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Original Article

Molecular Taxonomy Toward Personalized MDS Management

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Abstract

Myelodysplastic Syndromes (MDS) represent a heterogeneous group of clonal hematopoietic disorders characterized by ineffective hematopoiesis, cytopenias, and a risk of progression to acute myeloid leukemia (AML). Traditionally, MDS classification relied on morphological and cytogenetic assessments, but advancements in next-generation sequencing (NGS) have revealed recurrent genetic mutations that have reshaped the diagnostic and therapeutic landscape. This review article explores the clinical implications of molecular taxonomy in MDS, focusing on key mutations such as *SF3B1, TP53, TET2,* and *ASXL1*. The integration of molecular profiling into diagnostic frameworks, such as IPSS-Molecular (IPSS-M), has enhanced patient stratification and prognosis prediction. Moreover, targeted therapies, including Luspatercept for *SF3B1*-mutated MDS and hypomethylating agents for *TET2* mutations, have emerged as promising treatments. However, challenges persist, including interpatient heterogeneity, clonal evolution, and limited access to molecular testing in clinical practice. This review article emphasizes the need for ongoing research and innovation to overcome these challenges, further integrating molecular insights into personalized MDS management to improve patient outcomes.

Keywords: Myelodysplastic Syndromes (MDS), Molecular Taxonomy, Next-Generation Sequencing (NGS), SF3B1 Mutation, TP53 Mutation

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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders characterized by ineffective hematopoiesis, bone marrow failure, and an increased risk of transformation into acute myeloid leukemia (AML). [1, 2] These disorders arise from genetic abnormalities within hematopoietic stem cells, leading to defective production of one or more blood cell lines, including erythrocytes, leukocytes, and platelets. [3] MDS manifests clinically as varying degrees of cytopenia (anemia, neutropenia, or thrombocytopenia), with symptoms such as fatigue, infections, or bleeding episodes. [4, 5]

Historically, the classification and diagnosis of MDS relied on morphology, peripheral blood findings, and bone marrow examination. The World Health Organization (WHO) has defined specific subtypes of MDS using cytogenetic and morphologic criteria, classifying cases based on the presence of dysplasia, blast percentage, and genetic abnormalities. [6] However, traditional diagnostic methods fail to fully capture the biological complexity of MDS, and patients with similar morphological features often exhibit different clinical outcomes. [7-9]

In recent years, advances in high-throughput genomic technologies, such as next-generation sequencing (NGS), have enabled the identification of recurrent somatic mutations associated with MDS. [3, 10] These discoveries have shifted the diagnostic paradigm from morphology-based classification to molecular taxonomy, providing a deeper understanding of the pathogenesis, prognosis, and therapeutic potential of MDS. [11]

Several recurrent mutations have been identified in key regulatory genes involved in hematopoietic processes, including *SF3B1*, *TP53*, *ASXL1*, *DNMT3A*, *RUNX1*, and *TET2*. [12]. These mutations affect various pathways such as epigenetic regulation, RNA splicing, DNA repair, and transcription control, influencing disease progression and clinical outcomes. [13, 14]

NGS technologies have made it possible to detect these mutations with high sensitivity, facilitating the identification of genetic subgroups within MDS. [15] This genomic stratification enables personalized therapeutic strategies, tailored according to the mutational profile of each patient, and improves prognostic accuracy by revealing high-risk mutations that may not be evident through conventional diagnostics. [7]

Despite the progress in understanding MDS at the molecular level, significant clinical challenges remain. MDS is a highly heterogeneous disease, with overlapping clinical features between subtypes and between MDS and other hematologic malignancies, such as myeloproliferative neoplasms (MPN) and AML. [16, 17] Additionally, while traditional risk scoring systems, such as the International Prognostic Scoring System-Revised (IPSS-R), remain useful, they are insufficient in accounting for the complex molecular landscape driving disease heterogeneity. [18,19]

The incorporation of molecular findings into diagnostic frameworks, such as the WHO and International Consensus Classification (ICC), offers the potential for greater diagnostic precision. For instance, the presence of *SF3B1* mutations is now recognized as a defining feature of MDS with ring sideroblasts (MDS-RS), a subtype associated with better prognosis compared to other MDS forms. [12] This molecular refinement also helps differentiate between borderline cases of MDS, AML, and MDS/MPN overlap syndromes. [9]

This review article aims to explore the clinical implications of molecular taxonomy in MDS. It will provide an in-depth analysis of the current molecular landscape, focusing on key mutations and their functional roles. We will also examine how molecular findings are reshaping the diagnosis, prognosis, and treatment of MDS. Key challenges and future directions in molecular taxonomy will be discussed.

1- Current Molecular Landscape of MDS

The molecular landscape of MDS is complex and diverse, marked by the presence of several recurrent genetic mutations that affect key biological processes such as DNA methylation, RNA splicing, transcription regulation, and chromatin modification. [20] Understanding this intricate molecular framework helps in identifying subtypes of MDS, predicting disease progression, and designing targeted therapies. [3, 7, 21]

1.1.Key Mutated Genes in MDS

The molecular pathophysiology of MDS involves intricate signaling networks that regulate hematopoietic differentiation, cell proliferation, and epigenetic modification. As illustrated in the figure [1], key signaling pathways include the JAK-STAT, PI3K-AKT, and RAS-MAPK pathways, which interact to maintain normal cellular functions. Mutations in genes like *TET2*, *ASXL1*, and *RUNX1* disrupt epigenetic regulation and transcriptional differentiation, contributing to the abnormal hematopoiesis observed in MDS. [22] Similarly, abnormalities in *p53* and dysregulation of receptor tyrosine kinases (e.g., *FLT3* and *c-KIT*) further enhance disease progression by promoting ineffective hematopoiesis and clonal expansion. [3, 23, 24] (figure 1)

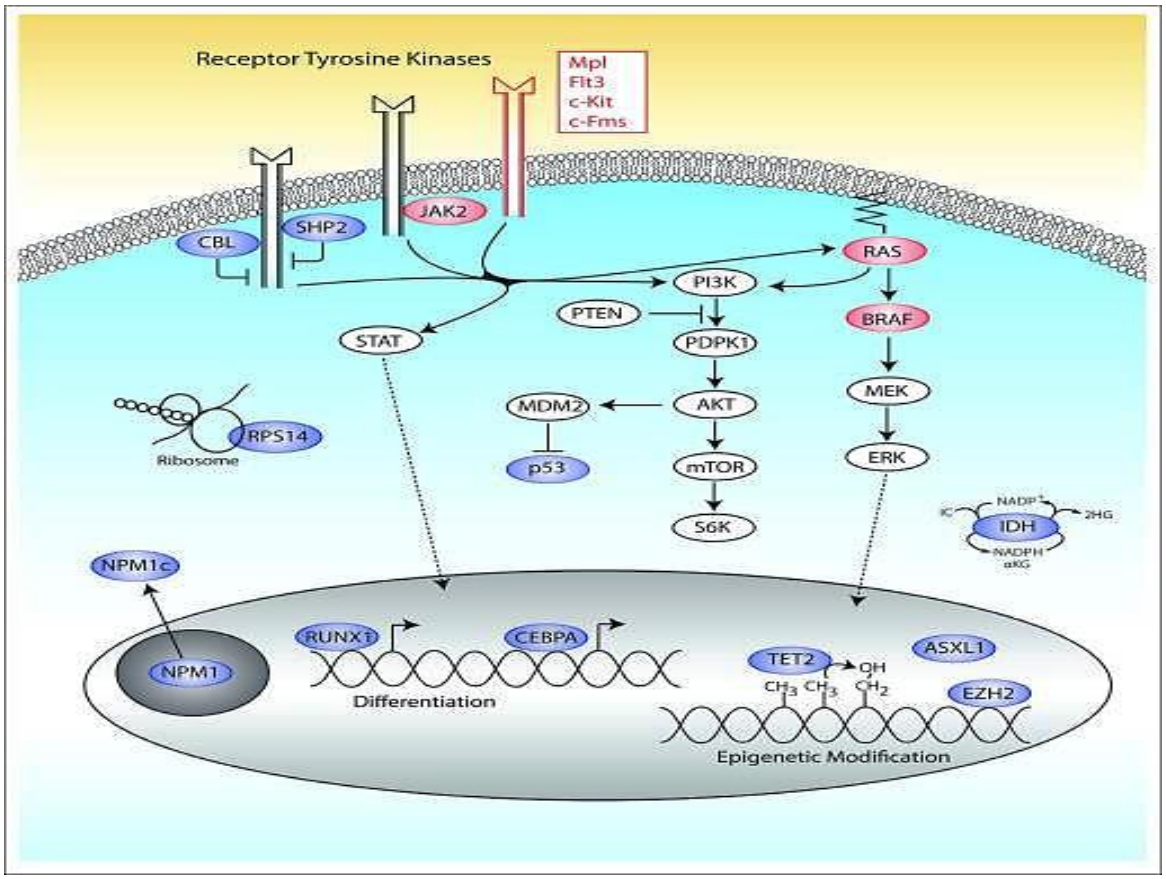

Figure 1: Molecular Pathways and Mutational Drivers in Myelodysplastic Syndromes (22)

1.2. Genetic Subgroups according to Molecular Taxonomy of MDS and their Functional Categories

Currently, the World Health Organization and the International Consensus categorization are the two main categorization systems used to categorize MDS. [25, 26]

Even while several unique genetic entities, such as del(5q), TP53-mutated, and SF3B1-mutated MDS, have been identified in their most recent iterations, they only constitute less than one-third of cases; the blast count determines the remaining MDS cases. Furthermore, phenotype —rather than genotype—is the primary defining characteristic of chronic myelomonocytic leukemia and other MDS/MPN groupings. [25-27] These categorization schemes are meant to identify biologically distinct entities, but they do not yet account for the genomic overlap with MDS/MPN entities and the genomic heterogeneity in MDS.

Crucially, classification systems are not the same as prognostic models (e.g., the Molecular International Prognostic Scoring System for

Myelodysplastic Syndromes [IPSS-M]. [25] which aid in risk-adapted treatment choices with a restricted range of noncurative treatments other than allogeneic bone marrow transplantation. Prognostic models are only useful for predicting outcomes.

Bernard et al. investigated complex gene-gene interactions to identify distinct genomic groups based on comutations, the presence or absence of genetic aberrations (mutations, copy number loss of heterozygosity, and aneuploidy), and the previous use of TP53 allelic state or IDH2 R140 vs. R172 status as inputs for unsupervised clustering (figure 2).

After clustering, a hierarchical classification system was created using 21 genes, 6 cytogenetic events, and 2 allelic states (TP53 and TET2) (figure 2). In addition to identifying eight novel subgroups, the scientists also confirmed five existing entities and three previously reported entities by identifying 16 genomically defined subgroups that classified 86% of patients with different genotype-phenotype relationships and clinical outcome .[27]

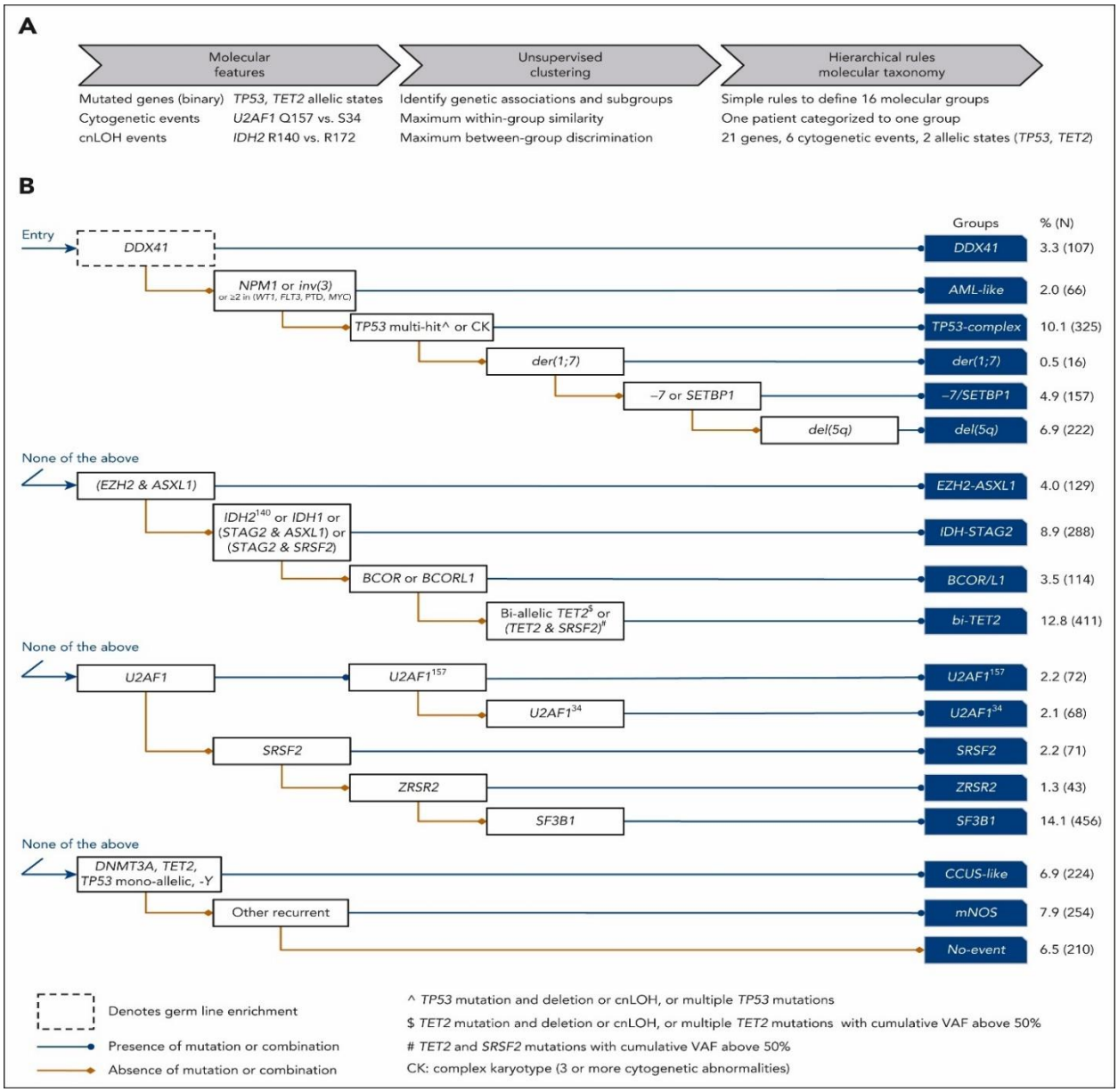

Figure 2: Derivation of 16 MDS molecular groups in molecular taxonomy of MDS (3).

The taxonomy further includes AML-like and DDX41 subtypes. AML-like MDS is defined by genetic mutations typically associated with highest percentage of BM blast. It was also associated with a younger age, a female predominance, short OS, and had the highest rate of leukemic transformation. The DDX41 group, notable for germline and somatic mutations in the DDX41 gene, presents clinical profile including elevated blasts and increased risk of leukemic transformation yet no excess risk of death, a relatively favorable prognosis when compared to other high-risk subtypes. The inclusion of these genetic profiles within the MDS classification underscores the shared pathogenetic pathways with AML, emphasizing the value of a molecular approach. [28, 29]

Del(5q) was associated with a female bias, low hemoglobin values, high platelet counts, and favorable OS. Notably, 22% of cases from del(5q) group would be excluded from the WHO 2022/ICC MDS with isolated del(5q) category because of excess blasts. The SF3B1 group was the most prevalent. SF3B1 mutations were frequently secondary to DNMT3A mutations and dominant to TET2 mutations. The group had low BM blasts and favorable outcomes.[3]

The second largest group was defined by biallelic TET2 mutations. Patients in this group had distinct clinicohematological features, including older age, milder anemia, increased monocytes, and a CMML enrichment. [3]

Novel molecular groups: for example, the −7/SETBP1 group was defined by SETBP1 mutations and/or −7 in the absence of CK. The −7/SETBP1 group was associated with a younger age, higher risk and poor outcomes.[3].

Two residual groups, mNOS (molecularly not otherwise specified) and No-event, capture patients without specific molecular drivers or those with less common genetic profiles. These groups exhibit milder clinical features and comparatively better outcomes, indicating that absence of significant driver mutations may correlate with lower disease aggressiveness. Such findings provide insight into the role of molecular complexity in MDS pathology.

In patients with MDS and chronic myelomonocytic leukemia, all 18 genetic entities were found, and many of them were also found in other MDS/MPN subtypes, albeit at varying frequencies.

A number of findings that are clinically important were found within the novel groups. GATA2 variations were common in the −7/SETBP1 group, with variable allelic frequencies indicating a germ line origin in 4% of cases. The results emphasize the necessity of further analyzing this genetic group that is probably enriched for patients with a germ line propensity, even if the targeted panel did not contain SAMD9 or SAMD9L and germ line tissue was not available. Most patients in the EZH2-ASXL1 group had at least five mutations, indicating a high level of genetic complexity. The poor survival results for both the EZH2-ASXL1 and −7/SETBP1 categories were unaffected by blast count.

As evidence of the prognostic value of genomes, this was also true for DDX41 and AML-like groups. Groups with IDH-STAG and BCOR/L1 had genomic landscapes resembling secondary AML, as well as increased blasts and a high incidence of leukemic transformation (figure 3&4). The use of blast percentage to establish diagnostic boundaries in these groups is often not supported by these results.

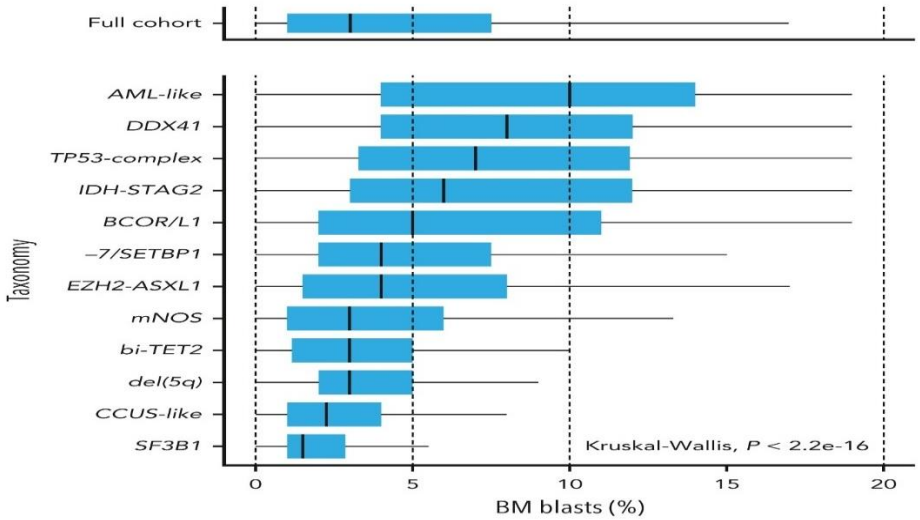

Figure 3: Distribution of the percentage of BM blast for 12 molecular groups [3].

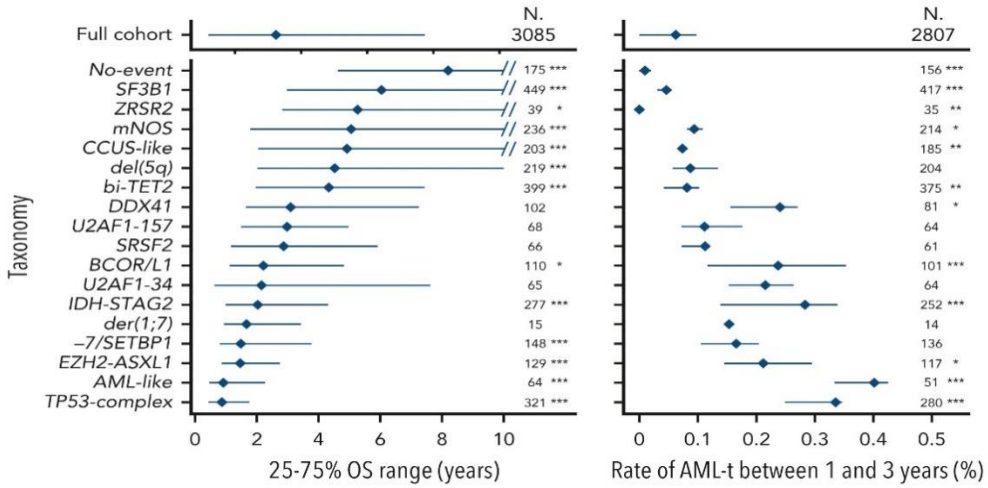

Figure 4: Association between molecular groups and outcomes, for OS (left) and AML transformation [(3)].

Bernard et al. provides a foundation for a more complex MDS classification system that would more accurately represent the underlying biology of these neoplasms, keeping in mind that this is a proposal for additional research rather than a consensus statement for a new MDS classification. It acts as a springboard for further studies that concentrate on comprehending the functional effects of these genomic occurrences and determining the biological distinctions or parallels among the suggested subgroups.

In order to facilitate medication discovery, such insights could be used to pinpoint certain weaknesses within particular populations. It is not, however, intended to take the place of the IPSS-M, which continues to perform better in terms of prediction than a model based on these chemical groupings. [(27)]

Bernard et al, evaluated the relationship between genetic subtypes and blasts. In several groups (AML-like, DDX41, −7/SETBP1, and EZH2-ASXL1), blast percentages did not stratify patient outcomes. However, for groups enriched for lower-risk disease (for example del(5q), bi-TET2, SF3B1, CCUS-like, and mNOS) blasts percentages differentiated outcomes. [(3)]

1.3.Clonal Evolution and Heterogeneity

MDS exhibits significant interpatient heterogeneity due to the dynamic nature of clonal evolution. This process begins with an initial driver mutation, followed by the accumulation of additional

mutations over time. As these subclones evolve, they compete for dominance, leading to a constantly changing genetic landscape within the same patient. [7, 23]

Early driver mutations, such as those in *TET2* or *DNMT3A*, typically establish the primary clone. Secondary mutations, including *ASXL1* or *TP53*, may develop later, giving rise to subclones with more aggressive phenotypes. This evolutionary pattern contributes to disease progression and therapy resistance (3, 30).

The presence of multiple mutated clones complicates the prediction of disease course. For instance, the acquisition of *TP53* mutations often indicates a transition to a more aggressive disease form or transformation into acute myeloid leukemia (AML). [16] Monitoring clonal dynamics is thus crucial for guiding treatment decisions and understanding therapy resistance. [31]

Molecular profiling not only informs diagnosis but also plays a critical role in therapeutic decisions. For example, *SF3B1* mutations are associated with responsiveness to Luspatercept, a therapy that targets ineffective erythropoiesis. [32] Similarly, mutations in *TET2* predict favorable responses to hypomethylating agents like azacitidine and decitabine. These associations between genotype and treatment response underscore the need for molecularly informed clinical trials that tailor therapies to individual patients. [33]

2. Clinical Implications of Molecular Taxonomy

The molecular taxonomy of MDS has introduced profound changes to how these disorders are diagnosed, stratified, and treated. Molecular insights allow more precise identification of disease subtypes, facilitate risk stratification, and promote the development of targeted therapies. [3] As genomic profiling becomes integrated into clinical practice, it significantly impacts diagnosis, prognosis, and therapeutic approaches, fostering a transition toward personalized medicine in MDS care. [34]

Molecular profiling has augmented traditional diagnostic frameworks, such as those established by the World Health Organization (WHO) and the International Consensus Classification (ICC). These frameworks increasingly incorporate mutational data to distinguish MDS subtypes more accurately (7). For example, the identification of *SF3B1* mutations is critical for diagnosing MDS with ring sideroblasts (MDS-RS). [35]

Genomic profiling reduces diagnostic ambiguity in cases where morphology or cytogenetic data are inconclusive. In situations with overlapping characteristics between MDS and other hematologic disorders, molecular markers offer a new level of diagnostic clarity. [3] Additionally, genomic classification helps differentiate MDS from related disorders, such as MDS/MPN overlap syndromes, by leveraging specific mutation patterns. [36]

Some patients with borderline features between MDS and acute myeloid leukemia (AML) or other hematopoietic neoplasms may now be better categorized using molecular insights. [25] This prevents misclassification and ensures that patients receive appropriate treatment.

Traditional prognostic tools, such as the International Prognostic Scoring System (IPSS) and its revised version (IPSS-R), have relied on factors like bone marrow blast percentage, cytopenias, and karyotype abnormalities to stratify patients into risk categories. [3] However, these models do not fully capture the heterogeneity of MDS, especially given the expanding knowledge of molecular alterations. Integrating molecular taxonomy into prognostic models offers more precise predictions of survival outcomes, disease progression, and treatment responses. [37]

The IPSS-M is an evolution of the IPSS-R, designed to include molecular data, particularly recurrent mutations in MDS-related genes such as *TP53*, *ASXL1*, *RUNX1*, and *SF3B1*. [16] This molecularly informed model provides superior predictive power by accounting for somatic mutations that influence the clinical trajectory of MDS patients.

IPSS-M integrates cytogenetics, clinical features, and somatic mutations, enabling more accurate risk stratification. [38] This model offers better predictions of overall survival (OS) and leukemia-free survival (LFS), compared to traditional scoring systems .[7] Patients previously classified as low risk may now be reclassified based on high-risk mutations, guiding more intensive surveillance or earlier treatment. [39]

Molecular profiling allows the customization of risk models for individual patients. The presence of multiple mutations (multi-hit status) in genes such as *TP53* can significantly downgrade a patient's prognosis, even if their cytogenetic profile suggests low risk. [3]

4.1. Impact of Key Mutations on Prognosis

TP53 is one of the most significant prognostic markers in MDS. It is often associated with high-risk disease, poor response to therapies, and shorter overall survival (OS). [40] Patients with multi-hit *TP53* mutations fare worse than those with single mutations, highlighting the importance of clonal burden in risk assessment. [16] This mutation is frequently linked with therapy-related MDS and complex karyotypes, compounding the challenges in management. [41]

Mutations in *ASXL1* and *RUNX1* are associated with aggressive disease behavior and unfavorable outcomes, especially in the context of other high-risk mutations. Their presence in low-risk patients can result in reclassification to a higher-risk group under IPSS-M, prompting earlier intervention. [7, 23]

In contrast to other high-risk mutations, *SF3B1* is associated with a more favorable prognosis. Patients with *SF3B1*-mutated MDS often present with ring sideroblasts (MDS-RS) and show prolonged survival with lower rates of progression to acute myeloid leukemia (AML). [12] Luspatercept, a novel erythropoiesis-stimulating agent, offers therapeutic benefits in these cases, reducing transfusion dependence and improving quality of life. [42, 43, 44]

Mutations in *TET2* and *DNMT3A* are early events in clonal hematopoiesis. Although they do not always correlate with poor prognosis, their presence can guide therapeutic decisions, especially concerning the use of hypomethylating agents. [3] Patients with these mutations may benefit from azacitidine or decitabine, which modulate epigenetic regulation.

4.2. Clonal Evolution and Its Role in Prognosis

MDS is a dynamic disease, with clonal evolution playing a significant role in its progression. New mutations or the expansion of specific subclones during treatment often herald disease progression or transformation to AML. [32] Monitoring clonal evolution through serial genomic testing is therefore essential for adaptive risk assessment. [45, 46]

The emergence of additional mutations, particularly in genes such as *TP53* or *ASXL1*, can change the risk profile during the course of the disease. [47] Tracking these changes in real-time allows clinicians to anticipate relapse or disease progression and modify treatment strategies accordingly. [48]

Clonal dynamics also affect therapeutic outcomes. For instance, the expansion of *TP53*-mutated clones during treatment with hypomethylating agents often indicates impending resistance, necessitating a switch to alternative therapies or enrollment in clinical trials. [3, 49]

4.3. Prognostic Tools in Clinical Practice

The incorporation of mutational data into everyday practice is becoming more accessible with the increasing availability of next-generation sequencing (NGS). Several clinical centers are now adopting molecularly informed scoring systems, such as IPSS-M, to guide decision-making. [36, 50, 51]

Patients stratified as high-risk based on molecular profiling may receive more aggressive treatment, such as allogeneic stem cell transplantation, at an earlier stage. Conversely, patients with favorable mutational profiles may benefit from less intensive therapy, preserving their quality of life. [52, 53]

As clonal evolution occurs during treatment, molecular profiles can shift. Repeated genomic testing enables adaptive management, where treatment plans are adjusted based on the changing mutational landscape. [12]

4.4. Challenges in Molecular Prognostication

While molecular profiling offers enhanced prognostic accuracy, several challenges remain. The diverse mutational landscape of MDS complicates the development of universal prognostic models. Some mutations may have different prognostic impacts depending on co-occurring mutations or clonal context. [16]

Although NGS has become more accessible, routine molecular profiling is still not available in all clinical settings. The cost and technical requirements pose barriers to widespread adoption. [7]

In some cases, the clinical significance of certain mutations remains unclear. More research is needed to fully understand how specific genotypes translate

into phenotypic outcomes, especially in the context of evolving disease.

5. Therapeutic Implications

The molecular taxonomy of MDS has profoundly changed the therapeutic landscape by shifting from generalized treatment approaches toward personalized medicine. By identifying specific gene mutations and understanding their functional impact, clinicians can now better align therapies to individual molecular profiles, improving treatment outcomes and reducing adverse effects. [12] This section explores the evolving therapeutic strategies informed by molecular findings and highlights the importance of molecular profiling in optimizing patient care.

5.1. Targeted Therapies and Molecularly Guided Treatments

Luspatercept, a recombinant fusion protein, targets the transforming growth factor-beta (TGF-β) signaling pathway. It is particularly effective in patients with *SF3B1*-mutated MDS who experience anemia and require frequent red blood cell transfusions. [12] By enhancing erythropoiesis, Luspatercept reduces transfusion dependency and improves quality of life for these patients. [44, 54]

Clinical trials have demonstrated that *SF3B1*-mutated patients treated with Luspatercept show significant improvements in hemoglobin levels and a reduction in transfusion requirements, reinforcing the importance of genomic profiling in treatment selection. [16, 55]

Hypomethylating agents (HMAs) such as azacitidine and decitabine have become the standard of care for high-risk MDS. These agents restore normal gene expression by modulating DNA methylation, making them particularly effective in cases with *TET2* mutations, which impair epigenetic regulation. [3, 56] [57]

Studies have shown that *TET2* mutations predict better responses to HMAs, with prolonged overall survival (OS) and improved hematologic function. [7] This highlights the importance of early molecular testing to identify candidates for HMA therapy. [58]

Patients with *TP53* mutations, especially multi-hit configurations, have poor prognoses and are less responsive to conventional therapies. Emerging therapies are now targeting this high-risk group, with clinical trials evaluating immune checkpoint inhibitors and gene-editing approaches. [12]

Novel agents targeting the p53 pathway aim to restore normal cell-cycle control, reduce leukemic transformation, and overcome resistance to existing treatments [59] Additionally, allogeneic stem cell transplantation is often pursued early for patients with *TP53* mutations due to their high relapse risk . [60, 61]

The heterogeneity of MDS demands combinatorial approaches to target multiple mutated pathways simultaneously. Molecular profiling identifies patients with complex mutational landscapes who may benefit from combination therapies. [3, 58, 62]

The combination of azacitidine with novel targeted agents, such as venetoclax (a BCL-2 inhibitor), is being tested in clinical trials to improve outcomes for high-risk MDS patients. These trials leverage molecular profiling to identify candidates with co-occurring mutations who are likely to benefit from these approaches. [63]

In cases where patients develop resistance to HMAs, combination therapies targeting multiple pathways are employed. For instance, combining immune checkpoint inhibitors with epigenetic agents may help overcome therapy resistance and delay disease progression. [64, 65]

5.2. Adaptive Therapy and Molecular Monitoring

Molecular monitoring allows clinicians to track clonal evolution and adapt treatment strategies accordingly. Serial genomic testing provides insights into the emergence of new mutations or clonal expansions, signaling the need for therapeutic adjustments. [16]

As clonal architecture shifts during treatment, therapeutic plans can be modified to address new resistance mechanisms or emerging high-risk mutations. This adaptive approach ensures that therapies remain effective over time, even as the disease evolves.

Patients whose molecular profiles change during treatment are often enrolled in clinical trials that explore innovative therapies for resistant MDS. Molecular profiling ensures that patients receive the most relevant experimental therapies, improving the likelihood of favorable outcomes. [12, 66]

5.3. Challenges in Molecularly Guided Therapy

Despite its promise, molecularly guided therapy faces several challenges. Not all clinical centers have access to next-generation sequencing (NGS), which is essential for molecular profiling. This limits the widespread adoption of personalized therapies. [36]

As MDS progresses, new subclones may emerge that are resistant to targeted therapies. Continuous monitoring of clonal evolution is necessary to address resistance, but frequent genomic testing can be cost-prohibitive. [3]

Patients with multiple co-occurring mutations pose therapeutic challenges. The presence of both favorable and unfavorable mutations complicates treatment decisions, necessitating further research to develop effective combination strategies. [12]

5.4. Future Directions in Therapeutic Development

The integration of molecular data into MDS treatment is still evolving, with several promising avenues under investigation:

Gene-editing technologies, such as CRISPR, offer the potential to correct mutations at the genomic level, providing a long-term solution for high-risk mutations like TP53. [16, 67]

Immune-based therapies, including immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapy, are being explored for MDS patients, particularly those with immune dysregulation linked to their mutational profile. [7]

Predictive models powered by artificial intelligence (AI) can integrate molecular data with clinical parameters to recommend optimal therapies, enhancing decision-making in complex cases. [12]

6. Challenges and Limitations in Molecular Taxonomy

Despite its promise, molecular taxonomy faces several challenges. The wide spectrum of mutations complicates the identification of universal biomarkers. Additionally, continuous clonal evolution creates difficulties in monitoring disease and predicting therapeutic responses. Also, the cost and technical demands of NGS limit its routine application. Finally, the link between specific mutations and clinical manifestations is not always clear, necessitating further studies.

7. Future Perspectives

The integration of molecular data with clinical practice holds promise for transforming MDS management. Predictive algorithms that combine molecular and clinical data may offer more accurate prognostic tools. In addition. synergistic approaches targeting multiple mutated pathways are under investigation to improve treatment outcomes. Future iterations of WHO and ICC guidelines are expected to incorporate molecular taxonomy, further embedding genetic data into everyday clinical practice.

8. Conclusion

The molecular taxonomy of MDS has transformed our understanding and management of this heterogeneous disease by identifying key mutations such as *SF3B1*, *TET2*, *TP53*, and *ASXL1*. These insights allow for more accurate diagnosis, prognosis, and personalized treatment, with targeted therapies like Luspatercept for *SF3B1*-mutated MDS and hypomethylating agents for *TET2* mutations. Molecularly informed models, such as IPSS-M, now offer improved patient stratification, guiding clinical decisions and ensuring appropriate therapeutic interventions. Additionally, molecular profiling plays a crucial role in selecting patients for clinical trials, promoting precision medicine.

However, challenges persist, including interpatient variability, clonal evolution, and limited access to next-generation sequencing in routine practice. Further research is needed to better understand genotype-phenotype relationships and address therapy resistance through adaptive treatment approaches. Despite these hurdles, molecular taxonomy marks a significant advancement in MDS care, paving the way for more personalized therapies and better outcomes, ultimately improving the quality of life for patients.

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