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, X, Y, 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

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology.
500 Chipeta Way, Salt Lake City, UT 84108 | (800) 522-2787 | (801) 583-2787 | www.arulab.com | www.arupconsult.com
© 2017 ARUP LABORATORIES | Content Review March 2018 | Last Update March 2018
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
- Triplody – 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

© 2017 ARUP LABORATORIES | Content Review March 2018 | Last Update March 2018
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,XY 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