ISSN: 3152-8686

Vol3; Issue4, Sep. 2026

JOURNAL OF
TAZEEZ FOR PUBLIC HEALTH

AN OFFICIAL JOURNAL OF SAUDI HEALTH PROMOTION AND EDUCATION ASSOCIATION

Systematic review

Incremental diagnostic yield and risk reclassification with optical genome mapping compared with conventional cytogenetics in myeloid neoplasms: a systematic review

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Abstract

Background: Optical genome mapping provides genome-wide detection of structural abnormalities in myeloid neoplasms. Its incremental clinical value depends on whether additional findings change diagnosis or established prognostic categories. This review evaluated diagnostic yield and risk reclassification relative to conventional cytogenetics. **Methods:** Eleven original comparative publications were examined through structured retrieval of indexed records and publisher sources. Disease-specific populations, comparator workflows, additional abnormalities, and classification outcomes were extracted. Heterogeneity in populations, outome definitions, and prognostic models supported narrative synthesis without quantitative pooling. **Results:** Additional findings were frequent, in consecutive myelodysplastic neoplasms, clinically significant cryptic findings affected 34% of 101 patients, whereas

Published: 14 Sep, 2026

https://doi.org/10.65759/gjd79t48

14/09/2026

reported prognostic reassignment included both category changes and newly assessable cases. A multicenter acute myeloid leukemia study identified additional clinically relevant findings in 13% of 100 patients. Another mixed cohort reported cytogenetic risk changes in 16%, with integrated prognostic changes in only three of 150 patients. In 252 high-grade myeloid neoplasms, six cryptic MECOM rearrangements were identified, with diagnostic or risk reclassification in five. **Conclusions:** Optical genome mapping adds clinically relevant structural information beyond conventional cytogenetics. The strongest evidence concerns cryptic rearrangements, complex abnormalities, and unsuccessful chromosome analysis. Incremental detection exceeds demonstrated risk reclassification, and evidence linking testing to improved patient outcomes remains limited. Standardized endpoints and prospective comparative studies are needed for clinical adoption.

Keywords: Optical genome mapping; myeloid neoplasms; cytogenetics; diagnostic yield; risk reclassification; structural variants; systematic review.

Introduction

Genetic abnormalities define important entities within myeloid neoplasms and contribute to diagnostic precision, prognostic assessment, and selection of disease-specific management strategies. The fifth World Health Organization classification places substantial emphasis on defining genetic alterations while retaining integration with morphology, clinical presentation, and other laboratory findings. Incomplete characterization of structural abnormalities affects more than descriptive cytogenetic reporting; it also influences the assignment of biologically meaningful disease categories (1).

The International Consensus Classification similarly integrates genomic findings into the classification of acute myeloid leukemia and related myeloid disorders, reinforcing the importance of reliable structural characterization. Differences between classification systems also mean that identical findings require interpretation against explicitly identified diagnostic criteria. A comparative assessment of laboratory technologies therefore requires separate consideration of abnormality detection and the resulting changes in formal disease classification (2). Prognostic assessment introduces an additional layer of interpretation because detecting an abnormality does not automatically change the risk category assigned to an individual patient. European LeukemiaNet recommendations integrate cytogenetic and molecular features into acute myeloid leukemia risk assessment, linking particular recurrent rearrangements with clinically relevant prognostic groups. An additional structural finding consequently has different implications depending on the abnormalities already identified and the classification framework applied (3).

In myelodysplastic neoplasms, the Revised International Prognostic Scoring System combines cytogenetic categories with marrow blasts and peripheral blood measurements to generate clinically established risk estimates. Improved structural characterization therefore has the potential to alter the cytogenetic component without necessarily changing the overall score (4). The Molecular International Prognostic Scoring System incorporates mutation information, further emphasizing the distinction between cytogenetic refinement and an actual change in integrated prognostic assignment (5).

Conventional cytogenetic workflows combine chromosome analysis with targeted fluorescence in situ hybridization and, in selected settings, chromosomal microarrays, each with distinct analytical strengths and limitations. Chromosome analysis depends on suitable dividing cells, whereas targeted assays interrogate predefined regions and

microarrays principally characterize genomic dosage (6). Optical genome mapping analyzes labeled long DNA molecules to identify balanced and unbalanced structural variation across the genome, providing a complementary approach to these established methods (7).

Despite increasing clinical interest, the meaningful endpoint is not simply the number of additional variants detected, because structural complexity and clinical actionability represent different outcomes. Genome-wide structural analysis also complements rather than duplicates sequence-level mutation testing, requiring an integrated interpretation of findings (7). This review therefore examines incremental diagnostic yield, recovery of unsuccessful cytogenetic assessments, and documented risk reclassification with optical genome mapping compared with conventional cytogenetic workflows.

Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review evaluated the incremental diagnostic yield and risk reclassification associated with optical genome mapping compared with conventional cytogenetic methods in myeloid neoplasms. Eligibility criteria, outcomes, and the approach to evidence synthesis were established before study selection.

PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library were searched from inception to September 2026. Search strategies combined controlled vocabulary and free-text terms relating to “optical genome mapping,” “myeloid neoplasms,” “acute myeloid leukemia,” “myelodysplastic syndromes,” “myelofibrosis,” “cytogenetics,” “diagnostic yield,” and “risk reclassification.” Boolean operators and database-specific syntax were applied, and reference lists of eligible publications were examined for additional studies.

Original human studies were eligible when they evaluated optical genome mapping in patients with myeloid neoplasms and included comparison with conventional cytogenetic testing. Eligible comparators included chromosome analysis, fluorescence in situ hybridization, and conventional workflows incorporating chromosomal microarrays or molecular testing. Studies were required to report additional abnormalities, diagnostic changes, prognostic reclassification, or resolution of unsuccessful cytogenetic assessments.

Reviews, editorials, commentaries, conference abstracts without sufficient extractable information, and studies without relevant comparative outcomes were excluded. Duplicate records were removed before screening. Two authors independently screened titles and abstracts, assessed potentially eligible full texts, and documented reasons for exclusion; disagreements were resolved through discussion and consensus.

Two authors independently extracted study characteristics and outcome data using a standardized extraction form. Extracted variables included publication year, study design, setting, disease population, sample size, comparator methods, additional abnormalities, diagnostic consequences, and prognostic frameworks. Extracted information was cross-checked against the source publications, and discrepancies were resolved by reviewing the relevant text and tables.

Incremental diagnostic yield was defined as additional clinically relevant findings identified by optical genome mapping beyond the reported conventional comparator. Risk reclassification was defined as a change in an established prognostic category, with initial risk assignment following failed cytogenetics recorded separately. Patient-level outcomes were distinguished from variant

counts, analytical concordance, karyotype refinement, and composite clinical endpoints.

Two authors independently appraised methodological limitations, including patient selection, comparator completeness, subclone detection, and consistency of outcome definitions. Findings were synthesized narratively because study populations, comparator workflows, and prognostic systems differed substantially. Results were presented in structured tables, without calculating a pooled effect or combined unique-patient total where cohort overlap remained uncertain.

Results

In 27 patients with acute myeloid leukemia or myelodysplastic neoplasms, Gerding and colleagues reported 93% concordance and 61 additional variants involving a predefined myeloid gene set. Karyotypes were redefined in 67%, an endpoint representing structural refinement rather than an equivalent frequency of risk change (8). In 101 patients with myelodysplastic neoplasms, Yang and colleagues identified clinically significant cryptic abnormalities in 34 patients; reported IPSS-R reassignment comprised 15 changes to existing categories and two first assignments following unsuccessful cytogenetics (9).

Balducci and colleagues identified additional abnormalities in nine of 27 myelodysplastic and 22 of 41 acute myeloid leukemia cases. Risk assignments differed in six and two patients, respectively, although some differences reflected abnormalities missed by optical genome mapping rather than beneficial incremental detection (10). In the multicenter study by Levy and colleagues, additional clinically relevant findings occurred in 13 of 100 acute myeloid leukemia cases, with modeled management changes in four and additional trial eligibility in eight (11).

In myelofibrosis, Díaz-González and colleagues detected 19 additional cryptic abnormalities in nine of 21 patients and recovered informative results in all ten cases with failed chromosome analysis. Three patients with an available conventional karyotype were assigned higher cytogenetic risk, highlighting the distinction between reclassification and recovery of previously unavailable information. Loghavi and colleagues reported additional cytogenomic or fusion information in 77 of 159 acute myeloid leukemia cases, including patients with normal or unsuccessful conventional studies (13).

In 15 selected complex-karyotype myelodysplastic cases, Valkama and colleagues reported concordance for 73 of 85 chromosome abnormalities and additional large structural findings in 93% of patients (14). These results reflect an enriched population and do not establish a corresponding rate of prognostic reclassification (14). Wei and colleagues reported additional information in 27% of 236 myelodysplastic cases, with diagnostic and/or risk changes in 14 of 149 newly diagnosed patients (15).

Among 150 patients studied by Torres-Hernández and colleagues, novel or refined cytogenetic information occurred in 80%, cytogenetic risk changed in 16%, and integrated prognosis changed in three patients (16). This discrepancy demonstrated the effect of molecular information already incorporated into baseline assessment (16). Mestre and colleagues documented additional abnormalities and prognostic upgrades in therapy-related neoplasms and younger myelodysplastic patients, although their exploratory IPSS-M analysis extended mutation inputs to selected structural gene disruptions (17).

Finally, Salcedo-Porras and colleagues identified 12 MECOM-rearranged cases among 252 high-grade myeloid neoplasms (18). Six rearrangements were cryptic to the conventional workflow, and five of

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these six prompted diagnostic or risk reclassification (18). Across the included evidence, broad structural yield, recovery of failed cytogenetics, and clinically consequential reclassification remained distinct endpoints requiring separate interpretation (8–18).

Eleven original publications evaluated optical genome mapping across acute myeloid leukemia, myelodysplastic neoplasms, myelofibrosis, and selected high-grade or therapy-related populations (8–18). Their designs ranged from selected complex-karyotype series to larger diagnostic cohorts, with considerable differences in baseline testing and endpoint definitions (8–18). Consequently, the evidence supported study-specific comparisons rather than a single pooled estimate of incremental diagnostic yield or risk reclassification (8–18). Separate reporting of newly informative testing, clinically relevant additional findings, and formal prognostic changes remains essential for interpreting these heterogeneous cohorts across different disease groups (8–18).

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Fig 1: PRISMA flow diagram

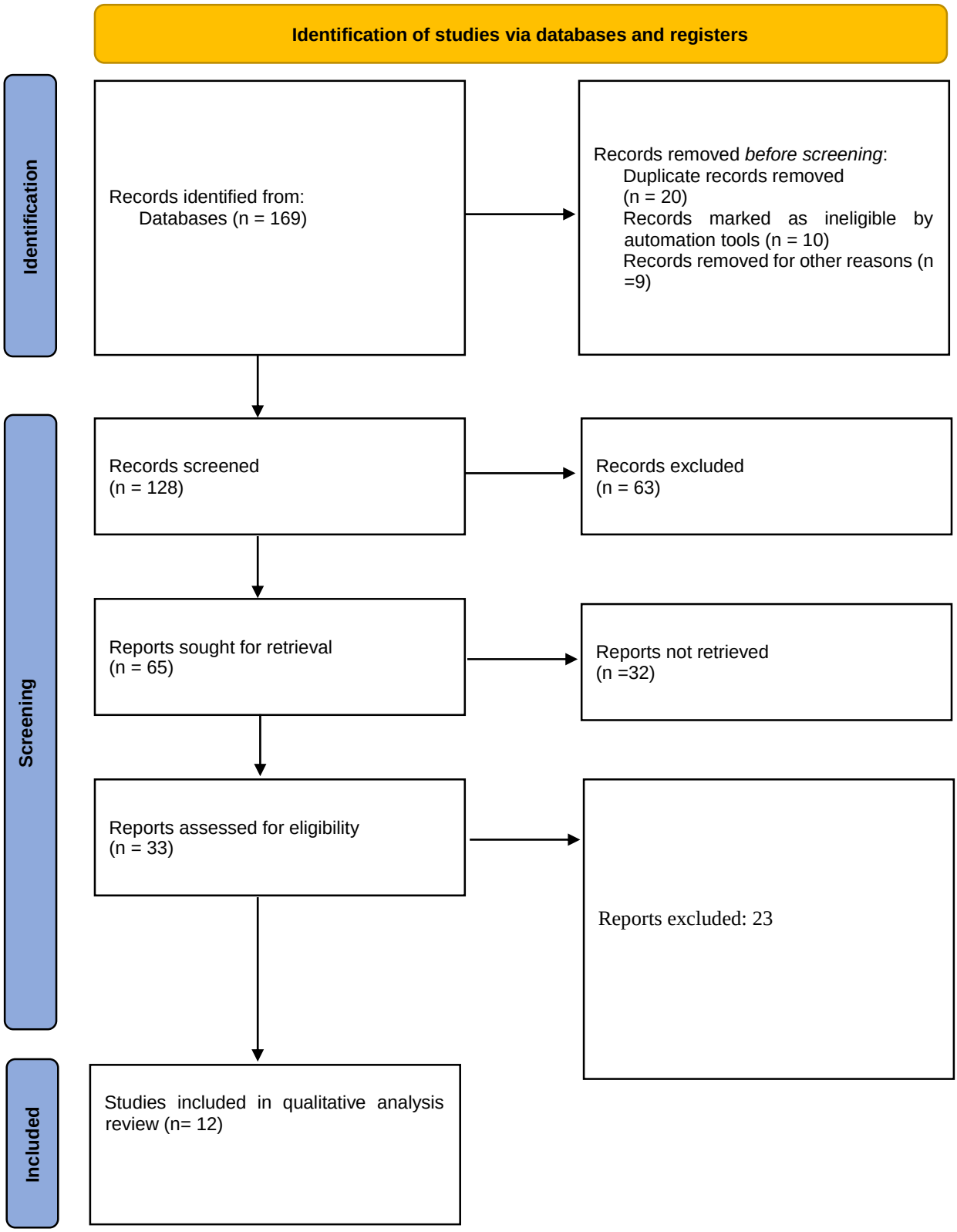

Table 1. Characteristics and incremental structural findings of included original studies

Study	Population	Comparator	Finding
Gerding, 2022	27 AML/MDS cases	Chromosome analysis with indicated supplementary testing	61 additional variants within a predefined myeloid gene set (8)
Yang, 2022	101 untreated MDS cases	Chromosome analysis; selected FISH/microarray studies	Clinically significant cryptic findings in 34 patients (9)
Balducci, 2022	27 MDS and 41 AML cases	Routine cytogenetic workup	Additional abnormalities in 9 MDS and 22 AML cases (10)
Levy, 2023	100 AML cases; multicenter	Previously characterized cytogenetic workup	Additional clinically relevant findings in 13 patients (11)
Díaz-González, 2023	21 MF cases	Conventional karyotyping	19 cryptic abnormalities in 9 patients; 10 failed karyotypes resolved (12)
Loghavi, 2024	159 AML cases	Integrated conventional cytogenomic assessment	Additional cytogenomic or fusion information in 77 patients (13)
Valkama, 2025	15 complex-karyotype MDS cases	Chromosome analysis	Additional large abnormalities in 93%; selected structurally complex population (14)
Wei, 2025	236 MDS cases	Conventional cytogenetic assessment	Additional information in 27%; newly diagnosed and relapsed populations included (15)
Torres-Hernández, 2026	150 MDS/AML cases	Conventional cytogenetics plus molecular assessment	Novel or refined cytogenetic information in 80% (16)
Mestre, 2026	48 therapy-related neoplasms; 65 younger MDS cases	Conventional cytogenetics	134 additional alterations; abnormal karyotypes refined in 52% (17)

Study	Population	Comparator	Finding
Salcedo-Porras, 2026	252 high-grade myeloid neoplasms	Karyotyping and reflex FISH	Six additional cryptic MECOM rearrangements (18)

Table 2. Diagnostic and prognostic consequences: endpoint-specific interpretation

Study	Clinical outcomes	Reported result	Interpretation
Gerding, 2022	Karyotype refinement	67% redefined	Structural refinement is not synonymous with a change in diagnosis or established prognostic category (8).
Yang, 2022	IPSS-R reassignment	15 existing categories changed; 2 categories newly assigned	Failed-test recovery requires separate reporting from reclassification of an established baseline risk category (9).
Balducci, 2022	Risk-category disagreement	6/27 MDS; 2/41 AML	Differences include effects of missed abnormalities; all disagreements are not evidence of improved risk assignment (10).
Levy, 2023	Anticipated clinical consequences	Management recommendations affected in 4%; additional trial eligibility in 8%	These are modeled consequences, not observed treatment benefit or isolated prognostic reclassification (11).
Díaz-González, 2023	Cytogenetic risk upgrade	Three patients with available baseline karyotypes	Upgrading and obtaining a first informative risk assessment represent different contributions of the test (12).
Loghavi, 2024	Diagnostic and/or risk change	14/149 newly diagnosed MDS cases	Composite endpoint; the denominator is the newly diagnosed subgroup, not the complete 236-patient cohort (15).
Valkama, 2025	Cytogenetic versus integrated risk	Cytogenetic risk changed in 16%; integrated prognosis changed in 3/150	Prior molecular results substantially reduced the incremental effect on final prognostic assessment (16).
Wei, 2025	Exploratory prognostic upgrading	IPSS-R and IPSS-M upgrades reported in evaluable subgroups	Structural gene disruptions were incorporated into exploratory IPSS-M

			inputs; these extensions require validation (17).
Torres-Hernández, 2026	Diagnosis or risk reclassification	Five of six cryptic MECOM-positive cases	This is a lesion-specific composite endpoint, not a measure of overall genome-wide reclassification (18).

Discussion

The evidence indicates that optical genome mapping improves structural characterization across several myeloid disease groups, with relevant findings in cryptic rearrangements, complex karyotypes, and unsuccessful chromosome analysis (8–18). The magnitude of additional detection nevertheless exceeds the frequency of integrated prognostic change, as illustrated by the 150-patient study reporting substantially fewer integrated than cytogenetic risk changes (16). These differences establish endpoint definition as a central issue when interpreting claims of clinical utility across laboratory studies (9–18).

Biological importance also depends on the identity and context of the detected lesion, rather than its size or visibility on a conventional karyogram (1–3). Cryptic MECOM rearrangements provide a direct example because their identification changes the interpretation of otherwise incompletely classified high-grade myeloid disease (18). Structural information is also relevant to TP53 allelic assessment, since the distinction between monoallelic and multihit involvement carries important biological and prognostic implications in myelodysplastic neoplasms (19). Optical mapping findings therefore require interpretation alongside sequence variants and other evidence needed to establish allelic state, rather than automatic assignment of molecular risk from structural data alone (5,19).

Additional benefits extend beyond changes in broad cytogenetic categories to recognition of lesions inadequately captured by routine chromosome analysis (7,20). A large diagnostic series demonstrated detection of KMT2A partial tandem duplications across myeloid neoplasms, supporting the value of structural interrogation for this alteration (20). Nevertheless, detection of a therapeutically relevant lesion, eligibility for a clinical trial, alteration of a treatment recommendation, and improved survival represent separate outcomes with different evidentiary requirements (11,20). The comparative literature establishes additional diagnostic information more firmly than improved outcomes following management directed by optical mapping (8–18).

Clinical implementation consequently requires validated thresholds, suitable DNA, standardized interpretation, and reporting that communicates both findings and analytical limitations (21). Missed low-level clones and difficulties involving selected chromosomal regions or ploidy states explain part of the discordance with conventional testing (8,10,15). International expert recommendations place optical genome mapping within an integrated cytogenomic and molecular workup, supporting complementary sequence analysis and appropriately selected confirmatory testing (22).

Replacement of an existing workflow therefore requires assessment against the complete local diagnostic pathway, including the consequences of both additional and missed abnormalities (21,22).

Methodological heterogeneity limits interpretation of apparent differences between studies, particularly when selected complex-karyotype populations are compared with consecutive diagnostic cohorts (9,14). Composite clinical endpoints obscure the fraction experiencing genuine risk changes, while newly assessable patients after failed cytogenetics require separate denominators (9,12,15). Exploratory incorporation of structural gene disruptions into IPSS-M also requires validation against the model's original inputs before resulting upgrades are treated as established prognostic improvements (5,17).

Conclusion

Optical genome mapping provides additional structural information beyond conventional cytogenetics in myeloid neoplasms, including cryptic rearrangements and resolution of unsuccessful chromosome analysis. Its clinical contribution depends on disease context, baseline molecular testing, and the prognostic framework applied. Additional abnormalities do not translate uniformly into diagnostic changes or risk reclassification. The strongest current evidence supports improved genomic characterization, with less direct evidence for improved treatment outcomes. Routine implementation requires validated analytical performance, integrated interpretation, and clearly separated clinical outcomes. Prospective comparative studies with reproducible methods and patient follow-up are required to establish the effect of mapping-guided decisions on management and survival.

List of abbreviations

Abbreviation	Definition
AML	Acute myeloid leukemia
DNA	Deoxyribonucleic acid
FISH	Fluorescence in situ hybridization
IPSS-M	Molecular International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
KMT2A	Lysine methyltransferase 2A
MDS	Myelodysplastic neoplasms
MECOM	MDS1 and EVI1 complex locus
MF	Myelofibrosis
OGM	Optical genome mapping
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TP53	Tumor protein p53

References

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*. 2022;36:1703–1719. doi:10.1038/s41375-022-01613-1.
2. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and

genomic data. *Blood*. 2022;140:1200–1228. doi:10.1182/blood.2022015850.
3. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140:1345–1377. doi:10.1182/blood.2022016867.
4. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120:2454–2465. doi:10.1182/blood-2012-03-420489.
5. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. *NEJM Evid*. 2022;1:EVIDoa2200008. doi:10.1056/EVIDoa2200008.
6. Rack KA, van den Berg E, Haferlach C, et al. European recommendations and quality assurance for cytogenomic analysis of haematological neoplasms. *Leukemia*. 2019;33:1851–1867. doi:10.1038/s41375-019-0378-z.
7. Smith AC, Neveling K, Kanagal-Shamanna R. Optical genome mapping for structural variation analysis in hematologic malignancies. *Am J Hematol*. 2022;97:975–982. doi:10.1002/ajh.26587.
8. Gerding WM, Tembrink M, Nilius-Eliliwi V, et al. Optical genome mapping reveals additional prognostic information compared to conventional cytogenetics in AML/MDS patients. *Int J Cancer*. 2022;150:1998–2011. doi:10.1002/ijc.33942.
9. Yang H, Garcia-Manero G, Sasaki K, et al. High-resolution structural variant profiling of myelodysplastic syndromes by optical genome mapping uncovers cryptic aberrations of prognostic and therapeutic significance. *Leukemia*. 2022;36:2306–2316. doi:10.1038/s41375-022-01652-8.
10. Balducci E, Kaltenbach S, Villarese P, et al. Optical genome mapping refines cytogenetic diagnostics, prognostic stratification and provides new molecular insights in adult MDS/AML patients. *Blood Cancer J*. 2022;12:126. doi:10.1038/s41408-022-00718-1.
11. Levy B, Baughn LB, Akkari Y, et al. Optical genome mapping in acute myeloid leukemia: a multicenter evaluation. *Blood Adv*. 2023;7:1297–1307. doi:10.1182/bloodadvances.2022007583.
12. Díaz-González Á, Mora E, Avetisyan G, et al. Cytogenetic Assessment and Risk Stratification in Myelofibrosis with Optical Genome Mapping. *Cancers*. 2023;15:3039. doi:10.3390/cancers15113039.
13. Loghavi S, Wei Q, Ravandi F, et al. Optical genome mapping improves the accuracy of classification, risk stratification, and personalized treatment strategies for patients with acute myeloid leukemia. *Am J Hematol*. 2024;99:1959–1968. doi:10.1002/ajh.27435.
14. Valkama A, Vorimo S, Tervasmäki A, et al. Structural Variant Analysis of Complex Karyotype Myelodysplastic Neoplasia Through Optical Genome Mapping. *Genes Chromosomes Cancer*. 2025;64:e70024. doi:10.1002/gcc.70024.
15. Wei Q, et al. Optical Genome Mapping in Myelodysplastic Syndromes: Clinical Value and Limitations Derived From a Cohort of 236 Patients. *Mod Pathol*. 2025;38:100862. doi:10.1016/j.modpat.2025.100862.
16. Torres-Hernández N, Mora E, García-Ruiz C, et al. Optical genome mapping as a high-resolution tool for uncovering cytogenetic complex and cryptic alterations in a cohort of patients with MDS and AML. *npj Precis Oncol*. 2026;10:85. doi:10.1038/s41698-025-01258-0.
17. Mestre J, Chaparro-González L, Ruiz Pérez-Hita L, et al. Optical genome mapping refines genomic risk stratification in therapy-related myeloid neoplasms and younger

myelodysplastic syndromes. *npj Precis Oncol*. 2026. Published online August 25, 2026. doi:10.1038/s41698-026-01671-z.

18. Salcedo-Porras N, et al. Optical genome mapping refines diagnosis of high-grade myeloid neoplasms through detection of MECOM rearrangements cryptic to conventional karyotype. *Am J Clin Pathol*. 2026;166:aqag087. doi:10.1093/ajcp/aqag087.
19. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med*. 2020;26:1549–1556. doi:10.1038/s41591-020-1008-z.
20. Wei Q, Hu S, Xu J, et al. Detection of KMT2A Partial Tandem Duplication by Optical Genome Mapping in Myeloid Neoplasms: Associated Cytogenetics, Gene Mutations, Treatment Responses, and Patient Outcomes. *Cancers*. 2024;16:4193. doi:10.3390/cancers16244193.
21. Levy B, Kanagal-Shamanna R, Sahajpal NS, et al. A framework for the clinical implementation of optical genome mapping in hematologic malignancies. *Am J Hematol*. 2024;99:642–661. doi:10.1002/ajh.27175.
22. Kanagal-Shamanna R, Puiggros A, Granada I, et al. Integration of Optical Genome Mapping in the Cytogenomic and Molecular Work-Up of Hematological Malignancies: Expert Recommendations From the International Consortium for Optical Genome Mapping. *Am J Hematol*. 2025;100:1029–1048. doi:10.1002/ajh.27688.
23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71.