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# Advancements in bone marrow biopsy: the role of omics and artificial intelligence in hematologic diagnostics

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Bone marrow biopsy remains central to the diagnosis, classification, and monitoring of hematologic disorders, providing essential morphologic and immunophenotypic information. However, conventional assessment is limited by interobserver variability and an inability to fully capture the molecular and spatial complexity of marrow pathology. Recent advances in multi-omics technologies, including genomic, epigenomic, transcriptomic, proteomic, lipidomic, metabolomic, and microbiomic, together with artificial intelligence (AI), are reshaping bone marrow evaluation. These approaches generate high-dimensional datasets that reveal disease-specific molecular signatures, refine diagnostic classification, improve risk stratification, and inform therapeutic decision-making. In parallel, AI-driven image analysis enhances objectivity, reproducibility, and integration of morphologic and molecular data across both biopsy histology and aspirate cytology. Despite their transformative potential, clinical translation remains challenged by issues of standardization, cost, data integration, and regulatory validation. This mini-review summarizes emerging applications of omics technologies and AI in bone marrow biopsy diagnostics, highlights current limitations, and discusses future directions toward integrated, data-driven precision hematology.

KEYWORDS
**artificial intelligence, bone marrow biopsy, digital pathology, hematologic malignancies, omics technologies, precision hematology**

## Introduction

Bone marrow biopsy is a cornerstone of diagnosing and managing a wide spectrum of hematologic disorders, including leukemias, lymphomas, myelodysplastic syndromes, myeloproliferative neoplasms, plasma cell dyscrasias, and marrow failure conditions (1). Conventional diagnostic modalities, including histomorphology, immunohistochemistry, flow cytometry, and cytogenetics, remain essential for classifying disease entities, assessing severity, and guiding initial treatment decisions (2). Despite their diagnostic value, these methods offer only a partial snapshot of the complex biological processes within the marrow. Overlapping morphological features, interobserver variability, and limited ability to capture molecular heterogeneity can lead to diagnostic uncertainty, difficulty predicting progression, and challenges in tailoring therapy (3).

Traditional histopathology in bone marrow biopsy diagnosis is limited by several inherent challenges. Interpretation of histologic features is largely subjective, leading to well-recognized inter- and intra-observer variability among pathologists (4–6). The diagnostic process is time-consuming and labor-intensive, particularly in complex cases or when multiple biopsies are

required, which can delay definitive diagnosis and clinical decision-making (7). Certain bone marrow and bone-related diseases exhibit indirect, heterogeneous, or ambiguous morphologic features, especially in rare or dedifferentiated tumors, making accurate diagnosis difficult without highly specialized expertise (8). These challenges are compounded by a global shortage of expert bone pathologists, resulting in increased workload, risk of diagnostic inconsistency, and limited access to specialist interpretation in resource-constrained settings (9, 10).

Advances in omics technologies have begun to overcome these limitations by enabling high-resolution interrogation of the marrow at genetic, transcriptomic, proteomic, metabolomic, and spatial levels (11–14). Genomic sequencing reveals clonal mutations and evolutionary trajectories; transcriptomic profiling uncovers dysregulated pathways; proteomics and metabolomics characterize functional alterations; and single-cell and spatial omics reconstruct the cellular ecosystems and microenvironmental interactions that drive hematologic disease. These approaches provide multilayered insights that complement, refine, and sometimes redefine traditional diagnostic categories (15).

In parallel, artificial intelligence (AI) has emerged as a powerful tool in hematopathology (16–19). Deep learning models can identify subtle morphological abnormalities, quantify features objectively, and improve reproducibility, while machine-learning algorithms integrate imaging, molecular data, and clinical variables to support risk stratification and prognostication (20–23). Multimodal AI systems are now bridging the gap between morphology and molecular biology, creating unified diagnostic frameworks capable of capturing disease complexity in ways previously unattainable.

Together, omics technologies and AI are transforming bone marrow biopsy from a largely morphology-based test into a comprehensive platform for precision hematology (24). By revealing molecular drivers, mapping cellular heterogeneity, and predicting clinical behavior, these innovations promise to enhance diagnostic accuracy, personalize treatment strategies, and deepen our understanding of marrow pathophysiology (25). As integration into clinical practice accelerates, bone marrow examination is poised to become not only a diagnostic tool but also a window into dynamic disease biology, supporting more informed and individualized patient care. An overview of how artificial intelligence and multi-omics technologies integrate with bone marrow biopsy histology and cytology to enhance diagnostic accuracy, prognostication, and workflow efficiency is illustrated in Figure 1.

## Omics technologies in bone marrow diagnosis

Multi-omics approaches have transformed bone marrow diagnostics by enabling comprehensive, multidimensional analysis of the molecular and cellular landscape underlying hematologic disorders, extending far beyond the limits of conventional morphology-based assessment (26). By interrogating genomic, epigenomic, transcriptomic, proteomic, lipidomic, metabolomic, and microbiome-derived features, omics technologies provide deeper insight into disease mechanisms, clonal evolution, and microenvironmental remodeling. Integration of these molecular layers allows refinement of diagnostic classification, detection of minimal residual disease, and identification of therapeutic vulnerabilities, supporting more precise risk stratification and personalized treatment strategies across a wide spectrum of bone marrow diseases (27).

Genomic technologies encompass a wide range of tools used to analyze the structure and function of DNA, providing deep insight

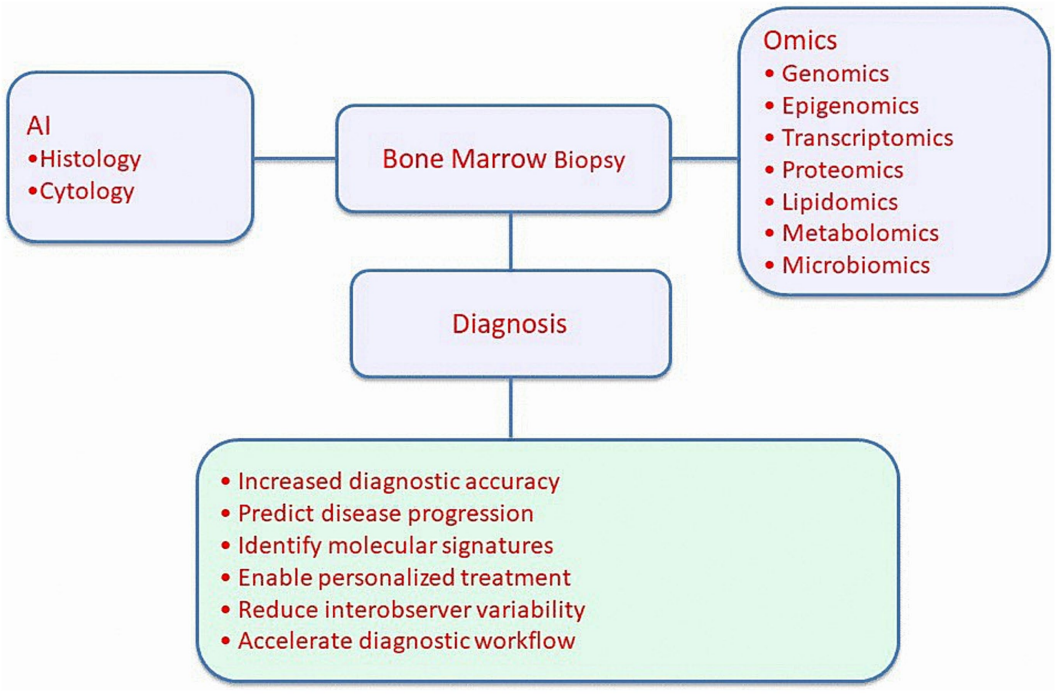


FIGURE 1
Integration of omics technologies and artificial intelligence in bone marrow biopsy diagnostics.

into the genetic architecture of hematologic diseases (28). Genomics has transformed bone marrow diagnostics by enabling detection of recurrent mutations associated with clonal hematopoiesis, leukemogenesis, and therapeutic response. Approaches such as targeted sequencing, whole-exome sequencing, and genome-wide association studies (GWAS) help refine disease classification and identify high-risk variants, as demonstrated by large cohort studies linking specific single nucleotide polymorphisms (SNPs) with altered disease susceptibility (29, 30).

Transcriptomics provides a global view of RNA expression profiles within bone marrow cells (31). Modern RNA-sequencing captures gene expression changes, splice variants, and fusion transcripts with high sensitivity (32). Transcriptomic studies have helped identify pathways associated with disease progression, clonal evolution, and inflammatory signaling by profiling expression patterns across diverse hematopoietic and stromal populations (33, 34).

Epigenomics, which investigates reversible modifications to DNA and histones across the genome (35), offers an additional layer of biological insight. Epigenetic mechanisms such as DNA methylation and histone acetylation regulate gene expression programs critical for hematopoietic differentiation and malignant transformation (36). Altered methylation patterns have been associated with dysregulated lineage commitment and aberrant marrow microenvironmental signaling in hematologic disorders (37, 38).

Lipidomics provides complementary insight into bone biology by identifying lipid species that regulate membrane structure, intracellular signaling, and stromal–hematopoietic interactions (39–41). When integrated with broader multi-omics approaches, lipidomic profiling has revealed distinct molecular signatures across diverse bone-related diseases, highlighting disruptions in the skeletal and marrow microenvironment that affect mesenchymal progenitors, osteoblasts, osteoclasts, chondrocytes, immune cells, and specialized stromal subsets (42–46). These disease-specific lipid and molecular patterns illuminate how altered cellular communication, microenvironmental remodeling, and inflammatory signaling drive pathological bone states and influence disease progression.

Proteomics expands this understanding by mapping protein abundance, interactions, and post-translational modifications within the marrow niche (47–49). Proteomic analyses have revealed alterations in extracellular matrix composition, cytokine networks, and signaling pathways that shape malignant hematopoiesis and niche remodeling (50, 51). Key regulatory proteins involved in angiogenesis, cellular proliferation, and immune modulation contribute to disease progression and therapeutic response (52).

Microbiomics research has shown that systemic immune function and inflammation, both influenced by gut microbiota, can indirectly impact marrow homeostasis and hematologic disease progression (53, 54). Dysbiosis-related immune dysregulation may contribute to marrow failure, cytokine imbalance, and treatment response variability (55).

Metabolomics further characterizes bone marrow biology by quantifying metabolites that reflect upstream genomic and proteomic dysregulation (56, 57). Metabolite profiling has identified markers of inflammation, oxidative stress, and aberrant metabolic states that contribute to hematologic disease pathophysiology and may serve as therapeutic targets (58).

A summary of the integrated multi-omics domains and their key contributions to bone marrow diagnostics, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, and lipidomics, is presented in Table 1. The table highlights the representative studies within each domain and outlines their principal insights and relevance to advancing molecular understanding and diagnostic precision in bone marrow and skeletal disorders.

## AI in bone marrow biopsy diagnosis

AI has become a powerful adjunct in hematopathology, transforming both bone marrow biopsy (histology) and bone marrow aspirate (cytology) evaluation. By providing objective, quantitative, and reproducible analysis, AI reduces the subjectivity and variability inherent in traditional microscopy (59). Across a wide spectrum of diagnostic tasks, including fibrosis grading, megakaryocyte assessment, mutation-associated morphology, plasma cell quantification, lineage recognition, and dysplasia detection, AI systems enhance diagnostic precision, streamline workflows, and deepen insight into the biological underpinnings of hematologic diseases. Together, AI-driven approaches in bone marrow histology and cytology support more accurate disease classification, prognostication, and monitoring, while facilitating scalable and standardized diagnostic practice in both routine and resource-limited settings (60).

## AI in bone marrow histology

AI enables precise and quantitative evaluation of bone marrow fibrosis, improving the detection and monitoring of reticulin changes and supporting accurate myeloproliferative neoplasm (MPN) subtyping. Machine learning–based fibrosis indices also help identify patients at risk of disease progression, refining prognostication in MPNs (61).

AI-driven analysis of megakaryocyte morphology provides automated, reproducible feature extraction that supports reliable MPN diagnosis and differentiation between key subtypes. These abstracted morphologic representations aid clinical interpretation and facilitate monitoring of disease evolution and treatment response (62). Convolutional neural network models can detect subtle morphologic signatures linked to genetic mutations, cytogenetic abnormalities, and prognostic categories. By integrating high-dimensional histologic features with molecular correlates, such as those associated with TET2 mutations or del(5q) MDS, AI enhances diagnostic precision and supports morphology–genotype interpretation in myelodysplastic syndromes (MDS) and MPN evaluation (63).

Deep learning approaches also improve quantification of plasma cells, offering precise and consistent measurements that closely align with expert assessment. These models reduce variability inherent in manual estimation and can be deployed on whole-slide images through workflow-friendly digital platforms, strengthening the diagnosis of plasma cell neoplasms (64). Beyond specific disease classifications, AI models streamline cell detection and classification tasks. A synchronized deep autoencoder enables simultaneous identification and categorization of cells, improving accuracy, reducing computational burden, and enhancing efficiency in bone marrow slide analysis (65).

AI-based image segmentation further standardizes bone marrow cellularity assessment, providing objective estimates that align with expert pathologists and allowing exploration of biologically relevant

TABLE 1 Integrated multi-omics approaches in bone marrow diagnostics.

| Omics domain/ technology | Key contributions/insights | Relevance to bone marrow diagnostics | Ref |
|---|---|---|---|
| Genomics | Genome-wide and targeted sequencing approaches; identification of SNPs, disease-associated variants, and regulatory elements influencing cell fate | Enables detection of clonal hematopoiesis, leukemogenic mutations, and inherited susceptibility variants; refines disease classification and risk stratification | (28–30) |
| Transcriptomics | Bulk and single-cell RNA-seq, transcriptome quantification, fusion detection, splice variant identification | Defines transcriptional programs of hematopoietic and stromal subsets; maps inflammatory and differentiation pathways underlying progression, clonal evolution, and niche remodeling | (31–34) |
| Epigenomics | Analysis of DNA methylation, histone modifications, chromatin remodeling pathways (Polycomb, COMPASS); epigenetic control of lineage specification | Reveals disrupted differentiation programs and microenvironmental signaling in marrow disorders; identifies mechanisms driving malignant transformation and stem cell dysfunction | (35–38) |
| Lipidomics | Mass spectrometry–based lipid profiling; integration of lipidomics with multi-omics and spatial analyses | Characterizes lipid species influencing membrane biology, signaling, and stromal–hematopoietic communication; reveals lipid-driven remodeling of bone and marrow microenvironments in disease | (39–46) |
| Proteomics | Protein abundance and interaction profiling, extracellular matrix characterization, cytokine and signaling pathway analysis | Identifies dysregulated ECM components, angiogenic factors, immune mediators, and signaling proteins contributing to marrow remodeling, malignant hematopoiesis, and therapeutic response | (47–52) |
| Microbiomics | Microbiome–immune interaction analysis; study of microbial metabolites influencing systemic inflammation | Highlights gut–marrow axis mechanisms; shows how dysbiosis alters systemic immunity, cytokine signaling, marrow homeostasis, and treatment response variability | (53–55) |
| Metabolomics | Mass spectrometry–based metabolite profiling; metabolic pathway mapping | Detects metabolic signatures associated with oxidative stress, inflammation, hypoxia, and altered energy states—key processes in marrow dysfunction and hematologic disease biology | (56–58) |

patterns such as age-related cellularity changes (66). Tools such as MarrowQuant automate the identification of hematopoietic cells, adipocytes, bone, and vascular structures, reducing user-dependent variability and enabling reproducible mapping of marrow composition across experimental and clinical contexts (67). Similarly, semantic segmentation models trained on expert-annotated slides accurately differentiate hematopoietic from adipose tissue on whole-slide images, offering a standardized and objective method for evaluating cellularity in Philadelphia chromosome-negative MPNs (68).

## AI in bone marrow cytology

AI enables automated, end-to-end analysis of bone marrow cytology by detecting optimal regions on aspirate slides, identifying individual cells, and classifying marrow cell types with high accuracy. The resulting quantitative differential (e.g., a 'Histogram of Cell Types') provides a reproducible cytological profile that minimizes inter-observer variability and supports more consistent hematological diagnosis (69). AI-driven digital pathology also facilitates deep learning–based assessment of digitized marrow slides, enabling reliable detection of malignant and reactive abnormalities and promoting more standardized, scalable evaluation workflows (19).

In routine practice, an implementable bone marrow aspirate (BMA) smear workflow begins with slide digitization (scanner settings and color calibration), followed by automated quality control to exclude thick areas, crush artifact, staining outliers, and poor focus regions The model then performs region selection, cell detection/segmentation, and cell-type classification to generate an automated differential alongside interpretable overlays and uncertainty flags for manual review (70, 71). Outputs can be triaged into concordant cases where AI-assisted differentials support faster sign-out, borderline/discordant cases routed for second review, and suspicious patterns (e.g., excess blasts, atypical promyelocytes, dysplastic forms) that trigger confirmatory testing (flow cytometry, cytogenetics/molecular assays) and structured reporting (72). Figure 2 summarizes these steps and highlights where human verification and ancillary testing remain essential.

Beyond tissue sections, AI-enabled cytomorphology on BMA smears provides a practical example of how computational modalities can be embedded into routine hematology workflows. Using large expert-annotated image datasets, deep neural networks have achieved highly accurate differentiation of bone marrow cell morphologies, supporting automated single-cell classification as a proof-of-concept for routine deployment (73). More recently, externally validated ensemble models have demonstrated expert-level or superior performance across independent centers and scanning systems, supporting generalisable AI-based bone marrow morphometry for hematological diagnosis and quantitative reporting (74).

Deep learning models have also been applied to automate detailed analysis of bone marrow smears in acute myeloid leukemia (AML), including cell segmentation, distinguishing AML from healthy samples, and predicting mutation status (e.g., NPM1) from morphology in research cohorts, which may enhance diagnostic

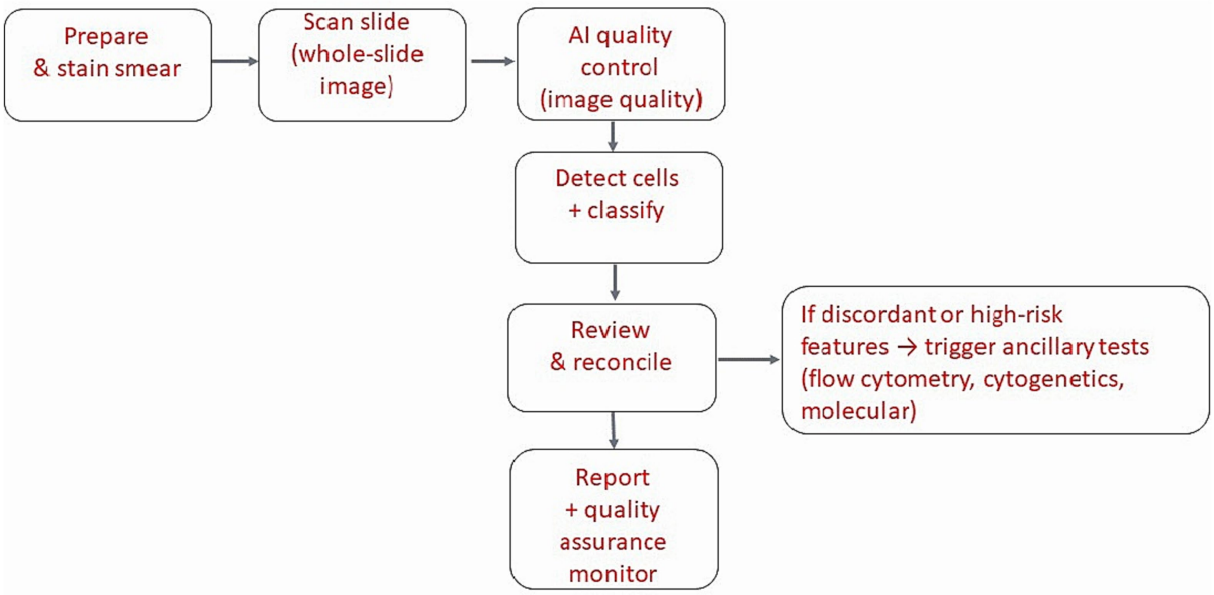


FIGURE 2
AI-assisted bone marrow aspirate smear cell-type classification integrated into routine clinical workflow.

precision (75). AI supports automated identification of hematopoietic lineages and detection of dysplastic cells in MDS, classifying normal and dysplastic forms with high accuracy and reducing the subjectivity of traditional smear evaluation (76). Models such as DysplasiaNet detect hypogranulated dysplastic neutrophils, a challenging but clinically relevant MDS feature, providing more objective granularity assessment and improving consistency in routine laboratory workflows (77). In acute promyelocytic leukemia (APL), AI enables rapid recognition of morphologic patterns associated with the t(15;17) translocation, reliably distinguishing APL from other AML subtypes and from normal marrow, which may be particularly valuable where molecular confirmation is delayed or unavailable (78).

## Limitations of AI in bone marrow biopsy

AI offers substantial advantages in bone marrow biopsy evaluation, yet several limitations constrain its routine clinical adoption. AI models rely heavily on large, well-annotated training datasets, which are difficult to obtain in hematopathology due to disease rarity, inter-institutional variability, and the time-intensive nature of expert annotation (79). Differences in staining quality, slide preparation, and scanning resolution can impair model generalizability, leading to reduced performance across laboratories (80). Many algorithms function as "black boxes," providing limited interpretability and posing challenges for clinical validation and regulatory approval (81, 82). Additionally, AI systems may overlook rare morphologic patterns or artifacts not well represented in training data (3, 19). Integration into clinical workflows requires robust computational infrastructure, quality control, and ongoing monitoring to prevent drift and ensure reproducibility (83, 84). These limitations highlight the need for standardized datasets, transparent algorithms, and multidisciplinary oversight to ensure safe and reliable deployment of AI in bone marrow biopsy diagnostics.

## Limitations of omics in bone marrow biopsy

Omics technologies have transformed bone marrow diagnostics, yet several limitations hinder their widespread clinical implementation. High-throughput genomic, epigenomic, transcriptomic, proteomic, and metabolomic assays are often costly, technically complex, and require specialized laboratory infrastructure that may not be accessible in all healthcare settings (85, 86). Variability in sample quality, particularly in small or hypocellular marrow biopsies, can affect data integrity and lead to incomplete or biased molecular profiles (87). Many omics datasets are high dimensional, requiring sophisticated bioinformatics expertise and computational resources to interpret, and results may vary depending on analytical pipelines and reference databases (88–90). Moreover, the integration of multi-omics data remains challenging due to differences in temporal resolution, dynamic biological processes, and limited consensus on standardized interpretation frameworks (13, 91). Finally, the clinical significance of certain molecular alterations may be unclear, leading to potential overinterpretation or uncertainty in diagnostic and prognostic decision-making (14, 92). These limitations underscore the need for harmonized protocols, improved analytic tools, and evidence-based validation to ensure reliable and clinically meaningful use of omics in bone marrow biopsy evaluation.

## Future directions

The future of bone marrow biopsy diagnostics lies in the integrated application of omics technologies and AI, enabling a shift

from descriptive morphology toward data-driven, precision hematopathology (24, 93, 94). Multi-omics profiling will increasingly be applied directly to bone marrow specimens to capture the complex molecular architecture of hematologic diseases and their microenvironment (95). These approaches will support refined disease classification, early detection of clonal evolution, minimal residual disease monitoring, and improved prediction of therapeutic response (96).

AI will play a central role in integrating and interpreting high-dimensional omics data alongside digital histopathology (97, 98). Deep learning models will increasingly link morphologic patterns in whole-slide images with underlying molecular signatures, enabling virtual molecular profiling from routine H&E or immunohistochemistry (99–101). Spatially resolved omics combined with AI-driven image analysis will allow precise mapping of genetic and proteomic alterations within specific marrow niches, improving understanding of tumor–stroma interactions, immune dysregulation, and treatment resistance (102, 103). Importantly, recent single-cell–resolved spatial mapping of human bone marrow using archival specimens has demonstrated that clinically relevant hematopoietic organization and niche biology can be recovered from pathology archives, including aging-associated remodeling of marrow topography and microvascular–cellular relationships (104).

Future workflows are expected to adopt end-to-end computational pathology pipelines, in which AI automates slide quality control, region selection, cell segmentation, and feature extraction, while multi-omics data provide complementary biological context (105–108). Federated learning and multi-center model training will enhance generalizability, address data-sharing constraints, and support regulatory approval (109). Additionally, explainable AI approaches will improve transparency, enabling pathologists to understand how morphologic and molecular features drive algorithmic predictions (110, 111).

Clinically, these advances will support personalized risk stratification and treatment planning, particularly in complex entities such as myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell dyscrasias (112). As costs decline and standardization improves, AI-integrated multi-omics bone marrow analysis is expected to transition from a research tool to a routine component of diagnostic and prognostic assessment, positioning the bone marrow biopsy as a central hub for precision hematology (113). These spatial multi-omic atlases of human bone marrow strengthen the case for cross-platform strategies in which spatial proteomics (e.g., CODEX) is co-registered with transcriptomic readouts to deliver clinically interpretable, niche-level biomarkers and standardized, reproducible neighborhood metrics (114).

## Conclusion

Bone marrow biopsy is undergoing a fundamental transformation driven by the convergence of omics technologies and AI. Together, these approaches extend diagnostic evaluation beyond morphology, enabling multidimensional characterization of genetic alterations, cellular heterogeneity, microenvironmental interactions, and disease dynamics. While important challenges remain, including technical complexity, interpretative standardization, and clinical validation, the integration of molecular profiling with AI-driven analytics represents a pivotal shift toward precision hematology. As these technologies mature and become increasingly standardized and accessible, they are poised to enhance diagnostic accuracy, refine prognostication, and support individualized therapeutic strategies, redefining the role of bone marrow biopsy as a central platform for integrated hematologic diagnosis and disease monitoring.

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## Generative AI statement

The author(s) declared that Generative AI was used in the creation of this manuscript. Generative AI (ChatGPT-5.2) was used solely for language refinement. All scientific content, interpretations, and conclusions were generated by the authors.

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