Name of Policy:
First-Trimester Detection of Down Syndrome Using Fetal Ultrasound Markers Assessment of Nuchal Translucency Combined with Maternal Serum Assessment

Policy #: 233                                Latest Review Date: April 2014
Category: Obstetrics                        Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**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 estimated at 0.5% to 1%. 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 two weeks later. Fetal nasal bone assessment can be done along with NT, or in the second step of a two-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.

**Policy:**

First trimester screening for detection of Down syndrome, which consists of a **calculation of risk based on maternal age, human chorionic gonadotropin, pregnancy-associated plasma protein A, and ultrasonic measurement of fetal nuchal translucency**, meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for **women who are adequately counseled and desire information on the risk of having a child with Down syndrome**.

First-trimester screening for detection of Down syndrome using **measurement of nuchal translucency alone does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage.

First-trimester screening for detection of Down syndrome incorporating **fetal nasal bone assessment translucency does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational**.

*Blue Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate 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.*

**Key Points:**

In studies of first-trimester screening, the laboratory and imaging components of the screening are performed in a coordinated fashion. This process results in a set of predictions of Down syndrome, which can be summarized by receiver operator characteristic (ROC) curve analysis or sensitivity and specificity estimates. Although multiple cutoff points are possible, a standard method of presenting results is to report the sensitivity at the cutoff that produces a 5% false-positive rate. In actual practice, however, patients are not just informed of a “positive” or “negative” result, but are given a numerical estimate (“1 of XX”) of the probability of Down syndrome. These probability estimates may help aid further decision making by the patient.
Trial design issues include the population of patients studied (i.e., high risk or average risk) and the quality of follow-up to avoid verification bias. Verification bias refers to a problem in which the outcome status (Down syndrome or normal) is not assessed or is not available in certain patients. In the context of Down syndrome screening, spontaneous abortion is more likely in fetuses with chromosomal anomalies. Fetuses that miscarry may be more likely to be Down syndrome fetuses, and may be missed among those who have negative screening tests. Therefore, unless karyotyping is performed in all cases of spontaneous abortion or stillbirth, it is likely that a certain percentage of Down syndrome fetuses will go undetected. Therefore, to avoid verification bias, it is important to have as complete a follow-up as possible of all pregnancy outcomes with karyotypic analysis on stillbirths and live births with dysmorphic features and phenotypic assessment of other live births.

First-Trimester Screening with Nuchal Translucency (NT) and Maternal (Biochemical) Markers
There are three large prospective, multicenter studies on the sensitivity of first-trimester screening that includes nuchal translucency (NT) measurements. The Serum, Urine, and Ultrasound Screening Study (SURUSS) study enrolled over 47,000 women, of whom 101 had fetuses with Down syndrome. This study evaluated several tests in parallel, including first-trimester testing with NT and maternal markers, the triple test, second-semester quadruple test, and a combined first- and second-trimester test (both with and without NT). There were very high rates of verification, and adjustments were applied to account for miscarriages. Calculation of risk for all tests was done with a similar analytic methodology. There was no abnormal cutoff threshold for any measurement of NT or maternal serum analyte, as all measurements were entered into the regression model as continuous variables. In a direct comparison of the first-trimester test to the triple test, at a threshold of 85% detection, the first-trimester test had a false-positive rate of 6.1%, and the triple test had a false-positive rate of 9.3%. The lower false-positive rate at the same sensitivity means that the first-trimester test had superior discriminative capacity. Setting the false-positive rate at 5% resulted in a sensitivity of 83%, which was superior to what was historically expected of the triple test. The study also evaluated NT measurement alone. Its performance was considerably worse than either first-trimester testing or the triple test, with a false-positive rate of 20% at a diagnostic sensitivity of 85%.

The BUN study was also published in 2003, and evaluated first-trimester screening using the NT and the same maternal markers (human chorionic gonadotropin and pregnancy-associated plasma protein A) as the SURUSS study. Approximately 8,500 patients were enrolled, and 61 cases of Down syndrome were identified. Using a screening threshold of 1 in 270, 52 of 61 (85%) of Down syndrome cases were detected with a false-positive rate of 9.4%. If the threshold were changed to produce a false-positive rate of 5%, the detection rate was 78.7%. Taking into account possible biases due to miscarriages, the authors calculated that second-trimester screening would have to be 75% sensitive to be equivalent to the 78.7% sensitivity they found for first-trimester screening.

Another large, prospective, multicenter study similar in design to the SURUSS study was published in 2005. This was the First and Second Trimester Evaluation of Risk (FASTER) trial, conducted in the U.S. and sponsored by the National Institutes of Health (NIH). The study enrolled 38,167 women, of whom 117 had a fetus with Down syndrome. All women underwent
first-trimester testing with NT and maternal markers, and second-trimester quadruple screening. The study compared the results of each test, as well as stepwise sequential screening (results provided after each test analyzed), fully integrated screening (results only provided after all tests analyzed), and serum-integrated screening (similar to fully integrated but NT results not included). At a threshold of 5% false-positive rate, the rate of detection of Down syndrome was 87% for first-trimester combined screening performed at 11 weeks, 63% for NT alone at 11 weeks, 81% with second-trimester quadruple screening, 88% with serum-integrated screening, and 96% for fully integrated screening (first-trimester at 11 weeks). The detection rate of first-trimester screening was somewhat lower if performed after 11 weeks: 85% at 12 weeks and 82% at 13 weeks. Results of the FASTER trial provided further evidence that first-trimester combined screening was effective, but not NT measurement alone, and that integrated first- and second-trimester screening provided higher detection rates.

Subsequent studies have confirmed that combined first-trimester screening that includes NT measurement and maternal serum markers is superior to NT measurement alone. For example, in 2013 Peuhkurinen et al in Finland reported on tests performed prospectively in 35,314 pregnant women. Ninety-five Down syndrome pregnancies were identified. The detection rate was 64.5% for NT alone and 72.4% for combined screening with NT and maternal serum markers. False positive rates were 4.4% with NT alone and 4.0% with combined screening. Moreover, Ranta et al, in a retrospective review of data on 76,949 women in Finland, found that combined screening with maternal serum markers and NT is especially preferable in women aged 35 years and younger.

Studies continue to investigate the optimal approach to testing that balances the desires to maximize detection, minimize false positive results, minimize unnecessary testing, and provide information to women as early in their pregnancies as possible. As stated, the SURUSS and FASTER studies have estimated the results of several approaches, including combination first-trimester testing only, stepwise sequential testing (results given after first-trimester testing, move on to second-trimester testing), and integrated screening (results given only after first- and second-trimester testing). A retrospective analysis of the prospectively collected FASTER data by Cuckle et al introduced another screening approach, called “contingent screening.” Initial risk was calculated from first trimester NT measurement and maternal serum markers and classified as positive (i.e., greater than 1 in 20), borderline (i.e., 1 in 30–1500), and negative (i.e., less than 1 in 1500). Women with positive tests were offered immediate prenatal diagnosis, and those with borderline tests underwent second-trimester quadruple screening and risks were recalculated. A final risk of greater than 1 in 270 was considered positive. This approach differs from stepwise sequential testing in that only women with borderline results continued to second-trimester testing. First-trimester testing identified 52 of 86 (60%) affected fetuses with a 1.2% false positive rate (401 false positive results). The final detection rate with the contingent approach was 91% with a 4.5% false positive rate. Detection rates were similar with the stepwise approach (92% with 5.1% false positive results) but substantially more women received second-trimester testing, 31,868 with stepwise testing versus 7360 with contingent testing.

Another retrospective analysis of prospectively collected screening data was published by Kagan et al in 2010. Contingent screening resulted in a better test performance than other
approaches. In this case, contingent screening involved first-stage screening using maternal age and NT thickness, with or without an additional ultrasound marker. Women with a risk of 1 in 50 or more were considered to test positive and those with a risk of less than 1 in 1000 were considered to test negative. Patients with intermediate risk (i.e., 1 in 51 to 1 in 1,000) underwent second-stage screening with the biochemical markers free beta subunit of human chorionic gonadotropin (B-hCG) and pregnancy-associated plasma protein A (PAPP-A). An adjusted risk of at least 1 in 100 was then considered positive. The analysis used data from 21,141 singleton pregnancies, 122 of which had fetal trisomy 21.

After first-stage screening using only maternal age and NT thickness, the risk was 1 in 50 or more in 1.4% of the euploid pregnancies and 75% of the trisomy 21 pregnancies. An intermediate risk was found in 28.3% of euploid pregnancies and 23% of the trisomy 21 pregnancies. After second-stage screening with serum markers, the overall detection rate for trisomy 21 was 89%, and the false-positive rate was 3.0%. The addition of fetal nasal bone evaluation in the first-stage screening resulted in a final detection rate of 90% with a false-positive rate of 2.6%. When first-stage screening consisted of maternal age and biochemical markers, and second stage screening included fetal NT thickness and fetal nasal bone, the final detection rate was 92% with a false-positive rate of 5.2%. Other ultrasound markers, not currently addressed in this policy, were also evaluated in the Kagan et al study. With first-stage screening consisting of the marker ductus venosus flow added to maternal age and NT and second-stage screening for biochemical markers, there was a trisomy 21 pregnancy detection rate of 96% with a false-positive rate of 2.7%. When tricuspid flow was assessed instead of ductus venosus in the strategy described above, there was a detection rate of 94% and a false-positive rate of 2.6%.

Several studies evaluating a particular screening approach in practice have been published. In 2009, Wald et al in the U.K. reported on use of the integrated screening strategy. Records from two London hospitals were reviewed for 15,888 women who presented in the first trimester and were screened. Ninety-eight percent accepted integrated screening, and 94% of women completed both testing stages. The Down syndrome detection rate was 87%, consistent with an estimate of 89% predicted by SURUSS. The observed false positive rate was 2.1%. A 2013 study by Torella et al in Italy reported the performance of two-stage first-trimester combined screening. Blood samples were taken at eight weeks 0 days to 10 weeks 6 days and NT measurement was performed at 12 weeks 0 days to 12 weeks 6 days. The combined screen was considered positive when the risk of Down syndrome was greater than 1 in 250. A total of 73 positive cases were identified among 713 women with singleton pregnancies who were screened. All 73 women underwent invasive testing and five cases of trisomy 21 were detected. There was also one false negative case. Using this approach, the Down syndrome detection rate was 83% and the false positive rate was 3.2%.

Studies have also addressed whether women whose fetuses have large NT measurements benefit from any additional screening tests or should move directly to diagnostic testing with chorionic villus sampling. A retrospective analysis of 36,120 patients in the prospective FASTER study, published in 2009, found no added benefit in waiting for serum screening results when NT was 4.0 mm or greater, and minimal benefit when NT was 3.0 mm or greater. In this study, there were 32 (0.09%) fetuses with NT of at least 4.0 mm. Among these 32 cases,
the lowest final Down syndrome risk after including first-trimester serum markers was 1 in 8. Similarly, a retrospective study of 77,443 women in Quebec found that final combined first-trimester screening results were always positive in the 197 (0.3%) when NT measurements were at least 4.0 mm. A study from Australia conducted first-trimester screening on 76,813 women and identified an extremely large NT (here defined as >6.5 mm) in 120 cases. Abnormal karyotypes were found in 89 of the 120 cases (74%).

An ongoing issue with NT measurement is the possible variability of ultrasonographic interpretation. The Fetal Medicine Foundation in the U.K. has a training program that offers an Internet-based certificate of competency in NT. Continuing medical education courses in the U.S. are also available through the Fetal Medicine Foundation’s U.S. affiliate. Training and certification, along with ongoing quality control, an appropriate reference database of patients and use of statistical methodology, are necessary to produce optimal diagnostic results. Two recent studies with large sample sizes estimated the impact of measurement error on the results of first-trimester screening by taking actual screening results and artificially altering the NT values. Both studies found that even small deviations in measurement of NT affect the false-positive and false-negative rates. For example, in the Schmidt et al study which analyzed data from 10,116 pregnancies, underestimating the NT by 0.5 mm increased the number of false-negative results from 12 to 20 (an increase of 66.7%) and decreased the number of false-positive results from 479 to 281 (a decrease of 41.3%). On the other hand, overestimating the NT by 0.5 mm decreased the number of false negative results from 12 to 11 (a decrease of 8.3%) and increased the number of false-positive results from 479 to 1,149 (an increase of 140%). Findings emphasize the importance of accurate measurement of NT and potential value of combining NT findings with maternal serum markers.

Section Summary
Evidence from multiple large prospective studies establishes that the accuracy of ultrasound assessment of NT assessment combined with maternal serum markers for detection of Down syndrome is similar or higher to other available methods. This combination of tests offers advantages over alternatives in that it can be performed earlier in the pregnancy than other methods and may lead to an earlier confirmation or exclusion of Down syndrome. The accuracy of either NT alone or serum markers alone is less than that of the combined tests. The optimal timing of this test, and/or the optimal sequence or combination of this screening test with other tests, is not certain at this time.

Fetal Nasal Bone
Performance of fetal nasal bone assessment
A 2006 systematic review by Rosen et al for the U.S.-based Maternal Fetal Medicine Foundation Nuchal Translucency Oversight Committee identified 10 on fetal nasal bone performance. A total of 35,312 women underwent first-trimester ultrasound assessment of fetal nasal bone. The fetal nasal bone was successfully imaged in 33,314 (94.3%) of cases and could not be imaged in 5.7% of cases. There were 479 Down syndrome fetuses, a prevalence of 13.6 in 1000. The authors note that this is 10 times the first-trimester incidence in the U.S., suggesting a high-risk population had been screened. The fetal nasal bone was absent in 310 of 479 (65%) Down syndrome cases and in 274 of 34,048 (0.8%) chromosomally normal cases.
One of the included studies, a subanalysis of the FASTER study, discussed above, involved a general population sample and had much lower rates of successful imaging than other studies. Assessment of fetal nasal bone was added to the FASTER protocol during the last seven months, but did not occur in all centers. A total of 6,324 women underwent fetal nasal bone sonography and pregnancy outcome data were available for 6228 (98.5%) of them. Sonographers failed to obtain an adequate view in 1,523 patients (24%). Among the 4,801 cases with adequate images of the fetal profile, the nasal bones were described as being absent in 22 (0.5%) of them. There were 11 identified cases of Down syndrome. Fetal nasal bone assessment did not identify any of these cases as potentially high risk. In nine of the 11 cases (92%), the fetal nasal bones were judged to be present, and in two cases, were unable to determined. There were also two cases of trisomy 18; nasal bones were present in one and absent in the other. The FASTER investigators concluded that first-trimester fetal nasal bone sonography does not seem to have a role in general population screening for Down syndrome. Other researchers have commented on the lower rate of successful fetal nasal bone assessment in the FASTER analysis. The Rosen review article noted that, although the sonographers were trained and experienced in NT measurement, they were new to fetal nasal bone assessment. Sonek et al states in another review article that the likely explanation for the FASTER findings is that their techniques were different from those used by others.

One study was identified that directly compared the performance of fetal nasal bone assessment in unselected and selected populations. This prospective study included a total of 7,672 pregnant women, 7116 of whom were at average risk and 510 at increased risk (more than 1 in 300) of Down syndrome based on age, family history, or previous pregnancy history. It was not possible to adequately assess the fetal nasal bones in 712 of 7,116 (10%) in a general population sample, and in 42 of 510 (8.2%) in a high-risk sample. A total of 35 cases of Down syndrome were identified, 23 in the selected group and 12 in the unselected group. Two Down syndrome cases in the selected group were excluded because there was not a satisfactory ultrasound examination. In the remaining cases, absent fetal nasal bones identified 10 of 21 (47.6%) Down syndrome cases in the selected population and 2 of 12 (16.7%) in the unselected group. An analysis including the two missing cases found that fetal nasal bone assessment was able to correctly identify 10 of 23 or 43.5% of Down syndrome cases. A logistic regression model including fetal nasal bone findings, as well as NT and demographic factors, absence of fetal nasal bone was found to be an independent predictor of trisomy 21 in the selected pregnancies group, but not in the unselected pregnancies group.

Fetal nasal bone assessment in first-trimester screening programs
Several studies were identified that evaluated the diagnostic accuracy of first-trimester screening programs that included fetal nasal bone measurements as part of a comprehensive screening program. None of these was multicenter and none was conducted in the U.S.

Cicero et al conducted a single-center prospective screening study in the UK. . Down syndrome screening including fetal nasal bone assessment was conducted in 21,074 singleton pregnancies at 11 to 13 weeks’ gestation. Data from 20,418 (97%) women were available for analysis. Chromosomal abnormalities were detected in 253 of the pregnancies; this included 140 cases of Down syndrome. An adequate view of the fetal profile could not be obtained in 243 (1.2%) of cases. Of the 20,175 cases in which the fetal profile could be obtained (i.e., “successful”
examination), the nasal bone was recorded as absent in 238 (1.2%) of cases and present in 19,937 (97.6%). Combined screening with NT assessment and maternal serum markers achieved a detection rate of 90% at a fixed false-positive rate of 5%. With the detection rate fixed at 90%, the inclusion of nasal bone measurements using either screening strategy decreased the false-positive rate to 2.5%. In another analysis at a fixed false-positive rate of 5%, the inclusion of fetal nasal bone assessment of all women in the sample increased the detection rate to 93.6% at the 5% false-positive rate. The same increase in the detection rate, to 93.6%, was obtained when fetal nasal bone assessment was included only for women of intermediate risk (one in 51 to one in 1,000).

A study by Sahota et al conducted in Hong Kong was a retrospective analysis of 10,767 women who had been screened in a comprehensive first-trimester screening program. The analysis compared several approaches to screening. Among the 10,854 fetuses with a known outcome, 32 had Down syndrome. In a screening approach that combined NT assessment and maternal serum markers in this group, 27 (94%) of the pregnancies would have been classified as high risk, four as low risk, and one as intermediate risk. The protocol included fetal nasal bone assessment of intermediate-risk pregnancies, with reclassification as high risk if the fetal nasal bone was absent. The one case classified as intermediate risk had an absent fetal nasal bone. In this study, too few cases were classified as intermediate risk to determine whether fetal nasal bone assessment in a contingent screening approach improves screening accuracy.

A 2014 prospective study conducted by Hsiao et al in Taiwan included 20,586 women who were screened with maternal serum markers and various ultrasound markers. The combination of maternal serum markers and NT measurement had a 66.7% detection rate of trisomy 21. The addition of fetal nasal bone measurement increased the detection rate to 88.2%. Further inclusion of more ultrasound markers i.e., tricuspid regurgitation and the Doppler velocity waveform of the ductus venosus continued to increase the detection rate.

Techniques for evaluating fetal nasal bone images continue to be refined. A 2014 article reported on the feasibility of assessing fetal nasal bone using the retronasal triangle view. A total of 1977 women pregnant with singletons were scanned using this approach. The retronasal triangle view was successfully obtained for 1970 (99.6%) fetuses. The prevalence of an absent or hypoplastic fetal nasal bone was 12 of 1728 (0.7%) in euploid fetuses and 12 of 17 (70.6%) in fetuses with trisomy 21. The sensitivity and specificity of an absent or hypoplastic fetal nasal bone for detecting trisomy 21 was 70.6% and 99.3%, respectively. Another technique under investigation is use of 3-dimensional ultrasound to measure fetal nasal bone during the first trimester. Nanni et al evaluated 161 women pregnant with singletons with both 2-dimensional and 3-dimensional ultrasound. There was high intraobserver and interobserver agreement using 3-dimensional ultrasound. The agreement between 2-dimensional and 3-dimensional ultrasound was moderate (correlation coefficient=0.77).

As with NT measurement, there are possible issues around variability of fetal nasal bone interpretation and the need for adequate training and quality control. A review article by Rosen et al states that mastering imaging of the nasal bone appears to be more difficult than mastering NT measurement. The Fetal Medicine Foundation in the U.K. has an Internet-based certificate of competency in fetal nasal bone assessment; their website does not state how long this
program has been available. Generalizability of nasal bone assessment to general clinical practice is also a consideration. A committee of the Fetal Medicine Foundation recommended further evaluation of nasal bone assessment in low-risk populations and additional availability of adequately trained centers before nasal bone assessment is introduced into general practice. They also suggested considering a contingent screening strategy. The approach they suggest is similar to that used in the Sahota et al study from Hong Kong, discussed earlier, in which fetal nasal bone assessment is used only in cases that have a borderline risk determination by screening with NT and maternal serum markers. If a contingency model were used, patients could be referred to centers with developed expertise, although the authors note that this may not be feasible or practical in all areas of the U.S.

Section Summary
Assessment of fetal nasal bone by ultrasound is another method of screening for Down syndrome phenotype in utero. The accuracy of this test in the published literature is variable, and some studies have reported a relatively low sensitivity. The variability in accuracy reported may reflect the difficulty in performing and interpreting this test, and the test results are likely prone to differences in operator characteristics. Limited evidence suggests that there may be modest incremental benefit when used in combination with ultrasound NT and serum markers, but the degree of benefit is not clear. As a result, the evidence is insufficient to determine the impact of this test on health outcomes.

Summary
Nuchal translucency (NT)
There is sufficient evidence from two large prospective multicenter studies (SURUSS and FASTER) and several smaller studies that first-trimester screening for Down syndrome with measurement of fetal nuchal translucency (NT) and maternal serum markers is at least as accurate as alternative tests and may allow earlier confirmation or exclusion of Down syndrome. Therefore, use of this test in the first trimester is a reasonable approach and may be considered medically necessary. The SURUSS and FASTER studies also found that overall first-trimester screening with NT alone is inferior to either 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 in these cases.

Fetal nasal bone assessment
Studies have found a high rate of successful imaging of the fetal nasal bone and an association between absent nasal bone and the presence of Down syndrome in high-risk populations. However, there is insufficient evidence on the performance of fetal nasal bone assessment in average-risk populations. Of particular concern is the low performance of fetal nasal bone assessment in a subsample of the FASTER study conducted in a general population sample. Two studies conducted outside of the U.S. have found that, when added to a first-trimester screening program evaluating maternal serum markers and NT, fetal nasal bone assessment can result in a modest decrease in the false positive rate. Several experts in the field are proposing that fetal nasal bone assessment be used as a second stage of screening, to screen women found to be of borderline risk using maternal serum markers and NT. Additional studies using this contingent approach are needed before conclusions can be drawn about its utility. In summary, given the uncertainty of test performance in average-risk populations and the lack of
standardization in the approach to incorporating this test into a first-trimester screening program, detection of fetal nasal bone is considered investigational.

**Practice Guidelines and Position Statements**

In 2011, two Canadian consensus documents on maternal screening for fetal aneuploidy were published; one on singleton pregnancies and one on twin pregnancies. Recommendations relevant to this policy are as follows:

**Singleton pregnancies:**
- All pregnant women, regardless of age, should be offered the option of pre-natal screening for significant fetal aneuploidies and a second trimester ultrasound for dating, assessment of fetal anatomy and detection of multiples.
- First trimester nuchal translucency should not be offered as a screen without biochemical markers. It should be measured by sonographers or sonologist trained and accredited for this service.

**Twin pregnancies:**
- Fetal nuchal translucency combined with maternal age is an acceptable first trimester screening test for aneuploidies in twin pregnancies.
- First trimester serum screening combined with nuchal translucency may be considered in twin pregnancies. It provides some improvement over the performance of screening by nuchal translucency and maternal age because the false-positive rate is lower.

In January 2007, the American College of Obstetricians and Gynecologists (ACOG) released an updated practice bulletin that recommended that all women, regardless of age, be offered aneuploidy screening before 20 weeks’ gestation. No single specific testing strategy was recommended. The recommendations state that first-trimester combined screening (NT and maternal serum markers) is effective for testing for Down syndrome. They further state that fetal nasal bone assessment in the general population is controversial, and that additional testing standardization, training for physicians and quality-control programs are needed.

**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

**Approved by Governing Bodies:**
Not applicable

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. Pre-certification requirements: Not applicable

**Current Coding:**

CPT codes:

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)

The following new codes should be used on or after 01/01/2013 to report the 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) *(Effective 01/01/2013)*

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) *(Effective 01/01/2013)*

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) *(Effective 01/01/2013)*

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) *(Effective 01/01/2013)*

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) *(Effective 01/01/2013)*

**Previous Codes:**

Any combination of these codes could be billed prior to 01/01/2013 based on the test performed:

82105 Alpha-fetoprotein (AFP); serum
82677 Estriol
84163 Pregnancy-associated plasma protein-A (PPA-A)
84702 Gonadotropin, chorionic (HCG); quantitative
84704 Gonadotropin, chorionic (HCG); free beta chain
References:
38. 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):788-9.

Policy History:
Medical Policy Group, June 2005 (1)
Medical Policy Administration Committee, July 2005
Available for comment July 28-September 10, 2005
Medical Policy Group, August 2007 (1)
Medical Policy Group, August 2010 (1): Medical policy completely updated with replacement of Description and Key Points
Medical Policy Administration Committee, September 2010
Available for comment September 4-October 18, 2010
Medical Policy Group, October 2010
Medical Policy Group, July 2011 (1): Updated Key Points & References related to MPP update; no change in policy statement
Medical Policy Group, March 2012 (1): Update to Key Points and References related to MPP update; no change in policy statement
Medical Policy Group, December 2012 (3): 2013 Code Update: Added Code range 81508 through 81512: Deleted 82105, 82677, 84163, 84702, 84704, and 86336 effective 01/01/2013
Medical Policy Panel, April 2014

Proprietary Information of Blue Cross and Blue Shield of Alabama
Medical Policy #233
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.