The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes

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Recently the World Health Organization (WHO), in collaboration with the European Association for Haematopathology and the Society for Hematopathology, published a revised and updated edition of the WHO Classification of Tumors of the Hematopoietic and Lymphoid Tissues. The 4th edition of the WHO classification incorporates new information that has emerged from scientific and clinical studies in the interval since the publication of the 3rd edition in 2001, and includes new criteria for the recognition of some previously described neoplasms as well as clarification and refinement of the defining criteria for others. It also adds entities—some defined principally by genetic features—that have only recently been characterized. In this paper, the classification of myeloid neoplasms and acute leukemia is highlighted with the aim of familiarizing hematologists, clinical scientists, and hematopathologists not only with the major changes in the classification but also with the rationale for those changes. (Blood. 2009;114:937-951)

Introduction

In 2001, the World Health Organization (WHO), in collaboration with the Society for Hematopathology and the European Association of Haematopathology, published a Classification of Tumors of the Hematopoietic and Lymphoid Tissues as part of the 3rd edition of the series, WHO Classification of Tumors.1 That classification reflected a paradigm shift from previous schemes in that, for the first time, genetic information was incorporated with morphologic, cytochemical, immunophenotypic, and clinical information into diagnostic algorithms for the myeloid neoplasms. The 2001WHO classification was prefaced with a comment predicting that future revisions would be necessary because of rapidly emerging genetic and biologic information. Recently, a revised classification has been published as part of the 4th edition of the WHO monograph series.2 The aim of the revision was to incorporate new scientific and clinical information to refine diagnostic criteria for previously described neoplasms and to introduce newly recognized disease entities. Our purpose in this communication is to highlight major changes in the revised WHO classification of myeloid neoplasms and acute leukemia and to provide the rationale for those changes.

Background of the WHO classification/revision

The principles of the WHO classification have been described previously.3,4 Briefly, the classification uses all available information—morphology, cytochemistry, immunophenotype, genetics, and clinical features—to define clinically significant disease entities. It is a consensus classification in which a number of experts have agreed on the classification and the diagnostic criteria used for defining the entities that compose it. Nearly 30 clinicians and clinical scientists from around the world who are recognized for their expertise in myeloid neoplasms and acute leukemia were invited to be members of the Myeloid and Acute Leukemia Clinical Advisory Committee (CAC). The CAC met with the pathology committee and made a number of recommendations that were incorporated in the revision to ensure that the classification would be clinically useful. Representatives of international consensus groups such as the International Working Group for Myelofibrosis Research and Treatment and the European Group for the Immunologic Classification of Leukemia were included in the CAC.

Proposals for revisions and for recognition of new entities for the 4th edition were based on studies published in the recent literature with the goal of providing a classification that can be used in daily clinical practice as well as serve as a common language for clinical trials and laboratory investigation. However, even during the revision process, new information was being published regarding a number of the myeloid neoplasms. To be incorporated in a universally accepted classification scheme, recent data need to “mature” and their significance needs to be widely acknowledged. Therefore, to accommodate such recent information, a number of “provisional entities” are found within the major subgroups of diseases. These are newly described or characterized disorders that are clinically and/or scientifically important and should be considered in the classification, but for which additional studies are needed to clarify their significance. It is likely that many of these
provisional categories will be incorporated as confirmed entities in the next revision process.

**Guidelines for using the WHO classification of myeloid neoplasms**

In the WHO classification, the term “myeloid” includes all cells belonging to the granulocytic (neutrophil, eosinophil, basophil), monocytic/macrophage, erythroid, megakaryocytic and mast cell lineages. The WHO criteria for myeloid neoplasms apply to initial diagnostic peripheral blood (PB) and bone marrow (BM) specimens obtained prior to any definitive therapy for a suspected hematologic neoplasm. Morphologic, cytochemical, and/or immunophenotypic features are used for establishing the lineage of the neoplastic cells and for assessment of their maturation. The blast percentage remains a practical tool for categorizing myeloid neoplasms and judging their progression. In the WHO scheme, a myeloid neoplasm with 20% or more blasts in the PB or BM is considered to be acute myeloid leukemia (AML) when it occurs de novo, evolution to AML when it occurs in the setting of a previously diagnosed myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm (MDS/MPN), or blast transformation in a previously diagnosed myeloproliferative neoplasm (MPN). In some cases associated with specific genetic abnormalities, however, the diagnosis of AML may be made regardless of the blast count in the PB or BM (see “Acute myeloid leukemia and related precursor neoplasms”). The 20% blast threshold is not a mandate to treat the patient as having AML or blast transformation; therapeutic decisions must always be based on the clinical situation after all information is considered. A tumoral proliferation of blasts in an extramedullary site (myeloid sarcoma) is also considered to be AML when it is found de novo or in a patient with MDS or MDS/MPN, and blast transformation in cases of MPN. Blast percentages should be derived, when possible, from 200-cell leukocyte differential counts of the PB smear and 500-cell differential counts of all nucleated BM cells on cellular marrow aspirate smears stained with Wright-Giemsa (see Table 1). Blasts are defined using the criteria recently proposed by the International Working Group on Morphology of Myelodysplastic Syndrome.5 Determination of the blast percentage by assessment of CD34+ cells by flow cytometry is not recommended as a substitute for visual inspection; not all leukemic blasts express CD34, and hemodilution and processing artefacts can produce misleading results. For acute leukemia, multiparameter flow cytometry (3 or more colors) is the method of choice for determining the blast lineage as well as for detecting aberrant antigenic profiles that may prove useful for disease monitoring.

Although a BM core biopsy may not be required in every case, an adequate biopsy does provide the most accurate assessment of the marrow cellularity, topography, stromal changes, and maturation pattern of the hematopoietic lineages, and it can be invaluable in detecting residual disease following therapy. In addition, the biopsy provides material for immunohistochemical detection of antigens that can be diagnostically and prognostically useful, such as CD34, TdT, and Ki67, particularly if marrow aspirate smears are poorly cellular.6

A complete cytogenetic analysis of BM cells is essential during initial evaluation for establishing a baseline karyotype; repeat analyses are recommended as needed thereafter for judging the response to therapy or for detecting genetic evolution. Additional genetic studies should be guided by the results of the initial karyotype and by the diagnosis suspected based on the clinical, morphologic, and immunophenotypic studies. In some cases, reverse transcriptase–polymerase chain reaction (RT-PCR) and/or fluorescence in situ hybridization (FISH) may detect variants of well-recognized cytogenetic abnormalities or submicroscopic abnormalities not detected by routine karyotyping, such as the FIP1L1-PDGFRα fusion in some myeloid neoplasms associated with eosinophilia.7 In addition, gene mutations are increasingly being recognized as important diagnostic and prognostic markers in myeloid neoplasms. These include, among others, mutations of JAK2, MPL, and KIT in MPN8-13; NRAS, KRAS, NF1, and PTPN11 in MDS/MPN14-19; NPM1, CEBPA, FLT3, RUNX1, KIT, WT1, and MLH in AML20-24; and GATA25 in myeloid proliferations associated with Down syndrome. Many of these gene mutations figure importantly in the revised WHO classification. Although over- and underexpression of genes has proved to affect the prognosis in some myeloid neoplasms,26 at the present time analyses of gene

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**Table 1. Guidelines for using the revised WHO classification of myeloid neoplasms**

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<th>Specimen requirements</th>
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<td>PB and BM specimens collected prior to any definitive therapy.</td>
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<td>PB and cellular BM aspirate smears and/or touch preparations stained with Wright-Giemsa or similar stain.</td>
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<td>BM biopsy, at least 1.5 cm in length and at right angles to the cortical bone, is recommended for all cases if feasible.</td>
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<td>BM specimens for complete cytogenetic analysis and, when indicated, for flow cytometry, with an additional specimen cryopreserved for molecular genetic studies. The latter studies should be performed based on initial karyotypic, clinical, morphologic, and immunophenotypic findings.</td>
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**Assessment of blasts**

- Blast percentage in PB and BM is determined by visual inspection.
- Myeloblasts, monoblasts, promonocytes, megakaryoblasts (but not dysplastic megakaryocytes) are counted as blasts when summing blast percentage for diagnosis of AML or blast transformation; count abnormal promyelocytes as “blast equivalents” in APL.
- Proerythroblasts are not counted as blasts except in rare instances of “pure” acute erythroleukemia.
- Flow cytometric assessment of CD34+ cells is not recommended as a substitute for visual inspection; not all blasts express CD34, and artifacts introduced by specimen processing may result in erroneous estimates.
- If the aspirate is poor and/or marrow fibrosis is present, IHC on biopsy sections for CD34 may be informative if blasts are CD34+.  

**Assessment of blast lineage**

- Multiparameter flow cytometry (at least 3 colors) is recommended; panel should be sufficient to determine lineage as well as aberrant antigen profile of neoplastic population.
- Cytochemistry, such as myeloperoxidase or nonspecific esterase, may be helpful, particularly in AML, NOS, but it is not essential in all cases.
- IHC on biopsy may be helpful; many antibodies are now available for recognition of myeloid and lymphoid antigens.

**Assessment of genetic features**

- Complete cytogenetic analysis from BM at initial diagnosis when possible. Additional studies, such as FISH, RT-PCR, mutational status, should be guided by clinical, laboratory, and morphologic information.
- Mutational studies for mutated NPM1, CEBPA, and FLT3 are recommended in all cytogenetically normal AML; mutated JAK2 should be sought in BCR-ABL1–negative MPN, and mutational analysis for KIT, NRAS, PTPN11, etc, should be performed as clinically indicated.

**Correlation/reporting of data**

| All data should be assimilated into one report that states the WHO diagnosis. |

WHO indicates World Health Organization; PB, peripheral blood; BM, bone marrow; IHC, immunohistochemistry; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; NOS, not otherwise specified; FISH, fluorescence in situ hybridization; RT-PCR, reverse transcriptase–polymerase chain reaction; and MPN, myeloproliferative neoplasm.
Table 2. WHO classification of myeloid neoplasms and acute leukemia

### Myeloproliferative neoplasms (MPN)
- Chronic myelogenous leukemia, BCR-ABL1-positive
- Chronic neutrophilic leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia, not otherwise specified
- Mastocytosis
- Myeloproliferative neoplasms, unclassifiable

### Myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of PDGFRα, PDGFRβ, or FGFR1
- Myeloid and lymphoid neoplasms associated with PDGFRα rearrangement
- Myeloid neoplasms associated with PDGFRβ rearrangement
- Myeloid and lymphoid neoplasms associated with FGFR1 abnormalities

### Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
- Chronic myelomonocytic leukemia
- Atypical chronic myeloid leukemia, BCR-ABL1-negative
- Juvenile myelomonocytic leukemia
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable

### Myelodysplastic syndrome (MDS)
- Refractory cytopenia with unilineage dysplasia
- Refractory anemia
- Refractory neutropenia
- Refractory thrombocytopenia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable

### Childhood myelodysplastic syndrome
- Provisional entity: refractory cytopenia of childhood

### Acute myeloid leukemia and related neoplasms
- Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- APL with t(15;17)(q22;q12); PML-RARA
- AML with t(9;11)(q22;q13); MLL3-MLL
- AML with t(6;9)(p23;q34); DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
- AML (megakaryoblastic) with t(1;22)(p13;q11); RBM15-MKL1
- Provisional entity: AML with mutated NPM1
- Provisional entity: AML with mutated CEBPA
- Acute myeloid leukemia with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Acute myeloid leukemia, not otherwise specified
- AML with minimal differentiation
- AML without maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemia
- Pure erythroid leukemia
- Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoesis
- Myeloid leukemia associated with Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

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Revised WHO classification of myeloid neoplasms and acute leukemia

Table 2 lists the major subgroups of myeloid neoplasms and acute leukemia in the WHO classification, and the specific entities of which they are composed. The nomenclature for the myeloproliferative entities is changed from "chronic myeloproliferative disease" to "myeloproliferative neoplasms" in order to accurately reflect their neoplastic nature. To be consistent, the subgroup formerly designated as "myelodysplastic/myeloproliferative diseases" has been renamed "myelodysplastic/myeloproliferative neoplasms." In addition, a new subgroup, "Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRα, PDGFRβ, and FGFR1," has been added. Within each of the major subgroups of myeloid neoplasms and acute leukemia, new entities have been added and/or diagnostic criteria have been changed.

Myeloproliferative neoplasms and myeloid neoplasms associated with eosinophilia

The MPNs are listed in Table 2. The revisions in the criteria for the WHO classification of MPN have been influenced by 2 factors: (1) the discovery of genetic abnormalities that can be used as diagnostic markers in BCR-ABL1–negative MPN and (2) better characterization of histologic features that aid in the identification of MPN subtypes. In the previous WHO scheme, detection of the Philadelphia (Ph) chromosome and/or BCR-ABL1 fusion gene was used to confirm the diagnosis of CML, whereas the BCR-ABL1–negative MPN subtypes were diagnosed according to their clinical and laboratory features supported by minor contributions from histopathology. A number of criteria were required for distinguishing the MPN subtypes not only from each other, but also from reactive granulocytic, erythroid, and/or megakaryocytic hyperplasia that often mimics MPN. Now it is recognized that in the other MPNs, as dosage by quantitative RT-PCR is not practical on a daily basis, nor have gene expression arrays been introduced into routine use, and therefore such data are not included in this revision.
reactive thrombocytosis does not exclude the possibility of ET if other criteria are met. Gery, infection, inflammation, connective tissue disease, metastatic cancer, and bulbous, or irregularly folded nuclei and dense clustering. Megakaryocyte morphology that is typical for primary myelofibrosis—small to large blood leukoerythroblastosis, or markedly hypercellular marrow accompanied by measurement is not required.

Table 3. Criteria for polycythemia vera (PV)

Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria:

Major criteria
1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume*
2. Presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation

Minor criteria
1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (pannerythosysis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. Serum erythropoietin level below the reference range for normal
3. Endogenous erythroid colony formation in vitro

*Hemoglobin or hematocrit > 99th percentile of method-specific reference range for age, sex, altitude of residence or hemoglobin > 17 g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from a person's baseline value that cannot be attributed to correction of iron deficiency or elevated red cell mass > 25% above mean normal predicted value.

Diagnosis requires meeting all 4 criteria
3. Not meeting WHO criteria for polycythemia vera,† primary myelofibrosis,‡ or metastatic malignancy, or toxic (chronic) myelopathies

Minor criteria
1. Leukocyte dysgranulopoiesis¶
2. Increase in serum lactate dehydrogenase level¶
3. Anemia¶
4. Palpable splenomegaly¶

¶Degree of abnormality could be borderline or marked.

Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria:

Major criteria
1. Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
2. Not meeting WHO criteria for polycythemia vera,† BCR-ABL1–positive chronic myelogenous leukemia,‡ myelodysplastic syndrome,§ or other myeloid disorders
3. Demonstration of JAK2 V617F or other clonal marker (eg, MPL W515K/L), or, in the absence of the above clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies

Minor criteria
1. JAK2 V617F or other clonal marker, or in the absence of JAK2 V617F, no evidence of reactive thrombocytosis¶
2. Serum erythropoietin level below the reference range for normal
3. Hemoglobin or hematocrit

*Clinical, laboratory, and/or morphologic features that allow the genetic abnormality to be used as a major criterion for diagnosis. Other abnormalities, such as mutated JAK2 or KIT, are not specific for any single MPN but provide proof that the proliferation is clonal and thus, when present, eliminate further consideration of a reactive process.

At the present time, the most commonly recognized mutation in BCR-ABL1–negative MPN is JAK2 V617F. This mutation is found in more than 90% of patients with polycythemia vera (PV) and in nearly one-half of those with primary myelofibrosis (PMF)

Table 4. Criteria for essential thrombocythemia (ET)

Diagnosis requires meeting all 4 criteria
1. Sustained platelet count > 450 × 10^9/L
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis.
3. Not meeting WHO criteria for polycythemia vera,† primary myelofibrosis,‡ BCR-ABL1–positive CML,§ or other myeloid neoplasm.
4. Demonstration of JAK2 V617F or other clonal marker, or in the absence of JAK2 V617F, no evidence of reactive thrombocytosis¶.

ET indicates essential thrombocythemia; BM, bone marrow; WHO, World Health Organization; and CML, chronic myelogenous leukemia.

*Sustained during the work-up process.
†Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required.
‡Requires the absence of dyserythropoiesis and dysgranulopoiesis.
§Requires the absence of BCR-ABL1.
¶Degree of abnormality could be borderline or marked.

Diagnosis requires meeting all 3 major criteria and 2 minor criteria
1. Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)

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<td>2. Not meeting WHO criteria for polycythemia vera,† BCR-ABL1–positive chronic myelogenous leukemia,‡ myelodysplastic syndrome,§ or other myeloid disorders</td>
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¶Degree of abnormality could be borderline or marked.

or essential thrombocythemia (ET). Therefore, JAK2 V617F is not specific for any single MPN, nor does its absence exclude any MPN. In the few PV patients who lack this mutation, a similar activating JAK2 exon 12 mutation may be found, and a small proportion of patients with PMF and ET who lack mutated JAK2 may instead demonstrate activating mutations of MPL, such as MPL W515K or MPL W515L. The WHO diagnostic algorithms for PV, ET, and PMF require analysis for mutated JAK2 and if absent, for other relevant genetic abnormalities that may provide proof of clonality of the proliferative process. Still, additional parameters are required to ensure accurate diagnosis and subclassification regardless of whether a mutation is or is not found. Clinical and laboratory findings form the backbone of these diagnostic criteria, but histopathologic findings characteristic of each MPN subtype have been included in the criteria as well. The revised criteria for PV, ET, and PMF are listed in Tables 3, 4 and 5, respectively. For ET some investigators have argued that patients with clinical and morphologic findings of ET may have platelet counts that exceed the normal range, but that fail to meet the diagnostic threshold previously required. In the revised criteria, the platelet threshold for the diagnosis of ET has therefore been lowered from 600 × 10^9/L to 450 × 10^9/L.

Recently, some authorities have raised concerns regarding the inclusion of histologic features as diagnostic parameters for PV, ET, and PMF. In particular, the histologic distinction between the “prefibrotic” stage of PMF (a stage often associated with marked thrombocytosis in the PB and granulocytic and atypical megakaryocytic proliferation with minimal, if any, fibrosis in the BM) and ET.

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has been questioned.\textsuperscript{34} It is important to note that the histopathologic features included in the WHO criteria for PV, PMF, and ET were derived from a number of clinical-pathologic studies\textsuperscript{35-37} and that the WHO classification does not advocate that any single histologic feature is sufficient for a diagnosis of any MPN, but must be interpreted in the context of other clinical and laboratory criteria.

Since the last edition of the WHO classification, it has been appreciated that some cases of eosinophilia, including cases formerly designated as chronic eosinophilic leukemia (CEL) or the “hypereosinophilic syndrome,” are caused by abnormalities in genes that encode the alpha or beta moieties of the platelet-derived growth factor receptor (PDGFR). Rearrangements of \textit{PDGFRB} at chromosome band 5q33 were first recognized in cases variably reported as chronic myelomonocytic leukemia (CMML) with eosinophilia, or less commonly, as CEL.\textsuperscript{38-41} More recently, the gene that encodes the alpha chain of PDGFR, \textit{PDGFRΑ}, located at chromosome band 4q12, was found to be involved in cryptic translocations in cases of CEL and in a substantial number of cases reported as idiopathic hypereosinophilic syndrome.\textsuperscript{42} Rearrangements of \textit{FGFR1} have also been implicated in myeloproliferations with prominent eosinophilia, that is, the “8p11.2 myeloproliferative syndrome.”\textsuperscript{42} Patients with \textit{FGFR1} rearrangements, however, may initially have T- or B-lymphoblastic leukemia/lymphoma associated with prominent tissue eosinophilia that may later evolve to a myeloid neoplasm with eosinophilia.\textsuperscript{42,43} Rare cases associated with \textit{PDGFRΑ} rearrangements have also been reported to initially have a lymphoblastic neoplasm.\textsuperscript{44} Therefore, although it might seem less confusing to categorize cases with rearranged \textit{PDGFRΑ}, \textit{PDGFRΒ}, or \textit{FGFR1} and eosinophilia as CEL within the MPN category, this would ignore cases with \textit{PDGFRΒ} rearrangements that have CMML as well as cases with rearrangements of \textit{FGFR1} and \textit{PDGFRΑ} that may have a lymphoid component. For these reasons, as well as for the therapeutic implications of specific identification of rearranged \textit{PDGFRΑ} and \textit{PDGFRΒ} that are sensitive to imatinib therapy, these cases were assigned to a new subgroup, “Myeloid/lymphoid neoplasms with eosinophilia associated with rearrangements of \textit{PDGFRΑ}, \textit{PDGFRΒ}, or \textit{FGFR1} and eosinophilia as CEL within the MPN category,” this would ignore cases with \textit{PDGFRΒ} rearrangements that have CMML as well as cases with rearrangements of \textit{FGFR1} and \textit{PDGFRΑ} that may have a lymphoid component. For these reasons, as well as for the therapeutic implications of specific identification of rearranged \textit{PDGFRΑ} and \textit{PDGFRΒ} that are sensitive to imatinib therapy, these cases were assigned to a new subgroup, “Myeloid/lymphoid neoplasms with eosinophilia associated with rearrangements of \textit{PDGFRΑ}, \textit{PDGFRΒ}, or \textit{FGFR1}.” Cases of myeloid neoplasms with eosinophilia that lack these rearrangements should be classified as CEL, not otherwise specified (NOS), if the neoplasms with eosinophilia that lack these rearrangements are categorized as a myeloid or lymphoid neoplasm with eosinophilia associated with rearrangements and/or abnormalities of \textit{PDGFRΑ}, \textit{PDGFRΒ}, or \textit{FGFR1}.

### Significant changes in the diagnosis and classification of MPN

1. The nomenclature has been changed from “myeloproliferative disorders” (MPDs) to “myeloproliferative neoplasms” (MPNs).
2. Diagnostic algorithms for PV, ET, and PMF have substantially changed to include information regarding \textit{JAK2} V617F and similar activating mutations. Additional clinical, laboratory, and histologic parameters have been included to allow diagnosis and subclassification regardless of whether \textit{JAK2} V617F or a similar mutation is or is not present.
3. The platelet count threshold for the diagnosis of ET has been lowered from \( \geq 600 \times 10^9/L \) to \( \geq 450 \times 10^9/L \).
4. Some cases previously meeting the criteria for chronic eosinophilic leukemia (CEL) may be categorized in a new subgroup, “Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of \textit{PDGFRΑ}, \textit{PDGFRΒ}, or \textit{FGFR1}.”
5. Systemic mastocytosis has been included in the MPN category.

### Myelodysplastic/myeloproliferative neoplasms

The MDS/MPN category was introduced in the 3rd edition to include myeloid neoplasms with clinical, laboratory, and morphologic features that overlap MDS and MPN. This subgroup includes chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), and a provisional entity within the MDS/MPN unclassifiable group, refractory anemia with ring sideroblasts and thrombocytosis (RARS-T). A few cases of CMML and aCML have been reported to demonstrate \textit{JAK2} mutations,\textsuperscript{27,46,47} but the proliferative aspects of most cases are related to aberrations in the RAS/MAPK signaling pathways. In JMML, nearly 75% of patients demonstrate mutually exclusive mutations of \textit{PTPN11}, \textit{NRAS} or \textit{KRAS}, or \textit{NF1}, all of which encode signaling proteins in RAS dependent pathways.\textsuperscript{14-16} Approximately 30% to 40% of cases of CMML and aCML also exhibit \textit{NRAS} or \textit{KRAS} mutations.\textsuperscript{17-19,48} There is therefore currently no convincing evidence to suggest that the MDS/MPN entities should be reclassified as either MPN or MDS, and the “mixed” MDS/MPN subgroup remains in the revised classification (Table 2). The distinction between CMML-1 and CMML-2, based on the percentage of blasts plus promonocytes in the PB and BM (CMML1 = < 5% blasts plus promonocytes in the PB and < 10% blasts plus promonocytes in the BM; CMML2 = 5% or more PB blasts plus promonocytes or 10% or more BM blasts plus promonocytes) suggested in the 3rd edition of the WHO classification has proved to be clinically significant\textsuperscript{49,50} and is again recommended in the revised edition. Cases of CMML with eosinophilia should be investigated for the \textit{PDGFRΑ} abnormality and if it is found, the case should be classified as a myeloid neoplasm with eosinophilia associated with \textit{PDGFRΑ} rearrangement.

During the revision process, the greatest controversy regarding MDS/MPN was related to the provisional entity RARS-T. A substantial proportion of cases of RARS-T are reported to demonstrate \textit{JAK2} V617F or, much less commonly, mutated \textit{MPL} (reviewed in Hellström-Lindberg\textsuperscript{51}), and the percentage of patients with RARS-T who have such mutations have been reported to vary directly with the height of the platelet count.\textsuperscript{52} These findings have prompted some authorities to suggest that RARS-T should be moved to the MPN category, whereas others argued that RARS-T is not a distinct entity at all, but rather an MPN that has undergone genetic
evolution to acquire ring sideroblasts. The few cases of RARS-T that have been studied by in vitro culture, however, including some with JAK2 V617F, have shown poor colony formation with lack of endogenous growth—features that are more in keeping with MDS than with MPN.\textsuperscript{53,54} Taken together, the JAK2 data and the in vitro culture studies suggest that RARS-T is probably a distinct disease that is appropriately classified in the MDS/MPN category. If so, the major question regarding RARS-T involves the precise criteria for its definition, and in particular, how to distinguish it from RARS, in which modestly elevated platelet counts are often reported. This point is even more important in view of the revised criteria for RARS-T that lower the platelet threshold from 600 x 10^9/L to 450 x 10^9/L (in keeping with the revised criteria for ET). The revised criteria for RARS-T require not only that there be refractory anemia accompanied by thrombocytosis (\geq 450 x 10^9/L) and dyserythropoiesis including ring sideroblasts that account for 15% or more of the erythroid precursors, but also that there is also a proliferation of large megakaryocytes, resembling those in ET or PMF. Such megakaryocytes are not likely to be seen in RARS. Still, because more studies are necessary for a clear definition of the boundaries of this disease, particularly the lower platelet threshold, RARS-T remains as a provisional entity in the revised classification.

**Significant changes in the diagnosis and classification of MDS/MPN**

1. Some cases of CMNL with eosinophilia are relocated to the category “Myeloid/lymphoid neoplasms with eosinophilia and PDGFRB rearrangement.”

2. The category atypical CML has been renamed atypical CML, BCR-ABL1-negative to emphasize that it is not merely a variant of CML, BCR-ABL1-positive.

3. RARS-T remains as a “provisional entity” classified as MDS/MPN, unclassifiable, RARS-T. The criteria have been modified to include refractory anemia, dyserythropoiesis in the bone marrow with ring sideroblasts accounting for 15% or more of erythroid precursors, and megakaryocytes with features resembling those in PMF or ET; the platelet threshold is lowered to 450 x 10^9/L.

**Myelodysplastic syndromes**

Myelodysplastic syndromes (MDS) remain among the most challenging of the myeloid neoplasms to diagnose and classify, particularly in cases in which the blast percentage is not increased in the PB or BM. Diagnostic problems can arise when the clinical and laboratory findings suggest MDS but the morphologic findings are inconclusive; when there is secondary dysplasia caused by nutritional deficiencies, medications, toxins, growth factor therapy, inflammation or infection; or when marrow hypocellularity or myelofibrosis obscures the underlying disease process.\textsuperscript{6,55-58} In addition, for occasional patients in whom the diagnosis of MDS is clear, there may be difficulties in subclassification according to the previous WHO scheme, for example, in patients with isolated refractory thrombocytopenia accompanied by unilineage dysplasia of megakaryocytes. Although some diagnostic issues can be addressed in individual patients only by clinical evaluation and follow-up, the members of the CAC recommended that the minimal diagnostic criteria be more clearly stated, particularly for cases in which there is no increase in the blast percentage in the PB and/or BM, that the diagnostic role of cytogenetics and flow cytometry be clarified, and that the classification be modified to allow for more clinically relevant classification of patients who currently may fall into the “MDS, unclassifiable” category. Lastly, the CAC suggested that the WHO monograph should address diagnostic problems related to hypocellular MDS and MDS with myelofibrosis (MDS-F).

The “minimal” morphologic criteria for the diagnosis of MDS remain similar to those stated in the 3rd edition: in the appropriate clinical setting, at least 10% of the cells of at least one myeloid BM lineage (erythroid, granulocytic, megakaryocytic) must show unequivocal dysplasia for the lineage to be considered as dysplastic.\textsuperscript{56,59,60} Causes of secondary dysplasia as well as congenital abnormalities such as congenital dyserythropoietic anemia should be excluded before a diagnosis of MDS is rendered. If, however, a patient with clinical and other laboratory features consistent with MDS has inconclusive morphologic features, a presumptive diagnosis of MDS can be made if a specific clonal chromosomal abnormality, listed in Table 6, is present. It is important to note that some recurring cytogenetic abnormalities observed in MDS, particularly del(20q), +8, and −Y, are not included in the list. These abnormalities have been reported to occur in some patients with aplastic anemia or other cytopenic syndromes who have a good response to immunosuppressive therapy and/or who show no morphologic evidence of MDS with prolonged follow-up.\textsuperscript{51-63} Moreover, loss of the Y chromosome in hematopoietic cells has also been reported to be a phenomenon associated with aging.\textsuperscript{64} Thus, it is not yet clear that these abnormalities are necessarily indicative of MDS when the morphologic features are not conclusive. If only unilineage dysplasia is present in the BM but one of the recurrent cytogenetic abnormalities listed in Table 6 is not present, and there is no increase in blasts in the PB or BM, and ring sideroblasts are less than 15% of the erythroid precursors, an observation period of 6 months and repeat bone marrow investigation is recommended prior to making the diagnosis of MDS. This will ensure that the clinical and morphologic features persist and are not secondary to any other disorder that emerges in that period.

Whether phenotypic abnormalities demonstrated by flow cytometry, such as asynchronous expression of maturation-associated antigens on myeloid cells, are diagnostic of MDS when morphologic features are inconclusive was considered at the CAC meeting. The consensus was that, although numerous authors have reported aberrant antigen expression patterns characteristic for MDS cells,\textsuperscript{65-67} sufficient numbers of cases with secondary dysplasia have not been adequately evaluated so that it can be proved that the changes are specific for MDS. Until such data are available, it is recommended that, if 3 or more phenotypic abnormalities are found involving one or more of the myeloid lineages the findings can be considered as

### Table 6. Recurring chromosomal abnormalities considered as presumptive evidence of MDS in the setting of persistent cytopenia of undetermined origin, but in the absence of definitive morphologic features of MDS

<table>
<thead>
<tr>
<th>Unbalanced abnormalities</th>
<th>Balanced abnormalities</th>
</tr>
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<tbody>
<tr>
<td>7 or del(7q)</td>
<td>i(11)(q13)(p13.3)</td>
</tr>
<tr>
<td>5 or del(5q)</td>
<td>i(3)(q21.2;q22.1)</td>
</tr>
<tr>
<td>i(17q) or t(17p)</td>
<td>i(1)(p36.3;q21.1)</td>
</tr>
<tr>
<td>13 or del(13q)</td>
<td>i(2)(11)(p21;q23)</td>
</tr>
<tr>
<td>del(11q)</td>
<td>inv(3)(q21q26.2)</td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
<td>i(6)(9)(p23;q34)</td>
</tr>
<tr>
<td>del(9q)</td>
<td></td>
</tr>
<tr>
<td>idel(13)(q13)</td>
<td></td>
</tr>
</tbody>
</table>

Complex karyotype (3 or more chromosomal abnormalities) involving one or more of the above abnormalities.
Refractory anemia with excess blasts-2 (RAEB-2) Cytopenia(s)

Refractory anemia with excess blasts-1 (RAEB-1) Anemia

Refractory cytopenia with multilineage dysplasia

Refractory cytopenia with unilineage dysplasia

Refractory cytopenia with multilineage dysplasia

Refractory anemia with ring sideroblasts (RARS) Anemia

Refractory cytopenia with unilineage dysplasia

“suggestive” of MDS, but in the absence of conclusive morphologic and/or cytogenetic features, flow cytometric abnormalities alone are not diagnostic of MDS. Patients whose cells exhibit aberrant phenotypic features suggestive of MDS should be carefully followed for morphologic features sufficient to substantiate the diagnosis.

Despite clarifications of the diagnostic criteria for MDS, there will be a number of patients with persistent cytopenia(s) who lack sufficient morphologic or cytogenetic evidence for a definitive diagnosis of MDS. Some authors have suggested the term “idiopathic cytopenia of undetermined significance” (ICUS) for such cases. Although this term is reasonable, it should be construed not as an entity in the WHO classification of MDS, but as a description for patients who do not fulfill the minimal WHO criteria. These patients should be carefully monitored for emerging morphologic or cytogenetic evidence of MDS.

The revised WHO classification of MDS has been further refined to allow for a more precise and prognostically relevant subclassification of patients with unilineage dysplasia who, in the previous scheme, were considered as “unclassifiable.” Such cases included patients with isolated thrombocytopenia with dysplasia limited to the megakaryocytic lineage or neutropenia with only granulocytic dysplasia, and no blasts in the blood and fewer than 5% blasts in the bone marrow. The category of “refractory cytopenia with unilineage dysplasia” has been expanded and redefined to include MDS patients with less than 1% blasts in the PB and less than 5% in the BM, but 10% or more dysplastic cells in a single myeloid lineage. This category includes the entities of refractory anemia (RA) for those with anemia and only dyserythropoiesis (but in whom ring sideroblasts account for less than 15% of the erythroid precursors), refractory neutropenia (RN) for those with neutropenia and only dysgranulopoiesis, and refractory thrombocytopenia (RT) for those with thrombocytopenia and morphologic dysplasia limited to the megakaryocytic lineage. The criteria also permit patients to be included in one of these categories if the dysplasia is unilineage but there is bi-cytopenia in the PB. On the other hand, patients with pancytopenia and unilineage morphologic dysplasia are classified as having MDS, unclassifiable, because of the uncertain clinical significance of such findings. These changes are outlined in Table 7.

Some authors suggested that the previous WHO classification failed to emphasize the prognostic significance of increased...
blasts in the PB. To address this criticism, the revised classification redefines the criteria for refractory anemia with excess blasts (RAEB-1) to include patients with PB smears that consistently show 2% to 4% blasts in the blood, even if the blast percentage in the BM is less than 5%. Patients with 5% to 19% PB blasts or 10% to 19% blasts in the BM are classified in the highest WHO grade, RAEB-2.

A minority of patients with MDS initially have hypocellular or myelofibrotic bone marrow specimens. Hypoplastic MDS has no independent prognostic significance per se, but such cases can pose diagnostic problems because they may show some morphologic similarities with aplastic anemia, such as macrocytic red blood cells. Also, MDS-F can be difficult to diagnose and subclassify because cellular BM aspirate smears cannot be obtained for evaluation of either dysplasia or blast percentage. Furthermore, distinction of MDS-F from other myeloid neoplasms with fibrosis, such as acute panmyelosis with myelofibrosis and acute megakaryocytic leukemia, is often difficult. Although criteria for the diagnosis of “hypocellular MDS” and “MDS-F” have been suggested by various investigators, none are universally accepted nor, in the opinion of the members of the CAC and pathology committees, is it clear that they define a unique type of MDS that cannot be otherwise accommodated within the framework of current MDS criteria. Therefore, the revised WHO classification does not recognize hypocellular MDS and MDS-F as distinct entities, but recommends that, once such cases are found to meet the criteria for MDS, they should be subclassified according to the MDS guidelines, followed by “hypoplastic” or “with myelofibrosis” as modifiers to the WHO subgroup, for example, “RAEB-2 with myelofibrosis.” In MDS with hypopcellularity or fibrosis, careful examination of the PB for dysplasia, estimation of CD34+ blasts by immunohistochemistry in the BM biopsy, and correlation with cytogenetic findings will usually allow the correct diagnosis and subclassification of the case. Most cases with myelofibrosis will demonstrate an excess of blasts that can be readily appreciated by immunohistochemical stains for CD34 on the biopsy, whereas those with hypocellular bone marrow specimens are often in the lower grade groups. On the other hand, in a hypocellular bone marrow that shows only unilineage dysplasia—particularly of the erythroid lineage—and no cytogenetic abnormalities or increase in blasts, a diagnosis of MDS should be deferred for an observation period of 6 months if possible, as suggested for cases of RA without cytogenetic abnormalities.

The 3rd edition of the WHO classification was criticized by some pediatric hematologists for failing to recognize differences between the clinical and pathologic features of MDS in children and MDS in adults. At the CAC meeting it was the consensus of the pediatric hematologists and hematopathologists that children with MDS and 2% to 19% blasts in the PB and/or 5% to 19% blasts in the BM may be categorized according to the same criteria as for adults with MDS. However, in contrast to adults, isolated refractory anemia is uncommon in childhood MDS, which more commonly is initially associated with thrombocytopenia and/or neutropenia, often accompanied by a hypocellular BM. In order to emphasize the unique features of these cases of childhood MDS, the 4th edition of the WHO devotes a section to childhood MDS, in which a provisional entity, refractory cytopenia of childhood (RCC), is introduced in the classification. The category of RCC is reserved for childhood cases with less than 2% blasts in the blood and less than 5% in the marrow and persistent cytopenias associated with dysplasia in at least 2 cell lineages. Often, BM specimens in RCC are hypocellular, and if no MDS-related cytogenetic abnormalities are present, the distinction between RCC and aplastic anemia or congenital bone marrow failure syndromes may be very difficult. Furthermore, the distinction, if any, between RCC and refractory cytopenia with multilineage dysplasia as defined in adults is not clear at this time. More study is needed to clarify these questions, thus RCC is considered as a provisional entity.

Significant changes in the diagnosis and classification of MDS

1. Patients with refractory cytopenia(s) suspected to have MDS, but who lack diagnostic morphologic features may be considered to have presumptive evidence of MDS if they have specific MDS-related cytogenetic abnormalities.

2. An over-arching category of MDS, refractory cytopenia with multilineage dysplasia, has been added to incorporate patients who exhibit unilineage dysplasia associated with refractory anemia (unilineage erythroid dysplasia), refractory neutropenia (unilineage dysgranulopoiesis), or refractory thrombocytopenia (unilineage dysmegakaryocytopoiesis), and who have fewer than 1% blasts in the blood and fewer than 5% in the bone marrow.

3. The category of refractory cytopenia with multilineage dysplasia is no longer subdivided according to whether 15% or more of the erythroid precursors are ring sideroblasts (RS), that is, the former category of RCMD-RS is now incorporated in RCMD.

4. Patients with 2% to 4% blasts in the blood and less than 5% blasts in the bone marrow should be diagnosed as having RAEB-1 if other clinical and laboratory findings of MDS are present.

5. A provisional entity, refractory cytopenia of childhood (RCC), has been added to include children with cytopenia(s) with less than 2% blasts in the peripheral blood and less than 5% in the bone marrow and evidence of dysplasia in 2 or more lineages. For children with 2% to 19% blasts in the blood and/or 5% to 19% in the bone marrow, the MDS subclassification should be made using the same criteria used for adults.

Acute myeloid leukemia and related precursor neoplasms

The previous edition of the WHO classification ushered in the era of incorporation of genetic abnormalities into diagnostic algorithms for the diagnosis of AML. The 4 abnormalities initially included in the subgroup “AML with recurring genetic abnormalities” involved rearrangements of genes (RUNX1, CBFB, RARA, and MLL) that encode transcription factors and that are associated with fairly distinct clinical and morphologic features. Since the publication of the 3rd edition of the classification, it has become more widely appreciated that multiple genetic lesions—including not only microscopically detectable chromosomal rearrangements or numerical abnormalities but also submicroscopic gene mutations—cooperate to establish the leukemic process and influence its morphologic and clinical characteristics. Although rearrangements of genes that encode transcription factors may lead to impaired maturation of one or more myeloid lineages, mutations of genes such as FLT3, JAK2, RAS, or KIT that encode proteins involved in signal transduction pathways may be required for the proliferation and/or survival of the neoplastic clone. The discovery of the importance of gene mutations in leukemogenesis has also paved the way for the genetic characterization of many cases of cytogenetically normal AML. In cytogenetically abnormal
as well as in cytogenetically normal AML, these newly discovered genetic abnormalities may be associated with clinical, morphologic, and/or phenotypic features that allow identification of a specific leukemic entity, and in other instances have proved to be powerful prognostic indicators even when they do not define a specific leukemic subtype.77

One of the major challenges in the revision of the WHO classification of AML was how to incorporate important and/or recently described genetic aberrations into a classification scheme of AML and yet adhere to the WHO principle of defining homogeneous, biologically relevant, and mutually exclusive entities based not only on the prognostic value of a genetic abnormality, but on morphologic, clinical, phenotypic, and/or other unique biologic properties. This was particularly problematic for the most frequent and prognostically important mutations currently recognized in cytogenetically normal AML, mutated FLT3, NPM1, and CEBPA. These mutations are associated with few, if any, entirely consistent morphologic or clinical features. Most notably, they are not entirely mutually exclusive of each other or, particularly in the case of FLT3, of other well-recognized cytogenetic defects.20,78 Yet, in the context of cytogenetically normal AML, they are each important prognostic factors. Mutated NPM1 is found in 50% to 60% of cases of cytogenetically normal AML, and when only the NPM1 mutation status is considered, is reported to be associated with approximately 50% survival at 4 years.21,77 The FLT3-ITD mutation is found in approximately 30% to 40% of cases of cytogenetically normal AML, and when only the FLT3-ITD status is considered is associated with a survival rate of only 20% to 25% at 4 years. Mutations of CEBPA are found in approximately 15% of cytogenetically normal AML cases and these patients have a nearly 60% 4-year survival rate. When NPM1 and FLT3-ITD status are considered together, patients who have mutated NPM1 and are FLT3-ITD–negative have a 4-year survival similar to that of the CEBPA-mutated cases at approximately 60%, whereas the remaining cases, being either NPM1 wild-type or FLT3-ITD–positive or both, have a dismal 30% survival rate at 4 years.21,77

Despite the dilemma and controversy regarding how to incorporate recently described and clinically important genetic lesions into the revised scheme, the framework of the classification proved flexible enough so that new, well-defined entities could be incorporated as could provisional entities—those for which more data need to be collected so that they can be better characterized. Table 2 shows the revised AML classification. In the subgroup of AML with recurrent genetic abnormalities, 3 entities included in the previous edition are retained: (1) AML with (t8;21)(q22;q22); RUNX1-RUNX1T1; (2) AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFB-MYH11; and (3) acute promyelocytic leukemia (APL) with t(15;17)(q22;q12). Although various RARA translocations, such as those involving ZBTB16 at 11q23, NUMA1 at 11q13, NPM1 at 5q35, or STAT5B at 17q11.2, should be diagnosed as AML with the variant partner specifically designated.79 For these entities alone [AML with (t8;21)(q22;q22), AML with inv(16)(p13.1q22) or t(16;16)(p13.1q22), and APL with t(15;17)(q22;q12)] the genetic abnormality is sufficient for the diagnosis of AML in the appropriate setting regardless of the blast percentage in the PB or BM. For all other entities within the category of AML with recurrent genetic abnormalities, 20% or more blasts must be present in the PB or BM to establish the diagnosis of AML. Although these leukemias are recognized as unique entities, it is important to realize that additional genetic abnormalities may coexist and influence their biologic and clinical behavior, including response to therapy and the overall survival (OS). For example, mutated KIT is not uncommon in core-binding factor AML, that is, those with rearranged RUNX1 and CBFB genes. In the case of t(8;21)(q22;q22); RUNX1-RUNX1T1, most published reports indicate a higher relapse rate and lower OS when mutated KIT is present, whereas its impact in the presence of the inv(16)(p13.1q22) or t(16;16)(p13.1;q22) remains to be firmly established.20,22 Deciding how to incorporate coexisting genetic abnormalities that are of prognostic importance or that provide a target for molecularly directed therapy will likely be increasingly important in future revisions of the classification, particularly as targeted therapies become available.

One entity included in the recurring genetic abnormality subgroup in the 3rd edition, “AML with abnormalities of 11q23; MLL,” has been revised to focus on the most frequent and best characterized of the MLL abnormalities, AML with t(9;11)(p22;q23); MLLT3-MLL. More than 80 partner genes participate in translocations with MLL, and in addition, “abnormalities of MLL,” as used in the previous edition, would include the partial tandem duplication of the gene.80,82 The AMLs that result from these various rearrangements and aberrations of MLL are not identical, and, in the case of translocations, the biology is influenced by the partner gene. Although the t(9;11)(p22;q23) is specifically listed in the classification, it is recommended that variant MLL translocations be also specified in the diagnosis, for example, AML with t(11;19)(q23;p13.3); MLL-ENL.

Studies of AML associated with the chromosomal rearrangements t(6;9)(p23;q34); DEK-NUP21, inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1, and t(1;22)(p13;q13); RBM15-MKL1 have provided evidence that these genetic rearrangements, although uncommon, are associated with distinctive morphologic and clinical features that argue for their incorporation in the revised listing of AML with recurrent genetic abnormalities.83,85 A more controversial issue is whether leukemia initially demonstrating a blastic myeloid proliferation associated with the Ph chromosome or BCR-ABL1 is a distinct and easily defined entity. Although BCR-ABL1–positive AML has been reported,86-88 criteria for its distinction from CML initially manifesting in a blast phase are not entirely convincing, and for this reason, BCR-ABL1–positive AML is not recognized in this classification. Many cases of BCR-ABL1–related acute leukemia will meet the criteria for acute lymphoblastic leukemia or mixed phenotype acute leukemia (see “Acute leukemia of ambiguous lineage”), provided that a blast phase of a previously unrecognized CML can be excluded.

In addition to the newly listed leukemias associated with cytogenetically detectable rearrangements, AML with mutated NPM1 or CEBPA have been added to the classification as “provisional entities.” Because mutated FLT3 frequently accompanies other genetic lesions, including well-recognized abnormalities such as the t(15;17)(q22;q12) and the t(6;9)(p23;q34), it is not included as a defining criterion for any distinct entity in this revision. Nevertheless, because of its prognostic importance, the mutational status of FLT3 should always be ascertained in AML, particularly in cytogenetically normal AML.

AML with multilineage dysplasia was initially introduced in the WHO classification to encompass cases of AML characterized by MDS-like features, including unfavorable cytogenetic abnormalities, overexpression of multidrug-resistance glycoprotein, and an unfavorable response to therapy. Dysplasia in at least 50% of the cells in 2 or more hematopoietic lineages was used as a surrogate marker for these MDS-related biologic features. Although the prognostic significance of AML with multilineage dysplasia has been verified in some studies,89,90 others showed that morphologic
multilineage dysplasia had no independent prognostic significance when cytogenetic findings were incorporated in the analysis. To address these studies, this subgroup has been renamed as “AML with myelodysplasia-related changes,” and the criteria have expanded to include a history of MDS or MDS/MPN and cytogenetic findings. Patients may be assigned to this category if they have 20% or more blasts in the PB or BM and (1) evolve from previously documented MDS or MDS/MPN, (2) have specific myelodysplasia-related cytogenetic abnormalities (see Table 8), or (3) exhibit dysplasia in 50% or more of the cells in 2 or more myeloid lineages. The diagnosis should state the reason(s) for placing the patient in this category, for example, “AML with myelodysplasia-related changes with myelodysplasia-related cytogenetic abnormalities.”

Patients who are categorized in this subgroup and have a normal karyotype should be analyzed for FLT3, NPM1, and CEBPA mutations, and, if present, the abnormality should be noted in the diagnosis. Currently, the significance of one or more of these mutations in the setting of morphologic dysplasia is not known.

Therapy-related myeloid neoplasms (t-AML/t-MDS and t-AML/t-MDS/MPN) remain as a distinct subgroup in the AML classification. Although cases may be designated as t-AML, or as t-MDS or t-MDS/MPN depending on the blast count, it is useful to think of them as a single biologic disease with similar genetic features, so that the designation as t-AML/t-MDS is appropriate as well. Most patients who develop therapy-related myeloid neoplasms have received alkylating agents and/or radiation as well as topoisomerase II inhibitors, so that a division according to the type of therapy is usually not practical and is no longer recommended. It has been argued that 90% of patients with therapy-related neoplasms have cytogenetic abnormalities identical to those observed in AML with myelodysplasia-related features or in AML with recurrent cytogenetic abnormalities, therefore such cases would be more appropriately classified in the appropriate subgroup rather than in a separate, therapy-related category. However, except for some patients with t-AML associated with inv(16)(p13.1q22), (t(16;16)(p13.1;q22) or (t(15;17)(q22;q12), patients with therapy-related myeloid neoplasms have a significantly worse outcome than those with de novo counterparts with the same genetic abnormalities, suggesting that there are biologic differences. Furthermore, the study of therapy-related neoplasms may provide valuable insight into the pathogenesis of de novo disease by providing clues as to why only a few patients develop leukemia, whereas most patients treated with the identical agents do not. It is recommended, however, that the cytogenetic abnormality be included in the diagnostic report, for example, “therapy-related AML with t(9;11)(p22;q23).”

Acute myeloid leukemia, not otherwise specified (AML, NOS) encompasses those cases that do not fulfill the criteria for any of the other AML categories. This category accounts for only 25% to 30% of all cases, and it will continue to diminish as more genetic subgroups are recognized. One of the lively discussions at the CAC meeting was whether to recommend continued subclassification within this group by criteria similar to those of the previous French-American-British (FAB) classification scheme for AML, or to designate all such cases merely as AML, NOS. The argument that specific genetic abnormalities may yet be found that will further characterize some AML, NOS subgroups prevailed as a reason for maintaining the subclassification. Furthermore, for prognostic purposes, it may still be important to recognize some disorders such as acute megakaryoblastic leukemia, acute panmyelosis with myelofibrosis, and pure acute erythroleukemia. However, it is important to note that the information used to characterize the subgroups in this category, such as epidemiologic or clinical outcome data, is often based on older studies that included patients who would now be assigned to different WHO diagnostic categories. Therefore, such information may no longer be reliable for patients now classified in this subgroup.

Three additional myeloid neoplasms in the AML listing include myeloid sarcoma, the myeloid proliferations related to Down syndrome, and blastic plasmacytoid dendritic cell neoplasm. Myeloid sarcoma, previously known as granulocytic sarcoma or chloroma, is a pathologic diagnosis for an extramedullary proliferation of blasts of one or more of the myeloid lineages that disrupts the normal architecture of the tissue in which it is found. Any site of the body can be affected, particularly the skin, gastrointestinal tract, lymph nodes, and bone. Most often, myeloid sarcoma is found concurrently in a patient with previously or recently recognized AML, but it may also precede the appearance of blood or bone marrow disease. In this latter case, the diagnosis of myeloid sarcoma should be considered as synonymous with AML, and the tumor should be evaluated for morphologic, phenotypic, and genetic features that would allow it to be classified further into one of the subgroups of AML. A myeloid sarcoma is evidence of relapse in a patient thought to be in remission of a previously diagnosed AML, is evidence of evolution to AML in a patient with a previously diagnosed MDS or MDS/MPN, and is blast transformation in a patient with MPN. The myeloid proliferations related to Down syndrome—transient abnormal myelopoiesis and myeloid leukemia—have unique morphologic, immunophenotypic, clinical, and molecular features, including GATA1 mutation, that justify their separation from other myeloid neoplasms. 3,102-103 MDS related to Down syndrome is biologically identical to Down-related AML; therefore they are considered as a single entity, myeloid leukemia associated with Down syndrome, in the classification. The neoplasm referred to in the WHO 3rd edition as “blastic NK-cell lymphoma” or in the literature as “agranular CD4+ CD56+ hematodermic neoplasm” is now known to be in virtually all cases a tumor that is derived from precursors of a specialized subset of dendritic cells, plasmacytoid dendritic cells, and hence is a myeloid-related neoplasm. It is a clinically aggressive neoplasm that is usually characterized at its onset by solitary or multiple skin lesions, often with associated regional lymphadenopathy. Many cases will ultimately progress to involve the PB and BM as well. The blasts in such cases do not express myeloperoxidase or...
nonspecific esterase, and they are characterized by the expression of CD4, CD43, CD56, CD123, BDCA-2/CD303, TCL1, and CLA; CD7 and CD33 are not uncommonly expressed as well, and TdT is expressed in approximately 30% of cases. There is no expression of CD34 or CD117.

Significant changes in the diagnosis and classification of AML and related precursor neoplasms

1. AML with recurrent genetic abnormalities
   a. As in the previous edition, AML with t(8;21)(q22;q22), inv(16)(p13q22) or t(16;16)(p13.1q22), and APL with t(15;17)(q22;q12) are considered as acute leukemia regardless of blast count in the PB or BM, but in contrast to the previous edition, for AML with t(9;11)(p22;q23) or other 11q23 abnormalities, as well as for all other subgroups (except the rare instance of some cases of erythroleukemia) blasts of 20% or more of white blood cells in PB or of all nucleated BM cells is required for the diagnosis of AML.
   b. In APL with t(15;17)(q22;q12), PML-RARA, variant RARA translocations with other partner genes are recognized separately; not all have typical APL features and some have all-trans retinoic acid (ATRA) resistance.
   c. The former category, AML with 11q23 (MLL) abnormalities has been redefined to focus on AML with t(9;11)(p22;q23); MLLT3-MLL. Translocations of MLL other than that involving MLLT3 should be specified in the diagnosis. Other abnormalities of MLL, such as partial tandem duplication of MLL should not be placed in this category.
   d. Three new cytogenetically defined entities are added: (1) AML with t(6;9)(p23;q34); DEK-NUP214, (2) AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1; and (3) AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1.
   e. Two provisional entities are added: AML with mutated NPM1 and AML with mutated CEBPA. Although not included as a distinct or provisional entity, examination for mutations of FLT3 is strongly recommended in all cases of cytogenetically normal AML.

2. AML with myelodysplasia-related changes
   a. The name was changed and expanded from “AML with multilineage dysplasia” to “AML with myelodysplasia-related changes.”
   b. Cases of AML are assigned to this category if (1) they have a history of MDS or MDS/MPN and have evolved to AML, (2) they have a myelodysplasia-related cytogenetic abnormality, or (3) at least 50% of cells in 2 or more myeloid lineages are dysplastic.

3. Therapy-related myeloid neoplasms
   Cases are no longer subcategorized as “alkylating agent related” or “topoisomerase II-inhibitor related.”

4. AML, NOS
   a. Some cases previously assigned to the subcategory of AML, NOS as acute erythroid leukemia or acute megakaryoblastic leukemia may be reclassified as AML with myelodysplasia-related changes.
   b. Cases previously categorized as AML, NOS, acute megakaryoblastic leukemia should be placed in the appropriate genetic category if they are associated with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1, or AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1. Down syndrome–related cases are excluded from this category as well.

5. Myeloid proliferations related to Down syndrome
   This new category incorporates transient abnormal myelopoiesis as well as MDS and AML that is Down syndrome–related. MDS and AML related to Down syndrome are biologically identical and thus are considered together as “Myeloid leukemia associated with Down syndrome.”

6. Blastic plasmacytoid dendritic cell neoplasm
   This is a new category that includes most cases previously classified as blastic NK-cell lymphoma/leukemia or agranular CD4+ CD56+ hemodermic neoplasm; it is derived from a precursor of plasmacytoid dendritic cells.

Acute leukemia of ambiguous lineage

Acute leukemias of ambiguous lineage show no clear evidence of differentiation along a single lineage. In some cases, no lineage-specific antigens are present, whereas in others the blasts express antigens of more than one lineage to such a degree that it is not possible to assign the leukemia to a specific lineage-related category. Historically, there has been confusion in the definition, terminology, and the criteria used for subclassification of such cases. In an attempt to clarify the definition of this group of diseases and to simplify their diagnosis, the 4th edition of the WHO classification not only places acute leukemias of ambiguous lineage in a chapter distinct from those of AML and ALL, but has significantly altered the criteria used to define the largest subset of these cases—those that express antigens of more than one lineage. Cases with no lineage-specific markers are designated as acute undifferentiated leukemia (AUL). Such cases often express CD34, HLA-DR, and/or CD38, and sometimes TdT, but lack specific myeloid or lymphoid antigens. Leukemias with blasts that coexpress certain antigens of more than one lineage on the same cells or that have separate populations of blasts that are of different lineages are referred to as mixed phenotype acute leukemia (MPAL). These cases may be further designated as B-myeloid or T-myeloid, irrespective of whether one or more than one population of blasts is found. The requirements for assigning specific lineages to the blasts are given in Table 9. Only a limited number of antigens are used in defining the pattern of lineage involvement. It should be pointed out that the requirement for myeloperoxidase positivity to prove myeloid lineage should be applied to MPAL only and not to

Table 9. Requirements for assigning more than one lineage to a single blast population in mixed phenotype acute leukemia (MPAL)

<table>
<thead>
<tr>
<th>Lineage</th>
<th>Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloid</td>
<td>Myeloperoxidase (flow cytometry, immunohistochemistry, or cytochemistry)</td>
</tr>
<tr>
<td></td>
<td>or Monocytic differentiation (at least 2 of the following: nonspecific esterase, CD11c, CD14, CD64, lysozyme)</td>
</tr>
<tr>
<td>T</td>
<td>Cytoplasmic CD3 (flow cytometry with antibodies to CD3 epsilon chain; immunohistochemistry using polyclonal anti-CD3 antibody may detect CD3 zeta chain, which is not T cell–specific)</td>
</tr>
<tr>
<td></td>
<td>or Surface CD3 (rare in mixed phenotype acute leukemia)</td>
</tr>
<tr>
<td>B</td>
<td>(multiple antigens required)</td>
</tr>
<tr>
<td>Strong CD19 with at least 1 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10</td>
<td></td>
</tr>
<tr>
<td>or Weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10</td>
<td></td>
</tr>
</tbody>
</table>
cases of AML with minimal differentiation that do not show any lymphoid-associated antigens. In general, leukaemias that can be classified according to a specific genetic defect, such as the t(8;21)(q22;q22), are excluded from the MPAL category, with the exception of some acute leukemias associated with the BCR-ABL1 fusion gene or with MLL rearrangements. In the specific case of acute leukemia with the Ph chromosome or BCR-ABL1 fusion, if the requirements for assigning the blast population to more than one lineage are fulfilled, a diagnosis of MPAL with t(9;22)(q34;q11.2) can be made, provided the blast phase of CML can be excluded.

There is one provisional entity included in this category, “natural killer cell lymphoblastic leukemia/lymphoma.” Most cases previously designated as “blastic natural killer cell leukemia/lymphoma” are now recognized as the myeloid-related “blastic plasmacytoid dendritic cell neoplasm.” The definition phenotype of true NK-cell precursor neoplasms is not clear, although the diagnosis might otherwise be considered when the blasts express CD56 with immature T-associated antigens such as CD7 and CD2, in the absence of any B or myeloid antigen expression, particularly if no rearrangement of T-cell receptor genes can be detected. However, this provisional subtype needs further study and clarification.

Summary of changes in the diagnosis and classification of acute leukemia of ambiguous lineage

1. Leukemia formerly designated as “bilineal acute leukemia” and “biphenotypic acute leukemia” are now collectively considered as “mixed phenotype acute leukemia” (MPAL).
2. The criteria that define the myeloid, T-lymphoid, and B-lymphoid components of mixed phenotype acute leukemia have been significantly altered (see Table 9).
3. Cases of BCR-ABL1–positive and MLL-positive acute leukemias may meet the criteria for MPAL; in the case of BCR-ABL1–positive disease, CML in blast phase should be excluded.
4. Blastic natural killer cell leukemia/lymphoma is not easily defined and is considered as a provisional entity in this category; most cases previously designated as such are now recognized as blastic plasmacytoid dendritic cell neoplasms.

Precursor lymphoid neoplasms: B lymphoblastic leukemia/lymphoma and T lymphoblastic leukemia/lymphoma

The classification of precursor B-cell and T-cell neoplasms is shown in Table 2. Although the distinction between lymphoblastic leukemia and lymphoblastic lymphoma is obvious when the patient has a mass composed of B or T lymphoblasts and no blasts in the blood or marrow, it is more arbitrary when there is a mass and limited marrow involvement. This revision follows the convention used in many treatment protocols and suggests that when a mass is present and 25% or more of the nucleated cells in the bone marrow are lymphoblasts, a diagnosis of lymphoblastic leukemia is preferred over lymphoblastic lymphoma. Because ALL rarely presents with low BM blast counts, the diagnosis of ALL should be deferred if there are fewer than 20% blasts in the BM until there is definitive evidence to confirm the diagnosis. However, in the unusual case that a patient presents with less than 20% lymphoblasts in the BM and no evidence of an extramedullary mass, but demonstrates one of the known recurring cytogenetic abnormalities associated with ALL (see Table 2), the patient may be considered to have lymphoblastic leukemia. However, the finding of less than 20% unequivocal lymphoblasts in the BM should also prompt a search for lymphoblastic lymphoma in an extramedullary location.

In the case of B lymphoblastic leukemia/lymphoma (a name change from the previous edition, in which “precursor B lymphoblastic leukemia/lymphoma” was used), numerous reports have demonstrated that recurring genetic abnormalities are associated with sufficiently unique clinical, immunophenotypic, and/or prognostic features so that they can be considered as distinct entities (Table 2). Although most of the specific chromosomal abnormalities may be detected by routine cytogenetic analysis, t(12;21)(p13;q22); ETV6-RUNX1 is a submicroscopic rearrangement that is usually detected by FISH analysis. This abnormality is very important prognostically and it should always be searched for in childhood B-ALL, as should the BCR-ABL1 in patients of any age, by routine cytogenetic analysis, FISH, or RT-PCR. Although rare, B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); IL3-IGH should be considered in the differential diagnosis of peripheral blood eosinophilia. The eosinophils are reactive, and in some patients the percentage of blasts is relatively low in the bone marrow, in which case the chromosomal abnormality is sufficient to confirm the diagnosis. The finding of prominent eosinophilia in either B or T lymphoblastic leukemia/lymphoma should be an additional consideration for rearrangement involving FGFR1, which, if present, will allow the case to be classified as lymphoblastic leukemia/lymphoma associated with an abnormality of FGFR1. If none of the specific genetic abnormalities listed in Table 2 are found, the designation of “B lymphoblastic leukemia/lymphoma, not otherwise specified,” is appropriate. It is important to understand that the term B-ALL should not be used for Burkitt lymphoma/leukemia, which is a neoplasm of mature B cells.

The neoplastic cells of 50% to 70% of patients with T lymphoblastic leukemia/lymphoma demonstrate abnormal karyotypes. The most common recurrent abnormalities are translocations that involve the alpha and delta T-cell receptor loci at 14q11.2, the beta locus at 7q35, or the gamma locus at 7p14-15 and that involve a growing list of partner genes. Although of pathogenetic significance, these abnormalities are not as clearly associated with unique biologic features as seen with some of the genetic abnormalities associated with B lymphoblastic leukemia/lymphoma, and thus the precursor T-cell neoplasms are not subdivided further according to their genetic defects.

Significant changes in the diagnosis and classification of precursor B- and T-cell neoplasms

1. The nomenclature has been changed from “precursor B lymphoblastic leukemia/lymphoma” and “precursor T lymphoblastic leukemia/lymphoma” to “B lymphoblastic leukemia/lymphoma” and “T lymphoblastic leukemia/lymphoma.”
2. B lymphoblastic leukemia/lymphoma is further divided into 7 distinct entities defined largely by specific recurring chromosomal abnormalities; cases of B-ALL lacking these abnormalities are considered as “not otherwise specified.”

Summary

The revised 2008 WHO classification of myeloid neoplasms and acute leukemia attempts to provide an up-to-date classification system that is based on recently published, peer-reviewed data. Already, in the few months since the publication of the 4th edition,
new information is accumulating that will eventually lead to our ability to recognize new diseases and change our criteria for the diseases already described. To continue to be useful in the clinics as well as in the evaluation of data from clinical trials and laboratory investigation, the classification must therefore be continually reviewed, updated, and tested. The exercise of developing the WHO document has produced a model of cooperation between pathologists, clinicians, and clinical scientists of all nationalities—a cooperation that must continue into the future for the benefit of patients with myeloid neoplasms and acute leukemia.

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Authorship

The WHO classification of myeloid neoplasms was developed and revised in part through discussions at the Myeloid Clinical Advisory Committee Meeting held in Chicago, Illinois, in February 2007. All authors of the manuscript served as session chairs and/or major presenters at the meeting and made major contributions to the classification described in this manuscript.

Contribution: J.W.V. drafted the initial manuscript; J.T. wrote and revised portions of the MPN section of the manuscript; D.A.A. wrote and revised portions of the AML section of the manuscript; R.D.B. wrote and revised portions of the MDS section of the manuscript; M.J.B. wrote and revised portions of the ALL and MPAL sections of the manuscript; A.P. wrote and revised sections pertinent to prognostic data; N.L.H. wrote and revised portions of the manuscript; M.M.L.B. wrote, reviewed, and revised genetic portions of the manuscript; E.H.-L. contributed to the MDS classification and partially revised the manuscript; A.T. contributed to the MPN classification and partially revised the manuscript; and C.D.B. chaired the CAC meeting, contributed to all portions of classification, and helped write and revise the manuscript.

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Appendix

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References


The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes

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