Noninvasive Prenatal Testing for Fetal Aneuploidy, With or Without Microdeletions

Indications for Ordering

- First- or second-tier screening test for the most common fetal aneuploidy disorders
  - Trisomy 13 (T13), trisomy 18 (T18), Down syndrome (trisomy 21 [T21]), Turner syndrome (TS), sex chromosome aneuploidies (XXX, XXY, XYY), and triploidy
- Test utilizes placental cell-free DNA (cfDNA) found in the maternal blood to identify women with a fetus at increased risk for the targeted disorders
- Screening test for pregnant women at 9w0d gestation to term

Test Description

PCR followed by next generation sequencing

Tests to Consider

Primary tests

Non-Invasive Prenatal Testing for Fetal Aneuploidy 2007537

- First- or second-tier screening test for the most common fetal aneuploidy disorders in pregnant women (9w0d-term)
  - T13, T18, T21, TS, triploidy
  - Sex chromosome aneuploidies (XXX, XXY, XYY) will be reported if identified
- Test may be ordered for
  - Singleton or twin pregnancies
  - Pregnancies achieved using an egg donor or surrogate
- Women at increased risk should be offered diagnostic testing (amniocentesis or chorionic villus sampling [CVS]) instead of screening
  - Increased risk includes
    - Women with a previous fetus with autosomal aneuploidy
    - Women ≥35 years at delivery
    - Women with an increased risk for aneuploidy based on multiple marker screening
    - Women with fetal ultrasound findings suggestive of T13, T18, T21, or TS
    - Either parent is a carrier of a Robertsonian translocation involving chromosomes 13 or 21
- Test 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)
- Test not recommended for women
  - Carrying triplets or higher-order multiples
  - Who have a known twin demise (vanished twin)
  - Who are carrying twins *and* used an egg donor/surrogate
    - Twin, egg donor/surrogate specimens will be run at Natera and reported through ARUP
  - Who have had an allogenic bone marrow transplant

Non-Invasive Prenatal Testing for Fetal Aneuploidy with 22q11.2 Microdeletion 2013142

- First- or second-tier screening test for the most common fetal aneuploidy disorders in pregnant women (9w0d-term)
  - T13, T18, T21, TS, X, Y, triploidy
  - Microdeletions causing 22q11.2 deletion syndrome (DiGeorge or velocardiofacial syndrome [VCFS])
    - Useful when the fetus is identified as having a heart defect and/or other findings suggestive of del22q11.2
    - May identify presence of 22q11.2 deletion in the patient
- Test may be ordered for
  - Singleton or monozygotic twin pregnancies
    - Monozygotic twin specimens will be run at Natera and reported through ARUP
- Test not recommended for women
  - Who are carrying dizygotic twins, triplets, or higher-order multiples
  - Who have a known twin demise (vanished twin)
  - Who have used an egg donor
  - Who are surrogates not using their own egg
  - Who have had an allogenic bone marrow transplant

Non-Invasive Prenatal Testing for Fetal Aneuploidy with Microdeletions 2010232

- First- or second-tier screening test for the most common fetal aneuploidy disorders in pregnant women (9w0d-term)
  - T13, T18, T21, TS, X, Y, and triploidy
- Microdeletion testing for
  - 22q11.2 deletion syndrome (DiGeorge or VCFS)
  - 1p36 deletion syndrome
  - Angelman syndrome
  - Prader-Willi syndrome
  - Cri-du-chat (5p-) syndrome
- Test not recommended for women
  - Who are carrying more than one fetus or who have a known twin demise (vanished twin)
  - Who have used an egg donor
  - Who are surrogates not using their own egg
  - Who have had an allogenic bone marrow transplant

Related tests (screening for low-risk individuals)

Maternal Serum Screening, Integrated, Specimen #1, PAPP-A, NT 3000147

Maternal Serum Screening, Integrated, Specimen #2, Alpha Fetoprotein, hCG, Estriol, and Inhibin A 3000149

Maternal Screening, Sequential, Specimen #1, hCG, PAPP-A, NT 3000146

Maternal Screening, Sequential, Specimen #2, Alpha Fetoprotein, hCG, Estriol, and Inhibin A 3000148

Maternal Serum Screen, First Trimester, hCG, PAPP-A, NT 3000145

Maternal Serum Screen, Alpha Fetoprotein, hCG, Estriol, and Inhibin A (Quad) 3000143

Alpha Fetoprotein (Amniotic Fluid) with Reflex to Acetylcholinesterase and Fetal Hemoglobin 3000142

Related tests (diagnostic testing)

Chromosome Analysis, Amniotic Fluid 2002293

Chromosome Analysis, Chorionic Villus 2002291

Cytogenomic SNP Microarray – Fetal 2002366

Disease Overview

Incidence at birth

- T13 – 1/5,000
- T18 – 1/3,000
- T21 – 1/700
- TS – 1/2,500 female births
- 1p36 deletion – 1/5,000
- 5p deletion – 1/20,000
- 22q11.2 deletion – 1/2,000
- Angelman – 1/12,000
- Prader-Willi – 1/10,000
- Sex chromosome aneuploidies – 1/250-300
- Triploidy – 1/50-100 conceptuses (very rare at birth)

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 >35 years
- High false-positive rates, associated with traditional prenatal aneuploidy screening methods, result in unnecessary invasive diagnostic procedures
  - Invasive procedures (eg, amniocentesis, CVS) carry a small risk of pregnancy loss
- cfDNA screening combines very high sensitivity (>99%) with very high specificity (>99%) for fetal aneuploidy
  - Should not be used in place of routine ultrasound or diagnostic testing for chromosomal aneuploidies
- Positive predictive value (PPV) is the likelihood that a positive NIPT screen will be confirmed as positive through a diagnostic test, which varies based on chromosome abnormality, maternal age, and gestational age
  - Average PPV by chromosome (Dar, 2014)
    - T13 – 38%
    - T18 – 93%
    - T21 – 91%
    - TS – 50%
- Microdeletion risk is very low (1/1,000) 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

Test Interpretation

Sensitivity/specificity

- Aneuploidy
  - Clinical sensitivity/specificity – >99%
- Microdeletions
  - Clinical sensitivity – >99%
  - Clinical specificity – >94%
- While the sensitivity and specificity are very high, both false-positive and false-negative test results can still occur due to confined placental mosaicism, fetal mosaicism, low fetal fraction, and the rarity of some of the disorders
- See positive predictive value above, or contact an ARUP genetic counselor if you have questions

Results

Each risk assessment includes the fetal fraction (FF), fetal sex (unless patient history form indicates this information is not desired), and the age-related/pretest risk

- High risk – significantly increased risk for fetus to have trisomy of chromosomes 13, 18, or 21; monosomy X; triploidy; or a deletion causing 22q11.2 microdeletion; 1p36 deletion; Angelman, cri-du-chat, or Prader-Willi syndromes
  - Although not specifically targeted, results that suggest fetal 47,XXX, 47,XXY, or 47,XYY will be reported
  - **As these are screening tests, diagnostic testing (eg, fetal karyotype by amniocentesis or CVS) is required to confirm abnormal results before irreversible action is taken**
- Low risk – very low risk for fetus to have abnormality of chromosomes 13, 18, 21, X, Y; triploidy; or a deletion causing 22q11.2 microdeletion (DiGeorge/VCFS); 1p36 deletion; Angelman, cri-du-chat, or Prader-Willi syndromes
  - Fetal karyotype, microarray, or other testing may still be appropriate if
    - Fetal anomalies are detected by ultrasound
    - Other concerns exist regarding the health of the fetus
- No result – unable to confidently report "high risk" or "low risk" test result (~3% of specimens) and may be due to
  - Insufficient fetal DNA in maternal specimen (low fetal fraction)
  - Presence of mosaicism in one of the targeted chromosomes in the fetus, placenta, or mother
  - Parents of fetus are blood relatives
- Unchanged (microdeletion test results only)
  - Unable to determine if the risk to have a child with a deletion is either increased or decreased, usually due to a low (<7%) fetal fraction
    - Population risk will be reported

Limitations

- Unless otherwise specified in the test descriptions above, inappropriate for women who
  - Are carrying more than one fetus
  - Are not carrying their biological offspring (eg, pregnancies resulting from an egg donor or when the woman is a surrogate)
  - Have undergone allogeneic bone marrow transplant
  - In any of the above circumstances, cfDNA screening by alternative method may be available
- 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 ability to report a result
  - Women with elevated body mass index (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 and should be counseled accordingly
    - Waiting to test until the second trimester, when FF is expected to be higher than in the first trimester, may increase the chances of obtaining a result for these women
- Maternal factors (eg, BMI or current cancer diagnosis) may affect FF or cfDNA analysis

References

- Dar P, Curnow KJ, et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. Am J Obstet Gynecol. 2014; 211(5):527.e1-527.e17
- Pergament E, Cuckle H, et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. Obstet Gynecol. 2014;124:210-218