

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

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

Table 1. (continued)

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

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 \geq 20%
Peripheral blood basophils \geq 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.

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

PV	Post-PV MF
<p>Major criteria</p> <ol style="list-style-type: none"> 1. Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass* 2. Presence of <i>JAK2</i> V617F or <i>JAK2</i> 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 <p>Minor criterion</p> <ul style="list-style-type: none"> • Subnormal serum erythropoietin level 	<p>Required criteria</p> <ol style="list-style-type: none"> 1. Previous established diagnosis of PV 2. Bone marrow fibrosis of grade 2 or 3 <p>Additional criteria</p> <ol style="list-style-type: none"> 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)
<p>The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion‡</p>	<p>The diagnosis of post-PV MF is established by all required criteria and at least 2 additional criteria</p>

*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.

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

ET	Post-ET MF
<p>Major criteria</p> <ol style="list-style-type: none"> 1. Platelet count $\geq 450 \times 10^9/L$ 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 <i>BCR::ABL1</i>-positive CML, PV, PMF, or other myeloid neoplasms are not met 4. <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation‡ <p>Minor criteria</p> <ul style="list-style-type: none"> • Presence of a clonal marker§ or absence of evidence of reactive thrombocytosis 	<p>Required criteria</p> <ol style="list-style-type: none"> 1. Previous established diagnosis of ET 2. Bone marrow fibrosis of grade 2 or 3 <p>Additional criteria</p> <ol style="list-style-type: none"> 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)
<p>The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criteria</p>	<p>The diagnosis of post-ET MF is established by all required criteria and at least 2 additional criteria</p>

*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
<p>Major criteria</p> <ol style="list-style-type: none"> 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. <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation† or presence of another clonal marker‡ or absence of reactive bone marrow reticulin fibrosis§ 3. Diagnostic criteria for <i>BCR::ABL1</i>-positive CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms are not met 	<p>Major criteria</p> <ol style="list-style-type: none"> 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* accompanied by reticulin and/or collagen fibrosis grades 2 or 3 2. <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation† or presence of another clonal marker‡ or absence of reactive myelofibrosis§ 3. Diagnostic criteria for ET, PV, <i>BCR::ABL1</i>-positive CML, myelodysplastic syndrome, or other myeloid neoplasms are not met
<p>Minor criteria</p> <ul style="list-style-type: none"> • Anemia not attributed to a comorbid condition • Leukocytosis $\geq 11 \times 10^9/L$ • Palpable splenomegaly • Lactate dehydrogenase level above the above the reference range 	<p>Minor criteria</p> <ul style="list-style-type: none"> • Anemia not attributed to a comorbid condition • Leukocytosis $\geq 11 \times 10^9/L$ • Palpable splenomegaly • Lactate dehydrogenase level above the above the reference range • Leukoerythroblastosis
<p>The diagnosis of pre-PMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations</p>	

*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.

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

<p>1. Peripheral blood white blood cell count $\geq 13 \times 10^9/L$* Segmented neutrophils plus banded neutrophils constitute $\geq 80\%$ 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.†</p>
<p>2. Hypercellular bone marrow with neutrophil granulocytes increased in percentage and absolute number, showing normal maturation.</p>
<p>3. <i>CSF3R</i> T618I or another activating <i>CSF3R</i> 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.</p>
<p>4. Not meeting diagnostic criteria for <i>BCR::ABL1</i>-positive CML, PV, ET, PMF or of a myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions.</p>

*At least $25 \times 10^9/L$ 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; $\geq 20\%$ blasts represents blast phase.

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

1. Peripheral blood hypereosinophilia (eosinophil count $\geq 1.5 \times 10^9/L$ and eosinophils $\geq 10\%$ 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 <i>BCR::ABL1</i> , other <i>ABL1</i> , <i>PDGFRA</i> , <i>PDGFRB</i> , <i>FGFR1</i> , <i>JAK2</i> , or <i>FLT3</i> 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 $\geq 5\%$ in the bone marrow and/or $\geq 2\%$ 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.

†Eosinophilia 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.

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

1. Persistent peripheral blood hypereosinophilia (eosinophil count $\geq 1.5 \times 10^9/L$ and $\geq 10\%$ 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. <i>JAK2</i> , <i>CALR</i> , or <i>MPL</i> mutation† or presence of another clonal marker‡
3. Diagnostic criteria for any other MPN, MDS, MDS/MPN,§ or <i>BCR::ABL1</i> -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.

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
<i>PDGFRA</i>	Cryptic deletion at 4q12/ <i>FIP1L1::PDGFRA</i>	<i>CDK5RAP2</i> ; <i>STRN</i> ; <i>KIF5B</i> ; <i>TNKS2</i> ; <i>ETV6</i> , <i>BCR</i>	Common: CEL-like BM with frequent extramedullary involvement Others: B-ALL/LL, AML or mast cell proliferations	Excellent response to TKI
<i>PDGFRB</i>	t(5;12)(q32;p13.2)/ <i>ETV6::PDGFRB</i>	>30 partners, cryptic	Common: CEL-like or monocytosis with eosinophilia Others: ALL/LL, AML or mast cell proliferations	Excellent response to TKI
<i>FGFR1</i>	t(8;13)(p11.2;q12.1)/ <i>ZMYM2::FGFR1</i>	15 other partners including <i>BCR</i>	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
<i>JAK2</i>	t(8;9)(p22;p24.1)/ <i>PCM1::JAK2</i>	<i>ETV6</i> and <i>BCR</i>	Common: MPN or MDS/MPN-like BM with eosinophilia Others: B- and T-ALL/LL with BM MPN	Limited responses to ruxolitinib
<i>FLT3</i>	t(12;13)(p13.2;q12.2)/ <i>ETV6::FLT3</i>	<i>ZMYM2</i> , <i>TRIP11</i> , <i>SPTBN1</i> , <i>GOLGB1</i> , <i>CCDC88C</i> , <i>MYO18A</i> , <i>BCR</i>	T-ALL/LL or myeloid sarcoma with CEL-like or MDS/MPN BM features	Various responses to specific FLT3 inhibitors
<i>ETV6::ABL1</i>	t(9;12)(q34.1;p13.2)/ <i>ETV6::ABL1</i>	Unknown	CML-like with frequent eosinophilia in chronic or blast phase	Various responses to second generation TKI

Table 11. Systemic mastocytosis: diagnostic criteria

Major criterion
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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 • <i>KIT</i> D816V mutation or other activating <i>KIT</i> 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.

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.

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

Monocytosis defined as monocytes $\geq 0.5 \times 10^9/L$ and $\geq 10\%$ 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 $\geq 1.0 \times 10^9/L$ 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: $\geq 5\%$ in the bone marrow and/or $\geq 2\%$ 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.

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

Persistent monocytosis defined as monocytes $\geq 0.5 \times 10^9/L$ and $\geq 10\%$ 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, $\geq 2\%$)†
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.

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

Leukocytosis $\geq 13 \times 10^9/L$, due to increased numbers of neutrophils and their precursors (promyelocytes, myelocytes and metamyelocytes), the latter constituting $\geq 10\%$ 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 \pm 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 <i>BCR::ABL1</i> 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 <i>SETBP1</i> mutations in association with <i>ASXL1</i> 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 $\geq 450 \times 10^9/L$
Anemia (threshold same as for MDS)
Blasts $< 1\%$ in blood and $< 5\%$ in bone marrow
Presence of <i>SF3B1</i> 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 <i>BCR::ABL1</i> or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no <i>t(3;3)(q21.3;q26.2)</i> , <i>inv(3)(q21.3q26.2)</i> , or <i>del(5q)</i> *
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 $\geq 450 \times 10^9/L$
Anemia associated with erythroid-lineage dysplasia, with or without multilineage dysplasia, and $\geq 15\%$ 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 <i>SF3B1</i> mutation; no <i>BCR::ABL1</i> or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no <i>t(3;3)(q21.3;q26.2)</i> , <i>inv(3)(q21.3q26.2)</i> , or <i>del(5q)</i> *
No history of MPN, MDS, or other MDS/MPN

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

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 $\geq 450 \times 10^9/L$ and/or a white blood cell count of $\geq 13 \times 10^9/L$
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 <i>BCR::ABL1</i> or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no <i>t(3;3)(q21.3;q26.2)</i> , <i>inv(3)(q21.3q26.2)</i> , [†] or <i>del(5q)</i> [‡]

*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)*.

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

<p>Fulfills the general criteria for a diagnosis of MDS/MPN, NOS</p> <ul style="list-style-type: none"> • Leukocytosis of $\geq 13 \times 10^9/L$ • 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 <i>BCR::ABL1</i> or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions • Absence of MPN-associated mutations (<i>JAK2</i>, <i>CALR</i> and <i>MPL</i>)* • No history of recent cytotoxic or growth factor therapy that could explain the MDS/MPN features
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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 <i>SF3B1</i> (MDS- <i>SF3B1</i>)	Typically $\geq 1\ddagger$	≥ 1	0	<5% BM <2% PB	Any, except isolated <i>del(5q)</i> , $-7/del(7q)$, <i>abn3q26.2</i> , or complex	<i>SF3B1</i> ($\geq 10\%$ VAF), without multi-hit <i>TP53</i> , or <i>RUNX1</i>
MDS with <i>del(5q)</i> [MDS- <i>del(5q)</i>]	Typically $\geq 1\ddagger$	≥ 1	Thrombocytosis allowed	<5% BM <2% PB§	<i>del(5q)</i> , with up to 1 additional, except $-7/del(7q)$	Any, except multi-hit <i>TP53</i>
MDS, NOS without dysplasia	0	≥ 1	0	<5% BM <2% PB§	$-7/del(7q)$ or complex	Any, except multi-hit <i>TP53</i> or <i>SF3B1</i> ($\geq 10\%$ VAF)
MDS, NOS with single lineage dysplasia	1	≥ 1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS- <i>del(5q)</i>	Any, except multi-hit <i>TP53</i> ; not meeting criteria for MDS- <i>SF3B1</i>
MDS, NOS with multilineage dysplasia	≥ 2	≥ 1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS- <i>del(5q)</i>	Any, except multi-hit <i>TP53</i> ; not meeting criteria for MDS- <i>SF3B1</i>
MDS with excess blasts (MDS-EB)	Typically $\geq 1\ddagger$	≥ 1	0	5-9% BM, 2-9% PB§	Any	Any, except multi-hit <i>TP53</i>
MDS/AML	Typically $\geq 1\ddagger$	≥ 1	0	10-19% BM or PB	Any, except AML-defining¶	Any, except <i>NPM1</i> , bZIP <i>CEBPA</i> or <i>TP53</i>

*Cytoses: Sustained white blood count $\geq 13 \times 10^9/L$, monocytosis ($\geq 0.5 \times 10^9/L$ and $\geq 10\%$ of leukocytes) or platelets $\geq 450 \times 10^9/L$; 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.

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.

Table 22. Diagnostic criteria for juvenile myelomonocytic leukemia

<p>I. Clinical and hematologic features (the first 2 features are present in most cases; the last 2 are required)</p> <ul style="list-style-type: none"> • PB monocyte count $\geq 1 \times 10^9/L^*$ • Splenomegaly† • Blast percentage in PB and BM < 20% • Absence of <i>BCR::ABL1</i>
<p>II. Genetic studies (1 finding required)</p> <ul style="list-style-type: none"> • Somatic mutation in <i>PTPN11</i>‡ or <i>KRAS</i>‡ or <i>NRAS</i>‡ or <i>RRAS</i>‡ • Germline <i>NF1</i> mutation and loss of heterozygosity of <i>NF1</i> or clinical diagnosis of neurofibromatosis type 1 • Germline <i>CBL</i> mutation and loss of heterozygosity of <i>CBL</i>§

*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.

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

	PB/BM blasts	Mutation	Secondary mutations	Karyotype
JMML	<20% PB <20% BM	<i>PTPN11</i> , <i>NRAS</i> , <i>KRAS</i> , <i>RRAS</i> , <i>NF1</i> *, <i>CBL</i> †	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	<i>PTPN11</i> ,‡ <i>NRAS</i> ,‡ <i>KRAS</i> ,‡ <i>RIT1</i> ‡	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 $\geq 10\%$ 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

Table 24. ICC of hematologic neoplasms with germline predisposition

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

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

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::KMT2A⁶; 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* <ul style="list-style-type: none"> • prior chemotherapy, radiotherapy, immune interventions
Progressing from MDS <ul style="list-style-type: none"> • MDS should be confirmed by standard diagnostics
Progressing from MDS/MPN (specify) <ul style="list-style-type: none"> • 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.

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

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

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 in AYA	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.