MAYO CLINIC LABORATORIES

Frequently Asked Questions: Cytogenetic Testing of Products of Conception by Chromosomal Microarray Analysis

1. Why is Chromosomal Microarray Analysis (CMA) recommended at Mayo Clinic for products of conception (POC) testing in place of traditional chromosome analysis (karyotype)?

- **More genomic aberrations are detectable by CMA versus karyotype.** Karyotyping will only reveal very large genomic changes that are visible by manual microscopic examination (>10 megabases for chromosome preparations from POC samples). In contrast, CMA analysis provides a high-resolution copy-number analysis of the entire genome and will reveal triploidy, chromosome-level, and gene-level copy-number imbalances. In addition, CMA can reveal data patterns suggestive of molar pregnancies not detectable by chromosome analysis.
- **CMA provides greater diagnostic clarity than karyotyping.** Even when large chromosome abnormalities are recognized by karyotype, unambiguous assessment of genomic content involved is not possible. Because the genomic content of detected imbalances is provided by CMA, this testing allows for greater accuracy in assessment of pathogenicity and better informs reproductive risk counseling for imbalances resulting from a parental chromosome rearrangement.
- **CMA has greater technical reliability than karyotyping.** Chromosome analysis requires viable tissue and cells grown in culture. Due to the nature of the sample type, approximately 15% of POC samples fail to grow in culture, leading to test failures. Whenever possible, CMA is performed from DNA extracted directly from uncultured tissue, leading to a significantly higher success rate (only approximately 3% of CMA testing for POC samples is unsuccessful in our laboratory).
- **DNA-based tests, such as CMA, can be directly tested for maternal cell contamination.** Since CMA is performed from extracted DNA, maternal cell contamination studies are available when a maternal blood specimen is provided. This testing can eliminate the possibility of erroneous test results representing sampling of maternal decidua.

2. Will chromosome rearrangements (eg, translocations) be detected by CMA?

CMA can only reveal the relative copy-number states of chromosomes and genomic segments, not their location. As such, structural abnormalities generating unbalanced rearrangements can only be inferred from CMA results, and balanced translocations with no associated imbalance are undetectable. Due to this limitation, our laboratory practice is to establish a limited culture from each fresh tissue POC ordered for CMA. Whenever a CMA result requires structural context for appropriate clinical guidance or parental follow-up, a limited karyotype analysis is provided at no additional charge. For example, all acrocentric aneuploidy results (chromosomes 13, 14, 15, 21, and 22) are examined by karyotype to identify a Robertsonian translocation in the fetus that may have parental recurrence risk implications. Importantly, this additional testing is not possible when paraffin-embedded samples are tested or when the fresh tissue sample does not yield a viable culture.

3. Will mosaic abnormalities by detected by CMA?

Mosaic abnormalities are detected by CMA with a comparable sensitivity to karyotype (in our experience ranging from about 10% to 15% for mosaic trisomy/monosomy to about 50% for smaller, focal imbalances).

4. Will CMA testing reveal genomic findings of uncertain significance?

Our laboratory strives to return only clinically relevant results with clear interpretations of all reported findings. However, it is the nature of any whole-genome test to occasionally reveal novel findings for which an unambiguous assessment of clinical significance is not possible. In an effort to minimize return of results of uncertain clinical significance, our laboratory policy is to: 1. report **all** pathogenic or likely pathogenic findings, regardless of size, and 2. report findings of uncertain significance only when exceeding size thresholds (1 Mb for deletions, 2 Mb for duplications). With these reporting rules, less than 2% of our CMA reports for products of conception testing have uncertain clinical interpretations. When such findings are reported, parental testing may be offered at no additional charge to help inform the clinical significance.

5. Are parental blood samples necessary for CMA testing of products of conception?

Ideally, a maternal sample should be submitted concurrently with the products of conception sample. Maternal blood samples are used for maternal cell contamination studies to ensure that the results obtained are reflective of the fetus and not maternal tissues.

Parental blood samples are occasionally requested to clarify the results of CMA testing. In the event of an uncertain finding (less than 2% of cases), parental blood samples may be requested to help clarify the clinical significance of the finding. There is no additional charge for this parental analysis.

6. What is the value of microarray for products of conception following prenatal screening?

Prenatal screening tests (via maternal serum screening or non-invasive/cell-free DNA screening) are not diagnostic assays and only reveal increased **risks** for specific aneuploidies or chromosome abnormalities. Regardless of methodology, a prior normal prenatal screening result does not exclude a cytogenetic basis for the pregnancy loss that may be revealed by CMA testing.

Similarly, CMA will provide diagnostic confirmation for screen-positive pregnancies. In straightforward cases, CMA will confirm or exclude the suspected aneuploidy or chromosome abnormality. CMA may also demonstrate a more complex finding not anticipated by the screening test result, which may inform the likelihood of a parental rearrangement with reproductive risk.

7. What are the available CMA tests for products of conception testing?

- **Test ID: CMAPC / Chromosomal Microarray, Autopsy, Products of Conception, or Stillbirth**
  - Performed for fresh tissue specimens
  - ThermoFisher CytoScan™ HD array
  - Reflex chromosome analysis for characterization of structural events is available
  - Processed immediately, cannot delay for preauthorization
  - Maternal cell contamination testing available
- **Test ID: CMAMT / Chromosomal Microarray, Autopsy, Products of Conception, or Stillbirth, Tissue**
  - Performed for FFPE specimens
  - ThermoFisher Oncoscan™ array
  - No reflex to chromosome analysis possible
  - Best for cases with preauthorization requirement
  - Maternal cell contamination testing available

8. If testing will not be ordered immediately, what options are available?

Because fresh tissue samples submitted for CMA testing (test ID CMAPC) are processed immediately with DNA isolation and tissue culture, delays cannot be accommodated. However, CMA can be performed on paraffin-embedded tissue (test ID CMAMT). This sample type will remain stable without compromising the quality of the testing results.

9. Is insurance preauthorization available through Mayo Clinic Laboratories (MCL)?

MCL does not offer insurance preauthorization services on CMA testing. However, clients may wish to determine insurance coverage prior to ordering and sending specimens.

10. What professional guidelines and published studies are available to support the use of CMA for the cytogenetic evaluation of products of conception?

There are numerous references, literature, and clinical studies available to support the use of CMA for POC specimens. The most informative references are listed below:

1. ACOG Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee opinion No. 682. Microarrays and next-generation sequencing technology: The use of advanced genetic diagnostic tools in obstetrics and gynecology. Obstet Gynecol. 2016;128(6):e262-e268. DOI: 10.1097/AOG.0000000000001817.
2. Armour CM, Dougan SD, Brock JA, et al. Practice guideline: joint CCMG-SOGC recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada. J Med Genet. 2018;55(4):215-221. DOI: 10.1136/jmedgenet-2017-105013.
3. Sahoo T, Dzidic N, Strecker MN, et al. Comprehensive genetic analysis of pregnancy loss by chromosomal microarrays: outcomes, benefits, and challenges. Genet Med. 2017;19(1):83-89. DOI: 10.1038/gim.2016.69.
4. Society for Maternal-Fetal Medicine (SMFM). The use of chromosomal microarray for prenatal diagnosis. Am J Obstet Gynecol. 2016;215(4):B2-9. DOI: 10.1016/j.ajog.2016.07.016.
5. Wang Y, Cheng Q, Meng L, et al. Clinical application of SNP array analysis in first-trimester pregnancy loss: a prospective study. Clin Genet. 2017;91(6):849-858. DOI: 10.1111/cge.12926.

For more background information regarding CMA, please view the educational webinar on the MCL Insights page:
Chromosomal Analysis vs. Chromosomal Microarray