# Know the facts before they're born

## Prenatal SNP array karyotyping
## Prenatal chromosome microarray analysis (CMA)

Conventional cytogenetic analysis (karyotyping) permits an analysis of the entire human genome, but does so at a relatively low-level of resolution (5-10 Mb). While this is more than adequate to diagnosis many constitutional cytogenetic disorders, such as trisomy 21 (Down syndrome), it will fail to identify smaller abnormalities which may be associated with significant genetic morbidity. Fluorescence in situ hybridization (FISH) provides a much higher level of resolution (150kb), but interrogates only a specific region of the genome. Chromosome microarray analysis (CMA) provides a genome-wide assessment of copy number changes (deletions and duplications) at a resolution far greater than what is achievable with other cytogenetic methodologies such as karyotyping and FISH.

## Clinical Utility

Note: This test requires insurance preauthorization. The Laboratory will not accept the specimen without preauthorization. Also note that CMA is generally performed in the outpatient setting.

CMA is now considered a first-line test, replacing the karyotype, in children with developmental delay/intellectual disability, multiple congenital anomalies, dysmorphic features and autism/autism spectrum disorder. Several recent multicenter studies have demonstrated the utility of prenatal CMA. In one study that compared karyotyping with CMA in 4,406 women (Wappner et al, 2012), clinically significant deletions and duplications were identified in 1.7 percent of cases with a normal karyotype referred for advanced maternal age or a positive screening result. If a structural fetal anomaly was identified by ultrasound, a clinically significant copy number change was observed in 6.0 percent of cases. In another study (Shaffer et al, 2012), the overall detection rate of clinically significant deletions or duplications was 5.3 percent for any indication for study and 6.5 percent for pregnancies with one or more fetal ultrasound anomalies. As in the previous study, many of the genomic changes identified by CMA were below the level of resolution achievable by karyotyping. **Prenatal CMA should be considered in any pregnancy with one or more fetal ultrasound anomalies and a normal karyotype.**

### Test limitations CMA cannot detect:

1. balanced chromosome rearrangements such as translocations, balanced insertions, or inversions
2. low-level mosaicism
3. an abnormality in a region not represented on the array


References

1 Wapner, RJ et al (2012): NEJM 367(23), 2175-2184.

2. Shaffer, LG et al (2012): Prenatal Diagn 32: 976-985.

3. Shaffer, LG et al (2012): Prenatal Diagn 32: 986-995.


### Yield of chromosome microarray analysis in prenatal cases with ultrasound anomalies and a normal karyotype

| Study | Multiple Anomalies | CNS Malformation | Cardiovascular | Hydrops/Cystic Hygroma/NT | Skeletal Anomalies | Diaphragmatic Hernia/ Gastrointestinal | Craniofacial |
|---|---|---|---|---|---|---|---|
| Vestergaard et al (2013), Acta Obstet Gynecol Scand, 90 cases | 1/22 (4.5%) | 2/17 (11.8%) | 2/9 (22%) | 2/6 (33%) | 3/19 (15.7%) | | |
| Lee et al (2012), BJOG 3171 patients | 6/39 (15.4%) | 4/22 (18.2%) | 7/50 (14%) | 1/17 (6.7%) | 2/23 (8.7%) | 1/7 (14.3%) | |
| Shaffer et al (2012), Prenat Diagn, 2858 patients | 58/579 (10%) | 23/326 (7.1%) | 6/193 (3.1%) | 10/232 (4.3%) | 15/165 (9.1%) | 1/9 (11.1%) | 3/70 (4.3%) |


Beaumont Laboratory

800-551-0488

# Principle of the test

At Beaumont, the CMA test utilizes the Affymetrix CytoScan HD single nucleotide polymorphism (SNP) array which can reliably detect 25-50 kb copy number changes across the genome. With more than 2 million copy number markers, including 750,000 SNPs, the Beaumont CytoScan Array offers high-density resolution of the entire genome. The Beaumont SNP array can also provide genotype information that allows for detection of uniparental disomy and consanguinity.

## Specimen collection

Collect: Amniotic fluid or tissue (chorionic villus tissue, fetal tissue, fetal membrane, umbilical cord) sample.

Collect specimen as follows:

- Amniotic fluid: Collect 20-30 mL amniotic fluid into sterile 15 mL centrifuge tubes.
- Chorionic villus sampling: Collect 10 mg chorionic villus tissue and place into a sterile 15 mL centrifuge tube containing tissue culture transport medium.
- Products of conception: Collect 1.0 x 1.0 cm piece of tissue (chorionic villus tissue, fetal tissue, fetal membrane, umbilical cord) and place into a sterile 15 mL centrifuge tube containing tissue culture transport medium.
- T-25 flasks: Amniotic fluid cells, chorionic villus cells, or products of conception cells in two sterile, confluent T-25 flasks containing tissue culture transport medium.

Additionally, collect 3-5 mL of maternal peripheral blood in one lavender-top (EDTA) tube with each specimen type for maternal contamination studies, if needed.

**Rejection criteria:**

- improperly labeled specimens
- frozen specimens
- cracked or compromised specimen tubes
- specimens received greater than 72 hours past the time of collection

**Test code: GSNPP**

## Results reported for:

- deletions of duplications larger than 500kb across the genome; deletions greater than 50kb and duplications greater than 100kb in known syndromic regions
- susceptibility genes associated with an unambiguous outcome
- uniparental disomy or clear consanguinity

## Specimen storage

Room temperature (20-25°C or 68-77°F): 24 hours

Refrigerated (2-8°C or 36-46°F): 72 hours

Frozen (-20°C/-4°F or below): Unacceptable

**Physician office /draw site specimen preparation**

Do not freeze specimen. Store all specimens at room temperature (20-25°C or 68-77°F) prior to courier pickup. For delays in transport (greater than 24 hours from the time of collection), refrigerate (2-8°C or 36-46°F) specimen.

## Transport

**Preparation for courier**

Room temperature (20-25°C or 68-77°F)

## Advantages of SNP array karyotyping for prenatal analysis

- one assay - whole genome copy number and UPD status
- permits evaluation of specific gene content involved in genomic imbalance
- chromosomal arm resolution is increased by several thousand fold when compared to FISH
- detects abnormalities missed by other techniques – including uniparental disomy
- detects atypical deletions missed by FISH
- can identify genomically complex chromosome abnormalities and genomic imhalance in an individual with a previously diagnosed “balanced” chromosome abnormality

- test performed Monday through Friday
- results available within seven to 14 days
- additional time may be needed for reflex testing of abnormal results
- positive or negative for chromosome abnormality; a comprehensive interpretative report will be provided

**For more information or questions about SNP Array, please contact Mark Micale, Ph.D. at 248-898-9063, or a Customer Service Agent at 800-551-0488.**

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