

## Whole-Genome Chromosomal Microarray (CMA) of Products of Conception

Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP) Array for Copy Number and Uniparental Disomy (UPD) Analysis

**Clinical Utility:** A miscarriage is the loss of pregnancy in the first 20 weeks and occurs in about 10-20% of known pregnancies. About half of these losses are caused by a chromosomal imbalance in the fetus.<sup>1,2</sup> 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. Chromosomal microarray (CMA) has overcome these limitations of conventional karyotyping and is viewed as a technological advancement for POC analysis.<sup>3-5</sup> The CMA performed by GeneDx has whole genome coverage with oligonucleotide probes for the detection of copy number abnormalities. In addition, this CMA also has probes for evaluating single nucleotide polymorphisms (SNP), which allows detecting long stretches of homozygosity, which may result from uniparental disomy (UPD). While relatively rare, some cases of uniparental disomy are relevant to disorders of imprinting as well as to recessive disorders caused by inheritance of a variant within a long stretch of homozygosity.<sup>6</sup>

### Test Method and Sensitivity:

The GenomeDx v5 (whole genome chromosomal microarray) contains 118,000 oligonucleotide probes used for detection of copy number variants (CNVs) and 66,000 probes for genotyping. The array detects CNVs of >200 kb, on average, across the entire unique sequence of the human genome and between 500 bp to 15 kb in more than 220 targeted regions. The genotyping probes contain single nucleotide polymorphisms and are used for genotyping to detect long stretches of homozygosity ranging from 5 Mb to the full length of a chromosome. Approximately 60 genes associated with neurodevelopmental disorders have enhanced coverage for detection of pathogenic partial gene copy number variants. In addition, this array contains 66,000 SNP probes throughout the genome and can detect stretches of homozygosity extending 5 Mb or longer. Interpretation of results sometimes depends on whether a CNV is inherited or de novo, and analysis of parental samples is useful for accurate interpretation.

### Test limitations:

CMA cannot detect balanced chromosomal rearrangements (inversions, balanced insertions, and reciprocal translocations), genomic alterations in regions that are not represented on the microarray, polyploidy, low-level mosaicism (<20%), rearrangements in repeat sequences

(e.g., short arms of acrocentric chromosomes and heterochromatic regions), and variants of single or small stretches of nucleotides (point variants, indels, etc.).

With GenomeDx v5, regions of homozygosity (ROH) will be reported if there is at least one region  $\geq 10$ Mb, or two regions each  $\geq 8$  Mb, suggesting identity by descent. The possibility of uniparental disomy (UPD) is reported when there is a terminal ROH  $\geq 10$  Mb or an interstitial ROH  $\geq 20$  Mb. Normal findings at a specific locus do not rule out the diagnosis of a genetic disorder associated with that locus since another abnormality may be present but undetectable by this cytogenetic array design. Test results are often complex and interpretation may be confounded by the detection of copy number variants that may be present in the general population.

**Parental testing policy:** GeneDx recommends parental testing when a patient is found to have a genomic imbalance. Parental analysis is used to evaluate the inheritance of an abnormality (familial or de novo) and may also clarify the clinical significance of copy number changes. GeneDx uses FISH, quantitative PCR (qPCR), targeted CMA or G-band chromosome analysis, as appropriate, for parental analysis. For clinically well-characterized genomic imbalances, parental analysis is available as a separate test for an additional cost (see Known Familial Deletion/Duplication testing). For genomic imbalances of unclear significance, GeneDx offers free parental analysis if clinical information on the parents is provided.

## References:

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