Non-Invasive Prenatal Testing (NIPT) for Fetal Aneuploidy, With or Without Microdeletions

Indications for Ordering

- Primary screening for women at increased risk of having a fetus with specific whole-chromosomal abnormalities
- Secondary/advanced screening for women with abnormal prenatal test results
  - Multiple marker screening and/or ultrasound suggestive of any of the disorders described under "Primary tests"

Test Description

- PCR followed by next generation sequencing
- Testing performed by Natera

Tests to Consider

Primary tests

Non-Invasive Prenatal Testing for Fetal Aneuploidy (Panorama) 2007537

- High-level screening for pregnant women (9w0d-term) at increased risk for having a fetus with specific chromosomal aneuploidies
  - Women with previous fetus with autosomal aneuploidy
  - Women >age 35 at delivery
  - Either parent is a carrier of a Robertsonian translocation involving chromosome 13 or 21
- Disorders include
  - Trisomy 13 (T13)
  - Trisomy 18 (T18)
  - Down syndrome (trisomy 21 or T21)
  - Turner syndrome (TS)
  - Triploidy
- Not recommended when the woman or her partner
  - Is a known carrier of a translocation or other chromosome rearrangement that will not result in a fetus with one of the above disorders
  - Has a known numerical abnormality in one of the targeted chromosomes (eg, mosaic T21 or TS)

Non-Invasive Prenatal Testing for Fetal Aneuploidy (Panorama) with Microdeletions 2010232

- Screens for whole-chromosome aneuploidy involving chromosomes 13, 18, 21, X, Y, and triploidy
- Also screens for microdeletions causing
  - 22q11.2 deletion syndrome (DiGeorge/velocardiofacial)
  - 1p36 deletion syndrome
  - Angelman syndrome
  - Prader-Willi syndrome
  - Cri-du-chat (5p minus) syndrome

Related tests (screening for low-risk individuals)

Maternal Serum Screening, Integrated, Specimen #1 0081062 (first trimester) **AND**
Maternal Serum Screening, Integrated, Specimen #2 0081064 (second trimester)

- Tests for DS, T18, and open neural tube defects (ONTD)
- Combines first and second trimester blood specimens, with or without a first trimester nuchal translucency (NT) measurement

Maternal Screening, Sequential, Specimen #1 0081293 (first trimester) **AND**
Maternal Screening, Sequential, Specimen #2 0081294 (second trimester)

- First trimester – screens for DS and T18
- Second trimester – screens for DS, T18, and ONTD
- Requires NT measurement performed by an ultrasonographer certified by the Fetal Medicine Foundation (FMF) or the Nuchal Translucency Quality Review (NTQR)

Maternal Serum Screen, First Trimester 0081150

- First trimester screening test for DS and T18
- Requires NT measurement performed by an ultrasonographer certified by FMF or NTQR

Maternal Serum Screen, Alpha Fetoprotein, hCG, Estriol, and Inhibin A 0080269

- Second trimester screening test for DS, T18, and ONTD

Related tests (diagnostic testing)

Chromosome Analysis, Amniotic Fluid 2002293

- Prenatal chromosome analysis after 14 weeks of gestation when individual
  - Is at increased risk for fetal aneuploidy based on maternal age, abnormal NIPT , abnormal multiple markers screening, or abnormal fetal ultrasound
  - Has a family history of chromosome abnormality or genetic disorder
  - Desires diagnostic testing instead of screening

Chromosome Analysis, Chorionic Villus 2002291

- Prenatal chromosome analysis at 10-13 weeks of gestation when individual
  - Is at increased risk for fetal aneuploidy based on maternal age, abnormal NIPT, abnormal multiple markers screening, or abnormal fetal ultrasound
  - Has a family history of chromosome abnormality or genetic disorder
  - Desires diagnostic testing instead of screening

Cytogenomic SNP Microarray – Fetal 2002366

- Diagnostic test designed to identify genomic abnormalities (eg, aneuploidy and microdeletions)
- Performed on cultured and direct amniotic fluid and CVS specimens

Disease Overview

Incidence at birth

- DS – 1/600
- T18 – 1/3,000
- T13 – 1/ 5,000
- TS – 1/2,500 female births
- Triploidy – 1/50-100 conceptuses
- 22q11.2 deletion – 1/2,000
- 1p36 deletion – 1/5,000
- Angelman – 1/12,000
- Prader-Willi – 1/10,000
- 5p deletion – 1/20,000

Diagnostic issues

- Traditional noninvasive screening methods (maternal serum biochemical markers with or without fetal NT)
  - Detect only 70-95% of fetal T21
  - Detect 60-90% of fetal T18
  - Do not detect microdeletions
  - Can have screen positive rate >20% in women >age 35
- High false-positive rates, associated with traditional prenatal aneuploidy screening methods, result in unnecessary invasive diagnostic procedures
  - Invasive procedures (eg, amniocentesis, chorionic villus sampling [CVS]) carry risk of pregnancy loss
- NIPT combines very high sensitivity (>99%) with very high specificity (>99%) for fetal aneuploidy
  - NIPT should not be used in place of routine ultrasound or diagnostic testing for chromosomal aneuploidies
- Microdeletion risk is very low in most pregnancies and does not increase with maternal age
  - Pretest genetic counseling should be considered to help women fully understand the benefits and limitations of microdeletion screening

Genetics

Panorama

- Detects aneuploidy of chromosomes 13, 18, 21, X, Y, and triploidy

Panorama XP

- Detects aneuploidy of chromosomes 13, 18, 21, X, Y, and triploidy
- Also detects deletions causing DiGeorge/velocardiofacial, 1p36 deletion, Angelman, cri-du-chat, and Prader-Willi syndromes

Test Interpretation

Sensitivity/specificity

- Aneuploidy
  - Clinical sensitivity/specificity – >99%
- Microdeletions
  - Clinical sensitivity – >99%
  - Clinical specificity – 97.9-99.9%

Results

Each risk assessment includes the age-related/pretest risk and the risk after NIPT

Providing a paternal buccal swab specimen along with the maternal blood specimen can increase test accuracy and decrease the chance of a no-call test result

- High risk – significantly increased risk for fetus to have either monosomy or trisomy of chromosomes 13, 18, or 21, monosomy X , or triploidy
  - Although not specifically targeted, results that suggest fetal 47,XXX, 47,XXY, or 47,XYY will be reported
  - Genetic counseling is available
  - Diagnostic testing (eg, fetal karyotype by CVS or amniocentesis) may be used to confirm results
- Low risk/very low risk for fetus to have abnormality of chromosomes 13, 18, 21, X, Y, or triploidy
  - Fetal karyotype or other test may still be appropriate if
    - Fetal anomalies are detected by ultrasound
    - Other concerns exist about the health of the fetus
- No call – unable to confidently report “high risk” or “low risk” test result (~6% of specimens) and may be due to
  - Insufficient fetal DNA in maternal specimen (low fetal fraction [FF])
  - Presence of mosaicism in one of the targeted chromosomes in the fetus, placenta, or mother
  - Unrecognized multiple-gestation pregnancy
  - Individual being tested is not the genetic mother of the fetus
  - Individual being tested has undergone allogeneic bone marrow transplant
  - Parents of fetus are blood relatives
- Unchanged (microdeletion test results only)
  - Unable to determine if the risk to have a child with a deletion was either increased or decreased
    - Population risk will be reported

Limitations

- Inappropriate for women who
  - Are carrying more than one fetus
  - Are not carrying their biological offspring (eg, pregnancies resulting from an egg donor, or if the woman is a surrogate)
  - Have undergone allogeneic bone marrow transplant
- Aneuploidy for chromosomes other than 13, 18, 21, X, and Y will not be detected
- Fetal mosaicism may not be detected
- Low FF may occur normally in some pregnancies and can affect the accuracy of the test
  - Individuals with elevated BMI are at increased risk of having a low FF
    - May result in increased chance of a false-positive, false-negative, or no-call test result