



BlueCross BlueShield
of Alabama

Name of Blue Advantage Policy:

**First-Trimester Detection of Down Syndrome Using Fetal
Ultrasound Markers Combined with Maternal Serum Assessment**

Policy #: 233

Latest Review Date: November 2024

Category: OB/Gyn

BACKGROUND:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
 - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - *Furnished in a setting appropriate to the patient's medical needs and condition;*
 - *Ordered and furnished by qualified personnel;*
 - *One that meets, but does not exceed, the patient's medical need; and*
 - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **first-trimester screening for detection of Down syndrome**, which consists of a calculation of risk based on patient's age, serum markers such as human chorionic gonadotropin and pregnancy-associated plasma protein A, and ultrasonic measurement of fetal nuchal translucency as a **covered benefit** for patients who are adequately counseled and desire information on the risk of having a child with Down syndrome. .

Blue Advantage will treat **first-trimester screening for detection of Down syndrome using measurement of nuchal translucency alone** as a **non-covered benefit** and as **investigational**.

Blue Advantage will treat **first-trimester screening for detection of Down syndrome incorporating fetal nasal bone assessment translucency** as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Ultrasound markers can potentially increase the sensitivity of biochemical measures for first trimester detection of Down syndrome. Nuchal translucency (NT) refers to the ultrasound detection of subcutaneous edema in the fetal neck between weeks 10 and 13 of gestation. Fetal nasal bone examination involves ultrasound assessment at 11-14 weeks' gestation to identify the presence or absence of the nasal bone.

Definitive diagnosis of Down syndrome and other chromosomal abnormalities requires amniocentesis or chorionic villus sampling (CVS), both of which are invasive procedures that carry a risk of miscarriage. Because of this risk, before biochemical screening existed, diagnosis was generally only offered to women 35 years or older, for whom the risk of the procedure approximated the risk of Down syndrome. However, the majority of babies with Down syndrome are born from mothers younger than 35 years, even though the mothers are at lower individual risk. This situation created interest in developing less-invasive screening programs based on assessment of serum markers that have shown associations with Down syndrome. In the late 1980s, biochemical screening at 16 weeks' gestation was developed and began to be offered to all pregnant women. Biochemical screening consists of maternal serum measurements of alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol (i.e., triple screen). More recently, there has been the option of a fourth marker, inhibin-A (quadruple screen). The triple screen identifies approximately 69% of Down syndrome pregnancies and the quadruple screen 81%, both at a 5% false-positive rate. This false-positive rate refers to the proportion of

all tests administered that are falsely positive at the cutoff point that produces that particular value of sensitivity. Among women who test positive, only about 2% actually have a fetus with Down syndrome.

There has also been interest in ultrasound markers to improve the accuracy of biochemical screening. One potential marker is fetal NT. This refers to the ultrasound detection of subcutaneous edema in the fetal neck, and is measured as the maximal thickness of the sonolucent zone between the inner aspect of the fetal skin and the outer aspect of the soft tissue overlying the cervical spine or the occipital bone. In the early 1990s, screening studies of pregnant women reported an association between increased NT in the first trimester of pregnancy (10–13 weeks of gestation) and chromosomal defects, most commonly Down syndrome, but also trisomy 18 and 13. NT could be done alone as a first-trimester screen, or in combination with the maternal serum markers, free beta subunit of human chorionic gonadotropin (B-hCG) and pregnancy-associated plasma protein-A (PAPP-A). These are different serum markers than those used in the second-trimester triple or quadruple screen.

Another potential ultrasound marker is fetal nasal bone examination. The technique for assessing the nasal bone using ultrasound involves viewing the fetal face longitudinally and exactly in the midline. The nasal bone synostosis resembles a thin echogenic line within the bridge of the nose. The nasal bones are considered to be present if this line is more echogenic than the overlying skin and absent if the echogenicity is the same or less than the skin, or if it is not visible. The absence of fetal nasal bone is considered to be a positive test result, indicating an increased risk of Down syndrome. In some cases, the sonographer will not be able to visualize the nasal area of the fetus's face and thus cannot make a determination of the presence or absence of nasal bone. The inability to visualize the nasal bone is regarded as an unsuccessful examination, rather than a positive test result. Fetal nasal bone examination can be done from 11 weeks to just before 14 weeks' gestation. It is sometimes recommended that, if the nasal bone is absent on ultrasound done between 11 and 12 weeks' gestation, a second examination be done 2 weeks later. Fetal nasal bone assessment can be done along with NT, or in the second step of a 2-stage screen for cases that are borderline using other first-trimester markers.

Note: This policy only addresses the ultrasound markers, nuchal translucency, and fetal nasal bone assessment.

KEY POINTS:

The literature was reviewed through November 14, 2024.

Summary of Evidence

For individuals who are pregnant and in the first trimester who receive first-trimester Down syndrome screening of maternal serum markers and nuchal translucency, the evidence includes observational screening studies. Relevant outcomes are test accuracy and validity and resource utilization. There is sufficient evidence from 2 large multicenter prospective studies- the Serum, Urine, and Ultrasound Screening Study (SURUSS) and the First and Second Trimester Evaluation of Risk (FASTER) trial- as well as several smaller studies, that first-trimester screening for Down syndrome with measurement of fetal NT and maternal serum markers is at

least as accurate as alternative tests and may allow earlier confirmation or exclusion of Down syndrome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are pregnant and in the first trimester who receive first-trimester Down syndrome screening of nuchal translucency alone, the evidence includes observational screening studies. Relevant outcomes are test accuracy and validity and resource utilization. The large multicenter prospective studies SURUSS and FASTER found, overall, that first-trimester screening with NT alone is inferior to first- or second-trimester combined screening. Additional testing may not be necessary in those few cases when NT is at least 4.0 mm due to the high likelihood of Down syndrome, but this would affect only a very small number of cases (0.09%-0.3%). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are pregnant and in the first trimester who receive first-trimester Down syndrome screening of fetal nasal bone, the evidence includes several observational studies. Relevant outcomes are test accuracy and validity and resource utilization. The accuracy of testing in the published literature is variable, with some studies reporting relatively low sensitivity rates. The variability in accuracy reported may reflect the difficulty in performing and interpreting this test, and test results are likely prone to differences in operator characteristics. Limited evidence has suggested that there may be modest incremental benefit when the test is used in combination with NT measurement and serum markers, but the degree of benefit is unclear. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists (ACOG)

In December 2016 (reaffirmed in 2022), ACOG issued practice bulletin 175 for ultrasound in pregnancy. The following recommendations and conclusions in the bulletin are relevant to this evidence review:

Level A recommendation (based on good and consistent scientific evidence):

“Measurement of nuchal translucency alone is less effective for first-trimester screening of the singleton pregnancy than is combined testing (nuchal translucency measurement and biochemical markers).”

There is no specific recommendation regarding nasal bone assessment, but they state the following:

“Other first trimester screening ultrasonographic markers such as nonvisualization of the nasal bone, tricuspid regurgitation, and abnormal ductus venosus waveforms have been associated with trisomy 21, but their clinical usefulness in the general population remains uncertain.”

U.S. Preventive Services Task Force Recommendations

Not applicable

KEY WORDS:

First trimester screening, nuchal translucency, NT, pregnancy-associated plasma protein, PAPP-A, serum estriol, Down syndrome, free beta-hCG, fetal nasal bone assessment, Maternal fetal screen, T1 SM, T1+Y Chromosome SM, free beta SM, Eurofins, triple screen, quadruple screen

APPROVED BY GOVERNING BODIES:

Fetal ultrasound uses available instrumentation and as a surgical procedure is not subject to regulation by the U.S. Food and Drug Administration.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:**CPT codes:**

The following codes should be used for ultrasound measurement of nuchal translucency:

76813	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation
76814	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; each additional gestation (list separately in addition to code for primary procedure)

There is no specific CPT code for ultrasound assessment of fetal nasal bone translucency. It should be reported using CPT code 76815- Ultrasound, pregnant uterus, real time with image documentation, limited (e.g., fetal heartbeat, placental location, fetal position and/or qualitative amniotic fluid volume), one or more fetuses.

The following codes should be used to report combination testing:

81508	Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score (Do not report 81508 in conjunction with 84163, 84702)
81509	Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score (Do not report 81509 in conjunction with 84163, 84702, 86336)
81510	Fetal congenital abnormalities, biochemical assays of three proteins (AFP, uE3, hCG [any

	form], utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)
81511	Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA) utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing) (Do not report 81511 in conjunction with 82105, 82677, 84702, 86336)
81512	Fetal congenital abnormalities, biochemical assays of five analytes (AFP, uE3, total hCG, hyperglycosylated hCG, DIA) utilizing maternal serum, algorithm reported as a risk score (Do not report 814XX5 in conjunction with 82105, 82677, 84702, 86336)

REFERENCES:

1. Adiego B, Martinez-Ten P, Illescas T, et al. First-trimester assessment of nasal bone using retronasal triangle view: a prospective study. *Ultrasound Obstet Gynecol* 2014; 43(3):272-276.
2. Alldred SK, Takwoingi Y, Guo B, et al. First trimester ultrasound tests alone or in combination with first trimester serum tests for Down's syndrome screening. *Cochrane Database Syst Rev*. 2017 Mar 15;3:CD012600.
3. American College of Obstetricians and Gynecologists. *Ultrasound in pregnancy* (No. 175). www.acog.org.
4. Audibert F, Gagnon A, Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada; Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Prenatal screening for and diagnosis of aneuploidy in twin pregnancies. *J Obstet Gynaecol Can* 2011; 33(7):754-767.
5. Baer RJ, Flessel MC, Jelliffe-Pawlowski LL, et al. Detection rates for aneuploidy by first trimester and sequential screening. *Obstet Gynecol*. Oct 2015; 126(4):753-759.
6. Berkthold L, C VK, Hillemanns P, et al. Analysis of the impact of PAPP-A, free beta-hCG and nuchal translucency thickness on the advanced first trimester screening. *Arch Gynecol Obstet* 2013; 287(3):413-420.
7. Brameld KJ, Dickinson JE, et al. First trimester predictors of adverse pregnancy outcomes. *Aust N Z J Obstet Gynaecol*, December 2008; 48(6): 529-535.
8. Caughey AB, Musci TJ, Belluomini J, et al. nuchal translucency screening: How do women actually utilize the results? *Prenat Diagn* 2007; 27(2): 119-123.
9. Chanprapaph P, Dulyakasem C, Phattanchindakun B. Sensitivity of multiple first trimester sonomarkers in fetal aneuploidy detection. *J Perinat Med*. May 2015; 43(3):359-365.
10. Chitayat D, Langlois S, Wilson RD. Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada; Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Prenatal screening for fetal aneuploidy in singleton pregnancies. *J Obstet Gynaecol Can* 2011; 33(7):736-750.
11. Cicero S, Avgidou K, Rembouskos G, et al. Nasal bone in first-trimester screening for trisomy 21. *Am J Obstet Gynecol*, July 2006; 195(1): 109-114.

12. Comstock CH, Malone FD, Ball RH, et al. Is there a nuchal translucency millimeter measurement above which there is no added benefit from first trimester serum screening? *Am J Obstet Gynecol* 2006; 195(3): 843-847.
13. Cuckle H, Malone F, Wright D et al. Contingent screening for Down syndrome—results from the FASTER trial. *Prenat Diag* 2008; 28(2):89-94.
14. Fetal Medicine Foundation website. Available online at: www.fetalmedicineusa.com.
15. Fetal Medicine Foundation website, Certificate of Competence in the Measurement of Nuchal Translucency. Available online at: www.fetalmedicine.com/fmf/training-certification/certificates-of-competence/11-13-week-scan/nuchal/.
16. Haddow JE, Palomaki GE, Knight GJ, et al. Screening of maternal serum for fetal Down's syndrome in the first trimester. *N Engl J Med* 1998; 338(14):955-961.
17. Has R, Kalelioglu I, Yuksel A, et al. Fetal nasal bone assessment in first trimester Down syndrome screening. *Fetal Diagn Ther* 2008; 24(1): 61-66.
18. Hsiao CH, Cheng PJ, Shaw SW, et al. Extended first-trimester screening using multiple sonographic markers and maternal serum biochemistry: a five-year prospective study. *Fetal Diagn Ther*. Feb 6 2014; 35(4):296-301.
19. IOM (Institute of Medicine). 2011. *Clinical Practice Guidelines We Can Trust*. Washington, DC: The National Academies Press.
20. Kagan KO, Etchegaray A, Zhou Y, et al. Prospective validation of first-trimester combined screening for trisomy 21. *Ultrasound Obstet Gynecol*, July 2009; 34(1): 14-18.
21. Kagan KO, Staboulidou I, Cruz J, et al. Two-stage first-trimester screening for trisomy 21 by ultrasound assessment and biochemical testing. *Ultrasound Obstet Gynecol* 2010; 36(5):542-547.
22. Kagan KO, Wright D, Etchegaray A, et al. Effect of deviation of nuchal translucency measurements on the performance of screening for trisomy 21. *Ultrasound Obstet Gynecol*, June 2009; 33(6): 657-664.
23. Leung TY, Chan LW, Leung TN, et al. First-trimester combined screening for trisomy 21 in a predominantly Chinese population. *Ultrasound Obstet Gynecol*, January 2007; 29(1): 14-17.
24. Malone FD, Canick JA, Ball RH, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. *NEJM* 2005; 353(19): 2001-2011.
25. Malone FD, Ball RH, Nyberg DA, et al. First-trimester nasal bone evaluation for aneuploidy in the general population. *Obstet Gynecol*, Dec 2004; 104(6):1222-1228.
26. McLennan A, Schluter PJ, Pincham V et al. First-trimester fetal nasal bone audit: evaluation of a novel method of image assessment. *Ultrasound Obstet Gynecol* 2009; 34(6):623-628.
27. Miron P, Cote YP and Lambert J. Nuchal translucency thresholds in prenatal screening for Down syndrome and trisomy 18. *J Obstet Gynaecol Can*, March 2009; 31(3): 227-235.
28. Mokhtar R, Hans P, Sinha A. Comparing Non-invasive prenatal testing with invasive testing for the detection of trisomy 21. *Cureus*. 2022 Nov; 14(11):e31252.
29. Mol BW, Lijmer JG, van der Meulen J, et al. Effect of study design on the association between nuchal translucency measurement and Down syndrome. *Obstet Gynecol* 1999; 94(5 pt 2):864-869.
30. Nanni M, Maroni E, Bevini M, et al. The usefulness of volume NT software in measuring the fetal nasal bone at 11 to 13 + 6 weeks of gestation. *Prenat Diag* 2014.

31. Peuhkurinen S, Laitinen P, Honkasalo T, et al. Comparison of combined, biochemical and nuchal translucency screening for Down's syndrome in first trimester in Northern Finland. *Acta Obstet Gynecol Scand*. Jul 2013; 92(7):769-774.
32. Platt LD, Greene N, Johnson A, et al. Sequential pathways of testing after first-trimester screening for trisomy 21. *Obstet Gynecol* 2004; 104(4): 661-666.
33. Prefumo F, Sairam S, Bhide A, Thilaganathan B. First-trimester nuchal translucency, nasal bones, and trisomy 21 in selected and unselected populations. *Am J Obstet Gynecol*, March 2006; 194(3): 828-833.
34. Ranta JK, Marttala J, Laitinen P, et al. First-trimester biochemistry at different maternal ages. *Clin Chem Lab Med*. Mar 2012; 50(3):549-555.
35. Rosen T, D'Alton ME, Platt LD, et al. First-trimester ultrasound assessment of the nasal bone to screen for aneuploidy. *Obstet Gynecol*, August 2007; 110(2 Pt 1): 399-404.
36. Sahota DS, Leung TY, Chan LW, et al. Comparison of first-trimester contingent screening strategies for Down syndrome. *Ultrasound Obstet Gynecol*, March 2010; 35(3): 286-291.
37. Schaelike M, Kossakiewicz M, et al. Examination of a first-trimester Down syndrome screening concept on a mix of 11,107 high- and low-risk patients at a private center for prenatal medicine in Germany. *Eur J Obstet Gynecol Reprod Biol* 2009; 144(2): 140-145.
38. Schmidt P, Staboulidou I, et al. How imprecise may the measurement of fetal nuchal translucency be without worsening first-trimester screening? *Fetal Diagn Ther* 2008; 24(3): 291-295.
39. Scott F, Evans J, McLennan A. Perinatal outcome in fetuses with extremely large nuchal translucency measurement. *Aust N Z J Obstet Gynaecol*, June 2009; 49(3): 254-257.
40. Senat MV, Bussieres L, Couderc S, et al. Long-term outcome of children born after a first-trimester measurement of nuchal translucency at the 99th percentile or greater with normal karyotype: A prospective study. *Am J Obstet Gynecol* 2007; 196(1): 53.e1-6.
41. Snijders RJ, Thom EA, Zachary JM et al. First-trimester trisomy screening: Nuchal translucency measurement training and quality assurance to correct and unify technique. *Ultrasound Obstet Gynecol* 2002; 12(4):353-359.
42. Sonek JD, Cicero S, Neiger R, Nicolaides KH. Nasal bone assessment in prenatal screening for trisomy 21. *Am J Obstet Gynecol*, November 2006; 195(5): 1219-1230.
43. Spencer K. What is the true fetal loss rate in pregnancies affected by trisomy 21 and how does this influence whether first trimester detection rates are superior to those in the second trimester? *Prenat Diagn* 2001; 21(9):788-789.
44. Torella M, Tormettino B, Zurzolo V, et al. Screening for trisomy 21 by maternal age fetal nuchal translucency thickness and maternal serum sample. *Minerva Ginecol* 2013; 65(6):653-659.
45. U.S. Preventive Services Taskforce. Guide to Clinical Preventive Services. Screening for Down syndrome. www.ncbi.nlm.nih.gov/books/NBK61778/.
46. Wald NJ, Rodeck C, Hackshaw AK, et al. First and second trimester antenatal screening for Down's syndrome: the results of the serum, urine and ultrasound screening study (SURUSS). *J Med Screen* 2003; 10(2):56-104.
47. Wald NJ, Rodeck C, Hackshaw AK, et al. SURUSS in perspective. *Semin Perinatol* 2005; 29(4): 225-235.
48. Wald NJ, Huttly WJ, Murphy KW, et al. Antenatal screening for Down's syndrome using the integrated test at two London hospitals. *J Med Screen* 2009; 16(1):7-10.

49. Wapner R, Thom E, Simpson JF et al. First-trimester screening for trisomies 21 and 18. N Engl J Med 2003; 349(15):1405-1413.
50. Wapner RJ. First-trimester screening: the BUN study. Semin Perinatol 2005; 29(4): 236-239.

POLICY HISTORY:

Adopted for Blue Advantage, August 2005

Available for comment August 30-October 13, 2005

Medical Policy Group, August 2007

Medical Policy Group, August 2010

Available for comment September 3-October 18, 2010

Medical Policy Group, October 2010

Medical Policy Group, July 2011

Medical Policy Group, March 2012

Medical Policy Group, December 2012

Medical Policy Group, April 2014

Medical Policy Group, April 2015

Medical Policy Group, December 2016

Medical Policy Group, November 2019

Medical Policy Group, August 2020: Removed codes 0124U, 0125U, 0126U.

Medical Policy Group, December 2020

Medical Policy Group, December 2021: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.

Medical Policy Group, November 2022: Reviewed by consensus. There is no new published peer-reviewed literature available that would alter the coverage statement in this policy.

UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.

Medical Policy Group, November 2024: Reviewed by consensus. There is no new published peer-reviewed literature available that would alter the coverage statement in this policy.

UM Committee, December 2024: Annual review of policy approved by UM Committee for use for Blue Advantage business.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.