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Optical Genome Mapping: Analysis of Hematological Malignancies

Optical genome mapping (OGM) has been evaluated for the analysis of hematological malignancies in a growing number of studies. Several key studies compared OGM results to traditional methods of karyotyping, fluorescence in situ hybridization (FISH), and chromosomal microarray (CMA) with consistently high concordance for previously detected aberrations while revealing new structural variants (SVs) and characterizing new gene fusion events.

Publication	Summary of Key Points
Clinical Validation and Diagnostic Utility of Optical Genome Mapping for Enhanced Cytogenomic Analysis of Hematological Neoplasms Kolhe Lab Augusta University *Sahajpal NS, et al. J Mol Diagn.* 2022 Oct 17 S1525-1578(22)00290-2. doi: https://10.1016/j.jmoldx.2022.09.009.	• Evaluated OGM performance, as compared to classical cytogenetic methods, across 59 myeloid and lymphoid neoplasms, and 10 controls • OGM Performance: 100% specificity, 98.7% sensitivity, 100% PPV, 98% NPV, 99.2% accuracy at a limit of detection of 5% VAF • OGM identified several additional structural variations, refined breakpoints, and corrected interpretations • Authors concluded that OGM outperformed classical methods in this study, and demonstrated potential to be a first tier cytogenetic assay for hematologic malignancies
Clinical Validation of Optical Genome Mapping for the Detection of Structural Variations in Hematological Malignancies Multicenter: Augusta University, University of Rochester, Children's Hospital of Los Angeles, Bionano Genomics *Pang A et al.,* Preprint: *medRxiv* 2022.Dec 27.	• Multi-site, IRB-approved study on hematological malignancies, conducted for the development of a laboratory developed test (LDT) • 68 hematological malignancy samples (multiple diseases), 27 controls, 2 cancer cell lines, included in study • OGM performance: 100% for accuracy, precision, PPV, NPV, sensitivity and specificity; 96% reproducibility among replicates; Limit of detection rates were ~5% for the SV algorithm and ~10% for the CNV algorithm • OGM found additional clinically significant variants in 37% of the cases • Authors concluded that OGM has superior performance as compared to traditional methods, and that its ability to detect both recurrent SVs and novel fusions positions it as a first-tier
Optical Genome Mapping in Acute Myeloid Leukemia: A Multicenter Evaluation Multicenter: Columbia University, Seattle Cancer Care Alliance, Mayo Clinic, Nationwide Children', Augusta University, PathGroup, MD Anderson Cancer Center, PennState College of Medicine, Fred Hutch Cancer Center, LabCorp, Quest Diagnostics, Case Western Reserve University *Levy et al., Blood Adv* 2022; doi: https://doi.org/10.1182/bloodadvances.2022007583	• Multi-center study from members of the Cancer Genomics Consortium • 100 AML samples evaluated with OGM, compared to classical cytogenetic methods (karyotyping, FISH, CMA) • OGM detected 100% of key pathogenic SVs and CNVs previously detected by SOC, with LOD of 5% allele fraction • For 13% of cases, OGM revealed additional pathogenic findings • For 12% of cases, OGM findings could have altered ELN risk-level classification, or identified eligibility for clinical trials

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High-resolution structural variant profiling of myelodysplastic syndromes by optical genome mapping uncovers cryptic aberrations of prognostic and therapeutic significance. Kanagal-Shamanna Lab MD Anderson Cancer Center *Leukemia*. 2022 Aug 1. doi: https://doi.org/10.1038/s41375-022-01652-8	• 101 consecutive MDS samples were evaluated with traditional cytogenetic methods (karyotyping, FISH, CMA), an 81-gene NGS panel, and OGM • OGM found nearly double the number of clinically relevant pathogenic variants compared to traditional cytogenetics • OGM findings could inform different prognostic risk classification or identify important additional variants in 28% of study participants • Changes to CCSS and IPSS-R risk scores in 21% and 17% of subjects, respectively. • Additional 13% of samples had additional alternations researchers suggest could be used for therapy selection/response and disease monitoring • The combination of OGM and NGS resulted in the detection of at least one clinically significant clonal abnormality in 97 of 101 samples
Next-generation cytogenetics: Comprehensive assessment of 52 hematological malignancy genomes by optical genome mapping. Hoischen Lab Radboud University Medical Center *Am J Hum Genet*. 2021 Aug 5;108(8):1423-1435. doi: https://doi.org/10.1016/j.ajhg.2021.06.001	• Evaluated OGM performance in 52 myeloid and lymphoid samples with clinically relevant aberrations detected with karyotyping, FISH, and/or CMA (36 simple; 16 complex) • Found 100% concordance of OGM in samples that traditional methods characterized as simple (46/46 aberrations in 36 samples) • Also found full concordance in 14/16 samples that traditional methods characterized as complex, with the remaining 2 cases largely concordant, while revealing additional new structural variants, gene fusion events, and greater detail about the structure of previously observed variants • OGM identified 15 additional candidate balanced translocations in 8 samples (4 simple; 4 complex) leading to potential gene fusion
Optimizing the diagnostic workflow for acute lymphoblastic leukemia by optical genome mapping. Dewaele Lab University Hospitals Leuven *Am J Hematol*. 2022 Apr;97:548-561. doi: https://doi.org/10.1002/ajh.26487	• Evaluated 41 samples of acute lymphoblastic leukemia (ALL): 29 B-ALL; 12 T-ALL • OGM detected all recurrent CNVs and SVs as well as additional recurrent SVs and resulting fusions • While traditional techniques (karyotype, FISH, MLPA, array) could assign only 23 samples to a major cytogenetic risk group, researchers conclude that OGM data would allow assignment of 32 subjects, potentially improving risk stratification

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Publication	Summary of Key Points
Optical genome mapping reveals additional prognostic information compared to conventional cytogenetics in AML/MDS patients. Nguyen and Vangala Labs Ruhr-University Bochum *Int J Cancer.* 2022 Jan 22;150(12);1998-2011. doi: https://doi.org/10.1002/ijc.33942	• Evaluated OGM performance in 27 samples from subjects with AML or MDS who underwent routine cytogenetic diagnostics (karyotype, FISH and RT-PCR when indicated) • OGM detected 31% more European Leukemia Net (ELN) and recurrent myeloid abnormalities compared to karyotyping and FISH • OGM also found abnormalities in 35% more samples than karyotyping, and in 67% of samples, the karyotype could be redefined by OGM. OGM refinement of the karyotype resulted in putative changes to the ELN risk classifications used in determining treatment plans
Clinical utility of combined optical genome mapping and 523-gene next generation sequencing panel for comprehensive evaluation of myeloid cancers. Kolhe Lab Augusta University Preprint: *medRxiv.* 2022 Jan 17. doi: https://doi.org/10.1101/2022.01.15.22269355	• Evaluated the use of OGM and a 523-gene NGS panel for genomic profiling of 15 myeloid tumors and compared results to karyotyping, FISH, and a 54-gene NGS panel • Results demonstrated 100% analytical concordance of OGM and the 523-gene NGS panel for variants found with traditional methods • In addition, the new proposed workflow revealed incremental findings, better characterized SVs and CNVs, detected compound heterozygous events, and enabled orthogonal validation of specific events between methods. • Demonstrated the combination of OGM and NGS is beneficial for comprehensive genomic profiling of myeloid neoplasm and N$_x$Clinical software enables simultaneous visualization and CNV confirmation
Optical genome mapping for structural variation analysis in hematologic malignancies. Adam C. Smith — University Health Network, Toronto Kornelia Neveling — Radboud UMC Rashmi Kanagal-Shamanna — MD Anderson *Am J Hematol.* 2022 May 12;1-8. doi: https://doi.org/10.1002/ajh.26587	• Highlights the performance of OGM in acute myeloid leukemia, myelodysplastic syndromes, and B cell acute lymphoblastic leukemia • Illustrates how the OGM workflow can solve common challenges in testing for hematologic malignancies • Discusses the strengths and weaknesses of OGM compared to traditional methods

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