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

GeneDx offers a whole-genome CMA which utilizes 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]

In addition, CMA has been shown to be valuable in cases of pregnancy loss. Pregnancy loss within the first 20 weeks of pregnancy occurs in 10-20% of known pregnancies. About half of these losses are caused by a chromosomal imbalance in the fetus.[3,4] Chromosome analysis of the products of conception (POC) is indicated for these losses. Karyotyping has been the conventional method used to analyze POC. However, this method has limitations including the inherent tendency towards microbiological contamination of this specimen type. Moreover, there is a high failure rate for cell culture due to the non-viability of the fetal tissues since many are missed abortions. CMA has overcome these limitations of conventional karyotyping and is viewed as a technological advancement for POC analysis.[5-7]

Test Method and Sensitivity:

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. 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. Result confirmation, when needed, is performed by MLPA, qPCR, FISH, or repeat array.

Maternal cell contamination studies are performed concurrently with the CMA.

Test Limitations:

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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.

Parental Testing Policy:

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), multiplex ligation-dependent probe amplification (MLPA), or targeted array, 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.

References:

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