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, 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