

Molecular Hematology: From Gene Profiles to Therapy Profiles at EHA 2026

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The management of hematological malignancies has evolved significantly, moving from broad cytotoxic chemotherapy to increasingly precise, molecularly targeted interventions. This shift necessitates a continuous re-evaluation of diagnostic and therapeutic paradigms to optimize patient outcomes. The upcoming EHA 2026 meeting will provide a comprehensive review of the last 25 years of molecular hematology, highlighting the transition from gene profiling to therapy profiling, and its implications for clinical practice.

KEY TAKEAWAYS

- **The Pivot:** Molecular hematology has transitioned from descriptive gene profiling to predictive therapy profiling, directly informing treatment selection.
- **The Data:** Integration of genomic and transcriptomic data has enabled identification of specific driver mutations, leading to targeted therapies with improved response rates in various hematological cancers.
- **The Action:** Clinicians should increasingly incorporate comprehensive molecular diagnostics into routine practice to guide personalized treatment strategies for hematological malignancies.

The field of hematology has undergone a profound transformation driven by advances in molecular biology. Initially, the focus was on identifying genetic aberrations associated with various blood disorders. Early efforts involved cytogenetic analysis and, subsequently, the sequencing of specific genes known to be recurrently mutated in conditions like acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). This foundational work established a link between specific genetic profiles and disease pathogenesis, laying the groundwork for more targeted approaches. For instance, the Philadelphia chromosome (BCR-ABL fusion gene) in chronic myeloid leukemia (CML) was one of the earliest and most impactful discoveries, directly leading to the development of tyrosine kinase inhibitors (TKIs).¹

Over the past 25 years, technological advancements, particularly in next-generation sequencing (NGS), have enabled a more comprehensive understanding of the genomic landscape of hematological malignancies. This has moved beyond single-gene analysis to broad gene panels, exome sequencing, and even whole-genome sequencing. The increased resolution has revealed the heterogeneity within disease classifications and identified novel driver mutations and co-mutations that influence disease progression and treatment response. For example, in AML, mutations in genes such as FLT3, NPM1, and IDH1/2 are now routinely assessed to guide therapeutic decisions.² Similarly, in lymphoid malignancies, the identification of specific translocations and mutations, such as MYC rearrangements or mutations in BTK, has informed the use of targeted agents.³

From Gene Profiles to Therapy Profiles

The evolution from simply identifying gene profiles to developing therapy profiles represents a critical advancement. This shift involves not only detecting genetic alterations but also understanding their functional consequences and, crucially, their predictive value for response to specific therapies. The goal is to match a patient's unique molecular signature with the most effective available treatment. This precision medicine approach has led to the development and approval of numerous targeted agents across various hematological cancers.⁴

In AML, for example, the presence of an FLT3 internal tandem duplication (ITD) mutation predicts a poorer prognosis with conventional chemotherapy but indicates sensitivity to FLT3 inhibitors like midostaurin or gilteritinib. A 2017 Phase III trial demonstrated that adding midostaurin to standard chemotherapy significantly improved overall survival (HR 0.78, 95% CI 0.63-0.96, P=0.009) in newly diagnosed FLT3-mutated AML patients.⁵ Similarly, IDH1 and IDH2 mutations, found in approximately 6-10% and 8-19% of AML patients respectively, are targets for specific inhibitors such as ivosidenib and enasidenib. A Phase III study showed that enasidenib monotherapy resulted in a complete remission or complete remission with partial hematologic recovery rate of 23% in relapsed/refractory IDH2-mutated AML.⁶ For lymphoid malignancies, the development of Bruton's tyrosine kinase (BTK) inhibitors, such as ibrutinib, acalabrutinib, and zanubrutinib, exemplifies therapy profiling. These agents are highly effective in B-cell lymphomas and chronic lymphocytic leukemia (CLL) with specific molecular characteristics. A randomized Phase III trial comparing ibrutinib with chlorambucil in previously untreated CLL patients showed a significantly longer progression-free survival (HR 0.16, 95% CI 0.10-0.25, P0.001) with ibrutinib.⁷ The identification of specific resistance mechanisms, such as mutations in BTK (C481S) or PLCG2, further refines treatment strategies, guiding the selection of next-generation BTK inhibitors or alternative agents.⁸

Myeloma also benefits from this approach, with agents targeting specific pathways. For instance, the identification of B-cell maturation antigen (BCMA) as a target has led to the development of BCMA-directed CAR T-cell therapies and bispecific antibodies, demonstrating high response rates in relapsed/refractory multiple myeloma.⁹

The integration of molecular diagnostics into routine clinical practice is now standard for many hematological malignancies. This includes not only initial diagnosis and risk stratification but also monitoring minimal residual disease (MRD) and detecting emergent resistance mutations. The continuous refinement of these molecular assays, coupled with the expanding arsenal of targeted therapies, underscores the dynamic nature of molecular hematology. Future directions include the incorporation of single-cell sequencing, spatial transcriptomics, and artificial intelligence to further enhance the precision of therapy profiling, moving towards even more individualized treatment paradigms.¹⁰

CLINICAL IMPLICATIONS

The shift from broad genomic characterization to actionable therapy profiling fundamentally alters the diagnostic and treatment algorithms for hematological malignancies. Clinicians are no longer simply identifying a disease; they are identifying a disease with specific vulnerabilities that can be exploited by targeted agents. This necessitates a deeper understanding of molecular pathology and a willingness to integrate complex genomic data into daily decision-making. The days of a 'one-size-fits-all' approach are receding, replaced by a nuanced strategy where molecular testing dictates the therapeutic path, often with superior outcomes compared to conventional chemotherapy.

For patients, this evolution offers the promise of more effective treatments with potentially fewer systemic side

effects. The availability of therapies like FLT3 inhibitors for AML or BTK inhibitors for CLL means that many individuals can achieve durable remissions or prolonged disease control, improving quality of life. However, this also places a greater burden on healthcare systems to provide timely and comprehensive molecular diagnostics. The cost of advanced sequencing technologies and novel targeted agents remains a significant consideration, requiring careful resource allocation and equitable access to these sophisticated tools. The pharmaceutical industry continues to invest heavily in developing agents that target specific molecular aberrations. This focus on precision oncology drives innovation but also creates a competitive landscape where demonstrating superior efficacy in molecularly defined subgroups is paramount. Regulatory bodies are adapting to this rapid pace, often granting accelerated approvals for therapies targeting rare mutations or highly aggressive diseases. The challenge for the industry, and indeed for clinicians, will be to navigate the increasing complexity of treatment options, understand the nuances of resistance mechanisms, and ensure that the right therapy reaches the right patient at the right time. The EHA 2026 review will undoubtedly reinforce that molecular hematology is not just a research endeavor, but the cornerstone of modern hematological practice.

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