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POSTER ABSTRACTS

803. EMERGING TOOLS, TECHNIQUES AND ARTIFICIAL INTELLIGENCE IN HEMATOLOGY

Assessment of Optical Genome Mapping for Front-Line Diagnostic Evaluation of Acute Leukemia: A Canadian Single-Center Evaluation of Added Yield in 69 Informative Cases

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Optical genome mapping (OGM) is a novel method currently being evaluated internationally as a diagnostic assay for genomic profiling of malignancies. OGM uses imaging and reference alignment of fluorescently labeled ultra-long DNA molecules to detect structural and copy number variants genome-wide at significantly higher resolution than is attainable with current standard-of-care (SOC) cytogenetic analysis. OGM is nearing deployment as a first-line diagnostic test for patients with acute leukemia at Vancouver General Hospital, the largest tertiary care hospital in British Columbia. Here, we describe our experience in the evaluation of OGM as a diagnostic assay relative to SOC karyotyping and fluorescence in situ hybridization (FISH) in newly diagnosed and relapsed acute leukemia.

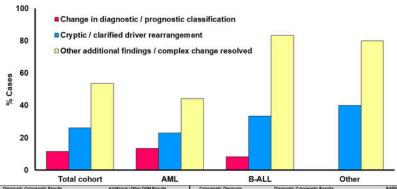
A selected cohort of 69 bone marrow specimens produced adequate quality OGM data for analysis: 52 acute myeloid leukemia (AML), 12 B-lymphoblastic leukemia (B-ALL), 4 mixed phenotype acute leukemia (MPAL; 2 B/myeloid, 1 B/T, and 1 T/myeloid), and 1 blast phase (T) myeloid/lymphoid neoplasm with tyrosine kinase gene fusion (M/L-N-Eo). Variants were filtered using population thresholds and with pan-cancer (669 genes) and disease targeted (myeloid: 185; B-lymphoid: 130) gene lists to facilitate detection of variants of interest. OGM results were compared to SOC to identify additional diagnostic yield and changes to risk stratification or diagnosis resulting from OGM findings.

In these 69 acute leukemias, filtering to remove common polymorphisms using a manufacturer-provided control dataset yielded a median of 53 variants (interquartile range (IQR) 39-86); using a pan-cancer list yielded a median of 6 (IQR 2-16); and disease-specific lists a median of 4 (IQR 1-10.5). In 11% of cases, diagnosis or risk stratification was altered by OGM (13% of AML; 8% of B-ALL), including a complex karyotype being resolved as normal, downgrading cytogenetic risk; identification of several cryptic KMT2A rearrangements, changing diagnostic classification; and identification of cryptic MECOM::RUNX1 (class-modifying), NUP98::NSD1 (risk-upgrading), and NUP214::ABL1 (potentially targetable and class- and risk-modifying) fusions. In 26% of cases, driver rearrangements were either newly identified by OGM or novel partner genes were resolved (23% of AML; 33% of B-ALL; 40% of others), including recurrent rearrangements of the IGH locus with MIR125B1/ BLID in B-ALL; KMT2A partial tandem duplication; novel MECOM::PAN3, JAKMIP2::PDGFRB, and NUP214::FRMD4B fusions; and a cryptic deletion juxtaposing FLT3 and PAN3 known to result in FLT3 overexpression. Additional findings, including copy number changes and clarifications of complex events, were seen in 54% of cases (44% of AML; 83% of B-ALL; 80% of others), mostly accounted for by small deletions or disruptive rearrangements in key disease genes, likely resulting in loss of function, including but not limited to RUNX1, GATA2 and ETV6 in AML; CDKN2A, PAX5, and RB1 in B-ALL; and TP53 in MPAL. Several cases harboured small MLLT4 copy number abnormalities that have been reported to be linked to cancer predisposition, and one potentially germline FANCA deletion was observed. Details of comparison between SOC methods (karyotyping and pertinent FISH where applicable) are detailed in the Figure and Table (bold text: newly resolved or clarified potential driver or resolution of normal karyotype; underline: change in diagnosis or risk stratification resulting from OGM findings). Notably, OGM failed to identify one hypodiploid B-ALL clone masked by endoreduplication, and further evaluation of this technology's performance in this context and in prospective practice is required.

This study demonstrates the significant potential added diagnostic yield of OGM relative to SOC as a clinical diagnostic and research assay. High-resolution genome-wide evaluation not reliant on cell culture substantially expands the scope of detectable variants, for many of which determining the biologic and clinical implications will require larger scale prospective study. Importantly, application of OGM in the clinical setting is likely to result in clinically meaningful disease reclassification and restratification of risk, and in some cases may permit patients access to previously inaccessible targeted therapies (as in the instance of cytogenetically cryptic tyrosine kinase gene fusions).

POSTER ABSTRACTS

Disclosures No relevant conflicts of interest to declare.



Cytogenetic Diegnosis	Diagnostic Cytogenetic Results	Additional / Other OGM Results	Cytogenetic Diagnosis	Diagnostic Cytogenetic Results	Additional / Other OGM Results
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		Rearangement BCORL1			
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Figure 1

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