Prenatal Chromosomal Microarray (CMA) For Copy Number Abnormalities and Uniparental Disomy

GeneDx offers two chromosomal microarrays (CMA) for prenatal testing: a whole-genome CMA and a targeted CMA. Both CMAs utilize the Affymetrix CytoScan HD microarray system for detection of copy number changes and uniparental disomy.

Clinical Utility:

The sensitivity of chromosomal microarray (CMA) in a prenatal setting was shown by a large multicenter study to be 5.8% greater than conventional chromosome analysis in fetuses with ultrasound abnormalities. Furthermore, in patients with advanced maternal age or abnormal maternal serum screen, an additional 1.7% of fetuses were found to have a clinically relevant copy number change not detected by karyotyping.[1] The American College of Obstetricians & Gynecology and the Society for Maternal Fetal Medicine have recommended CMA specifically for fetuses with abnormal ultrasound findings.[2] Additionally, their joint Committee Opinion states that CMA can be performed in fetuses without abnormal ultrasound findings if the mother is undergoing invasive prenatal diagnostic testing and that CMA should not be restricted to women aged 35 years and older.[2]

The *whole-genome CMA* contains 2.67 million probes placed throughout the genome that are spaced on average 880 bases apart in genic regions and approximately 1700 bases apart in non-genic regions. There are 1.9 million non-polymorphic probes for detection of copy number variants (CNVs). The array can identify deletions of ≥25 kb including at least 25 consecutive probes and duplications of ≥50 kb including at least 50 consecutive probes. Detected CNVs are reported if they have a clear or suspected clinical relevance. In addition, this CMA contains 750,000 single nucleotide polymorphism (SNP) probes spread throughout the genome, which provide information about regions of homozygosity (ROH) including uniparental disomy (UPD) and identity by descent (parental consanguinity) on all autosomes.

The *prenatal targeted CMA* focuses on detection of CNVs in approximately 150 cytogenetically relevant regions, including common or novel microdeletion and microduplication syndromes. Deletions ≥1 Mb and duplications ≥2 Mb in the remainder of the genome are also assessed. In addition, SNP probes covering only chromosomes known to contain imprinted regions (specifically, chromosomes 6, 7, 11, 14, 15, and 20) can provide information regarding ROH and UPD on those chromosomes.

GeneDx recommends parental testing when the fetus is found to have a genomic imbalance and the inheritance of an abnormality (familial or de novo) may help to clarify the clinical significance of copy number changes and also may be useful for future reproductive choices and follow-up testing of family members. GeneDx uses fluorescence in situ hybridization (FISH), quantitative PCR (qPCR), multiplex

ligation-dependent probe amplification (MLPA), or targeted microarray, as appropriate, for parental analysis. For clinically relevant genomic imbalances detected in the fetus, parental analysis is available as a separate test for an additional charge. For genomic imbalances of unclear significance, GeneDx offers free parental analysis if clinical information on the parents is provided.

Test Methods and Sensitivities:

Prenatal Whole-Genome CMA:

Identifies deletions of ≥25 kb including at least 25 consecutive probes as well as duplications of ≥50 kb including at least 50 consecutive probes throughout the entire genome. It also detects ROH, which may be indicative of uniparental disomy or identity by descent (parental consanguinity). Autosomal ROH is reported when at least one region of homozygosity of ≥10 Mb or two regions that are each ≥8 Mb are identified. Any additional ROH calls ≥5 Mb are included in the report.

Prenatal Targeted CMA:

Screens for common or novel microdeletion and microduplication syndromes, any other genomic deletions ≥1 Mb and duplications ≥2 Mb, and uniparental disomy of chromosomes 6, 7, 11, 14, 15, or 20.

For both Whole-Genome and Targeted CMAs:

Maternal cell contamination studies are performed concurrently.
Result confirmation, when needed, is performed by MLPA, qPCR, FISH, or repeat array.
Benign and likely benign variants and carrier status for autosomal recessive disorders are not routinely reported in either type of array.

Test Limitations:

CMA cannot detect balanced chromosomal rearrangements (inversions, balanced insertions, and balanced translocations), low-level mosaicism (<20%), and rearrangements in repeat sequences (e.g., short arms of acrocentric chromosomes and some heterochromatic regions). CMA also cannot identify pure uniparental heterodisomy (i.e., can only identify uniparental isodisomy, mixed hetero- and isodisomy, or segmental isodisomy). Technical limitations and inherent sequence properties may effectively reduce the resolution for some genes or regions. Erroneous results may occur in the setting of suboptimal DNA quality. The targeted SNP analysis in the prenatal targeted CMA limits detection of homozygosity to chromosomes with clinically relevant imprinting disorders; ROH present on other chromosomes will not be detected.

References:

1. Wapner et al. (2012) The New England Journal Of Medicine 367 (23):2175-84 (PMID: 23215555).
2. ACOG Committee Opinion No.682. Obstet Gynecol 128:e262– 8, 2016.