haematologica
Journal of the Ferrata Storti Foundation

Genomic proximity mapping: a promising next generation cytogenomic assay for comprehensive assessment of acute myeloid leukemia

by Lianqun Qiu

Received: January 19, 2026.
Accepted: January 28, 2026.

Citation: Lianqun Qiu. Genomic proximity mapping: a promising next generation cytogenomic assay for comprehensive assessment of acute myeloid leukemia.
Haematologica. 2026 Feb 12. doi: 10.3324/haematol.2026.000003 [Epub ahead of print]

Genomic proximity mapping: a promising next generation cytogenomic assay for comprehensive assessment of acute myeloid leukemia

Lianqun Qiu

Department of Hematopathology, Division of Pathology and Laboratory Medicine,

The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA

Running title: GPM in evaluation of AML

Key words: Genome proximity mapping; acute myeloid leukemia; optical genome mapping; structural variants; copy number alterations

Disclosures: No conflicts of interest to disclose.

CORRESPONDENCE:

Lianqun Qiu, MD, PhD
Department of Hematopathology
Division of Pathology and Laboratory Medicine
The University of Texas MD Anderson Cancer Center
Phone: 832-750-1427; Email: lqiu@mdanderson.org

Genetic abnormalities from cytogenetics and molecular profiling form the core of the 2022 European Leukemia Net (ELN) risk stratification guidelines for adult acute myeloid leukemia (AML) [1]. The current standard-of-care (SOC) techniques for assessment of cytogenomic aberrations include chromosome banding analysis (CBA), fluorescence in situ hybridization (FISH) and chromosomal microarrays (CMA) or array comparative genomic hybridization (array CGH). As each technique differs with respect to resolution and limitation, they are typically considered complementary to each other and performed in combinations to maximize detection sensitivity and capacity of all clinically relevant abnormalities.

High-throughput genome-wide technologies have evolved rapidly in recent years. Optical Genome Mapping (OGM) represents an emerging cytogenomic technique that has been successfully applied for systematic evaluation of AML in clinical laboratories [2-4]. In contrast, Genomic proximity mapping ™ (GPM) is one of relatively newer transformative tools for cytogenomic diagnostics and is a short-read sequencing based platform that utilizes high-throughput chromosome conformation capture (Hi-C) technology by retaining three-dimensional chromosomal structure conformation within genomic loci and permitting analysis of genome-wide chromatin interactions in the cell nucleus [5].

In this issue of *Haematologica*, Yeung and colleagues evaluate the clinical utility of GPM in identification of genomic aberrations using 48 archival cryopreserved specimens that have undergone conventional cytogenetic assessment at diagnosis [6]. The aim of this study was to evaluate the extent to which GPM enhances cytogenetic analysis compared to SOC cytogenetic methods in AML assessment.

Yeung and colleagues first evaluated GPM performance at the detection of cytogenetic risk variants specified by the ELN 2022 risk stratification scheme. In the categories classified either as favorable or adverse, GPM showed 100% concordance with the SOC cytogenetic methods, including translocations such as t(6;9)(p22.3;q34.1)/*DEK::NUP214,* inversions such as inv(3)(q21.3q26.1), and aneuploidies (monosomy 7). When considering variants in the intermediate risk category for cytogenetic and/or molecular abnormalities not classified as favorable or adverse, there was a lower concordance rate of 77.8% between GPM and conventional cytogenetics, with major discordant calls in aneuploidies, followed by copy number variants.

Besides the ELN-specified risk categories, GPM identified additional chromosomal rearrangements that were clinically significant variants but were not detected by the conventional cytogenetics. Such examples included t(11;12)(p15.4;p13.33)/*NUP98*::*KDM5A,* inv(3)(p24.3q26.2) with associated *MECOM* rearrangement and EVI1 over-expression [7], and t(6;7)(p23;q36.3) resulting in deletion of the *JARID2* gene, a known tumor suppressor in myeloid neoplasms. Furthermore, a complex karyotype was detected in this study that showed six inter-chromosomal breakpoints, -7 and dup(21)(q22.12q22.12), features compatible with chromoanagenesis described in the OGM study of AML case series [4]. In these cases, the

identification of clinically important variants has clinical impact on AML classification, risk stratification, and/or clinical trial eligibility.

In addition, GPM allows a more thorough description of small insertions and inversions with improved resolution compared to conventional cytogenetics. Novel inversions such as inv(12)(p13.32p13.2) and inv(9)(p13.3p13.1) have not been previously reported. Both variants are featured by para-centric inversion involving a sub-microscopic interval of the genome. inv(9)(p13) has been previously detected only through a targeted re-sequencing effort of this pericentromeric region in adult cases of lymphoblastic leukemia [8].

Of the other classes of structural variants (SVs), GPM was able to detect numerous aneuploidies and smaller deletions and duplications of unknown significance that were not previously identified by routine cytogenetic analysis. Unsurprisingly, most additional variants called by GPM involve copy number alterations (CNAs) below the level of cytogenetic resolution (< 5 Mb). Yeung and colleagues took extra effort by performing orthogonal testing with whole genome sequencing to validate GPM or cytogenetic findings. Fourteen GPM calls were confirmed, whereas only 4 cytogenetic calls were confirmed over their respectively counterparts. These observations corroborated increased detection capability of GPM for a variety of SVs or CNAs compared to traditional methods.

GPM offers several technologic advantages. First, it overcomes the limitation of short read sequencing by capturing ultra-long-range sequence information at a relatively low sequencing depth. Second, unlike FISH or targeted RNA sequencing, GPM is not restricted to specific targets, increasing the likelihood of identifying cryptic rearrangements and novel genomic aberrations that are often missed by conventional cytogenetics. Thirdly, GPM allows detection of CNAs below the level of cytogenetic resolution by overcoming the limitation of genomic location and/or size of the genomic interval in SOC cytogenetics. Lastly, the Hi-C technology uses cross-linked chromatin and is applicable to a wide variety of sample types including formalin-fixed paraffin-embedded (FFPE) tissues and fixed cell pellets. The sample pass rate was robust (~ 97%) in this study, even under suboptimal sample conditions.

Compared to OGM, GPM shows comparable performance in the identification of every major class of genomic aberrations in a single cost-effective assay for AML (Table 1), other hematologic malignancies and constitutional disorders [6, 9, 10]. In contrast, GPM differs from OGM by capturing preserved chromatin interactions, offering 3-dimentional genomic architecture, and allowing linkage of structural variants with functional outcomes; whereas OGM is a bulk DNA assay and cannot assess epigenetics or chromatin structure. In addition, OGM demands intact UHMW DNA, and requires fresh samples or live cells, restricting its clinical applicability in FFPE tissues and hypocellular specimens.

GPM has its own analytic limitations. The limit of detection is 5-10% leukemic blasts for confident variant calls [6, 9], lower than FISH and CMA, making it challenging to detect aberrations in specimens with low-level disease. GPM might struggle with detection of mosaic

changes, polyploidy variants and copy-neutral loss of heterozygosity (cnLOH). Its resolution is dependent on sequencing depth, limiting sensitivity for small-scale variants, like single-nucleotide variants, small inversions, or small insertions/deletions.

In summary, the study presented by Yeung and colleagues has clearly demonstrated that GPM is a promising next generation cytogenomic platform for comprehensive assessment of AML. GPM excels the conventional cytogenetics at detection of cryptic alterations and additional variants of known or unknown significance not specified in the ELN risk guidelines. The utility of GPM in detecting some other SVs, such as small duplications (like *KMT2A* partial tandem duplications), has not yet been fully evaluated, and awaits further exploration in more case scenarios and other myeloid neoplasms.

REFERENCES

1. Dohner 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(12):1345-1377.
2. Levy B, Baughn LB, Akkari Y, et al. Optical genome mapping in acute myeloid leukemia: a multicenter evaluation. Blood Adv. 2023;7(7):1297-1307.
3. 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(6):1029-1048.
4. 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(10):1959-1968.
5. Dixon JR, Xu J, Dileep V, et al. Integrative detection and analysis of structural variation in cancer genomes. Nat Genet. 2018;50(10):1388-1398.
6. Yeung CC, Eacker SM, Sala-Torra O, et al. Evaluation of acute myeloid leukemia using genomic proximity mapping-based next generation cytogenomics. Haematologica. xxx
7. Haferlach C, Bacher U, Grossmann V, et al. Three novel cytogenetically cryptic EVI1 rearrangements associated with increased EVI1 expression and poor prognosis identified in 27 acute myeloid leukemia cases. Genes Chromosomes Cancer. 2012;51(12):1079-1085.
8. Sarhadi VK, Lahti L, Scheinin I, et al. Targeted resequencing of 9p in acute lymphoblastic leukemia yields concordant results with array CGH and reveals novel genomic alterations. Genomics. 2013;102(3):182-188.
9. Chen X, Fang H, Wu Y, et al. Comprehensive Detection of Chromosomal and Genomic Abnormalities via Next-Generation Sequencing-Based Genomic Proximity Mapping Improves Diagnostic Classification of Hematologic Neoplasms. Cancers (Basel). 2025;17(23):3775.

10. Fang H, Eacker SM, Wu Y, et al. Evaluation of Genomic Proximity Mapping for Detecting Genomic and Chromosomal Structural Variants in Constitutional Disorders. J Mol Diagn. 2025;27(11):1054-1069.

Table 1. Comparison of Optical Genome Mapping (OGM) and Genomic Proximity Mapping (GPM) for Cytogenomic Assessment of Acute Myeloid Leukemia

	OGM	GPM
Technology		
Principle	Linear mapping of ultra-long DNA molecules with sequence-specific labels	Detects physical proximity of genomic regions inside the nucleus
Labeling strategy	Fluorescent labeling at specific motifs	Ligation of spatially proximal fragments
DNA preparation	UHMW DNA	Crosslinked chromatin
Sequencing	No (Imaging based)	NGS-based
Output	Lineage genome maps/Linear structural arrangement	Interaction heatmaps/3D spatial co-localization
Platform examples	Saphyr (Bionano Genomics)	CytoTerra (Phase Genomics)
Resolution	$\geq$ 500 bp ~ 5 kb	> 10-100 kb
Sensitivity	5-10%	5-10%
Sample		
Cell number	1-2 million	0.2-0.5 million
DNA amount	~ 750 ng	$\geq$10 ng
Sample type	Viable/Frozen cells	Viable/Frozen/Fixed cells/tissue
FFPE compatibility	No	Yes
Structural Variants*		
Translocations		
Intrachromosomal	Excellent	Excellent
Interchromosomal	Excellent	Excellent
Inversions	Excellent	Excellent
CNAs (indels/dups)	Excellent	Excellent
Aneuploidy		
Hypoploidy	Moderate	Moderate
Polyploidy	Poor	Poor
cnLOH	Moderate	Moderate
Chromoanagenesis	Yes	Possible
Regulatory interactions	No	Yes

*The performance of OGM and GPM was compared with standard-of-care cytogenetic methods, and is indicated as "excellent", "moderate", or "poor", if performance excels, equals to, or inferior to the routine cytogenetic methods, respectively.

Abbreviations: cnLOH, copy-neutral loss of heterozygosity; CNA, copy number alteration; Dups, duplications; FFPE, formalin-fixed paraffin-embedded; Indels, insertions and/or deletions; NGS, next generation sequencing; UHMW, ultra-high molecular weight.