

Genomic Microarray, Products of Conception

Indications for Ordering

- Intrauterine fetal demise or stillbirth (American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine, Committee Opinion, 2013)
- Pregnancy loss or termination in the presence of fetal anomalies
- Further characterization of fetal chromosomal abnormalities determined by conventional cytogenetic methods
- Multiple fetal losses of unknown etiology

Note

- If no living tissue is available, testing can still be performed using
 - Formalin-fixed, paraffin-embedded (FFPE) tissue
 - Products of conception (POC) specimens that fail to grow in culture

Test Description

Genomic SNP Microarray, Products of Conception

Chromosome Analysis, Products of Conception, with Reflex to Genomic Microarray

- Platform – Affymetrix CytoScan HD
 - Oligo copy number and single-nucleotide polymorphism (SNP) array
 - Contains >2.6 million copy number markers
 - Includes 750,000 SNP probes
 - Detects copy number changes and long continuous stretches of homozygosity (LCSH)
 - Average marker spacing
 - Intragenic – 880 base pairs (bp)
 - Intergenic (nongene backbone) – 1,700 bp
 - Overall (gene and nongene backbone) – 1,100 bp
 - Average functional resolution
 - Deletion of 25 consecutive markers
 - Duplication of 50 consecutive markers

Cytogenomic Molecular Inversion Probe Array, FFPE Tissue – Products of Conception

- Platform – Affymetrix OncoScan
 - Contains 220,000 SNP probes across the entire genome
 - Detects copy number changes and LCSH
 - Average functional resolution – 20 consecutive markers

Tests to Consider

Primary tests

[Genomic SNP Microarray, Products of Conception 2005633](#)

- Preferred test for further characterizing chromosomal abnormalities detected by conventional cytogenetic methods
- Preferred test for POC specimens that fail to grow in culture
- Fresh or frozen tissue
 - Fetal or placental

[Chromosome Analysis, Products of Conception, with Reflex to Genomic Microarray 2005762](#)

- Ensures best chance of obtaining meaningful results from fetal specimens
- When tissue culture is unsuccessful or if results of chromosome analysis are normal, testing reflexes to genomic microarray
- Fresh tissue
 - Fetal, placental, or umbilical cord

[Cytogenomic Molecular Inversion Probe Array, FFPE Tissue – Products of Conception 2010795](#)

- For detection of copy number alterations and loss of heterozygosity in FFPE specimens
- FFPE tissue
 - Fetal autopsy or POC

Related tests

[Chromosome Analysis, Products of Conception 2002288](#)

- Identifies
 - Aneuploidy – the most common cause of fetal loss
 - Duplications and deletions >~10-15 Mb
 - Large chromosomal rearrangements, including balanced/unbalanced translocations and inversions
 - May be unsuccessful in up to 50% of cases of POC
- Requires cell culture of fresh fetal or placental tissue studies to identify familial rearrangements or variants detected by microarray

[Chromosome Analysis, Constitutional Peripheral Blood 2002289](#)

- Routine chromosomal studies on parental blood specimens
- Culture of living cells

Disease Overview

Diagnostic issues

- Cytogenetic abnormalities are present in the majority of early fetal losses – 50-70%
 - Autosomal trisomies – 60%
 - Monosomy X (Turner syndrome) – 10%
 - Triploidy – 10%
- Age of fetus at time of loss is associated with probability of cytogenetic abnormality
 - ≤ 5 weeks of gestation (early loss) – 90%
 - > 10 weeks of gestation – 30%
 - ≥ 20 weeks (stillbirth) – 6-12%
- Conventional cytogenetic technique (karyotyping)
 - Requires cell culture – may be unsuccessful in up to 50% of POC cases
 - In successful cultures, the presence of maternally derived tissues can lead to overgrowth of the fetal cells by the maternal cells (maternal cell contamination)
 - Limited in ability to detect or characterize subtle or cryptic abnormalities
 - Cannot detect LCSH
- Identification of specific abnormalities may be helpful in determining
 - Recurrence risk
 - Medical management of future pregnancies

Genetics

- Whole-genome coverage, including subtelomeric and pericentromeric regions
- Detects common aneuploidy and triploidy present in majority of cases
- Detects > 50 known microdeletion/microduplication syndromes

Test Interpretation

Results

- Abnormal microarray
 - Copy number variation (CNV) detected
 - Clinically significant, even if penetrance and expressivity of the CNV are known to be variable
 - LCSH noted across either one region or multiple independent regions
 - Suggestive of either uniparental disomy (UPD) or increased risk of recessive condition
 - Unrecognized consanguinity of the parents of the tested individual may be revealed
- Copy number change detected, clinical significance unknown
 - CNV detected for which insufficient evidence is available to determine unequivocally its clinical significance
 - Deletions/duplications that confer carrier status for recessive conditions may be identified
- Normal microarray
 - No clinically significant abnormalities detected based on current knowledge at the time of reporting

Limitations

- Does not detect
 - Base pair mutations and very small deletions/duplications
 - Duplications < 400 kb and deletions < 50 kb may not be investigated or reported, depending on genomic content of the imbalance
 - Balanced rearrangements (translocations, inversions, and balanced insertions)
 - Positional information for chromosome rearrangements (eg, cannot differentiate between trisomy 21 and Down syndrome)
 - Imbalances of the mitochondrial genome
 - Tetraploidy
- Low-level mosaicism ($< 25\%$) may not be detected
- CNVs devoid of relevant gene content or reported as common findings in the general population are not reported
- LCSH on imprinted chromosomes < 8 Mb (telomeric) or < 15 Mb (interstitial) may not be investigated or reported
- LCSH < 10 Mb (telomeric) or < 15 Mb (interstitial) on non-imprinted chromosomes are generally not investigated or reported
- LCSH $< 3\%$ of the autosomal genome may not be reported