

Genomic SNP Microarray, Products of Conception (ARRAY POC)

FOR DETECTION OF GENOMIC IMBALANCES IN PRODUCTS OF CONCEPTION (POC) SPECIMENS. USEFUL AS A PRIMARY TEST, INSTEAD OF CHROMOSOME ANALYSIS, FOR DETECTION OF SUBMICROSCOPIC GAINS/LOSSES AND AS A FOLLOW-UP TEST FOR SAMPLES NOT YIELDING A KARYOTYPE DUE TO POOR GROWTH IN CULTURE, OR TO CLARIFY ABNORMAL-CHROMOSOME TEST RESULTS.

Test Highlights

- This array platform contains DNA sequences representing specific regions of the human genome designed to detect both copy-number variation (loss or gain of DNA) and loss of heterozygosity (LOH).
- This platform offers excellent performance and exceeds current guidelines for specificity, sensitivity, and resolution across the genome.
- This test is designed to identify hundreds of common microdeletion/microduplication syndromes, subtelomeric deletions or duplications, and LOH at thousands of loci throughout the genome.
- Patient DNA is hybridized to the chip in order to:
 - Identify unbalanced chromosomal abnormalities (copy-number variants [CNVs]) undetectable by conventional chromosome analysis
 - Further characterize cytogenetic abnormalities identified by conventional cytogenetic methods
 - Detect areas of the genome that have long contiguous stretches of homozygosity (LCSH)
- The very high probe density present on this chip provides the broadest coverage of RefSeq genes on a single array, with average probe spacing of one probe per 880 base pairs over all genes, with increased density over disease-causing OMIM, cancer, and ISCA constitutional genes.
- The large number of single-nucleotide polymorphisms (SNPs) also present on the array allows detection of gene-level, copy-neutral LOH, uniparental disomy (UPD), and regions “identical by descent,” which may indicate increased risk of a recessive condition.
- Fluorescence in situ hybridization (FISH) or routine chromosome studies on parental blood specimens may be recommended in order to identify familial rearrangements or variants detected by microarray.

Clinical Background

- Fetal loss is a common pregnancy complication. Cytogenetic abnormalities are present in the majority of losses (50%–70%), with 60% of those being comprised of autosomal trisomies, 20% monosomy X (Turner syndrome) and 20% polyploidy.
- Early losses (at or before five weeks of gestation) are most likely to be associated with a chromosome abnormality (90%), as compared to losses which occur after 10 weeks of gestation (30%). Stillbirths, defined as losses at or beyond 20 weeks of gestation, have a chromosome abnormality rate of 6%–12%.
- Conventional cytogenetic techniques are dependent on the successful culture of fetal or placental tissue.
- Cell culture on POC may be unsuccessful in up to 50% of cases. For those that are cultured successfully, the presence of maternally derived tissues can lead to overgrowth of the fetal cells by the maternal cells (maternal cell contamination).
- The POC array can be run on direct fetal or placental tissue, either fresh or frozen, and can therefore obtain results even when cell culture fails.
- Conventional cytogenetic techniques are limited in their ability to detect or characterize subtle or cryptic abnormalities and cannot detect LCSH that may be suggestive of UPD or an increased risk of a recessive condition, all of which may be implicated in an as-yet unknown proportion of pregnancy losses.
- The identification of specific abnormalities by array may be helpful in determining recurrence risk and/or medical management of future pregnancies.

Indications for Ordering

- In the presence of fetal anomalies, such as:
 - Growth retardation
 - Severe, single, fetal anomalies, such as cardiac defects or structural brain abnormalities
 - Multiple congenital anomalies

- Unexplained fetal death
- To further characterize chromosomal abnormalities seen by conventional cytogenetic methods, including marker chromosomes, ring chromosomes, apparent terminal deletions, unbalanced translocations, or an apparently balanced de novo rearrangement
- When the patient has had multiple losses of unknown etiology
- Identification of LCSH that may be suggestive of UPD or increased risk of a recessive disorder

Additional Ordering Notes

- **All samples must have a clinical indication for testing.** Please complete the Patient History Form for Cytogenetic (Chromosome) Studies, which can be found at http://www.aruplab.com/Testing-information/resources/consent_forms/history_cytogenetic.pdf, and submit it to the laboratory along with the patient sample.
- Sample requirements: products of conception in a sterile, screw-top container (wide-mouth containers: ARUP supply #42710) filled with tissue-culture transport medium (ARUP supply #32788). Available online through eSupply using ARUP Connect™, or contact ARUP Client Services at (800) 522-2787. If cytogenetics tissue medium is not available, collect in plain RPMI medium, Hanks solution, saline solution, or Ringer solution. **If autopsy is performed:** Chest wall cartilage (particularly if macerated), gonad, spleen, kidney, or other internal organs. **If no autopsy is performed:** Placenta from fetal side is preferred (e.g., chorionic villi). Also acceptable: umbilical cord or Achilles tendon.
- Samples may be shipped at ambient temperature, in transport media, or frozen (-20°). No media required.
- High-quality DNA may also be accepted. A minimum of 1 µg of DNA (concentration between 100 ng/µl and 400 ng/µl) will be required, with an OD260/280 ratio of 1.8–2.0 and an OD260/230 ratio of >1.5.
- Unacceptable conditions: paraffin-embedded specimens; DNA must not be degraded.

Interpretation

- A written summary and interpretation of the microarray findings are provided.
- Gains and losses are reported based on genomic content.
- Duplications smaller than 400 kb and deletions smaller than 50 kb may not be investigated or reported. CNVs devoid of relevant gene content or reported as common findings in the general population may not be reported.
- Regions of homozygosity are reported when a single LCSH is greater than 8 Mb–15 Mb (dependent upon chromosomal location and likelihood of imprinting disorder), or when the total autosomal LCSH proportion is greater than 3% (only autosomal LCSH greater than 3 Mb are considered for this estimate).
- Test results are often complex; a copy-number change of uncertain clinical significance may be detected.

Limitations

- This technique will detect only copy-number imbalances and LCSH in the nuclear genome. It will not detect balanced rearrangements, such as translocations, inversions, and balanced insertions. Additionally, base-pair mutations, imbalances of the mitochondrial genome, genomic imbalances below the resolution of this array platform, and aberrations in regions of the genome not represented on the array platform may not be detected. Tetraploidy cannot be detected by this methodology. Low-level mosaicism may also not be detected.

- As this array accurately detects copy-number changes below the resolution of FISH technologies, parental testing may not be available by alternative methodologies.

Methodology

- The technique involves DNA preparation, amplification, purification, labeling, hybridization, washing, array scanning, analysis, and interpretation.
- Copy-number changes are calculated based on hybridization signal intensity data from the experimental sample relative to data derived from phenotypically normal individuals.
- This cytogenomic single nucleotide polymorphism (SNP) test is run on the Affymetrix® CytoScan™ HD array, which interrogates the entire genome using more than 2.6 million markers for copy-number analysis and approximately 750,000 SNPs.
- Data is analyzed using Affymetrix Chromosome Analysis Suite software (ChAS).

Related Tests

- Chromosome Analysis, Products of Conception, with Reflex to Genomic Microarray (2005672)
- Conventional cytogenetic analysis (karyotyping) will detect large additions, deletions, and rearrangements, including balanced translocations and inversions. Conventional cytogenetics generally cannot detect duplications and deletions smaller than approximately 5 Mb–10 Mb (5,000 kb–10,000 kb) in size (the size of a chromosomal band), or larger changes that do not alter the karyotype banding pattern.
- Other molecular techniques (e.g., gene-scanning or PCR-based assays) are more sensitive than genomic microarray for detecting many intragenic alterations, such as point mutations and very small deletions or duplications, but are highly specific and restrictive for the genetic site or gene of interest.

Background Readings

1. Filges I, et al. aCGH on chorionic villi mirrors the complexity of fetoplacental mosaicism in prenatal diagnosis. *Prenat Diagn.* 2011;31:473–478.
2. Manning M, Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med.* 2010;12(11):742–745.
3. Schaeffer AJ, et al. Comparative genomic hybridization-array analysis enhances the detection of aneuploidies and submicroscopic imbalances in spontaneous miscarriages. *Am J Hum Genet.* 2004;74:1168–1174.
4. Shaffer LG, et al. Microarray analysis for constitutional cytogenetic abnormalities. *Genet Med.* 2007;9:654–662.
5. Warren JE, Silver RM. Genetics of pregnancy loss. *Clin Obstet Gynecol.* 2008;51:84–95.
6. Warren JE, et al. Array comparative genomic hybridization for genetic evaluation of fetal loss between 10 and 20 weeks of gestation. *Obstet Gynecol.* 2009;114:1093–1102.

Test Information

2005633

Genomic SNP Microarray, Products of Conception

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

AUTHORS

Katherine Geiersbach, MD, FCAP

Danielle LaGrave, MS, LCGC