

Maternal Serum Screening

Indications for Ordering

Low-risk individuals

Maternal Serum Screen, First Trimester

- First-trimester screening test for Down syndrome (trisomy 21 [T21]) and trisomy 18 (T18)

Maternal Serum Screen, Sequential

- Combined first- and second-trimester screening tests for T21, T18, and open neural tube defects (ONTD)

Maternal Serum Screen, Integrated

- Combined first- and second-trimester screening tests for T21, T18, and ONTD

Maternal Serum Screen, Quad

- Second-trimester (>14 weeks) screening test for T21, T18, and ONTD for individual who did not have first-trimester screening performed

High-risk individuals

All high-risk pregnant women should consider noninvasive prenatal testing (NIPT), chorionic villus sampling (CVS), or amniocentesis instead of the tests listed above

- High risk defined as
 - Women ≥ 35 years at delivery
 - Previous pregnancy with chromosome aneuploidy
 - Either parent is a known carrier of a chromosomal translocation or inversion
 - Abnormal fetal ultrasound
 - Increased risk of ONTD due to family history, patient use of specific medications (eg, valproic acid or carbamazepine), or diabetic status

Test Description

Methodology depends on test components

- Alpha fetoprotein (AFP) and human chorionic gonadotropin (hCG)
 - Noncompetitive (sandwich) immunoassay
 - Antibodies – capture protein to a solid phase and detect presence of protein
 - External calibrators used
- Unconjugated estriol (uE3)
 - Solid phase competitive immunoassay
 - Antiestriol polyclonal antibody (labeled estriol)
 - Solid phase antibody directed against the estriol antibody
 - External calibrators

- Dimeric Inhibin-A (DIA)
 - Noncompetitive (sandwich) microtiter immunoassay
 - Capture antibody to inhibin subunit β A
 - Detection antibody to subunit α
 - External calibrators
- Pregnancy-associated plasma protein-A (PAPP-A)
 - Sequential immunoenzymatic assay
 - Measures protein using monoclonal antibodies and external calibrators
- Post-test risks – calculations by a multivariate log Gaussian model
 - Risk estimates for T21 and T18 are strongly influenced by maternal age
- Refer to table for first- and second-trimester screening options

Tests to Consider

Primary tests

[Maternal Serum Screen, First Trimester, hCG, PAPP-A, NT 3000145](#)

- First-trimester screening test for T21 and T18
- Does not include AFP for ONTD screening
- Requires NT measurement performed by an ultrasonographer certified by the Fetal Medicine Foundation (FMF) or the Nuchal Translucency Quality Review (NTQR)

[Maternal Screening, Sequential, Specimen #1, hCG, PAPP-A, NT 3000146](#)

- First-trimester screening test for T21 and T18
- Requires NT measurement performed by an ultrasonographer certified by the FMF or NTQR
- Risks provided in both first and second trimesters

[Maternal Screening, Sequential, Specimen #2, Alpha Fetoprotein, hCG, Estriol, and Inhibin A 3000148](#)

- Second-trimester screening test for T21, T18, and ONTD
- Requires a previously submitted first-trimester specimen, Maternal Screening, Sequential, Specimen #1, hCG, PAPP-A, NT (3000146)
- Requires NT measurement performed by an ultrasonographer certified by the FMF or NTQR
- Risks provided in both first and second trimesters

[Maternal Serum Screening, Integrated, Specimen #1, PAPP-A, NT 3000147](#)

- First-trimester screening test for T21, T18, and ONTD
- Risks determined using a combination of first- and second-trimester serum markers, with or without first-trimester nuchal translucency (NT) measurement
- Risks provided after testing is completed for second-trimester specimen, Maternal Serum Screening, Integrated, Specimen #2, Alpha Fetoprotein, hCG, Estriol, and Inhibin A (3000149)

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

- Second-trimester screening test for T21, T18, and ONTD
- Requires a previously submitted first-trimester specimen, Maternal Serum Screening, Integrated, Specimen #1, PAPP-A, NT (3000147)
- Risks are determined after second-trimester specimen is received, using a combination of first- and second-trimester serum markers with or without first-trimester NT measurement

[Maternal Serum Screen, Alpha Fetoprotein, hCG, Estriol, and Inhibin A \(Quad\) 3000143](#)

- Second-trimester screening test for T21, T18, and ONTD

Related tests (screening)

[Non-Invasive Prenatal Testing for Fetal Aneuploidy 2007537](#)

[Non-Invasive Prenatal Testing for Fetal Aneuploidy with 22q11.2 Microdeletion 2013142](#)

[Non-Invasive Prenatal Testing for Fetal Aneuploidy with Microdeletions 2010232](#)

Related tests (diagnostic)

[Chromosome Analysis, Chorionic Villus 2002291](#)

[Chromosome Analysis, Amniotic Fluid 2002293](#)

[Cytogenomic SNP Microarray – Fetal 2002366](#)

Disease Overview

Incidence

- ONTD – 1/900 pregnancies
- T21 – 1/600 births
- T18 – 1/3,000 births

Background

ONTD

- Most common ONTDs include
 - Spina bifida
 - Often results in some degree of paralysis of lower limb, loss of bowel and bladder control, ventriculomegaly
 - Anencephaly
 - Incompatible with life
- Risk – independent of maternal age

T21

- Extra copy of chromosome 21
- Features
 - Moderate intellectual disability
 - Characteristic facial features
 - Variety of medical conditions (eg, cardiac abnormalities)
- Risk – increases with maternal age
 - ~50% of babies with T21 are born to women <35 years

T18

- Extra copy of chromosome 18
- Most newborns die within their first year of life
- Features
 - Severe to profound intellectual disability
 - Small size at birth/poor growth
 - Variety of medical conditions (eg, cardiac abnormalities) which are generally more severe than those seen in T21
- Risk – increases with maternal age

Screening/detection

- Maternal serum screening helps to identify pregnancies at risk for ONTD, T21, or T18
- Most families who have a child with ONTD, T21, or T18 have no obvious risk factor for the condition (eg, advanced maternal age, previous history)
- Refer to table for first- and second-trimester screening options
- Abnormal results for any screen requires followup
 - Targeted ultrasound (US)
 - Other prenatal diagnostic procedures
 - Genetic counseling

Test Interpretation

Results

T21 cutoffs listed below are ARUP default cutoffs

- Clients may request a different T21 cutoff

Maternal Serum Screen, First Trimester

- T21 screen – 1/230 or worse, reported as abnormal
- T18 screen – 1/100 or worse, reported as abnormal

Maternal Serum Screen, Sequential

- First trimester
 - T21 and T18 screen – 1/25 or worse, reported as abnormal
 - Second-trimester specimen not required if first-trimester result is abnormal
- Second trimester
 - T21 screen – 1/110 or worse, reported as abnormal
 - T18 screen – 1/100 or worse, reported as abnormal
 - ONTD screen
 - AFP ≥ 2.5 MoM – increased risk for ONTD
 - AFP < 2.5 MoM – screen will be reported as abnormal when the ONTD risk is 1/250 or worse
 - uE3 < 0.15 MoM – increased risk for congenital steroid sulfatase deficiency or Smith-Lemli-Optiz syndrome
 - hCG ≥ 3.5 MoM – increased risk for poor fetal outcome

Maternal Serum Screen, Integrated

- See maternal serum screen sequential for second trimester

Maternal Serum Screen, Quad

- See maternal serum screen sequential for second trimester

Limitations

- A screen interpreted as “normal” misses approximately 15-20% of ONTD cases, 10-20% of T21 cases, and 10-20% of T18 cases, depending on the test and maternal age
- AFP false positives occur with multiple gestation pregnancies, fetal ventral wall defects, fetal demise, and underestimated gestational age

First- and Second-Trimester Prenatal Screening Options					
	First Trimester Only	Serum Integrated (without NT)	Full Integrated (with NT)	Sequential Screen	Quad
Specimen(s) collected	First trimester	First and second trimester	First and second trimester	First and second trimester	Second trimester
First-trimester measurements	US – CRL, NT Blood – PAPP-A, total hCG	US – CRL (optional) Blood – PAPP-A	US – CRL , NT Blood – PAPP-A	US – CRL, NT Blood – PAPP-A, hCG	N/A
Gestational age	Blood – 43-83.9 mm (11w0d–13w6d) NT – 38-83.9 mm (10w3d-13w6d)	32.4-83.9 mm (10w0d-13w6d) by US or LMP	Blood – 32.4-83.9 mm (10w0d-13w6d) NT – 38-83.9 mm (10w3d–13w6d)	Blood – 43-83.9 mm (11w0d-13w6d) NT – 38-83.9 mm (10w3d-13w6d)	N/A
Second-trimester measurements	N/A	AFP, hCG, uE3, DIA	AFP, hCG, uE3, DIA	AFP, hCG, uE3, DIA	AFP, hCG, uE3, DIA
Gestational age	N/A	14w0d-24w6d (by previous CRL or LMP)	14w0d-24w6d (by previous CRL)	14w0d-24w6d (by previous CRL)	14w0d-24w6d
Down syndrome (T21)					
Detection rate	85%	85%	87%	86% (63% – first draw; 23% – second draw)	81%
Screen-positive rate	6%	3-4%	1%	1.6% (0.6% – first draw; 1% – second draw)	4-5%
Trisomy 18					
Detection rate	~80%	90%	90%	90%	~80%
Screen-positive rate	<1%	0.01%	0.01%	0.01%	<0.5%
Open neural tube defect					
Detection rate	N/A	80%	80%	80%	80%
Screen-positive rate	N/A	1-2%	1-2%	1-2%	1-2%
Results reported	First trimester	Second trimester	Second trimester	Both first and second trimesters	Second trimester