INDIANA UNIVERSITY
DEPARTMENT OF MEDICAL AND MOLECULAR GENETICS
School of Medicine

Indiana University Genetic Testing Laboratories (IUGTL)
975 W. Walnut St, IB 350, Indianapolis, IN 46202
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Information for Providers– Prenatal Chromosomal Microarray

Instructions: Please obtain patient signature on separate consent form and provide a signed copy to IUGTL to permit testing and processing. If a signed consent is not submitted, the laboratory assumes that the ordering clinician has discussed testing with the patient and obtained the patient's informed consent.

Genetic imbalances such as chromosomal deletions and duplications are known to be a significant cause of intellectual disability, birth defects, developmental disorders, and pregnancy loss. Traditional prenatal G-banded chromosome testing yields low-resolution structural and numerical analysis of the chromosomes, while prenatal Chromosomal Microarray (CMA) provides high-definition copy number analysis.

Genetic counseling is recommended prior to the ordering of prenatal CMA. To assist in counseling, the laboratory provides a patient consent form and informational brochure available at http://geneticslab.medicine.iu.edu/.

Approximately 1.7% of women who have invasive prenatal testing due to advanced maternal age (AMA) or abnormal serum screening will have an abnormal chromosomal microarray finding that would be missed by traditional karyotype.[1] This statistic rises to 6.0% for those pregnancies with structural fetal anomalies identified by ultrasound.[1] In response to these new data, the American College of Obstetricians and Gynecologists (ACOG) issued a committee opinion on the use of chromosomal microarray analysis in prenatal diagnosis, which provided the following practice recommendations to replace those set in 2009[2]:

- CMA is recommended for any patient undergoing an invasive diagnostic prenatal procedure because of the ultrasound indication of one or more major structural anomalies in the fetus. CMA replaces the need for fetal karyotype.
- CMA or karyotype may be offered in those patients undergoing invasive diagnostic prenatal testing if no structural fetal abnormalities are noted on ultrasound regardless of maternal age.
- CMA is recommended for products of conception in the case of intrauterine fetal demise or stillbirth.
- Patients choosing CMA should receive both pre-test and post-test genetic counseling.
- Since most abnormalities detected by CMA are not associated with AMA, the use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older.

References:

1. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med* 2012; 367:2175–8.
2. ACOG Committee Opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis. *Obstet Gynecol* 2013; 122:1374–7.

Method: Prenatal CMA is performed using the CytoScan™ HD microarray platform (ThermoFisher) with approximately 1.9 million non-polymorphic copy number probes and 743,000 single nucleotide polymorphism (SNP) probes. This test can detect chromosomal imbalances throughout the human genome related to congenital anomalies, ultrasound abnormalities, miscarriage and stillbirth. These imbalances include deletions, duplications and aneuploidy. The SNP probes also may identify copy neutral changes suggestive of uniparental disomy (UPD) and consanguinity or identity by descent, which are associated with an increased risk for autosomal recessive conditions and imprinting disorders, as well as triploidy. The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy or to test for mutations in genes associated with autosomal recessive disorders, present in regions of homozygosity and consistent with fetal clinical findings. Our laboratory has established criteria for reporting abnormalities based on size, gene content, and clinical significance. CMA is not able to detect low-level mosaicism, balanced rearrangements, point mutations, small deletions or insertions below the resolution of this assay, other types of mutations such as epigenetic changes, or some types of UPD. An abbreviated (5-cell) chromosome analysis is included to rule out tetraploidy and rearrangements not detected by microarray, such as balanced translocations and inversions. Maternal cell contamination studies are performed concurrently.

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Reporting Criteria:

Deletions ≥ 1 Mb of unknown clinical significance (at least 1 exon of 1 gene)
Duplications ≥ 2 Mb of unknown clinical significance (at least 1 exon of 1 gene)
Deletions ≥ 25 kb of known clinical significance
Duplications ≥ 50 kb of known clinical significance
Regions of absence of heterozygosity (AOH) on UPD-associated chromosomes ≥5 Mb (terminal) or ≥10 Mb (interstitial)
Whole genome AOH ≥10% of the genome

Specimen Collection:

Amniotic Fluid

- 20-25 ml amniotic fluid at 16 weeks of gestation or greater (30 ml fluid if additional studies are ordered).
- Discard first 2 ml to avoid maternal cell contamination. Transfer the remaining specimen to sterile 15 ml conical centrifuge tubes in 3-4 sterile aliquots, labeled 1st, 2nd, etc., and transport to the laboratory within 24 hours.
  - If the DNA yield from direct fluid is not adequate or the submitted sample is too small or suboptimal, analysis will be performed on cultured cells, which may require additional time for cell growth. Suboptimal specimens likely to cause longer turnaround times include bloody samples (fluid or cell pellet), low volume samples, gestational age < 16 weeks.

CVS

- 20-30 mg branched, clean fetal villi (50 mg if FISH/Chromosome testing also requested).
- Place in CVS transport media and transfer at room temperature to the laboratory within 24 hours.
  - If the DNA yield on uncultured cells is not adequate or the submitted sample is too small or suboptimal, analysis will be performed on cultured cells, which may require additional time for cell growth.

Parental Samples

- 3 ml whole blood in lavender top (EDTA) tube OR one buccal swab (if needed, please call laboratory). **Please note: MATERNAL samples are REQUIRED to accompany the fetal sample.** It is also recommended to send a paternal blood sample to determine the parental inheritance of CMA findings of uncertain clinical significance. Maternal cell contamination (MCC) studies will be performed in all cases.
  - When interpretation requires parental studies, these will be performed automatically to help clarify the significance of the fetal results.

All Specimens

- Collect aseptically.
- **Do not freeze.**
- **Do not place in formalin or any other fixative.**
- **Specimens should be received within 24 hours of collection.** Keep refrigerated until transport.
- Label all containers and requisition forms with patient name, MRN, date of collection, and physician name.
- Call the laboratory at (317) 274-2243 to order any collection containers/media/buccal swabs.

Turnaround Time

- 7-10 days. Suboptimal specimens may require additional time for cell growth.