

<b>Subject:</b> Antenatal Fetal Ultrasound Assessment for prenatal screening of chromosomal abnormalities		<b>Original Effective Date:</b> 5/20/10
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**PREFACE**

*This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion's or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: <http://www.cms.hhs.gov/center/coverage.asp>.*

**FDA INDICATIONS**

The U.S. Food and Drug Administration (FDA) do not regulate the specific screening procedures. The commercially marketed ultrasound scanners and tests utilized to conduct the procedure require FDA marketing clearance.

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

*The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.*

CMS has not established a national coverage determination or a local coverage determination for antenatal fetal ultrasound assessment for screening for chromosomal abnormalities.<sup>4</sup>

**INITIAL COVERAGE CRITERIA**

Fetal ultrasound assessment of nuchal translucency for screening of common chromosomal abnormalities (*Down's syndrome-Trisomy 21, Edward's syndrome-Trisomy 18, and Patau's syndrome- Trisomy 13*) in the first trimester is considered medically necessary and may be authorized when **all** of the following criteria are met: [ALL]

- A Board certified trained-Gynecologist (OB-GYN), Radiologist, or a Maternal-Fetal Medicine specialist with a certification in Obstetrical ultrasonography may perform the ultrasound if the center has an appropriate certification by either the Fetal Medicine Foundation (FMF) or the Nuchal Translucency Quality Review Program (NTQR) or an accreditation by the American Institute of Ultrasound Medicine or the American College of Radiology.<sup>1,6,8,72</sup>

- Documented evidence that nuchal translucency measurement is being performed for the screening of common chromosomal abnormalities in combination with the following maternal serum tests:<sup>1,3</sup>
  - Serum human chorionic gonadotropin (free b-hCG or total hCG); **AND**
  - Serum pregnancy-associated plasma protein A (PAPP-A)
- Documented evidence that nuchal translucency assessment will be performed between 10.4 and 13.6 weeks gestation<sup>3</sup>
- Documented evidence that member has received adequate counseling regarding possible positive screening outcomes and has expressed an interest in obtaining information regarding the risks of having a child with a common chromosomal abnormality through formal consent<sup>3</sup>

#### CONTINUATION OF THERAPY

N/A

#### COVERAGE EXCLUSIONS

All requests for fetal ultrasound assessment for nuchal translucency/nuchal fold that are not included in the 'Coverage Criteria' section above are considered **experimental/investigational**. This includes the following:

- Nuchal translucency assessment alone without maternal serum testing in the first trimester<sup>1,3</sup>
- Routine ultrasound screening for chromosomal anomalies:
  - Soft markers (e.g. nuchal fold measurement) in the second trimester<sup>48,49</sup>
- Nuchal fold ultrasound assessment in the second trimester used as sequential testing<sup>3,20,46,48, 49,54,72</sup>
- Screening for chromosomal abnormalities in the third trimester of pregnancy.
- Three-dimensional ultrasonography for nuchal translucency/nuchal fold testing<sup>3 78</sup>

#### DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Nuchal translucency is an ultrasound echo-free space between the skin and soft tissue overlying the cervical spine that appears only during the first trimester of pregnancy.<sup>2</sup> In fetuses with chromosomal abnormalities, cardiac defects, perinatal risks and certain genetic syndromes nuchal translucency is increased. The fetus is examined between 10 and 14 weeks of gestation when the fetus is between 45mm to 84mm long from crown to rump (sitting height).<sup>21, 44</sup> Normal nuchal translucency thickness ranges from 1.2 to 1.9mm (at crown to rump lengths of 45mm and 84mm respectively)<sup>6</sup> and the fluid at the fetal neck length from 45 to 84 millimeters is measured. An ultrasonographer performs this subjective measurement of nuchal translucency. Special training is required prior to an ultrasonographer producing standardized measurements of nuchal translucency.<sup>1, 3</sup>

All fetuses have nuchal (nape of the neck) translucency (thickening) detectable by a first trimester ultrasound.<sup>3,18</sup> The presence of nuchal translucency thickness, between 10 and 14 weeks gestation, is recognized as a marker of trisomy 21, Down's syndrome as well as other chromosomal anomalies. (e.g., trisomy 18, trisomy 13, and Turner's syndrome).<sup>3, 16, 59</sup> The probability that a fetus has a trisomy increases with nuchal translucency thickness. Nuchal translucency thresholds in the range of 3.0 to 4.0 mm have been reported based upon the high risk of Down syndrome associated at this level.<sup>17</sup> Sources including the American College of Obstetricians and Gynecology reference 3.5 mm or higher as the high risk marker for nuchal translucency for abnormality risk (Down's syndrome, major congenital heart defects, defects of the great vessels, fetal malformations, dysplasia's and other genetic syndromes).<sup>3, 36</sup>

The nuchal fold, rather than nuchal translucency, is measured in the second trimester.<sup>18</sup> The nuchal fold is the measurement between the outer edge of the occipital bone to the outer margin of the skin and is taken in the axial plane. An increase in this measurement is also associated with aneuploidy (chromosome abnormality).

Cystic hygroma is a congenital malformation of the lymphatic system in which obstruction between the lymphatic and venous pathways in the fetal posterior neck leads to lymph accumulation in the jugular lymphatic sacs of the nuchal region.<sup>18,59</sup> They tend to be largest in the nuchal region, but may extend along the entire length of the fetus.<sup>59</sup> First trimester cystic hygromas are often associated with trisomies and second trimester cystic hygromas are often associated with monosomy X (Turner's syndrome).

Women age 35 and older have an increased risk of having a baby with a chromosomal abnormality. Historically, amniocentesis and chorionic villus sampling with genetic testing were routinely offered to women age 35 or older prior to birth to assist in diagnosing affected fetuses.<sup>16</sup> However, amniocentesis and chorionic villus sampling are invasive procedures that carry higher risk for fetal loss. The majority of affected fetuses are conceived by younger women as there are a higher volume of pregnancies in younger women; although the risk of conceiving an affected fetus is higher in women older than age 35 years. It has been reported that approximately 80 percent of Down syndrome babies are born to mothers under age 35.<sup>38</sup> Using maternal age of 35 as a sole indicator for testing will detect only 30 percent of Trisomy 21. Routine screening in women over age 35 by invasive testing has not detected the majority of fetuses with chromosomal abnormalities.<sup>16</sup> Routine screening in women under age 35 by invasive testing is not considered an acceptable practice. As a result, noninvasive tests and combinations of noninvasive tests have been considered as screening tools for the most common autosomal aneuploidy<sup>39</sup> syndromes resulting in Down's syndrome-Trisomy 21, Edward's syndrome-Trisomy 18, and Patau's syndrome- Trisomy 13. The most common sex chromosome aneuploidy syndromes include Turner's syndrome-X, Klinefelter syndrome-XXY, XYY, and XXX.<sup>39</sup> Trisomy 21, 18 and 13 are associated with severe congenital anomalies and mental handicap.<sup>39,40</sup>

Combined prenatal screening tests during the first-trimester involves determination of maternal serum free  $\beta$ -human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A) levels in the maternal bloodstream between 10 and 13 weeks combined with ultrasonographic measurement of nuchal translucency between 10 and 14 weeks of gestation.<sup>1</sup> Software programs adjust the biochemical measurements of maternal age, gestational age, maternal race, maternal age and calculate patient-specific risk for fetal chromosomal disorders. The parents may be advised to undergo additional testing if the risk of the fetus affected by a trisomy is 1:300 or higher.<sup>5-8</sup> Women have the advantage of chorionic villus sampling (CVS) at 10 to 14 weeks of pregnancy to confirm a positive diagnosis when testing is performed within the first trimester. The goal of first-trimester prenatal screening is to provide risk information early in pregnancy, thereby allowing for additional diagnostic testing (amniocentesis or chorionic villus sampling) and optimal pregnancy management or early termination with less health risks. Triple and quadruple testing can only be performed in the second trimester and eliminates the advantage of early identification options.

Competing and Complementary Testing: *Triple Screening Test*- Triple screening is performed in the second trimester and tests maternal blood for total hCG, unconjugated estriol (uE3), and alpha fetoprotein (AFP) levels.<sup>20</sup>

*Quadruple Screening Test*- Quadruple screening is performed in the second trimester and tests maternal blood for levels of AFP, total hCG, uE3, and dimeric inhibin A.<sup>20</sup> The test is performed at 15 to 18 weeks gestation. On average, maternal serum AFP and uE3 are reduced by 25 percent in Down syndrome pregnancies. Inhibin A and hCG levels are, on average twice as high as found in unaffected pregnancies. This testing is considered the best available based upon detection rates for women presenting for care in the second trimester. Quadruple testing has proven to have a high detection rate for second trimester sequential testing.<sup>1, 20, 36, and 41</sup>

*Integrated Screening*- Integrated screening is a combination of various tests performed in both the first and second trimesters to screen for aneuploidy.<sup>19</sup> PAPP-A testing with nuchal translucency measurements in the first trimester with

uE3, AFP, inhibin-A, and hCG in the second trimester are the most common integrated testing combination.<sup>11</sup> The integrated test is reported to be highly accurate but second trimester testing is required before estimating risk, eliminating any potential choice for the parents to terminate an affected pregnancy.<sup>11,12</sup>

*Sequential Screening-* Sequential screening is performed during both the first and second trimesters.<sup>19</sup> This screening type was developed to address concerns in regard to integrated testing where first-trimester results were withheld from the patient pending completion of the second-trimester blood testing, eliminating early diagnostic testing. Sequential screening is reported as the most effective method of preventing live-born trisomy cases, it also may increase the rate of invasive testing and complications of fetal loss.<sup>6,10</sup> The two types of sequential screening available include:

- *Contingent Screening*<sup>19</sup>- Results of the first trimester combined screening are shared with the patient. If the risk of aneuploidy is greater than a predetermined cutoff, then the patient is offered the option of proceeding with a diagnostic test (e.g., amniocentesis or CVS).
- *Stepwise Screening*<sup>19</sup>- Results of the first trimester combined screening are shared with the patient. If the risk of aneuploidy is less than a predetermined cutoff, the patient proceeds with the quadruple screening and receives a revised final risk assessment based upon first and second trimester measurements.

*Serum Combined First-Trimester Screening* - The first trimester combined test incorporates beta-hCG, PAPP-A, and nuchal translucency testing.<sup>17</sup> The detection rate has been reported as the highest during the first trimester by using this testing methodology.

#### GENERAL INFORMATION

Summary of Medical Evidence: For each screening test individually, the average detection rate calculated for Down syndrome, with a fixed screen-positive rate (similar to false-positive) of 5%, has been reported to be approximately as follows:<sup>3,41</sup>

- triple screen 69%;
- quadruple screen 81%;
- PAPP-A and free B-hCG at 10 weeks 58%, at 12 weeks 53%; and
- Nuchal Translucency (NT) 64%-70%.

Combining these tests produces higher detection rates while keeping a fixed screen-positive rate; combining NT with PAPP-A and free B-hCG yields 84%-90% detection rates<sup>6,38</sup>

Nuchal Translucency Measurement Alone in First Trimester: There is insufficient evidence to support nuchal translucency measurement alone as a routine soft marker screening method to detect fetal cardiac anomalies, Down's syndrome, or other chromosomal abnormalities.<sup>18,27,28,34-37,41</sup> Nuchal translucency measurement has a detection rate of approximately 70 to 71 percent for Down syndrome and a 3.5 to 5 percent false-positive rate.<sup>34,35</sup> Studies have shown an increased nuchal translucency of greater than 3.5 mm is associated with genetic syndromes. Combined testing detection rates (blood testing with nuchal translucency) have shown more significant results when compared to nuchal translucency testing alone<sup>1,6,8,27</sup> (71% versus 85-96%).<sup>27,41</sup> Nuchal translucency performance has not been consistent in reported studies.<sup>17</sup> This inconsistency has been attributed to quality of equipment and variability in operator expertise.<sup>1</sup> Small errors in nuchal translucency measurement can cause large errors in the accuracy of first-trimester screening. In unaffected pregnancies, average nuchal translucency increases from approximately 0.8 mm to 1.2 mm during the 11th to 13th weeks of gestation.<sup>1</sup> During this time period, 95% of fetuses with trisomy 21 have an average nuchal translucency that is at least 2.3-fold greater than the normal average<sup>8</sup>; thus, ultrasonographers must be able to

distinguish very small differences accurately and reproducibly (e.g., a 1.0-mm nuchal translucency versus a 2.3-mm nuchal translucency). Since nuchal translucency changes with gestational age, ultrasonographers must also be able to determine gestational age accurately based on crown-rump length.<sup>1</sup> Specific factors that can influence and complicate nuchal translucency measurement include the following: ultrasonography equipment, equipment operator, proper caliper placement, contact or near contact between the fetus and the amnion, image contrast and magnification, flexion or extension of the fetal neck, maternal physique, and wrapping of the umbilical cord around the fetal neck. To ensure accuracy of nuchal translucency measurements, both the SURUSS project<sup>8</sup> and FASTER trial<sup>6</sup> involved special training of ultrasonographers and ongoing quality assurance programs. The FASTER and SURUSS<sup>6,8</sup> trials found that including nuchal translucency measurement in first-trimester screening protocols improved the accuracy of screening; however, these benefits may not be realized in the future if ultrasonographer training is inadequate or if a thorough quality assurance program is not established and maintained. Proper training and ongoing quality management have been highly recommended for screening programs that involve measurement of nuchal translucency.<sup>17,72</sup>

It has been reported that abnormal nuchal translucency may lead to an earlier diagnosis of congenital heart defects.<sup>37</sup> Studies evaluating nuchal translucency as a marker of cardiac anomaly associated with fetal aneuploidy reported poor sensitivity.<sup>18,29-33</sup> There were different cut-off points used across various institutions and for different cardiac defects that affected sensitivity and false positive rates. A review of eight independent studies with 58,492 pregnant women were included to assess the diagnostic performance of increased nuchal translucency for congenital heart defect detection.<sup>27,29</sup> There was significant heterogeneity among the studies. Nuchal translucency above the 99th percentile had a sensitivity of 31% and specificity of 98.7% (random effects calculations), with a positive likelihood ratio of 24. Summary receiver-operating characteristic estimates were consistent with these values. The ability of nuchal translucency measurements above this threshold to detect cardiac malformations varied non-significantly ( $P = .64$ ) for different congenital heart defects types (sensitivity range, 25%-55%). The authors concluded the use of the 99th percentile threshold may capture approximately 30% of congenital heart defects.<sup>29</sup>

A meta-analysis of 11 studies examining the diagnostic value of nuchal translucency measurement of low-risk or unselected populations on detecting cardiac anomalies were conducted. Cardiac defects showed a positive likelihood ratio of 5.01 (95% CI 4.42 to 5.68) and a negative likelihood ratio of 0.70 (95% CI 0.65 to 0.75). It has been reported that this technique provides poor diagnostic value.<sup>27</sup>

*Second Trimester Screening using Ultrasound Screening for Soft Markers “Nuchal Fold” (NF):* There is insufficient evidence to support the significance of soft markers, such as nuchal fold measurement, during the second trimester as a routine screening examination in a patient who appears to be at low risk for giving birth to a child with chromosomal abnormalities.<sup>3,20,46,54,72</sup> Studies in low-risk populations have suffered from lack of standardization of what is considered abnormal findings.<sup>3,55</sup> The relevance of genetic sonogram in a low-risk population remains to be proven. An evaluation of 36 studies involving more than 900,000 fetuses reported an overall sensitivity of 40% for detecting fetal anomalies, ranging from 13.3 -82.4.<sup>71,72</sup> The detection rate is not sufficiently high enough.<sup>68</sup> With the use of NF alone, the detection rate for Down syndrome ranged from 4-35% in a meta-analysis.<sup>67</sup> The RADIUS study identified that major anomalies are frequently missed by ultrasound examination.<sup>3,69</sup> A more recent evaluation reported a detection rate of 12%.<sup>66</sup> Nuchal fold for screening for Down’s syndrome in the second trimester has been reported as suboptimal for two reasons.<sup>68</sup> Nuchal fold thickness in unaffected pregnancies increases with advancing gestation; small thickening at an earlier gestation could be more important than larger thickening later. The use of a single cut-off with a fixed likelihood ratio throughout the entire second trimester can be misleading. The presence of these markers with the reported lower detection rates high false-positive rates (11-29%)<sup>3,6,55,70</sup> may lead to invasive diagnostic testing that are

unnecessary.<sup>3,54,68</sup> Several resources have not recommended ultrasound screening as primary screening tool for Down's syndrome and other chromosomal abnormalities in the second trimester.<sup>3,52,54,72</sup>

One meta-analysis included 56 studies involving 1930 babies to evaluate the accuracy of second trimester ultrasound in detecting Down's syndrome.<sup>46</sup> This analysis included all studies evaluating the soft markers –choroid plexus cyst, echogenic intracardiac focus, thickened nuchal fold, echogenic bowel, humeral and femoral shortening and renal pyelectasis. Retrospective studies were included when the original ultrasound interpretation was used. Wide ranges of sensitivity were reported ranging between 4 and 36 percent. The authors concluded that the overall sensitivity for nuchal fold is too low for it to be a practical screening test for Down syndrome alone. Using these markers as a basis for deciding to offer amniocentesis will result in more fetal losses than cases of Down syndrome detected, and will lead to a decrease in the prenatal detection of fetuses with Down syndrome.

A prospective multicenter cohort study of women who underwent an anatomic survey between 16 and 22 weeks of gestation.<sup>47</sup> Among 4373 pregnancies that were evaluated over a 5-year period, there were 50 pregnancies with Down syndrome. Nuchal fold was evaluated in all of the fetuses. Absent nuchal folds of 6mm was seen in 6 of 50 cases (12%) with Down syndrome. The authors concluded evaluation using nuchal fold alone results in a small detection rate of 12%. Using nuchal fold in this manner is not optimal as the nuchal fold thickness in unaffected pregnancies increases with advancing gestation, so a relatively small thickening could be more important at an earlier gestation than could a larger thickening later. Second, the reassuring value of a small nuchal fold is diminished because women with moderately increased nuchal folds are not treated differently than those with values near or below the median.

One prospective population-based cohort study of 9244 women with singleton pregnancies, including 245 whose fetuses had Down syndrome, concluded that the accuracy of the genetic sonogram in second trimester screening for Down's syndrome was less than previously reported.<sup>48</sup> The authors recommended that the sonogram should not be used as a sequential test following serum biochemistry, as this would substantially reduce the prenatal diagnosis of Down syndrome cases. In contrast to prior reports, most isolated soft markers were not associated with Down syndrome. One randomized controlled trial reported a detection rate of 47 percent.<sup>49</sup>

A large and randomized-control trial called the RADIUS study found that routine ultrasound scanning of a group of low-risk women provided no benefits in reducing neonatal deaths or reducing the incidence of moderate or severe illness.<sup>50</sup> Pregnant women without a specific indication for ultrasonography were randomly assigned to have either two screening sonograms (15 to 22 weeks and 31 to 35 weeks) or conventional obstetric care with ultrasonography. Major congenital malformations occurred in 2.3% of the 15,281 fetuses and infants in this study. Antenatal ultrasonography detected 35% of the anomalous fetuses in the screened group versus only 11% in the control population (relative detection rate 3.1; 95% confidence interval 2.0 to 5.1). Ultrasonography did not significantly influence the management or outcome of pregnancies complicated by congenital malformations. Only 9 abortions were performed for anomalies among 7685 fetuses in the screened group whereas 4 pregnancies were terminated for fetal anomalies detected among 7596 control subjects. Ultrasonography screening also had no significant impact on survival rates among infants with potentially treatable, life-threatening anomalies despite the opportunity to take precautionary measures such as delivery in a tertiary center.

**First Trimester Serum Combined Test:** Results from a good-quality large cohort study reported the serum combined test to have a detection rate of 92.6% with a false positive rate of 5.2% for the detection of Down's syndrome, and a slightly lower detection rate for trisomy 18 or 13 or other chromosomal anomalies in singleton pregnancies.<sup>18,21,56</sup> The detection rate of trisomy 13 and 18 is approximately 90 percent in combined testing.<sup>18,56-58</sup> One study screened over

8500 women with singleton pregnancies in the first trimester detected 10 of 11 fetuses with trisomy 18.<sup>17,45</sup> Similar results were reported in a second study.<sup>22</sup> A third study showed a lower detection rate but a higher false positive rate for the combined test.<sup>23</sup> The diagnostic accuracy results of three other very large prospective cohort studies reported similar positive results.<sup>1,6,8</sup> A large multicenter study<sup>24</sup> reported a detection rate of 79.6% with a false positive rate of 2.9%, a second study reported a detection rate of 90.3%<sup>25</sup> and 82%<sup>26</sup> with a fixed false positive rate of 5%.

Multiple resources and clinical practice guidelines exist and support first trimester serum combined testing as an effective method for prenatal screening and detection of chromosomal anomalies (e.g., Trisomy 21, 18, or 13, Turner's syndrome).<sup>3, 17,19,27,36,41</sup>

Marchini and colleagues (2010) evaluated the performance of the combined test (nuchal translucency, NT) and maternal serum free-beta human chorionic gonadotropin (free beta-hCG) and pregnancy-associated plasma protein-A (PAPP-A), compared to the NT measurement alone, in fetal aneuploidy screening in the general population and in pregnant women aged 35 years and over. In addition, the association between increased NT and presence of cardiac defects in fetuses with normal karyotype was evaluated. Screening at 11-14 weeks of gestation by NT measurement and combined test was carried out in 1521 pregnant women. The estimated risk for trisomy 21 and trisomy 13+18 was calculated (risk cut-off 1/300 and 1/750 respectively) and the outcomes was evaluated. Ten cases of trisomies (21 and 18) occurred, seven of which among the older group of pregnant women. The detection rate (DR) for the combined test was 80% in the general population and 85.7% in older pregnant women, which resulted higher rate than NT measurements alone. Detection rate of cardiac defects using NT measurements was 66.6%. The authors concluded the combined test is an effective screening for aneuploidies and reduces at 14% the need of invasive testing in the older obstetric population, detecting all the trisomies occurred in this group. The association between increased NT and cardiac defects is confirmed but it seems too weak to consider NT as a single screening strategy for these abnormalities.<sup>76</sup>

*First Trimester and Second Trimester Comparison Studies:* Three large multicenter trials have been conducted that compared first-trimester with second-trimester screening (e.g., the SURUSS (Serum, Urine, and Ultrasound Screening Study),<sup>8</sup> the First-And Second-Trimester Evaluation of Risk (FASTER Trial),<sup>6</sup> and a multicenter Korean study.<sup>1</sup> These studies evaluated integrated screening approaches combining a combination of the various tests performed in first or second trimester screening. The comparison of the protocols used a fixed sensitivity corresponding to the fraction of Down syndrome fetuses that could be detected by screening. The efficacy was evaluated by false-positive rates, lower rates indicating the potential for fewer unnecessary invasive diagnostic tests such as chorionic villus sampling or amniocentesis.

The SURUSS (Serum, Urine, and Ultrasound Screening Study) study enrolled 47,053 women, of whom 101 had fetuses with Down syndrome.<sup>8</sup> This study compared several tests, including first trimester testing with nuchal translucency and maternal markers, the triple test (maternal serum measurements of alpha-fetoprotein, human chorionic gonadotropin and unconjugated estriol), second semester quadruple test (similar to the triple test, but with the addition of inhibin A), and a combined first and second trimester test (both with and without nuchal translucency). There were very high rates of verification and adjustments applied to account for miscarriages. Study results showed that in antenatal screening for Down syndrome it is possible to detect approximately 90% of affected pregnancies with a false positive rate of 1-2%. The conclusions indicated that the following tests offer the most safe and effective method of screening: the integrated test combining first trimester and second trimester screening is the most effective strategy; if a nuchal translucency measurement is not available: the serum integrated test should be performed. Women who do not receive antenatal care until the second trimester of pregnancy: the quadruple test is most effective. The combined test is recommended for women who choose to have a screening test in the first trimester.

The FASTER (First and Second Trimester Evaluation of Risk) trial, sponsored by the National Institute of Child Health and Human Development (NIHCHD), is a multicenter, prospective study comparing (n=38,167) the accuracy of first and second trimester noninvasive screening methods for Down syndrome and other aneuploidies (n=117 for Down's syndrome) to diagnosis at delivery or miscarriage/fetal loss.<sup>6</sup> Participants underwent first trimester screening with measurement of nuchal translucency (7% failed to provide adequate images), b-hCG, and PAPP-A 10 weeks 3 days through 13 weeks 6 days of gestation) and second-trimester quadruple screening (measurement of alpha-fetoprotein, total human chorionic gonadotropin, unconjugated estriol, and inhibin A at 15 through 18 weeks of gestation). The results indicated that a combined first and second trimester screening is the most effective screening strategy.<sup>1,6</sup> First trimester screening provided better results performed during the 11<sup>th</sup> week of gestation. Quadruple screening at 13 weeks has similar results to second-trimester quadruple screening. Sequential screening and fully integrated screening have high detection rates for Down's syndrome, with low false positive rates.

A third multicenter prospective Korean study with 17,590 participants<sup>28</sup> reported that the integrated testing method was more accurate, these researchers only used 2 serum marker tests rather than the 5 serum markers that were included in the FASTER trial and SURUSS project protocols.<sup>1</sup> An accurate comparison with these trials cannot be conducted. The results do provide additional evidence that first trimester screening with nuchal translucency combined with second trimester double screen is more sensitive than first trimester screening with nuchal translucency or second trimester with double screening alone for Down syndrome screening (86% versus 61-73% accuracy rates).

***Integrated Screening Results:*** Studies have reported a higher rate of detection of trisomy 21 and (94 to 96% in the FASTER trial<sup>6</sup> and 94% in the SURUSS trial<sup>8</sup> with rates varying according to gestational age). Than either first or second trimester screening tests alone.<sup>6,11</sup> Noncompliance rates as high as 25% have been reported in routine practice with completing the second step.<sup>53</sup>

Ghaffari and colleagues (2012) sought to investigate the performance of first-trimester screening for chromosomal abnormalities by integrated application of nuchal translucency thickness (NT), nasal bone (NB), tricuspid regurgitation (TR) and ductus venosus (DV) flow combined with maternal serum free  $\beta$ -human chorionic gonadotropin (f $\beta$ -hCG) and pregnancy-associated plasma protein-A (PAPP-A) at a one-stop clinic for assessment of risk (OSCAR). In total, 13,706 fetuses in 13,437 pregnancies were screened for chromosomal abnormalities during a period of 5 years. Maternal serum biochemical markers and maternal age were evaluated in combination with NT, NT + NB, NT + NB + TR, and NT + NB + TR + DV flow data in 8581, 242, 236 and 4647 fetuses, respectively. In total, 51 chromosomal abnormalities were identified in the study population, including 33 cases of trisomy 21, eight of trisomy 18, six of sex chromosome abnormality, one of triploidy and three of other unbalanced abnormalities. The detection rate and false-positive rate (FPR) for trisomy 21 were 93.8% and 4.84%, respectively, using biochemical markers and NT, and 100% and 3.4%, respectively, using biochemical markers, NT, NB, TR and DV flow. The authors concluded that while risk assessment using combined biochemical markers and NT measurement has an acceptable screening performance, it can be improved by the integrated evaluation of secondary ultrasound markers of NB, TR and DV flow. This enhanced approach would decrease the FPR from 4.8 % to 3.4 %, leading to a lower number of unnecessary invasive diagnostic tests and subsequent complications, while maintaining the maximum level of detection rate. Pre- and post-test genetic counseling is of paramount importance in either approach.<sup>80</sup>

***Multiple Pregnancy:*** There is no proven evidence that nuchal translucency measurement alone in triplet and higher order multiple pregnancies is an effective method for prenatal screening in the first trimester.<sup>1</sup> A model developed by Spencer et al. predicts that using nuchal translucency measurements alone will detect 75% of trisomies, and the combination of nuchal translucency and maternal serum testing will result in detection rates approaching 80%.<sup>62</sup> These

results have not been clinically confirmed.<sup>1</sup> There have only been a few small published studies that are of sufficient quality.<sup>62-65</sup> The total number of pregnancies combined in one analysis screened only 477 pregnancies and detected nine fetuses (in 7 pregnancies) affected by trisomy 21, an insufficient number of cases to provide reliable estimates of the accuracy of this method. First or second trimester maternal serum testing is less sensitive on women with multiple gestation pregnancies with triplets or higher as the maternal serum value may represent an average of normal and abnormal fetuses and may mask an abnormal result.<sup>3,36</sup> Combined first trimester serum screening for multi-fetal gestation is less sensitive at approximately 70% than in singleton pregnancies.<sup>51</sup> Nuchal translucency alone has similar detection rates for Down syndrome in multiple gestations. One study enrolled 57 twin pregnancies in the study and reported screening data for the multiple gestations separately.<sup>60</sup> The sensitivity was reported 100% and specificity 92.9%. Only one fetus was identified as affected by trisomy 21. The study was considered low quality due to the small number of twin pregnancies evaluated.

*Second Trimester Triple or Quadruple testing:* Studies have reported that quadruple screening has an improved detection rate compared with the triple screening test by 5% to 7%.<sup>1,20,36,41</sup> Guidelines have supported this information.<sup>3,41</sup> It has been reported that the quadruple test is the best available screening test for Down syndrome if a woman presents for care after 13 weeks of gestation.<sup>3,19,20</sup>

*Three-dimensional ultrasonography (3D):* Antsaklis and colleagues (2011) sought to evaluate the use of three-dimensional ultrasonography (3D) as an alternative for examining fetal anatomy and nuchal translucency (NT) in the 1(st) trimester of pregnancy. A prospective study of 199 low risk pregnant women undergoing 1(st) trimester ultrasound scans for fetal anomalies. The NT and fetal anatomy were evaluated by three-dimensional (3D) ultrasonography after the standard two-dimensional (2D) examination. The gold standard in this study was the 2D ultrasonography. In some of the evaluated parameters the 3D method approaches the conventional 2D results. These parameters are the crown-rump length (CRL), the skull - brain anatomy (93.5%), the spine (85.4%), the upper (88.4%) and lower limbs (87.9%) and the examination of the fetal abdomen (98.5%). Some of the anatomic parameters under evaluation revealed a statistically significant difference in favor of the 2D examination. During the 3D examination the nasal bone was identified in 62.1% of the cases, the stomach in 85.9%, and the urinary bladder in 57.3% of the cases. The NT was assessed accurately in half of the cases compared to 2D examination. The authors concluded that the 3D ultrasound is insufficient for the detailed fetal anatomy examination during the 1(st) trimester of pregnancy. Nevertheless, the method might be improved in order to be considered as a screening method.<sup>77</sup>

*Combined, stepwise sequential and contingent screening versus the integrated test:* Guanciali-Franchi and associates (2011) sought to compare the efficacy of combined, stepwise sequential and contingent screening versus the integrated test in detecting fetal aneuploidies. First trimester combined test, sequential second trimester, and contingent risks were retrospectively calculated for 7292 unselected pregnant women with singleton pregnancies who had received integrated screening. The first trimester testing was based on nuchal translucency, pregnancy-associated plasma protein-A, and free-beta-human chorionic gonadotrophin (free  $\beta$ -hCG) and the second trimester tests were alpha-fetoprotein, hCG, and unconjugated estriol. A second trimester risk of 1:250 defined a positive result for all protocols with the contingent protocol based on additional second trimester testing for those with risks between 1:30 and 1:1200. Among the population submitted for the integrated test, the detection rate was 19/21 (90%) for Down syndrome (DS) and 6/6 (100%) for Edwards syndrome (ES) and the DS false-positive rate (FPR) was 247/7271 (3.4%). Provision of the first trimester combined test alone would have resulted in a 17/21 (81%) detection rate for DS, that of 4/6 (67%) for ES and a DS FPR of 292/7271 (4.0%). The sequential and contingent approaches had the same final detection rates as the integrated test but potentially allowed a high proportion of the affected pregnancies to be detected in the first

trimester. The lowest net DS FPR was seen with the contingent approach (2.6%) and using this protocol only 12.7% of women would have required second trimester testing. The authors concluded that the integrated, sequential, and contingent screenings are all more efficacious than the combined test. Overall, the contingent approach was the most efficient with a high-detection rate, the lowest FPR, and the least amount of testing.<sup>81</sup>

Hayes, Cochrane, UpToDate, MD Consult etc.: Hayes has a directory report entitled First Trimester Prenatal Screening (2009, archived 2011). According to the report, three large, multicenter trials have provided evidence indicating that integrated first- and second-trimester prenatal screening enables significant improvements in prenatal detection of aneuploidy in singleton pregnancies. If all facets of testing are performed correctly and results of testing are clearly and accurately communicated to pregnant women, integrated first- and second-trimester screening should provide benefits such as an optimization of treatment options and a decrease in the number of unnecessary amniocentesis procedures and concomitant procedure-related pregnancy losses. To obtain accurate measurements of nuchal translucency, the FASTER trial and SURUSS project established rigorous quality assurance programs. The establishment and maintenance of similar programs seems to be essential in order to obtain the full benefits of integrated first- and second-trimester screening on a routine basis. In addition, prenatal screening has limited applicability for multiple pregnancies, and practical difficulties will prevent completion of some or all first-trimester tests for some women. Prenatal screening is recommended for singleton pregnancies with first-trimester measurement of maternal PAPP-A level integrated with second-trimester screening using the “quad screen”; singleton pregnancies with the second-trimester “quad screen” if first-trimester screening is missed or not possible and for prenatal screening of singleton pregnancies with first-trimester measurement of nuchal translucency combined with maternal PAPP-A level integrated with second-trimester screening using the “quad screen”. Prenatal screening is not recommended for twin pregnancies with first-trimester measurement of maternal PAPP-A level integrated with second-trimester screening using the “quad screen”, with or without first-trimester measurement of nuchal translucency; for prenatal screening of triplet and higher order multiple pregnancies with first-trimester measurement of nuchal translucency; and for prenatal screening of triplet and higher order multiple pregnancies with first- or second-trimester maternal serum testing.<sup>1</sup>

UpToDate<sup>17</sup> has a report entitled First trimester combined test and integrated tests for screening for Down syndrome and trisomy 18. This report last updated Jan 2013, indicates the following summary of recommendations:

- The "combined test" is a first trimester screening test for Down syndrome. It consists of sonographic measurement of fetal nuchal translucency and maternal serum assessment of beta-hCG and pregnancy-associated plasma protein-A, and is commonly performed at 110/7ths to 136/7ths weeks of gestation. This test is indicated for patients who place a higher value on identifying Down syndrome during the first trimester than on the risk of procedure-related pregnancy loss (Grade 2C).
- The full integrated test (first trimester nuchal translucency, and pregnancy-associated plasma protein-A (PAPP-A) plus second trimester quadruple markers) detects 85 percent of Down syndrome fetuses at a 1 percent FPR. If a 90 percent detection rate is the target, the FPR will be 2 percent. The full integrated test is recommended for patients who place a higher value on minimizing the risk of invasive testing than on first trimester identification of an affected pregnancy (Grade 2C). Results are available in the second trimester and amniocentesis is offered to screen positive patients for definitive diagnosis. Alpha fetoprotein screening for neural tube defects is included.
- If nuchal translucency testing is not available, the serum integrated test (first trimester PAPP-A and second trimester AFP, uE3, beta-hCG, and inhibin A) is more efficient than the second trimester quadruple test. At the same detection rate, the serum integrated test has a lower FPR than the quadruple test.

Professional Organizations: The American College of Obstetricians and Gynecologists (ACOG) 2007 (reaffirmed in 2011) practice guideline for Fetal Chromosomal Abnormalities<sup>3</sup> states that ideally, screening for aneuploidy should occur before 20 weeks of gestation, regardless of maternal age. ACOG has recommended the following based on consistent scientific evidence:

- First-trimester screening using both NT and maternal serum blood testing is an effective screening test in the general population and is more effective than NT alone.
- Measurement of NT alone is less effective for first-trimester screening than is the combined test (NT measurement and biochemical markers).
- 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.
- 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.
- Neural tube defect screening should be offered in the mid-trimester to women who elect only first-trimester screening for Down syndrome.

All pregnant women should be offered first-trimester screening for chromosomal abnormalities using the combination of biochemical tests and nuchal translucency measurement.<sup>3</sup> Only specially trained ultrasonographers using standardized methods should perform the test. Genetic counseling and the option of chorionic villus sampling or mid-trimester amniocentesis should be offered to women that test positive. The committee opinion indicated that as data for screening multiple gestations for chromosomal abnormalities are limited, assessing risk in women with multiple gestations should be done with caution. Three dimensional ultrasonography have not proven to provide any clinical advantage in testing for fetal anomalies and is not recommended.<sup>72</sup>

The American College of Medical Genetics (ACMG) practice guideline updated in 2009 recommend that all women are offered screening tests in the first or second trimesters for fetal aneuploidy and neural tube defects.<sup>51</sup> Invasive diagnostic testing or CVS are options that should be available to all pregnant women. Combined screening tests are acceptable for first trimester screening before 14 weeks gestation. Multifetal pregnancies require women to be informed of the limitations of the screening.

The National Collaborating Centre for Women's and Children's Health developed a clinical guideline (2008) for antenatal care following evidence review.<sup>27</sup> The guideline recommends conducting the combined test (nuchal translucency, beta-hCG, PAPP-A) on all pregnant women between 11 and 13 weeks gestation to screen for Down's syndrome. The most clinically cost-effective serum screening test (triple or quadruple) should be offered between 15 and 20 weeks gestation for women who are evaluated later in pregnancy. Women may be offered triple or quadruple testing between 15 and 20 weeks when it is not possible to measure nuchal translucency, due to fetal position or raised body mass index. A routine anomaly scan at 18 to 20 weeks should not be given using soft markers. An isolated soft marker identified on the anomaly scan, with the exception of a nuchal fold, should not be used to adjust the priori risk for Down's syndrome. The identification of a nuchal fold (6mm or higher) or two soft markers on the anomaly scan should result in referral to a fetal medicine specialist. The guideline also does not recommend routine screening for cardiac anomalies using nuchal translucency.

The California Technology Assessment Forum provided evidence review for ultrasound nuchal translucency testing.<sup>16</sup> The recommendation indicates ultrasound nuchal testing in combination with biochemical screening for fetal aneuploidy meets review criteria but should be restricted to centers meeting California Department of Health Services designation for perinatal diagnostic centers.

CODING INFORMATION	
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CPT	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)
84163	Pregnancy-associated plasma protein-A (PAPP-A)
84702	Gonadotrophin, chorionic (hCG); quantitative

HCPCS	Description
	N/A

ICD-9	Description
655.13	Known or suspected chromosomal abnormality in fetus, antepartum condition
V28.89	Other specified antenatal screening-nuchal translucency testing. (Use as secondary code only in conjunction with 655.13)

ICD-10	Description
O35.1xx0	Maternal Care Chromosomal Abnormality Fet NA/UNS
O35.1xx1	Maternal Care Chromosomal Abnormality Fet Fet 1
O35.1xx2	Maternal Care Chromosomal Abnormality Fet Fet 2
O35.1xx3	Maternal Care Chromosomal Abnormality Fet Fet 3
O35.1xx4	Maternal Care Chromosomal Abnormality Fet Fet 4
O35.1xx5	Maternal Care Chromosomal Abnormality Fet Fet 5
O35.1xx9	Maternal Care Chromosomal Abnormality Fet Oth Fet
Z36	Encounter for Antenatal Screening of Mother

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