Chromosomal Microarray, Constitutional

The Molecular Pathology and Cytogenomics Laboratory within the Division of Laboratory Medicine, Robert J. Tomsich Department of Pathology and Laboratory Medicine, Diagnostics Institute, currently offers a genomic microarray (GGXChip + SNP v1.0) designed by Signature Genomic Laboratories (Perkin Elmer Inc.) and manufactured by Agilent technologies (Santa Clara, CA). The clinical utility of microarray analysis may include, but is not limited to, newborns with phenotypic abnormalities including congenital heart disease or individuals with unexplained developmental delay, intellectual disability, or autism spectrum disorders. Microarray analysis may also be used in cases of pregnancy loss using fetal or placental tissue particularly where there has been no karyotype result possible or when a normal karyotype result is obtained.

The array utilized by the Molecular Pathology and Cytogenomics Laboratory will identify DNA copy number gains and losses associated with chromosomal imbalances, as well as single nucleotide polymorphisms (SNP). It will detect aneuploidy, deletions, and duplications of the loci represented on the microarray. It will not detect balanced alterations (reciprocal translocations, Robertsonian translocations, inversions, and balanced insertions), tetraploidy, point mutations, or imbalances of regions not represented on the microarray. It may not detect low levels of mosaicism (less than 20%). The failure to detect an alteration at any locus does not exclude the diagnosis of any of the disorders represented on the microarray. A copy number loss will be reported if at least 5 consecutive probes reach a derivative log ratio (DLR) of -0.5, while a copy number gain will be reported if at least 5 consecutive probes reach a DLR of +0.5. In certain circumstances, a copy number loss or gain involving 3 consecutive probes meeting the DLR requirements may be reported (for example, if the loss or gain is within an exon(s) of known disease-causing genes).

In addition to the disorders detected by copy number changes, the SNP component of the microarray design has the capability to detect regions of homozygosity (ROH). ROH itself is not indicative of an abnormality but it will be reported, as it may be suggestive of uniparental disomy or an increased risk for recessive disorders. Clinical correlation and detailed family history is required to properly assess potential significance and guide any follow-up testing. Regions of homozygosity are reported when the total autosomal ROH is greater than 3% of the genome or when a single ROH of at least 8-10 Mb is identified, depending on the chromosome location and likelihood of an imprinting disorder. In cases of known consanguinity, all ROH may be reported. Please note that failure to detect ROH does not exclude the clinical diagnosis of an imprinting or recessive disorder.

While most copy number variation observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there may be limited data available to support definitive classification of a subset of findings into either of these categories. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance. After full review, the copy number variant (CNV) may be classified as a variant of unknown or uncertain clinical significance (VUS). A VUS could play an important role in the clinical diagnosis. In such cases, parental and family studies may be helpful in the clinical interpretation of these unknowns, as *de novo* occurrence of the CNV is more likely related to pathogenicity. The continual discovery of novel copy number variations and published clinical reports means that the interpretation of any given CNV may evolve with increased scientific understanding.

This microarray assay does not detect the origin of any abnormality i.e., paternal, maternal or de novo. Additional testing may be required.

Genes present within a CNV or an ROH will be included within the report. In the event of multiple ROH greater than 3%, the gene lists will be very large and will not be included on the report. Information regarding genes within the clinically significant CNV or ROH is dependent on literature and databases current at the time of reporting.

Of note, microarray analysis is not a recommended test for adult patients with multiple miscarriages or pregnancy losses and no abnormal phenotype. Chromosome analysis is

a better test to exclude the possibility of balanced parental rearrangements.

A referral to a clinical genetics professional is often appropriate for individuals and families undergoing chromosomal microarray testing. This may be valuable both before and after testing. Families should be aware of the possibility of a VUS and the need for parental blood samples to help interpret the change. In addition, families should be counseled that an incidental but pathogenic finding may be reported which is unrelated to the reason for referral. Families should also understand that findings of ROH may require additional testing of the proband before a diagnosis can be made. Clinical geneticists can guide testing strategies and further evaluate the patient in light of the test results. In some cases, it may be important to discuss the potential for discovery of parental consanguinity. Genetic counseling can also elicit a thorough family and social history, which can be critical in the interpretation of the array results, particularly the SNP results.

References

1. Hollenbeck D *et al.* Clinical relevance of small copy-number variants in chromosomal microarray clinical testing. *Genet Med.* 2017 Apr;19(4):377-385.
2. Riggs ER *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). *Genet Med.* 2020;22(2):245-257.
3. Shao L *et al*. ACMG Laboratory Quality Assurance Committee. Chromosomal microarray analysis, including constitutional and neoplastic disease applications, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021 Oct;23(10):1818-1829.

Test Overview

Test Name	Chromosomal Microarray, Constitutional, Blood
Ordering Mnemonic	CRMSNP
Specimen Requirements	Testing volume: 3–5 mL; minimum volume for pediatric samples: 1 mL or 500 µl (every attempt will be made to run the array with limited specimen) Type: Whole blood; Container: EDTA (Lavender); Transport Temperature: Ambient
Stability	Ambient: 48 hours. Frozen: Unacceptable; Refrigerated: 72 hours
Turnaround Time	10–14 days
Methodology	Genomic Oligonucleotide and SNP Microarray
Reference Range	Refer to report
Billing Code	30103595
CPT Code	81229(x1)

Laboratory Genetic Counselors:

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Scientific and Technical Information:

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