Cytogenomic Microarray, Oncology

Cytogenomic single nucleotide polymorphism (SNP) microarray testing (also referred to a genomic SNP microarray or SNP-A) is used to identify genomic imbalances (deletions and duplications) and may be used to further characterize abnormalities identified by chromosome analysis including ploidy states, unbalanced rearrangements, and unidentifiable additional material or marker chromosomes. Regions of homozygosity (ROH) can also be identified, which in cancer, are most often due to copy-neutral loss of heterozygosity (CN-LOH or simply, LOH).

For many tumors, genomic SNP microarray testing is an adjunct test. However, guideline recommendations continue to evolve. For certain hematologic malignancies and solid tumors with characteristic, prognostically important, and/or targetable array findings, copy number variant (CNV)/LOH detection is now recommended. Common diagnoses submitted for genomic SNP microarray testing include acute lymphoblastic leukemia, myeloid malignancies, chronic lymphocytic leukemia, plasma cell neoplasms (eg, multiple myeloma), lymphomas, central nervous system (CNS) tumors, and melanocytic tumors.

Depending on the specimen type, genomic SNP microarray testing is available for fresh/frozen and/or formalin-fixed, paraffin-embedded (FFPE) tissue specimens. These methods are also of value compared to other cytogenetic testing methods because they do not require living cells and offer increased resolution for detection of CNVs. LOH can only be detected by this methodology compared to other standard cytogenetic methods.

Results

- A written summary and an interpretation of the microarray findings are provided
- CNV evaluation is performed in accordance with recommendations by the American College of Medical Genetics and Genomics (ACMG)[1]:
  - Acquired/somatic or constitutional/germline cancer-associated CNVs and ROH are classified and reported using the following clinical significance categories:
    - Clinically significant CNVs and/or ROH (tier 1 and tier 2 variants)
    - Other clonal variants (tier 3)
    - Benign or likely benign (tier 4)
  - In general, only constitutional CNVs classified as pathogenic or likely pathogenic will be reported using the following clinical significance category:
    - Other variants (likely constitutional)
  - Constitutional/germline CNVs not associated with cancer are classified according to the ACMG recommended 5-tier classification system[2]:
    - Pathogenic
    - Likely pathogenic
    - Variant of uncertain significance (VUS)
    - Likely benign
    - Benign

Result	Description
Normal	No clinically significant CNV or ROH detected
Abnormal	One or more tier 1/2 or tier 3 findings detected
No evidence for acquired/somatic abnormality/other variants (constitutional)	One or more unrelated germline CNVs of pathogenic or likely pathogenic clinical significance or germline ROH/AOH detected; no tumor related findings detected

Featured ARUP Testing

Cytogenomic SNP Microarray - Oncology 2006325

Method: Genomic Microarray (Oligo-SNP Array)

- Performed using the CytoScan HD (Thermo Fisher Scientific) platform
- Detects CNVs and LOH and further characterizes chromosomal abnormalities identified by conventional cytogenetic methods
- Preferred test for fresh tissue specimens for patients with hematologic malignancies and diagnostically and/or prognostically important CNVs/LOH

Chromosome Analysis, Bone Marrow with Reflex to Genomic Microarray 2007130

Method: Giemsa Band/Genomic Microarray (Oligo-SNP array)

- Performed using the CytoScan HD (Thermo Fisher Scientific) platform
- Preferred test strategy with highest diagnostic yield for fresh tissue bone marrow specimens for patients with hematologic malignancies and diagnostically and/or prognostically important CNVs/LOH
- Microarray performed when karyotype results are reported as "normal" or "no growth"

Chromosome Analysis, Leukemic Blood with Reflex to Genomic Microarray 2007131

Method: Giemsa Band/Genomic Microarray (Oligo-SNP array)

- Performed using the CytoScan HD (Thermo Fisher Scientific) platform
- Preferred test strategy with highest diagnostic yield for fresh tissue leukemic blood specimens for patients with hematologic malignancies and diagnostically and/or prognostically important CNVs/LOH
- Microarray performed when karyotype results are reported as "normal" or "no growth"

Cytogenomic Molecular Inversion Probe Array FFPE Tissue - Oncology 3004275

Method: Molecular Inversion Probe Array

- Performed using the OncoScan CNV (Thermo Fisher Scientific) platform
- Detects CNVs and LOH and further characterizes chromosomal abnormalities identified by conventional cytogenetic methods
- Preferred test for FFPE tissue specimens for patients with hematologic malignancies or solid tumors and diagnostically and/or prognostically important CNVs/LOH

Technical Information and Reporting Criteria

- Detection sensitivity (resolution) varies dependent upon platform design, tumor content, and the size and type of genomic alteration (CNV or ROH).
- Genome-wide resolution for fresh tissue specimens (CytoScan platform) varies from approximately 25-50 kb for CNVs and approximately 3 Mb for ROH for samples with high tumor content (generally greater than 70%), to several Mb for samples with lower tumor content (20-30%).
- Genome-wide resolution for FFPE specimens (OncoScan platform) varies from approximately 300-400 kb for CNVs and approximately 5 Mb for ROH for samples with high tumor content to several Mb for samples with lower tumor content (greater than 50% tumor content is recommended for this assay).
- In general, genotype mixture due to mosaicism (distinct cell lines from the same individual) or chimerism (cell lines from different individuals) will be detected when present at greater than 20-30% in the sample.
- Acquired/somatic or constitutional/germline cancer associated CNVs and ROH classified as tier 1/2 or tier 3 variants are generally reported.
- Constitutional/germline CNVs not associated with cancer classified as pathogenic or likely pathogenic are generally reported.
- Tier 4 likely benign, or benign CNVs and ROH, and/or constitutional CNVs conferring noncancer recessive disease risk are generally not reported.
- Total autosomal homozygosity (only autosomal ROH greater than 3 Mb are considered for this estimate) consistent with genomic absence of heterozygosity (AOH) at a level of greater than 10% will generally be reported; AOH less than 10% may be reported, dependent upon on the concern for masked LOH and/or a recessive disorder.

For additional chromosome analysis options using alternate specimen types, refer to the Laboratory Test Directory.

- FISH testing for specific balanced translocations may be considered, based on indication.
- For a complete list of ARUP's oncology FISH tests, including probe targets and genes, see "Oncology FISH" on the ARUP Genetics website.

Limitations

- Does not detect:
  - CNVs below the limit of resolution of the testing platform
  - Balanced chromosomal rearrangements (ie, translocations, inversions, and insertions)
    - Chromosome analysis, fluorescence in situ hybridization (FISH), and/or molecular testing may be appropriate as a first-line test according to indication
  - Sequence-level variants (mutations), including point mutations and small insertions/deletions
  - Low-level mosaicism (generally less than 20-30%)
- FFPE specimens must contain a region with ≥50% tumor
- Not recommended for monitoring for minimal residual disease

References

1. Mikhail FM, Biegel JA, Cooley LD, et al. Technical laboratory standards for interpretation and reporting of acquired copy-number abnormalities and copy-neutral loss of heterozygosity in neoplastic disorders: a joint consensus recommendation from the American College of Medical Genetics and Genomics (ACMG) and the Cancer Genomics Consortium (CGC). *Genet Med*. 2019;21(9):1903-1916.

2. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) [published correction appears in *Genet Med*. 2021;23(11):2230]. *Genet Med.* 2020;22(2):245-257.

Related Information

Acute Lymphoblastic Leukemia - ALL
Acute Myeloid Leukemia - AML
Chronic Lymphocytic Leukemia - CLL
Mature B-Cell Lymphomas
Myelodysplastic Syndromes
Melanoma

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