of this approach and consequently strongly support the definition of an early/pre-fibrotic stage of PMF (pre-PMF).[23-26] In this context, dense clustering of megakaryocytes (3 or more megakaryocytes lying adjacent without other BM cells in between), which is generally accepted as the morphologic hallmark of PMF,[22,27] does not exclude the diagnosis of ET, because infrequently small megakaryocytic clusters may be present even in this subtype. Compared with pre-PMF, patients with ET usually present with normal white blood cell counts, no anemia, normal lactate dehydrogenase (LDH) values, less frequently splenomegaly, and lower numbers of CD34-positive progenitor cells in PB and BM.[23,24,26] Distinction is important because ET has a lower risk for major hemorrhagic events, a significantly lower risk of myelofibrotic progression (ie, post-ET myelofibrosis) ranging between 0.8% and 4.5% at 10 years, and a very low risk of transformation to BP with more than 20% of PB/BM blasts with a reported 10-year cumulative incidence between 0.7% and 1.9%.[28,29]

Table 2. Diagnostic criteria for accelerated and blast phase chronic myeloid leukemia (CML)

Accelerated phase	Blast phase
Bone marrow or peripheral blood blasts 10%-19%	Bone marrow or peripheral blood blasts ≥ 20%
Peripheral blood basophils ≥ 20%	Myeloid sarcoma†
Presence of additional clonal cytogenetic abnormality in Ph+ cells (ACA)*	Presence of morphologically apparent lymphoblasts (>5%) warrants consideration of lymphoblastic crisis‡

Ph, Philadelphia chromosome.

*Second Ph, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or abnormalities of 3q26.2.

†Extramedullary blast proliferation.

‡Immunophenotypic analysis is required to confirm lymphoid lineage.

Accurate identification of MPN-associated driver mutations, *JAK2* V617F, *JAK2* exon 12, *MPL* W515L/K, and calreticulin (*CALR*) by highly sensitive single target (quantitative reverse transcriptase-polymerase chain reaction [RT-qPCR], digital droplet PCR [ddPCR]) or multitarget panel/next generation sequencing (NGS) assays with a minimal sensitivity of variant allele frequency (VAF) 1%, is important to support a diagnosis of PV, ET, or PMF and to separate wild-type or triple-negative cases.[30,31] In triple-negative cases, the search for noncanonical *JAK2* and *MPL* mutations (the latter for suspected ET and PMF) is encouraged, whereas a *JAK2* V617F VAF of <1% should prompt the search for coexisting canonical *CALR* (and *MPL*) mutations. In PV, high VAF for *JAK2* V617F is associated with older age, higher hemoglobin level, leukocytosis, and lower platelet count.[32] *JAK2* exon 12 mutated cases are prognostically similar to *JAK2* V617F mutated cases, although they may occur at a younger age. Because a proportion of these cases may be characterized by isolated erythrocytosis associated with erythroid preponderance in the BM, the diagnostic criterion of panmyelosis may not be applicable to this patient subset.

Chronic neutrophilic leukemia (CNL) is a rare *BCR::ABL1* negative MPN (Table 6) characterized by persistent neutrophilia and often splenomegaly. Most patients with CNL have a poor prognosis, with a mean overall survival of 1.8 years.[33] The presence of driver mutations in the colony-stimulating factor 3 receptor (*CSF3R*) is the diagnostic genetic signature of CNL.[34-36] However, additional mutations can be seen in most cases. These include *SETBP1*, *ASXL1*, and *SRSF2*, as well as signaling mutations. The absence of a *CSF3R* mutation does not exclude the possibility of CNL.[35,37] At initial diagnosis of CNL, a predominance of granulocytes (≥80%) at the segmented or band stage in the PB is

Table 3. Diagnostic criteria for polycythemia vera (PV) and post-PV myelofibrosis (post-PV MF)

PV	Post-PV MF
Major criteria 1. Elevated hemoglobin concentration* or elevated hematocrit or increased red blood cell mass* 2. Presence of *JAK2* V617F or *JAK2* exon 12 mutation† 3. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia Minor criterion • Subnormal serum erythropoietin level	Required criteria 1. Previous established diagnosis of PV 2. Bone marrow fibrosis of grade 2 or 3 Additional criteria 1. Anemia (ie, below the reference range given age, sex, and altitude considerations) or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis 2. Leukoerythroblastosis 3. Increase in palpable splenomegaly of >5 cm from baseline or the development of a newly palpable splenomegaly 4. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)
The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion‡	The diagnosis of post-PV MF is established by all required criteria and at least 2 additional criteria

*Diagnostic thresholds: hemoglobin: > 16.5 g/dL in men and > 16.0 g/dL in women; hematocrit: > 49% in men and > 48% in women; red blood cell mass: > 25% above mean normal predicted value.

†It is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level < 1%); in negative cases, consider searching for noncanonical or atypical *JAK2* mutations in exons 12 to 15.

‡A bone marrow biopsy may not be required in patients with sustained absolute erythrocytosis (hemoglobin concentrations of >18.5 g/dL in men or >16.5 g/dL in women and hematocrit values of >55.5% in men or >49.5% in women) and the presence of a *JAK2* V617F or *JAK2* exon 12 mutation.

characteristic, whereas significant monocytosis, basophilia, eosinophilia, or the presence of dysgranulopoiesis should prompt a critical review of the diagnosis. In contrast to previously established criteria, the ICC suggests lowering the key diagnostic threshold for leukocytosis from ≥25 to ≥13 × 10^9/L in cases with *CSF3R* T618I or other activating *CSF3R* mutation. Because of expanded neutrophilic granulopoiesis in the BM, CNL is uniformly hypercellular with a myeloid to erythroid ratio that may exceed 20:1. In most cases, there are fewer than 5% myeloblasts and an absence of Auer rods, and there should be no dysplastic features in the granulocytic series. Increased numbers of circulating or BM blasts (10%-19%) along with progressive splenomegaly and worsening of thrombocytopenia indicate transformation to an AP, whereas ≥20% defines BP.[38]

Table 4. Diagnostic criteria for essential thromocythemia (ET) and post-ET myelofibrosis (post-ET MF)

ET	Post-ET MF
Major criteria 1. Platelet count ≥ 450 × 10^9/L 2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters*; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant BM fibrosis† 3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, PMF, or other myeloid neoplasms are not met 4. *JAK2*, *CALR*, or *MPL* mutation‡ Minor criteria • Presence of a clonal marker§ or absence of evidence of reactive thrombocytosis‖	Required criteria 1. Previous established diagnosis of ET 2. Bone marrow fibrosis of grade 2 or 3 Additional criteria 1. Anemia (ie, below the reference range given age, sex, and altitude considerations) and a >2 g/dL decrease from baseline hemoglobin concentration 2. Leukoerythroblastosis 3. Increase in palpable splenomegaly of >5 cm from baseline or the development of a newly palpable splenomegaly 4. Elevated LDH level above the reference range 5. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)
The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criteria	The diagnosis of post-ET MF is established by all required criteria and at least 2 additional criteria

*Three or more megakaryocytes lying adjacent without other BM cells in between; in most of these rare clusters ≤ 6 megakaryocytes may be observed, increase in huge clusters (>6 cells) accompanied by granulocytic proliferation is a morphological hallmark of pre-PMF (Table 5).

†Very rarely a minor increase in reticulin fibers may occur at initial diagnosis (grade 1).

‡It is recommended to use highly sensitive assays for JAK2 V617F (sensitivity level < 1%) and CALR and MPL (sensitivity level 1% to 3%); in negative cases, consider a search for noncanonical *JAK2* and *MPL* mutations.

§Assessed by cytogenetics or sensitive NGS techniques.

‖Reactive causes of thrombocytosis include a variety of underlying conditions like iron deficiency, chronic infection, chronic inflammatory disease, medication, neoplasia, or history of splenectomy.

Table 5. Diagnostic criteria for primary myelofibrosis (PMF)

PMF, early/prefibrotic stage (pre-PMF)	PMF, overt fibrotic stage
Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* bone marrow fibrosis grade < 2, increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis 2. *JAK2*, *CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive bone marrow reticulin fibrosis§ 3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms are not met	Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* accompanied by reticulin and/or collagen fibrosis grades 2 or 3 2. *JAK2*, *CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive myelofibrosis§ 3. Diagnostic criteria for ET, PV, *BCR::ABL1*-positive CML, myelodysplastic syndrome, or other myeloid neoplasms‖ are not met
Minor criteria • Anemia not attributed to a comorbid condition • Leukocytosis ≥ 11 × 10^9/L • Palpable splenomegaly • Lactate dehydrogenase level above the above the reference range	Minor criteria • Anemia not attributed to a comorbid condition • Leukocytosis ≥ 11 × 10^9/L • Palpable splenomegaly • Lactate dehydrogenase level above the above the reference range • Leukoerythroblastosis
The diagnosis of pre-PMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations	

*Morphology of megakaryocytes in pre-PMF and overt PMF usually demonstrates a higher degree of megakaryocytic atypia than in any other MPN subtype; distinctive features of megakaryocytes include small to giant megakaryocytes with a prevalence of severe maturation defects (cloud-like, hypolobulated, and hyperchromatic nuclei) and presence of abnormal large dense clusters (mostly > 6 megakaryocytes lying strictly adjacent).

†It is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level < 1%) and *CALR* and *MPL* (sensitivity level 1% to 3%); in negative cases, consider searching for noncanonical *JAK2* and *MPL* mutations.

‡Assessed by cytogenetics or sensitive NGS techniques; detection of mutations associated with myeloid neoplasms (eg, *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SF3B1*, *SRSF2*, and *TET2* mutations) supports the clonal nature of the disease.

§Minimal reticulin fibrosis (grade 1) secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or another lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

‖Monocytosis can be present at diagnosis or develop during the course of PMF; in these cases, a history of MPN excludes CMML, whereas a higher variant allelic frequency for MPN-associated driver mutations is supporting the diagnosis of PMF with monocytosis rather than CMML.

Chronic eosinophilic leukemia, not otherwise specified (CEL, NOS) is an MPN characterized by persistent eosinophilia not meeting the criteria for other genetically defined entities (Table 7). Mutations by NGS have helped to establish clonality in a significant subset of cases with eosinophilic disorders.[39-42] However, like other myeloid neoplasms, the application of NGS data in eosinophilic disorders can be challenging because of the prevalence of clonal hematopoiesis of indeterminate potential (CHIP) and technical limitations in using NGS data to define clonality. The BM of CEL, NOS typically shows hypercellularity with dysplastic megakaryocytes, with or without dysplastic features in other lineages, and often significant fibrosis associated with an eosinophilic infiltrate.[43,44] Abnormal BM histopathology is now incorporated into the diagnostic criteria for CEL, NOS, allowing for a more definitive confirmation of the neoplastic nature of CEL, NOS and providing a better separation from the related entities idiopathic hypereosinophilic syndromes (iHES) and HE of unknown significance (HEus).[45] iHES is characterized by (1) persistent PB hypereosinophilia; (2) organ damage related to infiltration by eosinophils; and (3) no known reactive, familial, or neoplastic etiology, as well as exclusion of lymphocyte-variant HES.[46] HEus presents with persistent HE, but has no associated organ damage. Except for increased eosinophils, the BM of iHES and HEus is morphologically unremarkable.[43,47] The refined criteria for CEL, NOS and iHES are shown in Tables 7 and 8.

MPN, unclassifiable (MPN-U) is an appropriate diagnosis for cases presenting with clinical, morphologic, and molecular features (Table 9) that prevent a clear diagnosis of a specific MPN subtype.[10,48-50] In addition, this category is appropriate for patients presenting in very early-phase disease in which the required diagnostic features are not yet fully developed and relevant diagnostic thresholds not met. These cases need to be

Table 6. Diagnostic criteria for chronic neutrophilic leukemia (CNL)

1. Peripheral blood white blood cell count ≥ 13 × 10^9/L* Segmented neutrophils plus banded neutrophils constitute ≥ 80% of the white blood cells. No significant dysgranulopoiesis. Neutrophil precursors (promyelocytes, myelocytes, and metamyelocytes) constitute < 10% of the white blood cells. Circulating blasts only rarely observed. Monocyte count < 10% of all leukocytes.†
2. Hypercellular bone marrow with neutrophil granulocytes increased in percentage and absolute number, showing normal maturation.
3. *CSF3R* T618I or another activating *CSF3R* mutation or persistent neutrophilia (≥3 mo), splenomegaly, and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or, if a plasma cell neoplasm is present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies.
4. Not meeting diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, PMF or of a myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions.

*At least 25 × 10^9/L in cases lacking *CSF3R* T618I or another activating *CSF3R* mutation.

†Ten percent to 19% blasts in peripheral blood or bone marrow represent CNL in accelerated phase; ≥ 20% blasts represents blast phase.

Table 7. Diagnostic criteria for chronic eosinophilic leukemia, not otherwise specified (CEL, NOS)

1. Peripheral blood hypereosinophilia (eosinophil count ≥ 1.5×10^9/L and eosinophils ≥ 10% of white blood cells)
2. Blasts constitute < 20% cells in peripheral blood and bone marrow, not meeting other diagnostic criteria for AML*
3. No tyrosine kinase gene fusion including *BCR::ABL1*, other *ABL1*, *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, or *FLT3* fusions
4. Not meeting criteria for other well-defined MPN; chronic myelomonocytic leukemia, or SM†
5. Bone marrow shows increased cellularity with dysplastic megakaryocytes with or without dysplastic features in other lineages and often significant fibrosis, associated with an eosinophilic infiltrate or increased blasts ≥ 5% in the bone marrow and/or ≥ 2% in the peripheral blood
6. Demonstration of a clonal cytogenetic abnormality and/or somatic mutation(s)‡
The diagnosis of CEL requires all 6 criteria.

*AML with recurrent genetic abnormalities with < 20% blasts is excluded.

†Eosinophila can be seen in association with SM. However, "true" CEL, NOS may occur as SM-AMN (SM with an associated myeloid malignancies).

‡In the absence of a clonal cytogenetic abnormality and/or somatic mutation(s) or increased blasts, bone marrow findings supportive of the diagnosis will suffice in the presence of persistent eosinophilia, provided other causes of eosinophilia having been excluded.

closely monitored to identify their specific MPN subtype, which tends to become manifest at follow-up. The category is also used to capture patients presenting with splanchnic or portal vein thrombosis that fail to meet specific criteria for a given MPN subtype. In cases with significant dysgranulopoiesis, dyserythropoiesis, or absolute monocytosis at the time of diagnosis, integration of molecular data and careful assessment of BM features is key to distinguish from myelodysplastic syndrome (MDS)

Table 8. Diagnostic criteria for idiopathic hypereosinophilic syndrome (iHES)

1. Persistent peripheral blood hypereosinophilia (eosinophil count ≥ 1.5 × 109/L and ≥ 10% eosinophils)*
2. Organ damage and/or dysfunction attributable to tissue eosinophilic infiltrate†
3. No evidence of a reactive, well-defined autoimmune disease or neoplastic condition/disorder underlying the hypereosinophilia
4. Exclusion of lymphocyte variant hypereosinophilic syndrome‡
5. Bone marrow morphologically within normal limits except for increased eosinophils
6. No molecular genetic clonal abnormality, with the caveat of clonal hematopoiesis of indeterminate potential (CHIP)
The diagnosis of iHES requires all 6 criteria.

*Preferably a minimal duration of 6 months if documentation is available.

†Hypereosinophilia of uncertain significance has no tissue damage, but otherwise fulfills the same diagnostic criteria.

‡An abnormal T-cell population must be detected immunophenotypically with or without T-cell receptor clonality by molecular analysis.

Table 9. Diagnostic criteria for MPN-U

1. Clinical and hematological features of an MPN are present*
2. *JAK2*, *CALR*, or *MPL* mutation† or presence of another clonal marker‡
3. Diagnostic criteria for any other MPN, MDS, MDS/MPN,§ or *BCR::ABL1*-positive CML are not met
The diagnosis of MPN-U requires all 3 criteria.

*In cases presenting with BM fibrosis reactive causes must be excluded, in particular BM fibrosis secondary to infection, autoimmune disorder or another chronic inflammatory condition, hairy cell leukemia or another lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathy.

†It is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level < 1%) and *CALR* and *MPL* (sensitivity level 1% to 3%); in negative cases, consider searching for noncanonical *JAK2* and *MPL* mutations.

‡Assessed by cytogenetics or sensitive NGS techniques; detection of mutations associated with myeloid neoplasms (eg, *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SF3B1*, *SRSF2*, and *TET2* mutations) supports the clonal nature of the disease.

§In cases presenting with myelodysplastic features effects of any previous treatment, severe comorbidity, and changes during the natural progression of the disease process must be carefully excluded.

or MDS/MPN and from advanced-stage MPN in disease progression.[51] Of note, MPN-U may include cases with molecular evidence of MPN, in which a coexisting neoplastic or inflammatory disorder may obscure some of the characteristic morphological diagnostic features.[10]

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

The category name is changed from the prior myeloid/lymphoid neoplasm with eosinophilia (M/LN-eo) and gene rearrangement to M/LN-eo with tyrosine kinase (TK) gene fusions (Table 10) to specify the molecular genetic changes underlying these hematopoietic neoplasms. M/LN-eo frequently manifests as a chronic myeloid neoplasm with eosinophilia, clinically and histopathologically resembling CEL, NOS, other MPN, myelodysplastic/myeloproliferative neoplasm (MDS/MPN), MDS, or systemic mastocytosis (SM), or presents as T- or B-acute lymphoblastic leukemia/lymphoma (ALL), acute myeloid leukemia (AML), BP of MPN, or mixed phenotype acute leukemia (MPAL).[52,53] Extramedullary presentation or involvement is common. For cases presenting as ALL with TK gene fusions, M/LN-eo differs from *BCR::ABL1*–like B-acute lymphoblastic leukemia (B-ALL) and de novo T-acute lymphoblastic leukemia (T-ALL) in its involvement not only of the lymphoblasts but also the background myeloid cells. Supported by a number of studies[53-55] after the initial proposal as a provisional entity,[8] M/LN-eo with t(8;9)(p22;p24.1)/*PCM1::JAK2* is now accepted as a formal member of this category. Other *JAK2*-rearranged neoplasms,[53-56] such as t(9;12)(p24.1;p13.2)/*ETV6::JAK2* and t(9;22)(p24.1;q11.2)/*BCR::JAK2*, show less distinctive histopathologic features such as characteristic erythroid microtumors[57] of *PCM1::JAK2* but demonstrate similar clinical and genetic features and are considered genetic variants of t(8;9)(p22;p24.1)/*PCM1::JAK2*. New additions to the category include M/LN-eo with t(9;12)(q34.1;p13.2)/*ETV6::ABL1* and M/LN-eo with *FLT3*-rearrangement. The most common *FLT3* rearrangement[58-61] is

Table 10. Genetic abnormalities, clinical presentations, and targeted therapy of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

TK gene	Most common fusion	Partner genes/ variants	Typical clinical and BM manifestations	Targeted therapy
PDGFRA	Cryptic deletion at 4q12/ *FIP1L1::PDGFRA*	*CDK5RAP2; STRN; KIF5B; TNKS2; ETV6, BCR*	Common: CEL-like BM with frequent extramedullary involvement Others: B-ALL/LL, AML or mast cell proliferations	Excellent response to TKI
PDGFRB	t(5;12)(q32;p13.2)/ *ETV6::PDGFRB*	>30 partners, cryptic	Common: CEL-like or monocytosis with eosinophilia Others: ALL/LL, AML or mast cell proliferations	Excellent response to TKI
FGFR1	t(8;13)(p11.2;q12.1)/ *ZMYM2::FGFR1*	15 other partners including *BCR*	Common: Extramedullary T-ALL/ LL with BM MPN-like or blast phase of MPN; Others: B-ALL/LL, myeloid sarcoma, AML or MPAL	High rate of response to FGFR inhibitor such as pemigatinib, especially for cases in chronic phase
JAK2	t(8;9)(p22;p24.1)/ *PCM1::JAK2*	*ETV6* and *BCR*	Common: MPN or MDS/MPN-like BM with eosinophilia Others: B- and T-ALL/LL with BM MPN	Limited responses to ruxolitinib
FLT3	t(12;13)(p13.2;q12.2)/ *ETV6::FLT3*	*ZMYM2, TRIP11, SPTBN1, GOLGB1, CCDC88C, MYO18A, BCR*	T-ALL/LL or myeloid sarcoma with CEL-like or MDS/MPN BM features	Various responses to specific FLT3 inhibitors
ETV6::ABL1	t(9;12)(q34.1;p13.2)/ *ETV6::ABL1*	Unknown	CML-like with frequent eosinophilia in chronic or blast phase	Various responses to second generation TKI

t(12;13)(p13.2;q12.2)/*ETV6::FLT3,* whereas various other partner genes have been reported (Table 10). *FLT3*-rearranged M/LN-eo frequently presents with T-ALL or myeloid sarcoma associated with MPN-like features in BM with or without eosinophilia. Irrespective of partner genes, *FLT3*-rearranged M/LN-eo appears to be sensitive to FLT3 inhibitors.[59-61] M/LN-eo with t(9;12)(q34.1;p13.2)/*ETV6::ABL1*[55,62,63] share a number of clinical and laboratory features with CML with frequent eosinophilia, mostly presenting in chronic phase, and some in myeloblastic or lymphoblastic phase. Tyrosine kinase inhibitors (TKIs), especially second-generation TKIs,[55] have shown therapeutic benefit for patients with *ETV6::ABL1*. *ABL1* with other fusion partner genes[64] (other than the well-known *BCR::ABL1* in CML), mostly presents as *BCR::ABL1*–like B-ALL[65] or de novo T-ALL,[66] very rarely manifesting as a myeloid neoplasm. However, with increased use of RNA sequencing technology in clinical samples, additional cryptic lesions may be identified in M/LN-eo with *ABL1* rearrangement.

Mastocytosis

Mastocytosis is a neoplastic disease characterized by infiltration of clonal mast cells in different tissues, including BM, skin, the gastrointestinal tract, the liver, and/or the spleen.[67] There are 2 main types of mastocytosis: cutaneous mastocytosis, which mainly affects children and where the disease is almost always confined to the skin, and SM characterized by extracutaneous involvement with or without evidence of skin involvement. The 5 SM subtypes (also termed variants) are indolent SM (ISM), smoldering SM (SSM), aggressive SM (ASM), mast cell leukemia, and SM with an associated hematologic neoplasm (SM-AHN). The latter subtype name is changed in the ICC to SM with an associated myeloid neoplasm (SM-AMN; supplemental Table 1 available on the *Blood* Web site). A clinicopathologic variant of ISM termed BM mastocytosis (BMM), characterized by a limited degree of BM infiltration, no skin lesions, normal or slightly elevated serum tryptase levels, older age, male predominance, and a strong association with severe allergic reactions to Hymenoptera sting, has also been described.[68,69]

The ICC has introduced refinements to the criteria for diagnosing SM (Table 11). These criteria are largely based on morphology. Because the pathognomonic multifocal dense mast cell aggregates may not be readily recognized in routinely stained sections, demonstration of tryptase and KIT (CD117) immunoreactivity has been added to ensure proper identification of mast cells.[70] CD30, which is found aberrantly expressed in a significant proportion of SM cases, has been added as an additional immunophenotypic finding to the second minor criteria.[71] An important modification addressing the presence of eosinophilia associated with a mast cell proliferation[53,72-77] is that the identification of 1 of the tyrosine kinase gene fusions associated with M/LN-Eo excludes a diagnosis of SM. The "burden of disease" criteria (ie, "B" findings), which have been used to differentiate smoldering SM from indolent SM, have been simplified

Table 11. Systemic mastocytosis: diagnostic criteria

Major criterion • Multifocal dense infiltrates of tryptase- and/or CD117 positive mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)*
In the absence of the major criterion, at least 3 of the following 4 minor criteria must be present • In bone marrow biopsy or in section of other extracutaneous organs > 25% of mast cells are spindle shaped or have an atypical immature morphology† • Mast cells in bone marrow, peripheral blood or other extracutaneous organs express CD25, CD2, and/or CD30, in addition to mast cell markers • *KIT* D816V mutation or other activating *KIT* mutation detected in bone marrow, peripheral blood, or other extracutaneous organs*,‡ • Elevated serum tryptase level, persistently >20 ng/mL. In cases of SM-AMN an elevated tryptase does not count as a SM minor criterion.

*In the absence of a *KIT* mutation particularly in cases with eosinophilia, the presence of tyrosine kinase gene fusions associated with M/LN-Eo must be excluded.

†Round-cell well-differentiated morphology can occur in a small subset of cases. In these cases, the mast cells are often negative for CD25 and CD2 but positive for CD30.

‡To avoid "false-negative" results, use of a high sensitivity PCR assay for detection of *KIT* D816V mutation is recommended. If negative, exclusion of *KIT* mutation variants is strongly recommended in suspected SM.

particularly in relation to criterion 2 (supplemental Table 2). "C" findings are unchanged from the prior classification.

In mastocytosis, the cytology of the mast cells is variable but atypical cytologic features (eg, marked spindling and hypogranularity) are almost always present. More pronounced degrees of cytologic atypia characterizes the aggressive SM variants. Mast cell leukemia, in particular, is defined as a proliferation of atypical immature mast cells including promastocytes, metachromatic blast-like forms, and multinucleated or highly pleomorphic mast cells.[78] These atypical immature mast cells must account for ≥20% of the BM cellularity (supplemental Table 3). A provision is made for diagnosing mast cell leukemia in the presence of a dry tap or an otherwise suboptimal BM aspirate. It is well recognized that mast cell leukemia may have circulating mast cells in a significant proportion of cases. It is recommended to document their presence in view of their prognostic relevance; however, the amount of circulating mast cells does not justify a separate subcategory of leukemic vs aleukemic mast cell leukemia.

Rare cases of SM characterized by a proliferation of mature, round shaped, well-granulated mast cells can also be observed. These cases which typically lack *KIT* D816V mutation, are often characterized by a CD25-negative, CD2-negative, CD30-positive mast cell immunophenotype and variable serum tryptase. They may display a higher rate of response to conventional tyrosine kinase ihibitors.

The SM subtype of SM-AHN is now modified to SM with an associated myeloid neoplasm (AMN), which allows a better framing of this disease entity (Table 12). Published work has demonstrated that the "hybrid" uniqueness of SM-AHN is limited to the presence of an associated myeloid neoplasm, with which it often also shares a *KIT* mutation and/or other clonal genetic abnormalities. In contrast, presence of *KIT* mutation is not observed in lymphoid neoplasms that can occur concomitantly with SM.[79,80] SM-AMN is an aggressive neoplasm, and its diagnosis should clearly indicate the precise nature of both components, which need to be separately classified and appropriately managed.

Table 12. Systemic mastocytosis with an associated myeloid neoplasm (SM-AMN)

1. Meets the diagnostic criteria for SM
2. Meets the criteria for an associated myeloid neoplasm (eg, CMML or other MDS/MPN, MDS, MPN, AML, or other myeloid neoplasm)*
3. The associated myeloid neoplasm should be fully classified according to established criteria†

*High degree of suspicion can be raised by the presence of monocytosis, eosinophilia, splenomegaly, elevated LDH, high *KIT* D816V variant allele frequency, and additional somatic mutations in genes associated with myeloid malignancies (particularly if occurring in combination) as they could be signs of an AMN.

†If eosinophilia is present, the presence of tyrosine kinase gene fusions associated with M/LN-eo should be excluded. Although usually mutually exclusive, rare cases with both a *KIT* mutation and a gene fusion associated with M/LN-eo have been reported. In these rare instances, the M/LN-eo would represent the SM-associated AMN, but it is recommended assigning such cases only in instances in which both a *KIT* mutation and an M/LN-eo gene fusion are present.

MDS/MPN

The MDS/MPN category comprises a heterogeneous group of diseases characterized by the co-occurrence of clinical and pathologic features of both myelodysplastic and myeloproliferative neoplasms.[81] The 2016 classification included chronic myelomonocytic leukemia (CMML), atypical CML, *BCR::ABL1* negative (aCML), juvenile myelomonocytic leukemia (JMML), MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), and MDS/MPN unclassifiable (MDS/MPN-U). The ICC now expands on these categories and moves JMML to be grouped with pediatric and/or germline mutation associated disorders.

The major changes in the classification of MDS/MPN and their rationale are presented herewith. They are summarized in Tables 13 to 19.

MDS/MPN are hybrid neoplastic myeloid diseases in which a myeloproliferative component coexists together with ineffective hematopoiesis leading to cytopenia. The lack of cytopenia as 1 of the explicit diagnostic requirements has muddled the distinction of MDS/MPN from MPN and from reactive noncytopenic conditions characterized by monocytosis and/or leukocytosis. Reliance on evidence of dysplasia, which can often be subtle (eg, in CMML cases), and/or subjective as a "surrogate marker" for ineffective hematopoiesis, seems unwarranted. Therefore now "cytopenia" in combination with "cytosis" becomes one of the stated key characteristics of the MDS/MPN diseases. The definition of cytopenia follows what is being used in MDS: anemia, hemoglobin < 13 g/dL (males), < 12 g/dL (females); neutropenia, absolute neutrophil count < 1.8×10^9/L; thrombocytopenia, platelets < 150×10^9/L.[82] An exception to the necessity of cytopenia is represented by patients with early-stage CMML who in a small proportion of cases may show only borderline or no cytopenia. Those cases would require marrow morphology, flow cytometric, and molecular data to support a

diagnosis of CMML.[83] The proliferative component in CMML is manifested as monocytosis often in association with splenomegaly and/or leukocytosis. The latter is characteristically seen in the myeloproliferative subtype of CMML (CMML-MP). Leukocytosis is also part of the definition of aCML and thrombocytosis of MDS/MPN-RS-T, whereas MDS/MPN, NOS requires leukocytosis and/or thrombocytosis.

CMML (Table 13)

The 2016 revision of the WHO classification introduced a 3-tier classification of CMML based blast percentage by adding CMML-0 for cases with <2% blasts in PB and <5% blasts in BM.[84] However, recent studies have shown that the prognostic impact of CMML-0 is absent or at best limited.[85,86] In addition, there is poor reproducibility in the setting of low blast counts, particularly in the case of CMML in which blasts include promonocytes whose distinction from abnormal monocytes can at times be problematic.[87] Thus, an additional change includes reverting to the fourth edition version 2-tiered system of CMML-1 (<5% blasts in PB, <10% in BM) and CMML-2 (5%-19% blasts PB, 10%-19% in BM, or Auer rods); CMML-0 is eliminated.

Mutations in splicing genes and epigenetic modifiers (eg, *SRSF2, TET2*, and/or *ASXL1*) are frequent in CMML and occur in up to 80% of cases. Other mutated genes that also occur commonly at lower frequency include *SETBP1, NRAS/KRAS, RUNX1, CBL*, and *EZH2*. Overall, >90% of patients with CMML would be expected to show at least 1 of these mutations with modern sequencing capabilities.[83,88-90] Therefore, presence of mutations as a means to demonstrate clonality was felt to be critical for confirming a diagnosis of CMML. Having established the need for clonality as 1 of the necessary diagnostic criteria, the presence of dysplasia as a surrogate marker of clonality becomes necessary only for rare patients who do not demonstrate a CMML-associated mutation. In addition to establishing clonality, mutations in CMML have prognostic implications (eg, *ASXL1* mutations).[89,91-93] Of note, *NPM1* mutation is seen in a rare subset of CMML (3%-5%), where it appears to herald a particularly aggressive clinical course with rapid progression to acute leukemia.[94] The development of an *NPM1* mutation in CMML should be noted, but such a finding does not define de novo AML in the setting of known CMML.

Table 13. Diagnostic criteria for chronic myelomonocytic leukemia (CMML)

Monocytosis defined as monocytes ≥ 0.5×10^9/L and ≥ 10% of the WBC
Cytopenia (thresholds same as MDS)*
Blasts (including promonocytes) < 20% of the cells in blood and bone marrow
Presence of clonality: abnormal cytogenetics and/or presence of at least one myeloid neoplasm associated mutation of at least 10% allele frequency†
In cases without evidence of clonality, monocytes ≥ 1.0×10^9/L and > 10% of the WBC, and increased blasts (including promonocytes),‡ or morphologic dysplasia, or an abnormal immunophenotype consistent with CMML would be required for its diagnosis.
Bone marrow examination with morphologic findings consistent with CMML (hypercellularity due to a myeloid proliferation often with increased monocytes), and lacking diagnostic features of acute myeloid leukemia, MPN or other conditions associated with monocytosis§
No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

*A small proportion of cases may show only borderline or no cytopenia usually in early phase disease.

†Based on International Consensus Group Conference, Vienna, 2018.[260]

‡Increased blasts: ≥5% in the bone marrow and/or ≥2% in the peripheral blood.

§For cases lacking bone marrow findings of CMML, a diagnosis of CMUS could be considered. If cytopenia is present, a diagnosis of CCMUS could be entertained. In these diagnostic settings, however, an alternative cause for the observed monocytosis would have to be excluded based on appropriate clinicopathologic correlations.

The integration of molecular genetics has further demonstrated that the so-called "oligomonocytic" CMML (cases with ≥10% circulating monocytes but an absolute monocyte count of 0.5 to $<1.0 \times 10^9$/L) and traditional CMML (absolute monocytes ≥ 1.0×10^9/L) share a similar genetic profile and should be considered 1 disease.[95,96] Consequently, in the presence of clonality the modified criteria for diagnosing CMML now require a lower level of absolute monocytosis, ≥0.5×10^9/L; however, monocytes must still comprise ≥10% of the white blood cell count (WBC).

Recent work has further confirmed the importance of identifying the myeloproliferative subtype of CMML (CMML-MP). In comparison with the myelodysplastic subtype, CMML-MP (cases with WBC of >13×10^9/L) is frequently associated with mutations affecting the RAS pathway (eg, *NRAS*, *KRAS*, *CBL*) and *JAK2* V617F and *SETBP1* mutations. The adverse prognosis of CMML-MP is captured by various CMML-specific prognostic scoring systems,[89,91-93] and its diagnostic recognition may help in developing innovative therapeutic strategies specifically tailored to those patients.

Clonal monocytosis of undetermined significance (Table 14)

Targeted sequencing in patients without signs of an overt myeloid neoplasm has revealed clonal hematopoietic states, which are also included elsewhere in this consensus report. In reported cases with persistent mild monocytosis, evidence of clonal hematopoiesis (CH) but indeterminate BM features not fulfilling criteria for CMML introduces specific forms of CH that predispose for an increased risk of MDS/MPNs. The types of myeloid mutations, number of mutations, and variant allele frequency largely but do not entirely overlap with overt CMML and are associated with higher risk of developing an overt myeloid malignancy.[83,97]

Notably, among patients with clonal cytopenia of undetermined significance (CCUS), a monocytosis ≥10% and ≥0.5×10^9/L of the WBC almost invariably segregated precursor conditions with potential to progress to MDS/MPN.[97] Thus, the ICC recognizes the CMML precursor condition of clonal monocytosis of undetermined significance (CMUS), based on persistent monocytosis (monocytes ≥ 10% and ≥ 0.5×10^9/L of the WBC), in the presence of myeloid neoplasm-associated mutation(s) without BM morphologic findings of CMML. If cytopenia is present, the nomenclature of clonal cytopenia and monocytosis of undetermined significance (CCMUS) is suggested.

Table 14. Diagnostic criteria for clonal monocytosis of undetermined significance (CMUS)

Persistent monocytosis defined as monocytes ≥ 0.5 × 10^9/L and ≥ 10% of the WBC
Absence or presence of cytopenia (thresholds same as for MDS)*
Presence of at least one myeloid neoplasm associated mutation of appropriate allele frequency (ie, ≥2%)†
No significant dysplasia, increased blasts (including promonocytes) or morphologic findings of CMML on bone marrow examination‡
No criteria for a myeloid or other hematopoietic neoplasm are fulfilled
No reactive condition that would explain a monocytosis is detected

*If cytopenia is present the nomenclature of CCMUS is suggested.

†VAF threshold based on International Consensus Group Conference, Vienna, 2018.[260]

‡Bone marrow findings of CMML include hypercellularity with myeloid predominance, often with increased monocytes and in a proportion of cases monoblasts and/or blast equivalents (ie, promonocytes) and/or dysplasia in at least 1 lineage.

aCML (Table 15)

Because the absence of *BCR::ABL1* is a requirement for diagnosing all subtypes of MDS/MPN, the notation "*BCR::ABL1* negative" is now dropped from the name aCML. It is also now explicitly acknowledged that aCML is not characterized by eosinophilia: eosinophils should account for <10% of the WBC,[98] and hypereosinophilia is clearly incompatible with this diagnosis. Having excluded the presence of significant eosinophilia, aCML can now be more easily separated from chronic eosinophilic leukemia, NOS, which can have variable morphologic dysplasia.[43] Although the presence of ≥10% circulating neutrophilic precursors and the usually severe granulocytic dysplasia support the neoplastic nature of the granulocytic proliferation in most cases, genetic analysis, which is always recommended, may be necessary to exclude M/LN-Eo (eosinophilia maybe absent in some cases) or other myeloid neoplasms, particularly from advanced-stage MPN, where myelodysplasia-like features can be encountered. In the latter setting, the absence of MPN-associated driver mutations (*JAK2, CALR, MPL*) is of diagnostic value in supporting a diagnosis of aCML.[99] A history of MPN and/or the presence of MPN-associated mutations (in *JAK2, CALR,* or *MPL*) tend to exclude the diagnosis of aCML; conversely, the diagnosis is supported by the presence of *SETBP1* mutations often in association with comutated *ASXL1*. *CSF3R* mutation is uncommon, and, if detected, should prompt a careful morphologic review to exclude an alternative diagnosis of CNL.

MDS/MPN with thrombocytosis and *SF3B1* mutation and myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, NOS (Tables 16 and 17)

After the discovery that MDS/MPN-RS-T is frequently associated with mutations in the spliceosome gene *SF3B1* (which in turn are associated with the presence of ring sideroblasts), there is now sufficient evidence to support recognition of MDS/MPN associated with thrombocytosis and *SF3B1* mutation.[100-102] In the presence of *SF3B1* mutation (>10% VAF), the identification of ring sideroblasts (although common) is no longer required. The *SF3B1* mutation is in most cases found in association with the *JAK2* V617F mutation and much less commonly (in <10% of cases) in association with the *CALR* or *MPL* W515 mutations. Although the presence of comutation in 1 of these genes is not required for the diagnosis, their presence supports the diagnosis.

Table 15. Diagnostic criteria for atypical chronic myeloid leukemia (aCML)

Leukocytosis ≥ 13 × 10^9/L, due to increased numbers of neutrophils and their precursors (promyelocytes, myelocytes and metamyelocytes), the latter constituting ≥ 10% of the leukocytes
Cytopenia (thresholds same as for MDS)
Blasts < 20% of the cells in blood and bone marrow
Dysgranulopoiesis, including the presence of abnormal hyposegmented and/or hypersegmented neutrophils ± abnormal chromatin clumping
No or minimal absolute monocytosis; monocytes constitute < 10% of the peripheral blood leukocytes
No eosinophilia; eosinophils constitute < 10% of the peripheral blood leukocytes
Hypercellular bone marrow with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages
No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions. The absence of MPN-associated driver mutations and the presence of *SETBP1* mutations in association with *ASXL1* provide additional support for a diagnosis of aCML

Table 16. Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis (MDS/MPN-T-*SF3B1*)

Thrombocytosis, with platelet count ≥ 450 × 10^9/L
Anemia (threshold same as for MDS)
Blasts < 1% in blood and < 5% in bone marrow
Presence of *SF3B1* mutation (VAF > 10%), isolated or associated with abnormal cytogenetics and/or other myeloid neoplasm associated mutations
No history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features
No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no t(3;3)(q21.3;q26.2), inv(3)(q21.3q26.2), or del(5q)*
No history of MPN, MDS, or other myelodysplastic/myeloproliferative neoplasm

*In a case that otherwise meets the diagnostic criteria for myelodysplastic syndrome with del(5q).

Table 17. Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, not otherwise specified (MDS/MPN-RS-T, NOS)

Thrombocytosis, with platelet count ≥ 450 × 10^9/L
Anemia associated with erythroid-lineage dysplasia, with or without multilineage dysplasia, and ≥ 15% ring sideroblasts
Blasts < 1% in blood and < 5% in bone marrow
Presence of clonality: demonstration of a clonal cytogenetic abnormality and/or somatic mutation(s). In their absence, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features
Absence of *SF3B1* mutation; no *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no t(3;3)(q21.3;q26.2), inv(3)(q21.3q26.2), or del(5q)*
No history of MPN, MDS, or other MDS/MPN

*In a case that otherwise meets the diagnostic criteria for MDS with del(5q).

For the rare cases of MDS/MPN with thrombocytosis and ≥15% ring sideroblasts that lack *SF3B1* mutation, a designation of MDS/MPN-RS-T, NOS is appropriate. In addition, in line with the criteria for other MDS/MPN, the thrombocytosis and anemia for both MDS/MPN-T-*SF3B1* and MDS/MPN-RS-T, NOS must both be present at the time of initial diagnosis. Cases of MDS-*SF3B1* that later develop thrombocytosis are now considered to represent thrombocytotic progression of MDS-*SF3B1*.

MDS/MPN, NOS (Tables 18 and 19)

MDS/MPN, unclassifiable although largely a diagnosis of exclusion, is now better refined with the adoption of newly specified diagnostic requirements. These include a need for the presence of cytopenia in association with myeloproliferative features in PB and lack of specific gene rearrangements/fusions of M/LN-Eo with tyrosine kinase gene fusions. Establishment of clonality is expected, although the diagnosis can be made in the absence of clonality or mutations if there is histopathologic evidence of MDS/MPN and exclusion of other MDS/MPN entities. The new name of MDS/MPN, NOS was adopted in lieu of MDS/MPN-U because what was priorly "unclassifiable" has become now a disease entity and that this category should not be used to diagnose (eg, advanced-stage MPN or triple negative MPN cases).

New provisional subentity MDS/MPN with isolated isochromosome (17q) [MDS/MPN with i(17q)] is added as a new provisional subentity under the diagnostic umbrella of MDS/MPN, NOS.[103] Whether this is a distinct entity or falls within the spectrum of aCML, with which it shares a similar genomic signature, is not yet clear. To this end, the designation of MDS/MPN with i(17q) is proposed until future studies indicate a more appropriate course. It is an aggressive condition, and its recognition may facilitate the development of targeted approaches.

Table 18. Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm, not otherwise specified (MDS/MPN, NOS)

Myeloid neoplasm with mixed myeloproliferative and myelodysplastic features, not meeting the criteria for any other MDS/MPN, MDS, MPN*
Cytopenia (thresholds same as for MDS)
Blasts < 20% of the cells in blood and bone marrow
A platelet count of ≥ 450 × 10^9/L and/or a white blood cell count of ≥ 13 × 10^9/L
Presence of clonality: demonstration of a clonal cytogenetic abnormality and/or somatic mutation(s). If clonality cannot be determined, the findings have persisted and all other causes (eg, history of cytotoxic or growth factor therapy or other primary cause that could explain the myelodysplastic/myeloproliferative features) have been excluded.
No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no t(3;3)(q21.3;q26.2), inv(3)(q21.3q26.2),† or del(5q)‡

*MPNs, in particular those in accelerated phase and/or in post–PV or post–ET myelofibrotic stage, may simulate MDS/MPN, NOS. A history of MPN and/or the presence of MPN-associated mutations (in *JAK2*, *CALR*, or *MPL*) particularly if associated with a high VAF, tend to exclude a diagnosis of MDS/MPN, NOS. The presence of hypereosinophilia would favor a diagnosis of CEL, NOS.

†In a case that otherwise meets criteria for MDS-NOS.

‡In a case that otherwise meets the diagnostic criteria for MDS with isolated del(5q).

Premalignant clonal cytopenias and MDSs

CH represents the underpinning of MDS. Although CH has wide-reaching effects outside the hematopoietic system,[104] its association with ineffective hematopoiesis comprises the group of clonal cytopenias spanning from CCUS to MDS. Cytopenia in the context of clonal cytopenias is defined as the presence of acquired and sustained anemia (hemoglobin < 12 g/dL in females and < 13 g/dL in males), neutropenia (absolute neutro-

Table 19. Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm with isochromosome (17q) [MDS/MPN with i(17q)]

Fulfills the general criteria for a diagnosis of MDS/MPN, NOS • Leukocytosis of ≥ 13 × 10^9/L • Cytopenia (thresholds same as for MDS) • Blasts < 20% of the cells in blood and bone marrow • Dysgranulopoiesis with non-segmented or Pseudo-Pelger Huët neutrophils • An i(17q), either isolated or occurring with one other additional abnormality [other than −7/del(7q)] • No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions • Absence of MPN-associated mutations (*JAK2, CALR* and *MPL*)* • No history of recent cytotoxic or growth factor therapy that could explain the MDS/MPN features

MDS/MPN with i(17q) is considered a provisional subentity of MDS/MPN, NOS.

*Presence of MPN features in the bone marrow, and/or MPN-associated mutations (in *JAK2, CALR,* or *MPL*) suggests progression of an underlying MPN that was not diagnosed and should be excluded; conversely, in the appropriate clinical context, mutations particularly co-mutations in *SRSF2* and *SETBP1* genes further support this diagnosis.

Table 20. Myelodysplastic syndromes (MDS) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics†	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1‡	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), −7/del(7q), abn3q26.2, or complex	*SF3B1* (≥ 10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1‡	≥1	Thrombocytosis allowed	<5% BM <2% PB§	del(5q), with up to 1 additional, except −7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS without dysplasia	0	≥1	0	<5% BM <2% PB§	−7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥ 10% VAF)
MDS, NOS with single lineage dysplasia	1	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*;not meeting criteria for MDS-*SF3B1*
MDS, NOS with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*,; not meeting criteria for MDS-*SF3B1*
MDS with excess blasts (MDS-EB)	Typically ≥1‡	≥1	0	5-9% BM, 2-9% PB§	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1‡	≥1	0	10-19% BM or PB‖	Any, except AML-defining¶	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

*Cytoses: Sustained white blood count ≥ 13 × 10^9/L, monocytosis (≥0.5 × 10^9/L and ≥10% of leukocytes) or platelets ≥450 × 10^9/L; thrombocytosis is allowed in MDS-del(5q) or in any MDS case with inv(3) or t(3;3) cytogenetic abnormality.

†*BCR*::*ABL1* rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.

‡Although dysplasia is typically present in these entities, it is not required.

§Although 2% PB blasts mandates classification of an MDS case as MDS-EB, the presence of 1% PB blasts confirmed on 2 separate occasions also qualifies for MDS-EB.

‖For pediatric patients (<18 y), the blast thresholds for MDS-EB are 5% to 19% in BM and 2% to 19% in PB, and the entity MDS/AML does not apply.

¶AML-defining cytogenetics are listed in the AML section.

phil count < 1.8 × 10^9/L), and/or thrombocytopenia (platelets < 150 × 10^9/L), that is not explained by another condition.[82]

Clonal cytopenia of undetermined significance (CCUS) and other pre-malignant clonal cytopenias (supplemental Table 4)

CH occurs when an expanded population of blood cells is derived from a single clone and is identified by the detection of somatic mutations or cytogenetic aberrations or copy number abnormalities on genetic testing. CHIP is defined by the presence of a somatic mutation in a myeloid neoplasm driver gene (at VAF ≥ 2%) or a non–MDS-defining clonal cytogenetic aberration in a patient lacking a myeloid neoplasm or unexplained cytopenia. Both cytopenia and CHIP increase with age and are relatively common in elderly individuals. In CCUS, the cytopenia is persistent (4 months or longer in duration), idiopathic, and not caused by another comorbid condition, which must be carefully excluded.[105] Clonal cytopenia also characterizes paroxysmal nocturnal hemoglobinuria and a subset of aplastic anemia, both of which may progress to MDS.[106] Clonal cytopenia cases with monocytosis are considered to represent CMUS, because they have different progression patterns from CCUS (see above).[97] CCUS and other premalignant clonal cytopenias are distinguished from MDS by lack of dysplasia or increased blasts on PB and BM examination. A threshold VAF of ≥2% is recommended for CCUS and other premalignant clonal cytopenias, recognizing that certain mutations and high VAF are associated with higher risk of progression to MDS.[107] Further study is warranted to better define high-risk CCUS and its relationship to bona fide MDS.[97,108] CH may also be detected in patients following treatment for a myeloid neoplasm (most commonly AML) or a solid tumor, and in such cases, the clinical and biological implications may be different from CHIP or CCUS occurring in patients lacking a history of myeloid neoplasia.[109] VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a unique autoinflammatory syndrome associated with anemia and CH caused by somatic mutation in the *UBA1* gene.[110] Because of its multisystem features, it is recommended to keep VEXAS separate from MDS, unless morphologic criteria of MDS are met (typically in the setting of acquired additional genetic aberrations).

MDS definition

MDSs are clonal hematopoietic neoplasms characterized by the combination of persistent unexplained cytopenia(s) and morphologic dysplasia and a propensity to progress to BM failure or AML. Although there is no formal requirement that the cytopenia persist for a specific duration of time, in general, there

Table 21. Myeloid neoplasms with mutated *TP53*

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF > 10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF > 10%)

*Defined as 2 distinct *TP53* mutations (each VAF > 10%) OR a single *TP53* mutation with (1) 17p deletion on cytogenetics; (2) VAF of >50%; or (3) Copy-neutral LOH at the 17p *TP53* locus.

†If *TP53* locus LOH information is not available.

should be clinical evidence that the blood count abnormality is chronic in duration (typically 4 months or longer) and is not explained by a drug, toxin, or comorbid condition. The threshold for defining dysplasia is recommended as 10% for all lineages; for megakaryocytes, micromegakaryocytes are the most specific indicator of MDS, and a higher threshold of dysplasia may be warranted when other types of dysmegakaryopoiesis are included.[111,112] All MDS cases are assumed to be clonal, and a somatic genetic aberration is identifiable on targeted NGS panels in approximately 90% and conventional karyotype in 50% of cases. In cases with no clonality proven by current testing methods, a diagnosis of MDS can still be made in the presence of qualifying dysplasia and persistent cytopenia.[113] Conversely, several genetic abnormalities in the context of persistent cytopenia are still considered to be MDS-defining irrespective of dysplasia; these have been updated from the revised fourth edition WHO classification (Table 20). MDS in children and adolescents lack recurrent mutations in genes of epigenetic regulation or RNA splicing known to expand clonal hematopoiesis in adults; instead, somatic aberrations in *SETBP1*, *ASXL1*, *RUNX1*, and RAS/MAPK pathway mutations define the genomic landscape.[114-116] In addition, most MDS cases in children have considerable hypocellularity of the BM.[117,118] Given its unique features, the entity known as refractory cytopenia of childhood (RCC) is included in a new section of pediatric disorders (see below).

Just as in the prior classification, the presence of persistent leukocytosis (WBC ≥ 13.0 × 10^9/L, not explained by clonal lymphocytosis or another comorbid condition), thrombocytosis (platelets ≥ 450 × 10^9/L, except in cases meeting criteria for MDS with del(5q) or with inv(3q)/t(3;3) cytogenetic aberrations), or monocytosis (monocytes ≥ 10% of leukocytes and absolute monocyte count ≥ 0.5 × 10^9/L) at the time of initial diagnosis excludes MDS and warrant classification as MDS/MPN or MPN.

MDS classification: subtypes without excess blasts

Recent studies have shown that in MDS without excess blasts, *SF3B1* mutation defines a more homogeneous group than ring sideroblasts.[101] For this reason, the prior entity of MDS with ring sideroblasts (MDS-RS) has been replaced by MDS with *SF3B1* mutation (MDS-*SF3B1*; Table 20). *SF3B1*-unmutated MDS-RS cases have clinical features and outcomes similar to MDS with single or multilineage dysplasia and are now classified as MDS, NOS, irrespective of the number of RS. Genetic risk stratification appears to supersede any effect of single vs multilineage dysplasia on the prognosis of lower risk MDS, but these are currently retained as subtypes of MDS, NOS.[101] MDS with isolated del(5q) has been retained with no changes from the revised fourth edition WHO classification, although the name has been simplified to MDS with del(5q), with the understanding that the del(5q) must be isolated or accompanied by only one other cytogenetic aberration except for −7 or del(7q). A new genetic subtype of MDS has been introduced, defined by the presence of multihit *TP53* mutations,[119,120] and is discussed below.

The prior category of MDS, unclassifiable (MDS-U) has been eliminated. Aside from del(5q), −7/del(7q), or a complex karyotype, the previous MDS-defining cytogenetic abnormalities in cytopenic patients lacking dysplasia are now considered as CCUS. Cytopenic cases with del(5q), multihit *TP53* mutation, or −7/del(7q) or complex karyotype that lack dysplasia or excess blasts are classified as MDS with del(5q), MDS with mutated *TP53*, or MDS, NOS. Although present in most cases, neither dysplasia nor ring sideroblasts are required to diagnose MDS-*SF3B1*. The MDS-U subtype with single lineage dysplasia and pancytopenia is no longer relevant, because cytopenias are already incorporated into the Revised International Prognostic Scoring System for MDS.[121] The presence of 1% PB blasts on 1 occasion is acceptable in any nonexcess blast MDS subtype; however, these patients should be followed closely and classified as MDS with excess blasts if PB blasts of 1% are confirmed on another occasion, or reach 2% or higher.[122]

The classification of lower-risk MDS has thus been simplified into 3 subtypes: 2 defined mainly by genetic features (*SF3B1* mutation and del(5q)) and the remainder in MDS, NOS. Although there is poor reproducibility in distinguishing single lineage vs multilineage dysplasia in MDS,[123] this distinction has been retained in the subclassification of MDS, NOS. In the near future, genetic clustering analysis will likely aid in establishing additional genetic subgroups within MDS-NOS.[124,125]

MDS with excess blasts

MDS with excess blasts (MDS-EB) is separated from lower risk MDS subtypes by the presence of at least 5% myeloid blasts in the BM or at least 2% blasts in the PB (or 1% documented on 2 occasions; Table 20). With the introduction of the new MDS/

AML category (discussed below), there is now only 1 MDS-EB subtype. The presence of excess blasts supersedes any of the above MDS subtypes, except for MDS with mutated *TP53* (discussed below).

MDS/AML

Although the blast threshold of 20% defining AML remains, several additional genetic lesions are now considered to be defining of AML for myeloid neoplasms with ≥10% BM or blood blasts (see AML section below). To acknowledge the biologic continuum between MDS and AML, the name of the previous category of MDS-EB2 in adults with 10% or more blasts is changed to MDS/AML, defined as a cytopenic myeloid neoplasm and 10% to 19% blasts in the blood or BM. However, given their unique biological features and treatment approach, pediatric (age < 18 years) MDS-EB will continue to include patients with 10% to 19% blasts. Patients with MDS/AML should be eligible for both MDS and AML trials, which will facilitate optimizing the management of such patients. In the future, genetic features rather than an arbitrary blast cutoff may drive treatment decisions in this group.[126]

Myeloid neoplasms with mutated *TP53* (Table 21)

This disease category encompasses separate diagnoses of MDS, MDS/AML, and AML with mutated *TP53* (including pure erythroid leukemia), according to the blast percentage. These diseases are grouped together because of their overall similar aggressive behavior irrespective of the blast percentage, warranting a more unified treatment strategy across the blast spectrum.[120,127] The presence of multihit *TP53* mutations in cytopenic myeloid neoplasms corresponds to a highly aggressive disease with short survival. Unlike other MDS, the prognosis of MDS with multihit *TP53* does not appear to depend on the blast percentage, although multihit *TP53* abnormalities appear to be more common in cases with increased blasts.[119,120] Multihit *TP53* can be confirmed by the presence of 2 or more distinct *TP53* mutations (VAF ≥ 10%) or a single *TP53* mutation associated with (1) a cytogenetic deletion involving the *TP53* locus at 17p13.1; (2) a VAF of >50%; or (3) copy-neutral loss of heterozygosity (LOH) at the 17p *TP53* locus.[119,127] In the absence of LOH information, the presence of a single *TP53* mutation in the context of any complex karyotype is considered equivalent to a multihit *TP53*.[119,127] Complex karyotype alone in the absence of a *TP53* mutation (even in the presence of 17p deletion) does not qualify for this category, as these cases have superior prognosis to *TP53*-mutated MDS.[120,128] Monoallelic *TP53* mutations in MDS have a less adverse effect on prognosis and different biology from cases with multihit *TP53*, and are not included in the MDS entity.[119] However, monoallelic mutated *TP53* AML has a poor prognosis, and thus monoallelic somatic mutations are allowed in MDS/AML and AML with mutated *TP53*.[127]

Patterns of progression in clonal cytopenias

The premalignant clonal cytopenias CCUS, aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH), and VEXAS can progress to MDS once dysplasia, excess blasts, or MDS-defining genetic lesions occur. In the setting of a germline predisposition condition, progression to MDS follows different criteria and is discussed in the Pediatric and/or Germline Mutation-Associated Disorders section. Any nonexcess blast MDS subtypes may progress to MDS-EB, MDS/AML, or AML and similarly, MDS-EB may progress to MDS/AML or AML. These progression events should be documented in the pathology report. MDS may also progress to MDS, MDS/AML, or AML (depending on the blast count) with mutated *TP53* with the acquisition of *TP53* mutations and should be designated as such if a *TP53* mutation develops later in the course of disease. Unlike the prior classification, cases of MDS with *SF3B1* mutation that later develop thrombocytosis (with or without a *JAK2* mutation) are no longer reclassified as MDS/MPN. Similarly, the development of leukocytosis, thrombocytosis, or monocytosis in an established MDS case generally does not warrant reclassification as MDS/MPN. Such cases can be designated as MDS (and subtyped) with neutrophilic, thrombocytotic, or monocytic progression. However, cases resembling bona fide CMML or, rarely, aCML, may rarely develop in patients previously diagnosed with MDS. Further study is needed to distinguish between MDS progression and true conversion to an MDS/MPN disease in these instances.[129-131]

Diagnostic qualifiers

All MDS cases that are therapy related should be qualified as such by entering a "therapy-related" statement after the diagnosis. Although it remains important to recognize therapy-relatedness of myeloid neoplasms, the first priority is to classify the disease according to its morphologic and genetic features.[132] As CCUS and CHIP can occur as a consequence of cytotoxic therapy and are a precursor to therapy-related MDS and AML,[133] it is recommended to also qualify a diagnosis of CHIP and non-MDS clonal cytopenias as therapy related if they follow marrow exposure to chemotherapy or radiation therapy. Any underlying germline predisposition mutation or syndrome should also be specified as a qualifier after the MDS diagnosis and subtype (see further discussion on qualifiers in the AML section below).

Pediatric disorders and/or germline mutation-associated disorders

Although virtually any of the disorders in the ICC can occur in children, some are unique to childhood, and some are associated with germline genetic predisposition. Disorders arising from germline abnormalities, however, often present in adulthood. Because of the unique and overlapping features of these disorders, they are presented together in the classification.

JMML and related disorders (Tables 22 and 23; supplemental Table 5)

JMML is a unique clonal disorder of childhood characterized by constitutive activation of the RAS signal transduction pathway that was previously considered an MDS/MPN. Nearly all patients harbor mutations in the RAS pathway that define genetic and clinical subgroups. The ICC refines JMML as a genetic entity with the presence of molecular alteration of 1 of these RAS pathway genes as requirement for diagnosis. The diagnostic criteria for JMML are listed in Table 22. It is noted that approximately 7% of cases may not meet the criteria for monocytosis listed in the table and approximately 3% will not demonstrate splenomegaly at presentation. Correlation with more detailed clinical features is needed in such cases.[134] The frequency of

Table 22. Diagnostic criteria for juvenile myelomonocytic leukemia

I. Clinical and hematologic features (the first 2 features are present in most cases; the last 2 are required) • PB monocyte count ≥ 1×10^9/L* • Splenomegaly† • Blast percentage in PB and BM < 20% • Absence of *BCR::ABL1*
II. Genetic studies (1 finding required) • Somatic mutation in *PTPN11*‡ or *KRAS*‡ or *NRAS*‡ or *RRAS*‡ • Germline *NF1* mutation and loss of heterozygosity of *NF1* or clinical diagnosis of neurofibromatosis type 1 • Germline *CBL* mutation and loss of heterozygosity of *CBL*§

*This monocyte threshold is not reached in approximately 7% of cases.

†Splenomegaly is absent in 3% of cases at presentation.

‡Germline mutations (indicating Noonan syndrome) need to be excluded.

§Occasional cases with heterozygous splice site mutations.

signs and symptoms of JMML are summarized in supplemental Table 5. JMML typically presents in early childhood with marked hepatosplenomegaly, lymphadenopathy, interstitial lung disease, and skin rash. Most cases show leukocytosis and leukoerythroblastosis associated with monocytosis (monocyte count $> 1 \times 10^9$/L).[134] Blasts and promonocytes account for <20% of white blood cells in PB and nucleated cells in BM.

JMML pathobiology is characterized by constitutive activation of the RAS signal transduction pathway. Canonical RAS pathway mutations in the *PTPN11*, *NRAS*, *KRAS*, *NF1*, *CBL*, and rarely *RRAS* genes are present in leukemic cells of more than 95% of patients and define genetically and clinically distinct subtypes.[135,136] Two subtypes are defined by germline events in either *NF1* or *CBL*, which progress to malignancy with acquired biallelic inactivation of the respective genes in hematopoietic cells. The other subtypes, *PTPN11*-, *NRAS*-, and *KRAS*-mutated JMML, are characterized by heterozygous, somatic gain-of-function mutations in children without germline disease. *KRAS*- and *NRAS*- mutated JMMLs with a normal karyotype share overlapping features with a rare disorder called RAS-associated autoimmune leukoproliferative disorder, which may represent different phenotypes of the same disorder.[137]

Clonal disease that phenotypically mimics JMML but does not harbor 1 of these RAS pathway mutations is classified as JMML-like neoplasm. Noonan syndrome–associated myeloproliferative disorder, a transient disease thought to be of polyclonal origin, can in its severe form clinically resemble JMML.

JMML-like neoplasms Cases in nonsyndromic patients that phenotypically resemble JMML but lack a RAS pathway mutation are referred to as JMML-like in the ICC (Table 23). This group includes JMML mimics with rare rearrangements, like *ALK*,[138,139] *ROS1*,[139] *FIP1L1::RARA*,[140,141] or *CCDC88C::FLT3*[142,143] fusions. Disorders with AML-defining recurrent genetic aberrations or M/LN-eo associated with tyrosine kinase gene fusions are excluded from JMML-like neoplasms.

Noonan syndrome–associated myeloproliferative disorder Patients with Noonan syndrome and germline mutations in *PTPN11*, *KRAS*, *NRAS*, or *RIT1* can experience a transient myeloproliferative disorder in the first year of life.[135] Although this disorder may be indistinguishable from JMML by clinical and hematologic parameters, acquired somatic mutations are conspicuously absent.[144]

Refractory cytopenia of childhood (Box 1)

RCC represents a well-recognized type of BM failure seen in children. Both persistent cytopenia and evidence of dysplasia are required for its diagnosis. Because of the marked BM hypocellularity found in ≥80% of children with RCC, its recognition requires BM biopsy examination to identify its characteristic histopathologic appearance.[145] The diagnostic criteria described in the revised fourth edition WHO have now been updated (Box 1). It has become evident that only in a proportion of cases diagnosed as RCC can acquired somatic mutations or cytogenetic abnormalities be identified.[146] In others, a germline predisposition may have been present that preceded the evolution to RCC. These conditions include Fanconi anemia,[147] dyskeratosis congenita, Shwachman-Diamond syndrome,[148] GATA2 deficiency,[149] and SAMD9/SAMD9L syndromes.[150] In these settings, RCC represents progression to BM failure or frank MDS. Although it is apparent that not all RCC cases are bona fide MDS, monosomy 7 and del(7q) are the most frequent MDS-defining genetic abnormalities.[118,151] Recent insight into karyotype instability and somatic rescue mechanisms[150,152,153] demonstrated, however, great plasticity of hematopoiesis in

Table 23. JMML, JMML-like neoplasms, and Noonan syndrome-associated myeloproliferative disorder

	PB/BM blasts	Mutation	Secondary mutations	Karyotype
JMML	<20% PB <20% BM	*PTPN11*, *NRAS*, *KRAS*, *RRAS*, *NF1**, *CBL*†	Any	Any (monosomy 7 in 25%)
JMML-like neoplasms	<20% PB <20% BM	Absence of RAS-pathway mutation	Any	Any
Noonan syndrome–associated myeloproliferative disorder	<20% PB <20% BM	*PTPN11*,‡ *NRAS*,‡ *KRAS*,‡ *RIT1*‡	None	Normal§

*Germline mutation with additional aberration resulting in biallelic inactivation of the *NF1* gene.

†Germline mutation with additional aberration resulting in biallelic inactivation of the *CBL* gene; some cases with heterozygous germ line mutation only.

‡Germline mutation, patients generally display syndromic features of Noonan syndrome.

§In rare instances, monosomy 7 can develop.[261,262]

BOX 1

ICC diagnostic criteria for RCC

1. Persistent cytopenia

Number of cytopenias (1-3). Cytopenia is defined according to age-adjusted values for hemoglobin, absolute neutrophil count, and platelets

2. Manifestation of dysplasia

Dysplastic changes in at least 2 lineages or in ≥10% in 1 lineage

Typical dysplastic features of RCC (not all are required)

Specimen	Cellularity	Erythropoiesis	Granulopoiesis	Megakaryopoiesis*
Bone marrow aspirate		Nuclear budding Multinuclearity Megaloblastoid changes	Pseudo–Pelger-Huët cells Hypo- or agranularity	Separated nuclear lobes Round monolobated nucleus Micromegakaryocytes
Bone marrow biopsy	Patchy pattern in otherwise hypocellular marrow or rarely diffuse pattern in normo- or hypercellular marrow†	Patchy (few multifocal clusters or unifocal cluster) Left-shift Increased mitosis	Marked decrease	Marked decrease or aplasia Round monolobated nucleus Separated nuclear lobes Micromegakaryocytes

*Immunohistochemistry for megakaryocyte markers is required.

†Normo- or hypocellular RCC requires significant dysplasia in megakaryocytes (>30%).

3. Other required criteria

Blast percentage in peripheral blood <2% and bone marrow <5%

No prior cytotoxic chemotherapy or radiation therapy

No fibrosis

young patients. Risk-based treatment strategies for children with RCC must account for this heterogeneity.

Hematologic neoplasms with germline predisposition (Table 24)

The identification of hematologic neoplasms with germline mutations is critical for proper diagnosis, patient management, screening of related donors for stem cell transplantation, selection of therapeutic conditioning, and genetic counseling for affected family members. A high index of suspicion of germline mutation is important particularly for younger patients diagnosed with hematologic neoplasms and for patients that will be transplanted using related donors. The unwitting use of related transplant donors who harbor the same germline mutation as the patient has led to donor-derived MDS and AML and poor outcomes, underscoring the need for increased awareness and recognition of hematologic neoplasms with germline predisposition.[154-157]

The ICC of hematologic neoplasms with germline predisposition includes 4 major subgroupings (Table 24) with new entities added in comparison with the 2016 WHO classification. Increasing data have demonstrated that many genes in the prior classification predispose not only to myeloid malignancy but also to lymphoid malignancy. Hence, the title is changed from "myeloid neoplasms" to "hematologic neoplasms" with germline predisposition. Several genes have emerged with substantial data documenting germline predisposition to hematologic malignancy that warranted incorporation into the new ICC (including *SAMD9*, *SAMD9L*, *IKZF1*, *PAX5*, and *TP53*). Any underlying germline predisposition mutation or syndrome should also be specified as a qualifier after the MDS, AML, or other malignancy diagnosis and subtype.

Hematologic neoplasms with germline predisposition without a constitutional disorder

The genes in this group include *CEBPA*, which predisposes to AML, and *DDX41*, which predisposes to both myeloid and lymphoid neoplasms. *TP53* is added, recognizing the importance of Li-Fraumeni syndrome and predisposition to myeloid and lymphoid malignancies in both treatment-naive and therapy-related settings.[158-162]

Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder

The genes in this group have not changed and include *RUNX1*, *ANKRD26*, and *ETV6*. It is noted that morphologic megakaryocytic dysplasia is common in the BMs of these patients in the setting of isolated thrombocytopenia and absence of MDS.[163,164] Lymphoid malignancies have been reported with germline *RUNX1* or *ETV6* in addition to myeloid neoplasia.

Table 24. ICC of hematologic neoplasms with germline predisposition

Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems
Myeloid neoplasms with germline *CEBPA* mutation
Myeloid or lymphoid neoplasms with germline *DDX41* mutation
Myeloid or lymphoid neoplasms with germline *TP53* mutation
Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder
Myeloid or lymphoid neoplasms with germline *RUNX1* mutation
Myeloid neoplasms with germline *ANKRD26* mutation
Myeloid or lymphoid neoplasms with germline *ETV6* mutation
Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems
Myeloid neoplasms with germline *GATA2* mutation
Myeloid neoplasms with germline *SAMD9* mutation
Myeloid neoplasms with germline *SAMD9L* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
Fanconi anemia
Shwachman-Diamond syndrome
Telomere biology disorders including dyskeratosis congenita
Severe congenital neutropenia
Diamond-Blackfan anemia
JMML associated with neurofibromatosis
JMML associated with Noonan-syndrome-like disorder (CBL-syndrome)
Myeloid or lymphoid neoplasms associated with Down syndrome
Acute lymphoblastic leukemia with germline predisposition*
Acute lymphoblastic leukemia with germline *PAX5* mutation
Acute lymphoblastic leukemia with germline *IKZF1* mutation

*Down syndrome and germline mutations in *ETV6* or *TP53* also predispose to acute lymphoblastic leukemia.

Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems

Similar to the prior 2016 WHO classification, this group includes germline mutations in *GATA2*, germline mutations associated with classical BM failure disorders, germline mutations in RAS-pathway genes (*NF1, PTPN11, CBL*) associated with neurofibromatosis, Noonan-like syndromes predisposing to JMML, and Down syndrome, which predisposes to both myeloid and lymphoid neoplasia. Additions to this group include *SAMD9* and *SAMD9L*, which predispose to acquired monosomy 7/del(7q) and MDS.[116,150,165]

ALL with germline predisposition

Germline mutations of *IKZF1*[166] and *PAX5*[167,168] are both associated with predisposition to ALL. These germline mutations also predispose to loss of B-cell subsets and immune deficiency. Down syndrome and germline mutations in *ETV6* and *TP53* (Li-Fraumeni syndrome) also predispose to ALL and myeloid malignancies.

Other germline mutations

Other germline mutations also result in predisposition to hematologic malignancies, including Bloom syndrome (*BLM*),[169] ataxia-telangiectasia, Nijmegen breakage syndrome, Noonan syndrome, constitutional mismatch repair deficiency syndrome,[170,171] and germline mutations in *DNMT3A*,[172] *ERCC6L2*,[173] *MBD4*,[174] and *XPC*.[175] Limited cases of hematologic malignancies have been reported for germline genetic mutations in *CSF3R*,[176] *MECOM*,[177] *SRP72*,[178] and *TET2*.[179,180]

Diagnosis of MDS in the setting of germline predisposition

The ICC recognizes that many of the genes predisposing to myeloid malignancy also predispose to baseline changes in BM cells that overlap with dysplastic features. These dyspoietic changes may be present irrespective of whether the patient has a myeloid malignancy. For this reason, a germline predisposition should be considered for cases with morphologic atypia in the absence of additional factors supporting a diagnosis of MDS or other myeloid malignancy. In general, the development of MDS in patients with germline predisposition is associated with new or progressive cytopenia(s) often in the setting of rising marrow cellularity, overt multilineage dysplasia, increased blasts, and/or acquired pathogenic genetic alterations. Emergence of del(5q), −7/del(7q), complex karyotype, multihit *TP53* mutations (VAF > 10%), or *SF3B1* mutation (VAF > 10%) is considered MDS defining. Acquired genetic changes must be interpreted in the context of the specific germline genetic mutation: for example, patients with Shwachman Diamond syndrome frequently develop small stable clones with monoallelic *TP53* mutations, and in isolation, these are not considered to represent development of MDS; however, biallelic *TP53* mutations in this context are associated with myeloid malignancy.[181]

Acute myeloid leukemia (Tables 25 and 26; supplemental Table 6)

AML represents a heterogenous group of genetically distinct disorders. The updated classification retains many of the previously defined AML types with recurrent genetic abnormalities and includes other genetically related entities (Table 25; supplemental Table 6) to move to a more genetically defined classification. Although the importance of prior therapy, antecedent myeloid neoplasms (ie, MDS or MDS/MPN), or underlying germline genetic disorders predisposing to the development of AML is well recognized, the classification now identifies such associations as qualifiers to the diagnosis rather than as specific disease categories (Table 26) in an attempt to reduce confusion caused by the substantial overlap of prior AML categories. Using this approach, the prior stand-alone categories of therapy-related myeloid neoplasms and AML with myelodysplasia-related changes are eliminated.

The ICC AML categories are listed in Table 25, with several key differences from prior classifications.

The prior category of AML with myelodysplasia-related changes (AML-MRC) was an attempt to identify patients with a worse

Table 25. Classification of AML with percentage of blasts required for diagnosis

Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML*::*RARA* ≥ 10%
APL with other *RARA* rearrangements* ≥ 10%
AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* ≥ 10%
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* ≥ 10%
AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* ≥ 10%
AML with other *KMT2A* rearrangements† ≥ 10%
AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214* ≥ 10%
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*; *MECOM*(*EVI1*) ≥ 10%
AML with other *MECOM* rearrangements‡ ≥ 10%
AML with other rare recurring translocations (see supplemental Table 5) ≥ 10%
AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*§ ≥ 20%
AML with mutated *NPM1* ≥ 10%
AML with in-frame bZIP *CEBPA* mutations ≥ 10%
AML and MDS/AML with mutated *TP53*† 10-19% (MDS/AML) and ≥ 20% (AML)
AML and MDS/AML with myelodysplasia-related gene mutations 10-19% (MDS/AML) and ≥ 20% (AML) Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
AML with myelodysplasia-related cytogenetic abnormalities 10-19% (MDS/AML) and ≥ 20% (AML) Defined by detecting a complex karyotype (≥ 3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), −7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), −17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities
AML not otherwise specified (NOS) 10-19% (MDS/AML) and ≥ 20% (AML)
Myeloid sarcoma

*Includes AMLs with t(1;17)(q42.3;q21.2)/*IRF2BP2*::*RARA*; t(5;17)(q35.1;q21.2)/*NPM1*::*RARA*; t(11;17)(q23.2;q21.2)/*ZBTB16*::*RARA*; cryptic inv(17q) or del(17) (q21.2q21.2)/*STAT5B*::*RARA*, *STAT3*::*RARA*; Other genes rarely rearranged with *RARA*:*TBL1XR1* (3q26.3), *FIP1L1* (4q12), *BCOR* (Xp11.4).

†Includes AMLs with t(4;11)(q21.3;q23.3)/*AFF1*::*KMT2A*#; t(6;11)(q27;q23.3)/*AFDN*::*KMT2A*; t(10;11)(p12.3;q23.3)/*MLLT10*::*KMT2A*; t(10;11)(q21.3;q23.3)/*TET1*::*KMT2A*; t(11;19)(q23.3;p13.1)/*KMT2A*::*ELL*; t(11;19)(q23.3;p13.3)/*KMT2A*::*MLLT1* (occurs predominantly in infants and children).

‡Includes AMLs with t(2;3)(p11∼23;q26.2)/*MECOM*::?; t(3;8)(q26.2;q24.2)/*MYC*, *MECOM*; t(3;12)(q26.2;p13.2)/*ETV6*::*MECOM*; t(3;21)(q26.2;q22.1)/*MECOM*::*RUNX1*.

§The category of MDS/AML will not be used for AML with *BCR*::*ABL1* due to its overlap with progression of CML, *BCR*::*ABL1*-positive.

Table 26. Diagnostic qualifiers that should be used following a specific MDS, AML (or MDS/AML) diagnosis

Therapy-related* • prior chemotherapy, radiotherapy, immune interventions
Progressing from MDS • MDS should be confirmed by standard diagnostics
Progressing from MDS/MPN (specify) • MDS/MPN should be confirmed by standard diagnostics
Germline predisposition

Examples: AML with myelodysplasia-related cytogenetic abnormality, therapy-related; AML with myelodysplasia-related gene mutation, progressed from MDS; AML with myelodysplasia-related gene mutation, germline *RUNX1* mutation.

*Lymphoblastic leukemia/lymphoma may also be therapy-related, and that association should also be noted in the diagnosis.

prognosis compared with AML, NOS.[5,8,182] Although the identification of multilineage dysplasia was a crude proxy for underlying myelodysplasia-related cytogenetic abnormalities, the association of multilineage dysplasia in a subset of patients with low-risk gene mutations, especially *NPM1* or biallelic *CEBPA*,[183-185] highlighted the need for molecular refinement of that category. Additionally, overlapping features between AML with myelodysplasia-related changes and therapy-related AML occur, further identifying a need for a better-defined approach to AML classification.

AML with mutated *TP53* is now recognized as a separate entity within the group of myeloid neoplasms with mutated *TP53* (which also includes MDS and MDS/AML with mutated *TP53*, discussed above and in Table 21). Like MDS, AML with mutated *TP53* is typically associated with complex cytogenetic abnormalities and with a very poor outcome.[120,127,186-188] Additionally, a panel of genes has been identified to be strongly associated with secondary AML arising from prior myeloid neoplasia.[187,189-193] Both categories were previously identified as AML genomic classes (TP53/chromosomal aneuploidy-complex karyotypes with abnormalities of chromosomes 5 and/or 7, often called monosomal karyotypes and chromatin/spliceosome, respectively).[187] The myelodysplasia-related mutations confer a similarly adverse prognosis to cases presenting as de novo AML that would previously fall into the category of AML, NOS. Based on these findings, the category of AML-MRC is eliminated while retaining a category of AML with myelodysplasia-related cytogenetic abnormalities and with new categories of AML with mutated *TP53* and AML with myelodysplasia-related gene mutations. *TP53* mutations define a distinctly aggressive AML category, whether they present de novo, as progression of MDS, or as therapy-related disease. Although multihit *TP53* mutation is required for MDS with mutated *TP53*, in AML and MDS/AML with mutated *TP53*, any pathogenic *TP53* mutation VAF of >10% is sufficient.[119,120,127] Mutations of *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2* qualify for a diagnosis of AML with myelodysplasia-related gene mutations (now encompassing the prior provisional entity of AML with mutated *RUNX1*). Finally, in the absence of a myelodysplasia-related gene mutation, *TP53* mutation, or other recurring genetic abnormalities definitional of specific AML categories, a case may be diagnosed as AML with myelodysplasia-related cytogenetic abnormalities based on specific karyotype findings.

The WHO fourth edition and revised fourth edition classifications included 3 specific categories of AML (other than pure erythroid leukemia) that defined AML without regard to myeloblast percentage in the appropriate clinical setting: AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*, AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*, and acute promyelocytic leukemia with t(15;17)(q24;q21)/*PML*::*RARA*. Cases in these categories diagnosed with very low blast counts (<20%) are uncommon. The ICC expands the categories that may be diagnosed as AML with <20% blasts to encompass additional recurring genetic abnormalities (including gene mutations),[194-203] with at least 10% blasts (or so-called "blast equivalents" including promonocytes and neoplastic promyelocytes in the appropriate pathologic setting) in the blood or marrow for such a diagnosis. The remaining AML categories retain the 20% or more blast requirement. MDS cases with 10% to 19% blasts are now diagnosed as MDS/AML, as described above, reflecting the diagnostic continuum between AML and MDS and clinical and genetic heterogeneity among individual patients with these lower blast counts.[126,204-207] Cases of MDS/AML are subclassified as MDS/AML with mutated *TP53*, MDS/AML with myelodysplasia-related gene mutations, MDS/AML with myelodysplasia-related cytogenetic abnormalities, or MDS/AML, NOS.

Several prior AML-related disease categories, including myeloid sarcoma, myeloid neoplasms associated with Down syndrome, and blastic plasmacytoid dendritic cell neoplasm are unchanged. Changes to acute leukemias of ambiguous lineage were not addressed in the CAC, but an ICC working group will report on them separately in the future. One significant change, however, relates to the prior category of AML with biallelic mutations of *CEBPA*. Several studies now demonstrate it is the presence of in-frame bZIP mutations of *CEBPA* that define the prognostic entity with a unique gene expression profile,[208-210] and this favorable category is now updated to include this abnormality, without the requirement of biallelic mutations.

The hierarchy of disease categories generally follows the order of entities listed in Table 25. The traditional genetic disease groups named after a single abnormality rarely show overlap. Such rare occurrences should be viewed as exceptions and clearly identified. Although *TP53* mutations may overlap with other categories, their presence is usually predictive of a worse prognosis and such a mutation should be noted with the other genetic abnormality. The single gene mutation or gene fusion categories take precedent over the myelodysplasia-related gene mutation and the myelodysplasia-related cytogenetic groups, although such findings, may again impact prognosis in the genetic groups and should be noted. After excluding all other genetic categories, some cases will remain unclassified and those will continue to be diagnosed as AML, NOS. Previously used morphologic or cytochemical subtypes of AML, NOS have limited prognostic significance, but pathologists may continue to subclassify such cases if desired. Of note, pure erythroid leukemia is typically associated with *TP53* mutations, and these cases are now classified within the category of AML with *TP53* mutations.

B-ALL, T-ALL (Tables 27 and 28; supplemental Table 7)

Synonym: B-(T-)lymphoblastic lymphoma/leukemia

The updated classification includes some revisions to entities previously present in the 2016 WHO classification and introduces a number of new subtypes (Table 27). *BCR*::*ABL1*-positive ALL from the prior classification is now divided into 2 biologically distinct subsets, 1 of which appears more closely related to CML presenting in lymphoid blast phase.[211,212] These subsets cannot be distinguished by the use of p190 vs p210 fusion proteins, but rather can by fluorescence in situ hybridization (FISH), based on whether the translocation can be detected in granulocytes, indicating a multilineage *BCR*::*ABL1* fusion, as opposed to a lymphoid-only rearrangement in which FISH is only positive in lymphoblasts.[211-213] In some cases, it may be necessary to sort cells to obtain enough myeloid cells to do this.[211] Further evidence comes from the finding that RT-PCR studies for *BCR*::*ABL1* following treatment may show high level positivity when both flow cytometry and molecular MRD methods show no or little evidence of MRD.[212,214] Prognosis and optimal treatment of these 2 variants may also differ.[211] Cases of *B-ALL, BCR*::*ABL1 like* are now recognized as having a wide variety of genetic lesions including *JAK-STAT* alterations (including *CRLF2*-rearrangement, *JAK* fusions, and *EPOR* rearrangement, among others), *ABL1* class fusions, and others, so that this entity has now been subdivided. It is particularly important to recognize those with *ABL-class fusions* because of their unique pattern of response to various *ABL1*-class tyrosine kinase inhibitors[215]; some other fusions, such as those involving *NTRK*, may also respond.[216] The most common alteration in the *JAK-STAT* category is a *CRLF2 rearrangement*, which in many cases can be detected by FISH (or screened by CRLF2 flow cytometry as CRLF2 is upregulated). *CRLF2* rearrangement is accompanied by *JAK* mutations in approximately half of cases, with other kinase activating mutations in additional cases, resulting in activation of *JAK-STAT* signaling. Responsiveness to approved JAK inhibitors such as ruxolitinib is variable in preclinical models and is being formally evaluated in clinical trials.

Table 28 lists new subcategories of ALL with driver structural lesions, commonly also recognizable by their distinct gene expression signatures. Several have translocations most readily detected by whole transcriptome sequencing, although nonsequencing approaches using RT-PCR or commercially available FISH probes are possible for many of these. A few entities are defined by mutations resulting in single amino acid substitutions.

B-ALL with *MYC* rearrangement In contrast to Burkitt or other *MYC*-rearranged lymphomas, these have an immature phenotype, generally positive for terminal deoxynucleotidyl transferase (TdT), although not CD34, and often are negative or partly positive for CD20. Surface immunoglobulin may be positive.[217] Some resemble Burkitt lymphoma morphologically. There may be accompanying *BCL2* and less commonly *BCL6* translocations.[218] These cases mostly have a leukemic rather than lymphomatous presentation. Cases of aggressive B-cell lymphomas may sometimes express TdT and have other phenotypic markers of immaturity, and follicular lymphomas may

Table 27. Classification of ALL (synonym: lymphoblastic leukemia/lymphoma)

B-ALL
B-ALL with recurrent genetic abnormalities
B-ALLwith t(9;22)(q34.1;q11.2)/*BCR::ABL1*
with lymphoid only involvement
with multilineage involvement
B-ALLwith t(v;11q23.3)/*KMT2A* rearranged
B-ALL with t(12;21)(p13.2;q22.1)/*ETV6::RUNX1*
B-ALL, hyperdiploid
B-ALL, low hypodiploid
B-ALL, near haploid
B-ALL with t(5;14)(q31.1;q32.3)/*IL3::*IGH
B-ALL with t(1;19)(q23.3;p13.3)/*TCF3::PBX1*
B-ALL, *BCR::ABL1*–like, ABL-1 class rearranged
B-ALL, *BCR::ABL1*–like, JAK-STAT activated
B-ALL, *BCR::ABL1*–like, NOS
B-ALL with iAMP21
B-ALL with *MYC* rearrangement
B-ALL with *DUX4* rearrangement
B-ALL with *MEF2D* rearrangement
B-ALL with *ZNF384(362)* rearrangement
B-ALL with *NUTM1* rearrangement
B-ALL with *HLF* rearrangement
B-ALL with *UBTF::ATXN7L3/PAN3,CDX2* ("CDX2/UBTF")
B-ALL with mutated *IKZF1* N159Y
B-ALLwith mutated *PAX5* P80R
Provisional entity: B-ALL, *ETV6::RUNX1*-like
Provisional entity: B-ALL, with *PAX5* alteration
Provisional entity: B-ALL, with mutated *ZEB2* (p.H1038R)/IGH::*CEBPE*
Provisional entity: B-ALL, *ZNF384* rearranged-like
Provisional entity: B-ALL, *KMT2A* rearranged-like
B-ALL, NOS
T-ALL
Early T-cell precursor ALLwith *BCL11B* rearrangement
Early T-cell precursor ALL, NOS
T-ALL, NOS
Provisional entities (see supplemental Table 7)
Provisional entity: natural killer cell ALL

undergo lymphoblastic transformation[219,220]; such cases should be classified under the appropriate lymphoma rather than in this category. These high-grade, but TdT+ (usually partial), lymphomas may have *MYC* or even "double hit" rearrangements, but have a different mutational profile from B-ALL with *MYC* rearrangement[220] and show evidence of somatic hypermutation, whereas B-ALL with *MYC* rearrangements have unmutated immunoglobulin V(H) genes.[217]

New ALL entities defined by translocations *DUX4* is most commonly rearranged to IGH, and the IGH::*DUX4* translocation is typically cryptic because of the repetitive, duplicated nature of the *DUX4* locus and the rearrangement to IGH enhancers. *DUX4*-rearranged ALL is relatively common in children and associated with excellent prognosis in both children and adults, even when associated with other poor risk features, including *IKZF1* deletion.[221-223] Detection by FISH is difficult, but overexpression of *DUX4* is specific and can be detected by quantitation of *DUX4* gene expression or immunohistochemistry[224]; expression of CD371 is associated with *DUX4* rearrangement and may be identified by flow cytometry.[225] *MEF2D*-rearranged *B*-ALL has a poor prognosis. Cases with the common 3′ *BCL9* fusion partner can be detected with available fusion FISH probes, and cases can be suspected based on a CD10-/dim, CD38+, cμ+ immunophenotype.[226,227] The mechanism of leukemogenesis, involving deregulation of the MEF2D target gene *HDAC9*, may sensitize cells to histone deacetylase (HDAC) inhibitors.[226] *ZNF384*-rearranged leukemia represents a distinct entity with characteristic gene expression profile, lineage ambiguity, and patterns of concomitant mutation that may manifest as B-ALL (often with aberrant myeloid antigen expression insufficient to result in classification as MPAL) or B/myeloid MPAL.[228] Shift in lineage during disease evolution is common and further supports *ZNF384* rearrangement defining a distinct entity irrespective of initial immunophenotype. *ZNF384* is rearranged to a diverse range of fusion partners, commonly *EP300*, *TCF3*, and *TAF15*. Additional cases have a similar gene expression profile but harbor rearrangement of *ZNF362*. Both leukemias typically lack expression of CD10, as well as having variable expression of myeloid antigens, with expression of MPO often distinguishing B-ALL (MPO negative) from B/myeloid MPAL (MPO positive).[229-232] Prognosis varies with fusion partner, with *EP300* having the best prognosis and *TCF3* the worst.[233] *NUTM1*-rearranged leukemia is rare and most common in infants that lack *KMT2A* rearrangements but has a much more favorable prognosis than *KMT2A*-R leukemias.[234] It can be diagnosed using standard *NUTM1* breakapart FISH probe set.[235] *TCF3/4::HLF* rearranged leukemia is exceptionally rare and probably only found in children; it has a very poor prognosis,[236] although anti-CD19 therapy and transplant has shown some promise.[237] *CDX2/UBTF*-deregulated B-ALL is characterized by 2 concomitant genomic alterations in all cases: a focal deletion on chromosome 13 upstream of *FLT3* that results in retargeting of the PAN3 enhancer and deregulation of *CDX2* and a focal deletion of the 3′ region of *UBTF* that results in expression of the chimeric *UBTF::ATXN7L3* fusion oncoprotein.[238-240] This leukemia is most common in female adolescents and young adults and appears to have poor outcome if treated with conventional chemotherapy.

New ALL entities with point mutations Two uncommon entities with hotspot point mutations produce leukemias with unique gene expression patterns distinct from all other subtypes. *IKZF1* N159Y is rare and produces a missense mutation leading to upregulation of several oncogenic genes.[222,241] *PAX5* P80R[241,242] is more common, especially in adults and has a relatively favorable prognosis; leukemogenesis depends on biallelic alteration of *PAX5*, with either deletion of the wild-type allele or copy neutral loss of heterozygosity.[241]

Table 28. New entities in B-ALL defined by structural alterations

Subtype	Frequency	Prognosis	Diagnostic approach	Partner genes	Immunophenotype	Comment	References
B-ALL with *MYC* rearrangement	2-5%, higher in adults and AYA)	Poor	FISH *MYC/BCL2/BCL6*; Ig V(H) mutational status	IGH	TdT+CD34-CD20$^{+/-}$; may be SIg+	May have *BCL2/ BCL6* rearrangements	217,218,241
B-ALL with *DUX4* rearrangement	5-10%, highest in AYA and adult	Excellent	WTS,* IHC for DUX4 overexpression	Enhancers, most commonly IGH	CD371+; CD2+	Common *ERG* and *IKZF1* deletions	221-225
B-ALL with *MEF2D* rearrangement	3-5%	Poor	WTS; FISH *MEF2D*	*BCL9*, *HNRNPUL1*	CD10-/dim; CD38+; cu+		226,227
B-ALL with *ZNF384 or ZNF362* rearrangement	5-10%, higher inAYA	Variable	WTS; FISH possible	*EP300* (most common and good prognosis), *TCF3*, *TAF15*, *CREBBP*	CD10-/dim; myeloid antigen +	~50% of B/My MPAL in children, but not adults; FLT3 overexpression	229-232
B-ALL with *NUTM1* rearrangement	2% or less; rare in adults, mostly in infants lacking *KMT2A* rearrangements	Good	FISH *NUTM1*; WTS; NUTM1 overexpression (WTS, RT-PCR, IHC)	*ACIN1*, *ZNF618*, *BRD9*, *IKZF1*, *CUX1*	CD10-/dim; expression of myeloid markers (CD13/CD15/CD33)	Common overexpression of HOXA9	234,235
B-ALL/LL with *HLF* rearrangement	<<1% children	Very poor	WTS; FISH HLF	*TCF3*; *TCF4*	Unknown	May respond to anti-CD19 therapy	237
CDX2/UBTF	<1%; higher in AYA and females	Poor	RT PCR, WTS	*UBTF*::*ATXN7L3* by cryptic deletion of 17q21.31; high expression of CDX2 by deletion *FLT3/PAN3* at 13q12.2)	CD10 negative and cytoplasmic IgM positive		238-240
B-ALL/LL with mutated *IKZF1* N159Y	<1% all ages	Intermediate	Exome/gene panel sequencing	N.A.	Unknown	Distinct gene expression profile; gain of chromosome 21 in 75% of cases	241,244
B-ALL/LL with mutated *PAX5* P80R	2-5% higher in adult	Intermediate, good in adults	Exome/gene panel sequencing	N.A.		Biallelic *PAX5* alterations from deletion or LOF mutation of second allele; *CDKN2A* loss; *JAK* and *RAS* signaling gene mutations	241,242,263

AYA, adolescents and young adults; WTS, whole transcriptome sequencing

*Whole transcriptome sequencing may not detect *DUX4* rearrangements in all cases due to repetitive genomic features at both *DUX4* and IGH loci.

Provisional entities (supplemental Table 7) Some cases are phenocopies of several of the subtypes described above and have identical gene expression profiles but lack the requisite structural lesion. Because these cannot yet as a rule be diagnosed by methods other than gene expression profiling, they are considered provisional. *ETV6*::*RUNX1*-like B-ALL cases share the CD27^{+},CD44 dim/neg phenotype of *ETV6*::*RUNX1* B-ALL[223,243] and in pediatrics appear to have the same favorable prognosis.[244] A relatively large subtype is *PAX5*-altered B-ALL (PAX5alt), which is characterized by a variety of different alterations in *PAX5*, including rearrangements, point mutations, and intragenic lesions[241,245]; although many of these can be identified directly, complete definition of the group requires gene expression profiling. Cases with the H1038R mutation in *ZEB2* co-cluster with those with IGH::*CEBPE*[244] and have a poor prognosis,[246] but these lesions do not appear to define this group uniquely.

T-ALL

Early T precursor ALL (ETP ALL) ETP ALL is currently diagnosed by immunophenotype, and the definition has not changed. It is now recognized that about a third of ETP ALL is characterized by rearrangement and deregulation of the T-lineage transcription factor gene *BCL11B* in hematopoietic stem cells.[247-249] More than 80% of cases have activating *FLT3* mutations, with all cases exhibiting high FLT3 expression. Most cases may be detected by FISH to detect disruption of the *BCL11B* locus. Also, there are some cases of T-ALL that are phenotypically similar to ETP except that CD5 is present on >75% rather than ≤75% of cells; these have been referred to as "near-ETP ALL" and have different genomic lesions from those of ETP, with some overlap,[250,251] and there are minor differences from ETP in clinical presentation and response to therapy.[251]

The remainder of T-ALL can be subclassified based on aberrant activation of different families of transcription factors (see reviews for detailed discussion),[251-259] although the underlying lesions are complex so that diagnosis is challenging, and subclassification is not typically used in clinical trials. Moreover, there is some variability in how different authors define different subtypes.[252,255,258] For these reasons they are considered provisional entities in this classification.

Authorship

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Footnotes

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