



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Down Syndrome Screening**

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Hyperlink to Related Coverage Policies

Genetic Counseling
Genetic Testing of Heritable Disorders
Preimplantation Genetic Diagnosis
Ultrasound in Pregnancy (including 3D and 4D ultrasound)

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers the following prenatal screening tests for the detection of Down syndrome as medically necessary for women who have received adequate counseling and information regarding the risk of having a child with Down syndrome:

- first-trimester ultrasonic measurement of nuchal translucency (NT), combined with serum levels of pregnancy-associated plasma protein A (PAPP-A) and free beta human chorionic gonadotrophin (b-HCG)
- second-trimester quadruple screening (alpha-fetoprotein [AFP], unconjugated estriol [uE3], free beta-human chorionic gonadotrophin [b-HCG] or total human chorionic gonadotrophin [HCG], and inhibin-A, together with maternal age)

CIGNA does not cover the use of invasive trophoblast antigen (ITA) as a biochemical marker for Down syndrome screening because it is considered experimental, investigational or unproven.

CIGNA does not cover first-trimester ultrasonic measurement of nuchal translucency (NT) when performed alone for the detection of Down syndrome in singleton pregnancies because this use is considered experimental, investigational or unproven.

General Background

Down syndrome is a variable combination of congenital malformations caused by trisomy 21, a triplication of chromosome 21. Characteristic physical and facial features associated with Down syndrome include epicanthal folds, narrow palate, short broad hands and transpalmar crease. Down syndrome is also associated with congenital heart defects, disorders of the immune and endocrine systems, and mild to moderate mental retardation. The risk of having a baby with Down syndrome increases with maternal age, significantly so after age 35. Age cannot serve as the sole screening factor, however, as 70% of Down syndrome babies are born to women under 35.

Until recently, maternal serum multiple-marker testing was typically performed in the second trimester as the standard screening for Down syndrome. Prenatal detection methods utilized during the second trimester do not allow much time for the patient and physician to evaluate alternatives. The advent of first-trimester screening using ultrasonic nuchal translucency (NT) measurement combined with serum testing has allowed for earlier decision-making about invasive testing such as amniocentesis. First-trimester screening does not eliminate the need for second-trimester ultrasound for detecting gross structural fetal anomalies. Currently, many healthcare providers recommend that one ultrasound examination be performed, usually between 18 and 20 weeks of pregnancy, as a routine part of prenatal care.

Screening Methods

Triple Screen: The triple screen screens by maternal age and a low maternal serum alpha-fetoprotein (AFP) level, along with high serum levels of human chorionic gonadotrophin (HCG) and unconjugated estriol (uE3). These screens are performed between 17 and 19 weeks' gestation to calculate the risks of specific chromosomal abnormalities and open neural tube defects. The triple screen is currently the basis for most Down syndrome screening tests which are performed in the second trimester. This testing detects only 60–76% of Down syndrome cases, leaving over 20% of cases concealed until birth.

Quadruple Screen: The quadruple screen includes all the parameters of the triple screen, plus a high serum level of inhibin-A. Also done in the second trimester, the quad screen has a 67–76% detection rate for a false-positive rate of 5%. This method has replaced the triple screen in many clinical settings. A significant limitation of the triple and quadruple screens is the false-positive rate, which has been reported to result in as many as 60 amniocenteses being done for each case of Down syndrome identified. Approximately 0.5% of unnecessary amniocenteses result in miscarriage of healthy pregnancies. The pregnancy loss rate associated with amniocentesis is one in 200. Within this protocol, approximately one normal fetus is lost for every three fetuses with Down syndrome identified.

Nuchal Translucency (NT): The term nuchal translucency refers to the space between the back of the fetal neck and the overlying skin. An association between increased NT and aneuploidy, particularly Down syndrome, was first noted in populations at high risk for chromosomal abnormality (i.e., advanced maternal age with previous pregnancy involving aneuploidy). In many cases, NT can be measured accurately and reproducibly on ultrasound between 10 and 14 weeks' gestation. NT is measured in the sagittal plane between 10 and 13 weeks' gestation. NT measurement is, on average, almost two times larger in Down syndrome pregnancies than in unaffected pregnancies. Values depend on crown-rump length (CRL). Measurements equal to or greater than 3 mm are considered abnormal (Agarwal, 2003). It is commonly believed that the larger the NT measurement, the greater the association with Down syndrome and other aneuploidy. The detection rate for Down syndrome using NT measurement is approximately 70% with a 5% false-positive rate. NT measurement in the absence of serum screening has a low specificity; therefore, it is not recommended as a screening test for aneuploidy in singleton pregnancies.

Combined Screening: This protocol involves NT measurement and screening for a low maternal serum level of pregnancy-associated plasma protein A (PAPP-A) with a high level of free b-HCG in the first trimester. There is no interdependence between fetal NT and maternal free b-HCG or PAPP-A, so the two methods can be combined to provide more effective screening than either would yield individually. The Down syndrome detection rate for combined screening has been reported to range from 79% to 90 % with a 5% false-positive rate. It is acknowledged combined ultrasound and serum screening for multifetal gestations remains less sensitive than in singleton pregnancies (Driscoll, et al., 2008).

Hyperglycosylated HCG, also known as invasive trophoblast antigen (ITA), has been investigated as a biochemical marker for Down syndrome. In Down syndrome pregnancies, ITA has been found to be increased

in maternal urine in the first trimester and both maternal urine and serum in the second trimester. Detection rates of 67–81% have been reported for the use of ITA second-trimester screening.

The Ultra-Screen[®] Instant Risk Assessment (NTD Laboratories, Inc. Huntington Station, NY) has been introduced as an in-home blood collection system that utilizes the combined test to assess the risk of Down syndrome, trisomy 18, and other chromosomal abnormalities. A blood sample obtained via finger-stick as early as nine weeks, but optimally between 11 and 13 weeks of pregnancy, is sent to the laboratory for analysis of free b-HCG and PAPP-A levels. Ultrasound measurement of NT taken at 11–13 weeks' gestation is entered into the laboratory database. Aneuploidy risk is then calculated by computer algorithm based on maternal age, NT measurement and free b-HCG and PAPP-A levels (NTD, 2005).

Integrated Screening: The integrated test refers to integrating NT and PAPP-A measurements in the first-trimester with the quadruple test (AFP, unconjugated estriol, free b-HCG or total HCG, and inhibin-A, together with maternal age) early in the second trimester. Indicated risk is not presented to patients until completion of the second-trimester component.

Stepwise Sequential Screening: In the stepwise sequential approach, a serum PAPP-A and NT measurements are both obtained between 10 and 13 weeks. The results of these studies are combined with the woman's age-associated risk, and a risk assessment for aneuploidy is provided. The woman may then choose to undergo either invasive testing (e.g., amniocentesis or chorionic villas sampling [CVS]), or a triple or quad screen at 15 weeks. If second trimester testing is performed, a new risk is assessed based on age and both the first and second trimester screening test results.

Contingent Sequential Screening: In contingent sequential screening, the majority of women receive their results after first-trimester screening. Women determined to be at high risk are offered invasive testing, while women at low risk require no further testing. A proportion of women identified as being at intermediate risk are offered second trimester serum testing. The final risk assessment incorporates first- and second-trimester results.

Literature Review

A number of large-scale prospective studies (n= 8514–47,000) have demonstrated that the detection rate of first-trimester screening is comparable to that of serum-marker screening done in the second trimester (e.g., First and Second Trimester Evaluation for Aneuploidy Risk [FASTER] trial; Serum Urine and Ultrasound Screening Study [SURUSS]; Blood, Ultrasound and Nuchal Translucency [BUN] study). The studies also showed that integrating first- and second-trimester screening yields the highest detection rate for Down syndrome (Malone, et al., 2005; Wald, et al., 2004; Wapner, et al., 2004).

An evidence report by ECRI examined six prospective cohort screening studies (n=135,304), conducted in four different countries. The evidence base was rated as low in quality primarily due to the presence of obvious spectrum and patient selection bias. The specificity of the first-trimester test in detecting trisomy 21 was found to be 94% (95% CI: 92.8% to 95.0%). The data were found to be too unstable to support an estimate of the sensitivity of the test in detecting trisomy 21. It was concluded that the available evidence indicates that for women aged 20 to 40 carrying a single fetus the first-trimester screening test is accurate enough to warrant its use in guiding decisions as to whether to undergo invasive testing for trisomy 21 or 18 (ECRI, 2008).

A comparison study by Palomaki et al. (2005) assessed the performance of ITA in first-trimester Down syndrome screening. ITA measurements were performed in 54 Down syndrome pregnancies and 276 matched unaffected pregnancies. The combination of maternal age, PAPP-A and ITA compared to that of maternal age, PAPP-A and free b-HCG was reported to be equivalent with a detection rate of 67%, at a 5% false-positive rate. Several small, retrospective studies have also evaluated the efficacy of ITA as a component of screening panels (Weinans, et al., 2005; Pandian, et al., 2004). However additional studies with larger patient populations are needed to validate the accuracy of ITA for Down syndrome screening.

Professional Societies/Organizations

The American College of Medical Genetics has issued practice guidelines for fetal aneuploidy diagnosis and screening. The ACMG recommendations include the following (Driscoll, et al., 2008):

1. First trimester screening (NT, PAPP-A, and hCG) is an acceptable, option for DS risk screening for women who present in early pregnancy (i.e., before 14 weeks' gestation).
2. Women presenting in the second trimester should be offered multiple marker screening.
3. First trimester screening can be used in multifetal pregnancies; however, women should be made aware of the limitations of screening in this setting.
4. First trimester screening requires adherence to strict standards and maintenance of quality, both in the laboratory and ultrasound units. Sonographers must be appropriately trained in the proper technique of NT measurement and have appropriate certification through available organizations.

The National Institute for Clinical Excellence (NICE) guideline for routine antenatal care states that all pregnant women should be offered screening for Down syndrome. The NICE states that the screening test for Down syndrome offered should be the combined test (NT, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A) between 11 weeks and 13 weeks and 6 days. Women should be offered the most clinically effective serum screening test (e.g., triple or quadruple test between 15 and 20 weeks of gestation (NICE, 2008).

The ACOG Practice Bulletin entitled Screening for Fetal Chromosomal Abnormalities states that ideally, screening for aneuploidy should occur before 20 weeks of gestation, regardless of maternal age. The bulletin further states that the options for women whose initial prenatal visit occurs during the second trimester are limited to quadruple screening and ultrasound examination. A strategy that incorporates both first- and second-trimester screening should be offered to women who seek prenatal care in the first trimester. ACOG has made the following recommendations based on consistent scientific evidence (ACOG, 2007):

1. First-trimester screening using both NT, an ultrasound exam that measures the thickness at the back of the neck of the fetus, and a blood test is an effective screening test in the general population and is more effective than NT alone.
2. Measurement of NT alone is less effective for first-trimester screening than is the combined test (NT measurement and biochemical markers).
3. Women found to be at increased risk of having a baby with Down syndrome with first-trimester screening should be offered genetic counseling and the option of CVS or mid-trimester amniocentesis.
4. Specific training, standardization, use of appropriate ultrasound equipment, and ongoing quality assessment are important to achieve optimal NT measurement for Down syndrome risk assessment, and this procedure should be limited to centers and individuals meeting this criteria.
5. Neural tube defect screening should be offered in the mid-trimester to women who elect only first-trimester screening for Down syndrome.

ACOG guideline also states that NT measurements may be useful in the evaluation of multifetal gestations, for which serum screening is not as accurate (twins) or is unavailable (triplets or higher), compared with a singleton gestation (ACOG, 2007).

The Nuchal Translucency Quality Review (NTQR) credentialing program supported by the SMFM, ACOG and the American Institute of Ultrasound in Medicine (AIUM) was initiated in February 2005. The NTQR program goals include the following (NTQR, 2005):

- educating providers on how to obtain reproducible NT measurements
- providing a method to evaluate and track provider proficiency
- providing ongoing NT quality review

The 1996 guide from the U.S. Preventive Services Task Force (USPSTF) stated that the offering of screening for Down syndrome by maternal serum multiple-marker testing at 15–18 weeks of gestation is recommended for all pregnant women who have access to counseling and follow-up services, skilled high-resolution ultrasound

and amniocentesis capabilities, and reliable, standardized laboratories. There is insufficient evidence to recommend a specific multiple-marker screening protocol (USPSTF, 1996). The USPSTF is currently updating these recommendations to incorporate new evidence. According to the USPSTF, the 1996 recommendation may contain information that is out of date.

Summary

There is sufficient evidence in the published, peer-reviewed medical literature to demonstrate that the combination of nuchal translucency (NT) measurement and serum testing (i.e., pregnancy-associated plasma protein A [PAPP-A] and free beta human chorionic gonadotrophin [b-HCG]) in the first trimester is an effective screening tool for Down syndrome. Ultrasonic NT measurement used alone as a screening for aneuploidy has a lower detection rate and therefore is not as effective as combined screening methods. NT measurement alone has an established role in Down syndrome risk assessment for multifetal pregnancies, as the use of serum analytes is less accurate in this population. There is insufficient evidence to support the use of invasive trophoblast antigen (ITA) as a substitute for free b-HCG in any screening panel. Larger, well-designed studies are needed to further define the role of this biochemical marker.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
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)
82105	Alpha-fetoprotein, serum
82677	Estriol
84163	Pregnancy-associated plasma protein-A (PAPP-A)
84702	Gonadotrophin, chorionic (hCG), quantitative
84703	Gonadotrophin, chorionic (hCG), qualitative
84704	Gonadotrophin, chorionic (hCG),; free betachain
86336	Inhibin A

HCPCS Codes	Description
S3626	Maternal serum quadruple marker screen including alpha-fetoprotein (AFP), estriol, human chorionic gonadotropin (HCG), and inhibin a

ICD-9-CM Diagnosis Codes	Description
V28.3	Encounter for routine screening for malformation using ultrasonics
V28.89	Other specified antenatal screening
V28.9	Unspecified antenatal screening

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	10/15/2008	0211	Down Syndrome Screening
Great-West Healthcare	8/23/2007	05.304.02	Ultrasound of Fetal Nuchal Translucency (NT) in the First-Trimester

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.