Myeloid Neoplasms in the WHO 5th Edition and the International Consensus Classification: A Rigorous Narrative Review

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Abstract

Background

The classification of myeloid neoplasms has undergone substantial transformation with advances in molecular genetics, genomics, and precision medicine. In 2022, two major classification systems were introduced simultaneously: the **5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours** and the **International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukemias**. Although both systems are founded on contemporary molecular and clinicopathological evidence, they differ in selected diagnostic criteria, disease nomenclature, genetically defined entities, and classification of specific myeloid disorders. Understanding these similarities and differences is essential for accurate diagnosis, prognostic assessment, therapeutic decision-making, and harmonization of clinical practice.

Objective

To critically review the major diagnostic, molecular, and conceptual advances introduced in the WHO 5th Edition and the International Consensus Classification of myeloid neoplasms, and to compare their implications for contemporary hematopathology and clinical management.

Data Sources

A rigorous narrative review was conducted using the WHO Classification of Haematolymphoid Tumours (5th edition), the original International Consensus Classification, European LeukemiaNet (ELN) recommendations, National Comprehensive Cancer Network (NCCN) guidelines, and peer-reviewed literature indexed in PubMed, including original research articles, expert consensus documents, and contemporary review articles.

Content

This review summarizes the evolution of myeloid neoplasm classification from earlier WHO editions to the current molecularly integrated systems. Major updates include revised classification of acute myeloid leukemia, myelodysplastic neoplasms, myeloproliferative neoplasms, myelodysplastic/myeloproliferative overlap neoplasms, mast cell disorders, eosinophilic neoplasms, and germline predisposition syndromes. The review also examines the incorporation of recurrent genetic abnormalities, next-generation sequencing, molecular prognostic models, and disease-defining genomic alterations into routine diagnostic practice. Similarities and differences between the WHO and ICC classifications are discussed together with their impact on precision medicine, standardized reporting, prognostic stratification, and multidisciplinary patient care.

Conclusion

The WHO 5th Edition and the International Consensus Classification represent major advances in the classification of myeloid neoplasms by integrating morphology with cytogenetics, immunophenotyping, and molecular genetics. Although differences exist in selected diagnostic thresholds and genetically defined entities, both systems reflect a common transition toward biologically driven disease classification and precision hematology. Continued advances in genomics, measurable residual disease assessment, artificial intelligence, and multi-omics technologies are expected to further refine future classifications and improve personalized management of patients with myeloid neoplasms.

Keywords: Myeloid neoplasms, World Health Organization, WHO 5th Edition, International Consensus Classification, Acute myeloid leukemia, Myelodysplastic neoplasms, Myeloproliferative neoplasms, Molecular classification, Precision hematology, Narrative review.

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Introduction

Myeloid neoplasms comprise a heterogeneous group of clonal hematopoietic disorders arising from genetically altered hematopoietic stem and progenitor cells. These disorders encompass acute myeloid leukemia (AML), myelodysplastic neoplasms (MDS), myeloproliferative neoplasms (MPNs), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), mastocytosis, and myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions. Although traditionally classified according to morphological appearance and clinical presentation, advances in molecular genetics have substantially transformed the understanding of these diseases. Recurrent somatic mutations, cytogenetic abnormalities, and germline predisposition syndromes have demonstrated that myeloid neoplasms represent biologically diverse entities with distinct pathogenetic mechanisms, prognostic implications, and therapeutic responses. Consequently, modern classification systems increasingly integrate morphology, immunophenotyping, cytogenetics, and genomic information to provide biologically meaningful diagnostic categories that support precision medicine and individualized patient care.[1]

The publication of the **5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours** in 2022 marked a major milestone in hematopathology by incorporating recent advances in molecular biology and genomic medicine into the classification of myeloid neoplasms. The revised classification reflects the rapid expansion of knowledge regarding disease-defining genetic abnormalities, clonal evolution, measurable residual disease, inherited predisposition syndromes, and novel molecular biomarkers. Compared with earlier editions, the WHO 5th edition places greater emphasis on integrating genetic findings with traditional morphological evaluation while maintaining the practicality and global applicability of diagnostic criteria. This integrated approach recognizes that morphology alone is often insufficient to define biologically distinct disease entities and that molecular alterations increasingly influence diagnosis, prognosis, and therapeutic selection.[1]

In parallel with the publication of the WHO 5th edition, the **International Consensus Classification (ICC)** of Myeloid Neoplasms and Acute Leukemias was independently developed by an international panel of hematopathologists, hematologists, and molecular experts. The ICC incorporated many concepts shared with the WHO classification but also introduced several important modifications regarding disease nomenclature, diagnostic thresholds, molecularly defined entities, and categorization of specific myeloid disorders. Although both classifications are evidence-based and largely concordant, differences exist in diagnostic criteria for selected entities, particularly acute myeloid leukemia, myelodysplastic neoplasms, myelodysplastic/myeloproliferative overlap neoplasms, and genetically defined disease categories. These distinctions have generated considerable discussion regarding diagnostic harmonization and the practical implications of using one classification system over the other in routine clinical practice.[2]

The WHO 5th edition further represents a transition from organ-based pathology toward biologically integrated disease classification. Rather than considering genetic abnormalities as ancillary findings, disease-defining molecular alterations are increasingly incorporated into the primary diagnostic framework. This evolution reflects the expanding role of next-generation sequencing, high-resolution cytogenetics, and molecular diagnostics in routine hematology laboratories. The classification therefore provides a standardized framework capable of accommodating rapidly emerging molecular discoveries while remaining

sufficiently practical for implementation across healthcare systems with differing diagnostic resources.[3]

The evolution of contemporary classification systems cannot be understood without acknowledging earlier WHO revisions. The 2016 WHO revision introduced several landmark concepts, including recognition of recurrent genetic abnormalities in acute myeloid leukemia, refinement of myelodysplastic syndrome subtypes, updated diagnostic criteria for myeloproliferative neoplasms, and improved characterization of overlap disorders. These revisions represented the first major incorporation of molecular genetics into routine classification and established the conceptual foundation upon which both the WHO 5th edition and the International Consensus Classification were subsequently developed. Many diagnostic principles introduced in 2016—including integration of morphology, immunophenotyping, cytogenetics, and molecular findings—remain fundamental components of current classification systems.[4]

Advances in molecular diagnostics have simultaneously transformed therapeutic decision-making. The identification of recurrent mutations involving genes such as **NPM1, FLT3, CEBPA, RUNX1, TP53, ASXL1, SF3B1, IDH1, IDH2, TET2, DNMT3A, JAK2, CALR,** and **MPL** has significantly improved understanding of disease pathogenesis while facilitating the development of targeted therapies. These molecular discoveries have shifted treatment paradigms from conventional chemotherapy toward individualized therapeutic strategies based on specific genomic alterations. Consequently, accurate molecular characterization has become indispensable for risk stratification, prognostic assessment, treatment selection, measurable residual disease monitoring, and clinical trial eligibility.[5]

The integration of molecular diagnostics into classification systems has important implications for contemporary clinical practice. Current recommendations from the National Comprehensive Cancer Network (NCCN) emphasize comprehensive diagnostic evaluation incorporating morphology, flow cytometry, cytogenetics, fluorescence in situ hybridization, and next-generation sequencing for patients with suspected acute myeloid leukemia. Such integrated diagnostic assessment enables identification of disease-defining genetic abnormalities, facilitates appropriate risk stratification, and supports selection of targeted therapeutic agents including FLT3 inhibitors, IDH inhibitors, BCL-2 inhibitors, and other precision medicine approaches.[6]

Similar advances have occurred in the management of myelodysplastic neoplasms. Modern diagnostic evaluation extends beyond conventional bone marrow morphology to include comprehensive cytogenetic and molecular analysis capable of identifying prognostically significant mutations and disease-defining abnormalities. The NCCN guidelines emphasize that integration of clinical, morphological, cytogenetic, and molecular findings is essential for establishing an accurate diagnosis, determining prognosis, and selecting appropriate therapeutic interventions. These recommendations closely parallel the principles incorporated within both the WHO 5th edition and the International Consensus Classification.[7]

Likewise, classification of myeloproliferative neoplasms has evolved substantially with increasing recognition of driver mutations involving **JAK2, CALR,** and **MPL**, together with improved understanding of additional cooperating molecular abnormalities influencing disease progression and transformation. Current NCCN recommendations advocate integrated pathological and molecular assessment to distinguish between individual myeloproliferative disorders, evaluate thrombotic risk, predict disease progression, and guide therapeutic management. The WHO and ICC classifications have incorporated these molecular discoveries to improve diagnostic precision while supporting individualized patient care.[8]

One of the most significant developments accompanying contemporary classification systems is the introduction of molecular prognostic models. The Molecular International Prognostic Scoring System (IPSS-M) for myelodysplastic neoplasms represents an important advancement by integrating somatic mutation profiles with traditional clinical and cytogenetic variables. Compared with earlier prognostic models, IPSS-M provides more accurate risk stratification by incorporating the prognostic significance of multiple recurrent genetic mutations, thereby improving prediction of leukemic transformation, overall survival, and treatment response. These developments illustrate the increasing convergence between molecular diagnostics, disease classification, and prognostic modelling in modern hematology.[9]

Long before the development of molecular classification systems, the European LeukemiaNet emphasized the importance of standardized diagnostic criteria, multidisciplinary evaluation, and evidence-based management of myelodysplastic syndromes. These recommendations established internationally accepted principles for diagnosis, prognostic assessment, and therapeutic decision-making that continue to influence contemporary classification systems. Many concepts originally proposed by the European LeukemiaNet—including integration of clinical findings, morphology, cytogenetics, and standardized reporting—have

subsequently been expanded within both the WHO 5th edition and the International Consensus Classification through incorporation of genomic medicine and precision oncology.[10]

Aim of the Review

This narrative review critically examines the contemporary classification of myeloid neoplasms by comparing the WHO 5th Edition and the International Consensus Classification. Particular emphasis is placed on the evolution of disease classification, major diagnostic updates, molecular and genomic advances, similarities and differences between the two systems, and their implications for clinical practice, prognostic assessment, precision medicine, and future research in hematopathology.

Disease-Specific Updates and Emerging Concepts in the WHO 5th Edition and International Consensus Classification

Refinement of Myeloproliferative Neoplasm Classification

Among the most important developments incorporated into both the WHO 5th Edition and the International Consensus Classification (ICC) is the continued refinement of myeloproliferative neoplasms (MPNs). These disorders, characterized by clonal proliferation of one or more myeloid cell lineages, have undergone significant conceptual evolution following the identification of recurrent driver mutations involving **JAK2, CALR,** and **MPL**. Contemporary classification systems emphasize integration of clinical presentation, bone marrow morphology, molecular findings, and laboratory parameters to improve diagnostic precision and facilitate individualized patient management.

Recent recommendations for **polycythemia vera (PV)** and **essential thrombocythemia (ET)** further reinforce this integrated diagnostic approach. Diagnostic confirmation now requires careful correlation of clinical features with hematological parameters, bone marrow histopathology, serum erythropoietin levels where appropriate, and molecular detection of canonical driver mutations. Molecular characterization not only establishes clonality but also contributes to risk stratification and therapeutic planning. Current management strategies increasingly incorporate genomic information to estimate thrombotic risk, predict disease progression, and guide selection of cytoreductive therapy. Consequently, both the WHO and ICC classifications recognize molecular diagnostics as indispensable components of routine evaluation for PV and ET rather than optional ancillary investigations.[11]

Primary myelofibrosis (PMF) has similarly undergone important refinements in diagnostic criteria. Distinguishing prefibrotic primary myelofibrosis from essential thrombocythemia remains one of the most challenging areas of hematopathology because these disorders may share overlapping clinical and laboratory features while exhibiting markedly different prognoses and therapeutic requirements. The WHO 5th Edition and ICC continue to emphasize detailed bone marrow histomorphology combined with molecular characterization to improve diagnostic reproducibility. Identification of driver mutations together with assessment of additional high-risk molecular abnormalities contributes to prognostic stratification, prediction of leukemic transformation, and selection of targeted therapeutic approaches including JAK inhibitors and allogeneic hematopoietic stem cell transplantation for appropriate patients.[12]

Advances in Mast Cell Disorders

Mast cell disorders represent another important category that has undergone progressive refinement in recent classification systems. Mastocytosis is now widely recognized as a distinct clonal hematopoietic neoplasm characterized by abnormal proliferation and accumulation of neoplastic mast cells within one or more organs. Advances in molecular biology, particularly the identification of activating **KIT** mutations, have significantly improved understanding of disease pathogenesis while facilitating more accurate diagnosis and classification.

Both the WHO and ICC emphasize standardized diagnostic criteria incorporating clinical manifestations, bone marrow morphology, immunophenotypic characterization, and molecular testing. Expression of aberrant immunophenotypic markers together with identification of **KIT D816V** and related mutations has become central to confirming clonality and distinguishing neoplastic mast cell disorders from reactive conditions. Updated classification systems also recognize the biological diversity of mastocytosis, ranging from indolent disease with excellent long-term prognosis to aggressive systemic mastocytosis and mast cell leukemia requiring intensive therapeutic intervention. These refinements have strengthened diagnostic consistency while supporting individualized management strategies based upon disease subtype and molecular profile.[13]

Myeloid/Lymphoid Neoplasms with Eosinophilia

The classification of myeloid and lymphoid neoplasms associated with eosinophilia has similarly evolved with increasing recognition of recurrent tyrosine kinase gene rearrangements. Advances in molecular diagnostics have

demonstrated that abnormalities involving **PDGFRA, PDGFRB, FGFR1, JAK2, FLT3,** and additional kinase genes define biologically distinct disorders with unique therapeutic implications. Identification of these molecular alterations has fundamentally transformed patient management because many affected individuals respond dramatically to targeted kinase inhibitors.

The WHO 5th Edition and ICC therefore place substantial emphasis on comprehensive molecular evaluation whenever persistent eosinophilia is accompanied by clinical or laboratory features suggestive of a clonal hematologic disorder. Molecular confirmation not only establishes diagnosis but also directs individualized therapy and facilitates prediction of clinical outcome. The recognition of genetically defined eosinophilic neoplasms represents one of the clearest examples of precision medicine within modern hematopathology and illustrates the increasing integration of molecular diagnostics into disease classification.[14]

Germline Predisposition to Myeloid Neoplasms

Recognition of inherited susceptibility to myeloid malignancies represents one of the most significant conceptual advances incorporated into the WHO 5th Edition. Although traditionally regarded as sporadic diseases, increasing evidence demonstrates that a subset of patients develops myeloid neoplasms because of inherited pathogenic variants involving genes responsible for hematopoietic regulation, DNA repair, and genomic stability. Identification of these germline alterations has important implications for diagnosis, surveillance, family counselling, donor selection for stem cell transplantation, and long-term clinical management.

The WHO classification now recognizes **myeloid neoplasms with germline predisposition** as a distinct diagnostic category rather than simply recording inherited mutations as ancillary observations. This approach reflects the growing importance of integrating family history, clinical findings, cytogenetics, and molecular genetics into routine diagnostic practice. Recognition of germline predisposition also emphasizes the expanding role of hematopathologists in identifying patients who require confirmatory genetic testing and multidisciplinary evaluation involving clinical geneticists and specialized hereditary cancer services.[15]

Comparative Perspectives: WHO 5th Edition versus ICC

Although the WHO 5th Edition and International Consensus Classification were published during the same year and share many common principles, several important differences distinguish the two systems. Both classifications acknowledge the central importance of integrating morphology, immunophenotyping, cytogenetics, and molecular genetics; however, they differ in the relative emphasis placed upon selected molecular abnormalities, disease nomenclature, blast count thresholds, and recognition of emerging disease entities.

The WHO classification generally adopts a more conservative approach by incorporating molecular discoveries supported by robust evidence while maintaining broad international applicability across laboratories with varying diagnostic resources. In contrast, the ICC places greater emphasis on recently identified genomic abnormalities and introduces several molecularly defined disease categories that anticipate future developments in precision hematology. Differences are particularly evident in the classification of acute myeloid leukemia with recurrent genetic abnormalities, myelodysplastic neoplasms, overlap syndromes, and genetically defined precursor conditions. Despite these differences, both systems reflect a shared movement toward biologically driven classification that prioritizes disease pathogenesis over purely morphological categorization.[16]

Molecular Basis of Myelodysplastic Neoplasms

Myelodysplastic neoplasms (MDS) continue to represent one of the most heterogeneous groups of clonal hematopoietic disorders. Advances in genomic medicine have demonstrated that recurrent mutations involving genes responsible for RNA splicing, epigenetic regulation, transcriptional control, DNA repair, and signal transduction contribute to disease initiation, clonal evolution, and leukemic transformation. These molecular discoveries have profoundly influenced both disease classification and prognostic assessment.

The WHO and ICC classifications increasingly recognize that molecular abnormalities define biologically distinct disease subsets with differing clinical behavior and therapeutic responsiveness. Incorporation of recurrent genetic alterations into diagnostic algorithms has improved risk stratification while facilitating individualized management strategies. Contemporary classification therefore extends beyond traditional assessment of dysplasia and blast percentage to include integrated evaluation of cytogenetic and molecular abnormalities, reflecting the transition toward precision hematology.[17]

Genomic Classification of Acute Myeloid Leukemia

Among all myeloid neoplasms, acute myeloid leukemia has experienced perhaps the greatest transformation following advances in genomic

sequencing. Large-scale genomic studies have demonstrated that AML comprises multiple genetically distinct diseases rather than a single clinicopathological entity. Recurrent mutations involving **NPM1, FLT3, CEBPA, RUNX1, TP53, IDH1, IDH2, ASXL1, DNMT3A, TET2**, and numerous additional genes contribute to disease heterogeneity, influence prognosis, and determine response to targeted therapies.

These discoveries have fundamentally altered contemporary classification systems. Both the WHO 5th Edition and ICC now classify several AML subtypes primarily according to defining genetic abnormalities rather than morphology alone. This genomic framework has improved diagnostic precision, enhanced prognostic accuracy, and accelerated development of individualized therapeutic strategies that increasingly form the basis of modern precision oncology in hematologic malignancies.[18]

Contemporary Advances in Myeloid Neoplasm Classification: Bridging Molecular Biology and Clinical Practice

The rapid expansion of molecular genetics has fundamentally transformed the understanding of myeloid neoplasms. Comprehensive genomic studies have demonstrated that acute myeloid leukemia (AML), myelodysplastic neoplasms (MDS), myeloproliferative neoplasms (MPNs), and overlap disorders comprise biologically heterogeneous diseases characterized by distinct genomic alterations, patterns of clonal evolution, and variable therapeutic responses. Rather than serving merely as ancillary diagnostic information, molecular abnormalities have become central determinants of disease classification, prognostic stratification, and therapeutic decision-making. Consequently, contemporary classification systems increasingly prioritize genetically defined disease entities over classifications based solely on morphology or blast percentage.[19]

The evolution of modern classification systems has been progressive rather than revolutionary. The 2008 revision of the WHO Classification represented one of the earliest major efforts to integrate emerging molecular discoveries into routine hematopathology. It introduced refined diagnostic criteria for acute myeloid leukemia, recognized recurrent cytogenetic abnormalities as disease-defining entities, improved classification of myelodysplastic syndromes and myeloproliferative neoplasms, and established internationally standardized terminology for myeloid malignancies. Although molecular diagnostics were relatively limited at that time, the 2008 classification laid the conceptual foundation for subsequent revisions by acknowledging that genetic abnormalities possess diagnostic significance beyond conventional morphology.[20]

Building upon these earlier developments, the WHO 5th Edition substantially expanded the role of molecular pathology within myeloid neoplasm classification. Disease-defining genetic abnormalities now occupy a central position in diagnostic algorithms, reflecting the increasing availability of next-generation sequencing and comprehensive genomic profiling in routine clinical practice. The classification emphasizes integrated interpretation of clinical findings, peripheral blood examination, bone marrow morphology, immunophenotyping, cytogenetics, and molecular genetics to establish biologically meaningful diagnoses. This multidimensional framework improves diagnostic reproducibility while supporting precision medicine across the entire spectrum of myeloid disorders.[21]

Recent practical reviews have further highlighted the diagnostic implications of these revisions for routine hematopathology laboratories. Contemporary diagnostic evaluation increasingly requires integration of morphologic findings with genomic information, particularly in patients presenting with borderline blast counts, ambiguous dysplastic features, or overlapping clinicopathological characteristics. The WHO 5th Edition recognizes that molecular alterations frequently precede overt morphological transformation and may identify biologically distinct disease entities before conventional pathological criteria become fully established. Consequently, incorporation of molecular diagnostics has enhanced both diagnostic sensitivity and disease classification while improving clinicopathological correlation.[22]

Despite broad agreement regarding the importance of molecular pathology, important conceptual differences remain between the WHO 5th Edition and the International Consensus Classification (ICC). Both systems recognize recurrent genetic abnormalities as fundamental determinants of disease classification; however, they differ in several aspects of disease nomenclature, diagnostic thresholds, and categorization of genetically defined entities. The ICC adopts a more genomically driven approach, introducing several molecularly defined categories and emphasizing genetic abnormalities that may establish diagnosis even in the presence of blast counts below traditional thresholds. In contrast, the WHO classification generally adopts a more conservative framework, balancing incorporation of emerging genomic evidence with the need for global applicability across healthcare systems possessing variable molecular diagnostic capabilities.[23]

These differences are particularly evident in the classification of acute myeloid leukemia. The ICC gives greater emphasis to recurrent molecular abnormalities, permitting diagnosis of selected genetically defined AML subtypes despite lower blast percentages under specific circumstances. Conversely, the WHO classification continues to maintain broader reliance upon integrated clinicopathological assessment while recognizing an expanding number of genetically defined AML entities. Although these differences may influence classification of a relatively small proportion of patients, they have important implications for therapeutic eligibility, prognostic stratification, and enrollment into molecularly targeted clinical trials.[23]

One area that has undergone substantial refinement is the classification of myelodysplastic/myeloproliferative overlap neoplasms. Historically, these disorders presented considerable diagnostic challenges because they exhibit simultaneous dysplastic and proliferative features that overlap with both MDS and MPN categories. Recent advances in molecular genetics have improved understanding of their biological basis, enabling more precise distinction between chronic myelomonocytic leukemia, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, and other overlap disorders. Both WHO and ICC acknowledge the importance of integrating clinical findings with cytogenetic and molecular abnormalities; however, subtle differences in diagnostic criteria remain for selected entities. Continued refinement of these overlap disorders reflects the broader movement toward biologically based disease classification rather than reliance upon purely morphological definitions.[24]

The WHO 5th Edition further strengthens the concept that classification should remain dynamic and evidence based. Rather than serving solely as a diagnostic reference, the classification functions as an evolving framework capable of incorporating newly identified molecular biomarkers, inherited predisposition syndromes, measurable residual disease assessment, and future genomic discoveries. This approach ensures that disease classification remains closely aligned with advances in hematologic research while maintaining sufficient flexibility to accommodate future revisions.[25]

Similarly, the International Consensus Classification represents an important complementary framework that reflects expert consensus regarding rapidly emerging molecular evidence. Although developed independently, the ICC shares many conceptual similarities with the WHO classification and reinforces the transition toward integrated genomic medicine. The coexistence of these two contemporary classification systems has stimulated constructive scientific discussion regarding optimal diagnostic thresholds, nomenclature, and molecular categorization while accelerating harmonization of international hematopathology practice.[26]

The practical relevance of these classifications extends directly into patient management. Contemporary European LeukemiaNet (ELN) recommendations strongly advocate comprehensive diagnostic evaluation incorporating morphology, immunophenotyping, conventional cytogenetics, fluorescence in situ hybridization, and next-generation sequencing for newly diagnosed acute myeloid leukemia. Molecular characterization is now indispensable for establishing risk categories, selecting targeted therapies, monitoring measurable residual disease, and determining eligibility for hematopoietic stem cell transplantation. Consequently, both the WHO 5th Edition and ICC provide the essential diagnostic framework upon which modern evidence-based management strategies are built.[27]

Collectively, these developments illustrate a paradigm shift in the classification of myeloid neoplasms. Traditional morphology-based systems have progressively evolved into integrated histomolecular frameworks that combine clinical, pathological, cytogenetic, and genomic information to define biologically meaningful disease entities. Although differences persist between the WHO 5th Edition and the International Consensus Classification, both systems acknowledge that molecular pathology has become central to diagnosis, prognostic assessment, and therapeutic decision-making. Future revisions are expected to further integrate genomic technologies, measurable residual disease assessment, artificial intelligence, and multi-omics approaches, ultimately advancing precision hematology and improving outcomes for patients with myeloid malignancies.

Clinical Implications, Future Perspectives, and Conclusions

Translation of Contemporary Classification into Clinical Practice

The ultimate value of any disease classification lies in its ability to improve patient care. Both the WHO 5th Edition and the International Consensus Classification (ICC) have shifted the classification of myeloid neoplasms from a predominantly morphology-based system to one that integrates morphology, immunophenotyping, cytogenetics, molecular genetics, and clinical features. This multidimensional approach has enhanced diagnostic precision while allowing clinicians to select therapies based on disease biology rather than solely on conventional pathological findings. The incorporation of molecular biomarkers into

diagnostic criteria has also strengthened risk stratification, therapeutic selection, and measurable residual disease monitoring, making classification an essential component of modern precision hematology.

Current **National Comprehensive Cancer Network (NCCN)** recommendations for acute myeloid leukemia emphasize comprehensive baseline evaluation including peripheral blood examination, bone marrow morphology, multiparametric flow cytometry, conventional cytogenetics, fluorescence in situ hybridization, and next-generation sequencing. Molecular characterization is now mandatory for identifying recurrent genetic abnormalities involving genes such as **FLT3, NPM1, CEBPA, IDH1, IDH2, TP53, RUNX1**, and others because these findings directly influence prognosis and determine eligibility for targeted therapies. Consequently, the WHO 5th Edition and ICC provide the diagnostic framework upon which current AML management guidelines are based.[29]

Similarly, contemporary NCCN recommendations for **myelodysplastic neoplasms (MDS)** advocate integrated clinicopathological and molecular evaluation. Bone marrow morphology remains fundamental for diagnosis; however, cytogenetic analysis and comprehensive genomic profiling have become indispensable for identifying disease-defining abnormalities, estimating prognosis, and selecting individualized treatment strategies. The incorporation of molecular findings into routine clinical practice has significantly improved diagnostic confidence while enabling more accurate prediction of leukemic transformation and overall survival.[30]

The classification of **myeloproliferative neoplasms (MPNs)** has also evolved substantially through integration of molecular diagnostics. Current NCCN guidelines emphasize evaluation of **JAK2, CALR,** and **MPL** mutations together with detailed bone marrow histopathology for accurate distinction among polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Identification of these driver mutations has improved diagnostic accuracy, facilitated risk stratification, and supported the development of targeted therapies that have transformed the management of MPNs over the past decade.[31]

Precision Medicine and Genomic Classification

Large-scale genomic sequencing studies have fundamentally changed the understanding of acute myeloid leukemia by demonstrating that AML comprises numerous biologically distinct diseases characterized by unique combinations of genetic alterations rather than a single clinicopathological entity. Genomic classification has shown that recurrent mutations involving **NPM1, FLT3, CEBPA, TP53, RUNX1, ASXL1, DNMT3A, TET2, IDH1**, and **IDH2** influence disease pathogenesis, prognosis, and therapeutic responsiveness. These discoveries have accelerated development of targeted therapies while supporting individualized treatment strategies based upon genomic profiling.[32]

The increasing incorporation of molecular information into disease classification has also transformed the approach to myelodysplastic neoplasms. Contemporary evidence indicates that MDS represents a heterogeneous spectrum of clonal disorders driven by abnormalities affecting RNA splicing, epigenetic regulation, transcriptional control, DNA repair, and signal transduction pathways. Recognition of these molecular mechanisms has improved disease subclassification and strengthened the biological basis of contemporary classification systems. Rather than relying exclusively upon morphological dysplasia and blast percentage, modern diagnostic algorithms integrate molecular findings to provide more accurate prognostic assessment and individualized patient management.[33]

Disease-Specific Clinical Implications

Advances in molecular diagnostics have had a particularly important impact on the management of **polycythemia vera** and **essential thrombocythemia**. Contemporary diagnostic criteria incorporate clinical findings, bone marrow morphology, laboratory parameters, and molecular detection of **JAK2, CALR,** and **MPL** mutations to establish clonality and distinguish between individual myeloproliferative neoplasms. Risk-adapted therapeutic strategies now consider age, thrombotic history, cardiovascular risk factors, and molecular abnormalities to guide selection of cytoreductive therapy and antithrombotic management.[34]

Likewise, classification of **primary myelofibrosis** increasingly incorporates molecular profiling to distinguish prefibrotic disease from overt fibrotic stages while identifying patients at increased risk of leukemic transformation. Integration of driver mutations with additional high-risk molecular abnormalities improves prognostic stratification and supports individualized therapeutic planning, including consideration of JAK inhibitors, investigational therapies, and hematopoietic stem cell transplantation.[35]

The WHO and ICC classifications have similarly strengthened recognition of **myeloid and lymphoid neoplasms associated with eosinophilia**. Identification of recurrent kinase gene rearrangements involving **PDGFRA, PDGFRB, FGFR1, JAK2**, and related genes has transformed

diagnosis and treatment by identifying patients who benefit from highly effective targeted therapies. Molecular confirmation is therefore considered essential for both disease classification and therapeutic selection.[36]

Contemporary classification systems have also refined diagnostic criteria for **mast cell disorders**, recognizing mastocytosis as a clonal hematopoietic neoplasm characterized by characteristic morphological, immunophenotypic, and molecular features. Detection of activating **KIT** mutations, particularly **KIT D816V**, together with immunophenotypic abnormalities has improved diagnostic specificity while facilitating distinction between indolent and aggressive disease subtypes with markedly different prognostic implications.[37]

Diagnostic Challenges and Future Directions

Despite substantial advances, important diagnostic challenges remain. Distinguishing early myelodysplastic neoplasms from age-related clonal hematopoiesis, differentiating overlap disorders, interpreting variants of uncertain significance identified through next-generation sequencing, and integrating increasingly complex genomic information into routine clinical practice continue to present significant difficulties for hematopathologists and clinicians. International consensus recommendations therefore emphasize multidisciplinary interpretation of clinical findings, morphology, cytogenetics, and molecular genetics to ensure accurate diagnosis and appropriate patient management.[38]

Rapid expansion of genomic technologies is expected to further refine disease classification during the coming decade. Increasing use of whole-genome sequencing, single-cell sequencing, transcriptomics, epigenomics, proteomics, and measurable residual disease assessment will likely identify additional biologically distinct disease subsets that cannot be recognized through conventional morphology alone. These technologies may eventually redefine disease boundaries while supporting increasingly individualized therapeutic strategies.

The genomic landscape of AML continues to evolve as new pathogenic mutations and cooperative genetic interactions are identified. Understanding clonal evolution, subclonal architecture, and treatment-associated molecular changes will likely contribute to future revisions of classification systems and improve prediction of disease progression and therapeutic resistance.[39]

Future classifications are also expected to build upon the principles established in earlier WHO revisions. The 2008 WHO classification represented the first major step toward integrating molecular findings with traditional pathology, whereas subsequent editions progressively expanded the role of genomics within disease classification. The WHO 5th Edition and ICC represent the current culmination of this evolutionary process while remaining adaptable to future scientific discoveries.[40]

Harmonization of Future Classification Systems

Recent expert recommendations from the International Consortium for Myelodysplastic Neoplasms/Syndromes emphasize continued refinement of diagnostic criteria through integration of morphology, cytogenetics, molecular genetics, and standardized reporting. Such collaborative initiatives are expected to facilitate greater harmonization between future WHO and ICC classifications while reducing diagnostic variability across institutions.[41]

Current evidence also highlights the importance of integrating genomic information into routine diagnosis of myelodysplastic neoplasms. Improved understanding of recurrent molecular abnormalities has strengthened disease classification, enhanced prognostic modelling, and accelerated development of personalized therapeutic approaches that increasingly define modern hematology practice.[42]

The classification of **chronic myelomonocytic leukemia (CMML)** has similarly benefited from advances in molecular genetics and improved recognition of clinicopathological heterogeneity. Integration of molecular abnormalities with conventional diagnostic criteria has enhanced risk stratification while improving distinction from other overlap neoplasms.[43]

Myelodysplastic/myeloproliferative overlap neoplasms remain among the most diagnostically challenging myeloid disorders because they combine dysplastic and proliferative features. Comparative analyses of the WHO and ICC classifications indicate that although substantial agreement exists regarding major disease entities, differences persist in diagnostic thresholds and categorization of selected overlap disorders. Continued refinement of molecular criteria is expected to improve diagnostic consistency in future classifications.[44]

Practical comparative studies have demonstrated that the WHO 5th Edition and ICC are highly concordant in their overall diagnostic philosophy despite differences in nomenclature and specific disease definitions. Both systems recognize that integrated interpretation of morphology, immunophenotyping, cytogenetics, and molecular genetics provides the most accurate approach for

classification of myeloid neoplasms. Rather than competing frameworks, they should be viewed as complementary systems reflecting the continuing evolution of precision hematology.[45]

Table 1. Evolution of WHO Classification of Myeloid Neoplasms

WHO Edition	Year	Major Features	Impact on Classification
WHO 2001	2001	First integrated classification combining morphology, immunophenotyping, cytogenetics and clinical findings	Established standardized diagnostic criteria for myeloid neoplasms
WHO 2008	2008	Recognition of recurrent cytogenetic abnormalities, refinement of MDS and MPN categories, introduction of provisional entities	Improved disease classification and international diagnostic uniformity
WHO 2016 Revision	2016	Incorporated recurrent molecular abnormalities, revised AML criteria, updated MDS, MPN and MDS/MPN overlap disorders	Introduced molecular pathology into routine classification
WHO 5th Edition	2022	Integrated genomic medicine, hereditary predisposition syndromes, disease-defining molecular abnormalities, updated nomenclature	Established biologically driven classification supporting precision medicine

Table 2. Comparison between WHO 5th Edition and International Consensus Classification (ICC 2022)

Parameter	WHO 5th Edition	International Consensus Classification (ICC)
Philosophy	Evidence-based global classification with emphasis on worldwide applicability	Genomically driven classification incorporating recent molecular discoveries
Diagnostic approach	Integrated morphology, immunophenotyping, cytogenetics and molecular genetics	Greater emphasis on molecular genetics and disease-defining mutations
AML classification	Molecular abnormalities incorporated while maintaining established diagnostic framework	Greater recognition of genetically defined AML entities and molecular thresholds
MDS classification	Updated terminology and molecular integration	Greater emphasis on genetically defined disease subsets
MDS/MPN overlap neoplasms	Conservative diagnostic approach	Expanded molecular categorization of overlap disorders
Germline predisposition	Separate disease category included	Similar recognition with emphasis on genomic characterization
Clinical application	Broad international applicability	Precision medicine-oriented classification

Table 3. Major Molecular Markers Incorporated into Contemporary Classification

Gene / Biomarker	Associated Disease	Clinical Importance

NPM1	Acute Myeloid Leukemia	Disease-defining mutation, prognostic marker
FLT3	Acute Myeloid Leukemia	Prognostic significance and targeted therapy
CEBPA	Acute Myeloid Leukemia	Favorable-risk molecular subgroup
TP53	AML, MDS	High-risk disease, adverse prognosis
RUNX1	AML, MDS	Diagnostic and prognostic significance
ASXL1	MDS, CMML, PMF	Poor prognostic marker
SF3B1	Myelodysplastic Neoplasms	Defines specific MDS subtype with ring sideroblasts
JAK2	Polycythemia vera, ET, PMF	Driver mutation and diagnostic marker
CALR	Essential thrombocythemia, PMF	Driver mutation and prognostic value
MPL	Essential thrombocythemia, PMF	Driver mutation in MPNs
KIT D816V	Mastocytosis	Diagnostic marker and therapeutic target
PDGFRA / PDGFRB / FGFR1	Eosinophilic neoplasms	Defines tyrosine kinase-associated neoplasms responsive to targeted therapy

Table 4. Clinical Impact of the WHO 5th Edition and ICC

Clinical Domain	Impact of Updated Classification
Diagnosis	Greater diagnostic accuracy through integrated morphology and molecular genetics
Prognosis	Improved risk stratification using genomic abnormalities
Precision Medicine	Selection of targeted therapies based on molecular biomarkers
Risk Assessment	Better prediction of leukemic transformation and overall survival
Hereditary Disorders	Improved recognition of germline predisposition syndromes
Standardization	Uniform diagnostic terminology across institutions
Clinical Trials	Harmonized eligibility criteria and molecular stratification
Personalized Medicine	Individualized treatment planning based on genomic profiling
Future Research	Supports incorporation of artificial intelligence, multi-omics, and measurable residual disease into future classifications

Conclusion

The WHO 5th Edition and the International Consensus Classification represent major advances in the contemporary classification of myeloid neoplasms by integrating molecular genetics with conventional hematopathology. Both systems have substantially improved diagnostic precision, prognostic assessment, and therapeutic decision-making through incorporation of disease-defining genetic abnormalities and biologically meaningful disease categories. Although differences remain regarding selected diagnostic criteria and molecularly defined entities, the overall direction of both classifications reflects a common transition

toward precision medicine. Continued advances in genomics, artificial intelligence, single-cell technologies, and measurable residual disease assessment are expected to further refine future classifications, ultimately improving individualized patient care and advancing the field of hematologic oncology.

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