

January 27, 2025

Re: Optical Genome Mapping at BC Cancer Vancouver

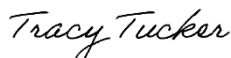
Dear colleagues,

We write to inform you that the Cancer Genetics and Genomics Laboratory (CGL) at BC Cancer Vancouver has recently received full accreditation from the Diagnostic Accreditation Program (CPSBC) for Optical Genome Mapping (OGM) using the Bionano platform. In addition to performing a karyotype, when the appropriate specimens are received (see sample requirements below), OGM will also be performed for all hematological malignancies where karyotype is indicated, allowing for a higher resolution whole genome analysis. This means that two CGL reports - one for karyotype and one for OGM - will be issued for a comprehensive chromosomal analysis in acute myeloid leukemia, myelodysplastic disorders, and myeloproliferative disorders. This technology does not detect sequence-level DNA mutations and so a Myeloid Panel is still necessary for these patients when indicated.

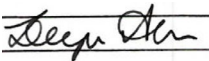
Since OGM has a higher resolution, more abnormalities may be reported than those identified by karyotype analysis. Copy number variants (CNVs) > 5Mb will be reported within all areas of the genome, while smaller CNVs will be reported within a panel of genes relevant to the disease (see CGL website for more information). All variants will be interpreted and tiered using the same classification system as our Myeloid Panel. Important details regarding this testing are outlined below.



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What is detected by Optical Genome Mapping?

OGM will detect most balanced rearrangements, with the exception of whole arm translocations, and copy number variants down to an allele fraction of 15%, although this is dependent on the genomic region and may be higher in different regions of the genome. CGL will report CNVs larger than 5 Mb across the whole genome and will report smaller CNVs in genes relevant to the disease in question.

Is karyotype being replaced?

No. Karyotype analysis will continue routinely in parallel with OGM.. In the future, karyotype may be performed only on select cases, but this change in testing strategy would be communicated by CGL in advance.

Who qualifies for testing?

Any patient who currently qualifies for a karyotype analysis will qualify for OGM analysis.

How is the test ordered?

OGM analysis can be ordered by any physician ordering a karyotype on a bone marrow specimen. This can be ordered by checking off karyotype on our myeloid requisition and the samples will be processed accordingly. The myeloid requisition is pending updates, at which point OGM will be ordered by checking off karyotype/OGM.

What sample is required for OGM?

OGM analysis requires 0.5 mL-1.0mL of bone marrow to be collected in EDTA, similar to our myeloid panel. Currently, we require a separate EDTA tube for myeloid panel and OGM because the DNA extraction process for each of these two techniques are different. So, for karyotype, OGM analysis and myeloid panel the specimens required are:

- 2x1.0 mL of bone marrow into transport media, for karyotype
- 2x0.5 mL of bone marrow into EDTA
 - One tube will have DNA extracted for myeloid panel
 - One tube will have DNA extracted for OGM
- If the patient has AML, another 0.5mL tube is required for RNA banking in the event they have an abnormality qualifying for MRD analysis

How will chromosomal abnormalities be reported?

Every attempt will be made to describe abnormalities similar to karyotype following the International System for Human Cytogenomic Nomenclature (ISCN) for OGM results (Moore et al PMID: 38071973). Historically, cytogenetics reports have provided a prognosis based on the whole karyotype, however, for consistency, OGM abnormalities will be interpreted and reported similar to our myeloid panel, using a modified version of published recommendations for OGM (Levy et al Am J Hematol. 2024 Apr;99(4):642-661. PMID: 38164980) and are as follows:

TIER I - VARIANTS OF STRONG CLINICAL SIGNIFICANCE

Variants in this tier have known clinical implications according to professional guidelines and can be acted upon using standard of care practices. These variants:

- Define a specific entity in the WHO and/or ICC classification.
- Are included in professional clinical practice guidelines as clinically significant variants (e.g., NCCN, Children’s Oncology Group (COG), Myelodysplastic Syndromes (MDS) International Prognostic Scoring System, International Myeloma Working Group Criteria).
- Have high quality evidence (level 1 CEBM evidence) in the literature showing association with a specific neoplasm, prognosis, or treatment response. This includes well-powered studies in the form of randomized controlled clinical trials, systematic review and meta-analysis of these studies, and cohort studies with consensus from experts in the field.
 - Can be treated by an approved targeted therapy.

TIER II - VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

Variant in this tier include acquired variants or a specific pattern of acquired variants with existing but limited evidence supporting their diagnostic, prognostic, and/or therapeutic clinical significance. These variants:

- Have good quality evidence (level 2 CEBM evidence) in the literature showing association with a specific neoplasm, prognosis, or treatment response. This includes multiple (at least two) smaller clinical studies in the form of cohort or case–control studies that have been confirmed and reproduced by different independent groups.
- Have been observed in different neoplasms but not specific to a particular tumor type; these variants usually affect genes associated with cancer and are included in the Catalogue of Somatic Mutations in Cancer (COSMIC) census cancer genes(s).

TIER IIIA –VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE

Variants are known or presumed to alter normal gene function, however no convincing published evidence of a predictive, prognostic or diagnostic association was found or evidence is sufficiently conflicting that a conclusion cannot be reached.

TIER IIIB – VARIANTS OF UNCERTAIN FUNCTION

Variants are not observed at a significant allele frequency in population, pan-cancer or tumour-specific variant databases and their effect on normal gene function cannot be confidently predicted. No convincing published evidence of a predictive, prognostic or diagnostic association was found or evidence is sufficiently conflicting that a conclusion cannot be reached.

TIER IV – BENIGN AND LIKELY BENIGN VARIANTS

[NOTE: Tier IV variants are not routinely reported.] Variants are known or presumed to not disrupt normal gene function, and/or are found at a significant frequency (>1%) within the population and are cataloged in the Database of Genomic Variants (DGV), and usually do not encompass COSMIC cancer gene(s).

What is the expected turn-around time (TAT) for results?

Once the sample is received in the CGL, the anticipated TAT for routine OGM is 21 days from activation based on bone marrow morphology. Karyotype TAT will continue to be 14 days from activation based on bone marrow morphology.. Acute leukemias will be treated as STAT and have a verbal preliminary karyotype communicated in 3-5 days and a final report within 14 days after sample receipt..

Once the sample is received in CGL, CGL will monitor CareConnect for the completed BM report which is required prior to routine OGM and karyotype activation. If a BM report is not available within 7 days, then the testing will be suspended. OGM and karyotype can be activated by faxing the BM report with appropriate morphology to CGL at 604-877-6294.

How can I access the OGM clinical report results for my patient?

The OGM report will be generated using the CGL SHIRE platform which is used for all CGL reporting. Both the karyotype and OGM report will be uploaded to CAIS, CST Cerner and CareConnect. For individuals who have not opted out of receiving a paper copy of our report, these will also be mailed out via Canada Post (see <https://cancer-genetics-lab.ca/2024/05/14/cancer-genetics-and-genomics-laboratory-reports-are-now-viewable-in-careconnect/> on how to opt out of receiving paper reports from CGL).

REFERENCES

1. Levy et al. A framework for the clinical implementation of optical genome mapping in hematologic malignancies. *Am J Hematol.* 2024 Apr;99(4):642-661. PMID: 38164980.
2. Moore et al. ISCN Standing Committee. *Genome Mapping Nomenclature.* *Cytogenet Genome Res.* 2023;163(5-6):236-246 PMID: 38071973.
3. Levy et al. Optical genome mapping in acute myeloid leukemia: a multicenter evaluation. *Blood Adv.* 2023 Apr 11;7(7):1297-1307. PMID: 36417763.