Soft markers were originally introduced to prenatal ultrasonography to improve the detection of trisomy 21 over that achievable with age-based and serum screening strategies. As prenatal genetic screening strategies have greatly evolved in the last 2 decades, the relative importance of soft markers has shifted. The purpose of this document is to discuss the recommended evaluation and management of isolated soft markers in the context of current maternal serum screening and cell-free DNA screening options. In this document, “isolated” is used to describe a soft marker that has been identified in the absence of any fetal structural anomaly, growth restriction, or additional soft marker following a detailed obstetrical ultrasound examination. In this document, “serum screening methods” refers to all maternal screening strategies, including first-trimester screen, integrated screen, sequential screen, contingent screen, or quad screen. The Society for Maternal-Fetal Medicine recommends the following approach to the evaluation and management of isolated soft markers: (1) we do not recommend diagnostic testing for aneuploidy solely for the evaluation of an isolated soft marker following a negative serum or cell-free DNA screening result (GRADE 1B); (2) for pregnant people with no previous aneuploidy screening and isolated echogenic intracardiac focus, we recommend no further evaluation as this finding is a normal variant of no clinical importance with no indication for fetal echocardiography, follow-up ultrasound imaging, or postnatal evaluation (GRADE 1C); (3) for pregnant people with no previous aneuploidy screening and isolated thickened nuchal fold or isolated absent or hypoplastic nasal bone, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for noninvasive aneuploidy screening through cell-free DNA or quad screen if cell-free DNA is unavailable or cost-prohibitive (GRADE 1B); (4) for pregnant people with no previous aneuploidy screening and isolated choroid plexus cysts, we recommend counseling to estimate the probability of trisomy 18 and a discussion of options for noninvasive aneuploidy screening with cell-free DNA or quad screen if cell-free DNA is unavailable or cost-prohibitive (GRADE 1C); (5) for pregnant people with negative serum or cell-free DNA screening results and isolated echogenic intracardiac focus, we recommend no further evaluation as this finding is a normal variant of no clinical importance with no indication for diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference (GRADE 1B); (6) for pregnant people with negative serum or cell-free DNA screening results and isolated fetal echogenic bowel, urinary tract dilatation, or shortened humerus, femur, or both, we recommend no further aneuploidy evaluation as this finding is a normal variant of no clinical importance with no indication for fetal echocardiography, follow-up ultrasound imaging, or postnatal evaluation (GRADE 1B); (7) for pregnant people with negative serum screening results and isolated thickened nuchal fold or absent or hypoplastic nasal bone, we recommend counseling to estimate the probability of trisomy 21 and discussion of options for no further aneuploidy evaluation, noninvasive aneuploidy screening through cell-free DNA, or diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference (GRADE 1B); (8) for pregnant people with negative cell-free DNA screening results and isolated thickened nuchal fold or absent or hypoplastic nasal bone, we recommend no further aneuploidy evaluation (GRADE 1B); (9) for pregnant people with negative serum or cell-free DNA screening results and isolated choroid plexus cysts, we recommend no further aneuploidy evaluation, as this finding is a normal variant of no clinical importance with no indication for follow-up ultrasound imaging or postnatal evaluation (GRADE 1C); (10) for fetuses with isolated echogenic bowel, we recommend an evaluation for cystic fibrosis and fetal cytomegalovirus infection and a third-trimester ultrasound examination for reassessment and evaluation of growth (GRADE 1C); (11) for fetuses with an isolated single umbilical artery, we recommend no additional evaluation for aneuploidy, regardless of whether results of previous aneuploidy screening were low risk or testing was declined. We recommend a third-trimester ultrasound examination to evaluate growth and consideration of weekly antenatal fetal surveillance beginning at 36 0/7 weeks of gestation (GRADE 1C); (12) for fetuses with isolated urinary tract dilatation A1, we recommend an ultrasound examination at ≥32 weeks of gestation to determine if postnatal pediatric urology or nephrology follow-up is needed. For fetuses with urinary tract dilatation A2-3, we recommend an individualized follow-up ultrasound assessment with planned postnatal follow-up (GRADE 1C); (13) for fetuses with isolated shortened humerus, femur, or both, we recommend a third-trimester ultrasound examination for reassessment and evaluation of growth (GRADE 1C).

**Key words:** aneuploidy assessment, aneuploidy screening, cell-free DNA screening, serum markers, soft markers, ultrasound
Introduction

Soft ultrasound markers were initially described as a screening method for trisomy 21 to improve the detection rate (DR) over that based on age-related risk alone. Soft markers are minor ultrasound findings identified in the midtrimester of pregnancy that most commonly do not represent a structural abnormality and may be normal variants but are noteworthy because of their association with an increased aneuploidy risk. Commonly identified soft markers addressed in this document include echogenic intracardiac focus (EIF); echogenic bowel, choroid plexus cysts (CPCs); single umbilical artery (SUA); urinary tract dilation (UTD); shortened humerus, femur, or both; thickened nuchal fold; and absent or hypoplastic nasal bone (Table 1).4 Several other ultrasound findings associated with trisomy 21 include mild ventriculomegaly, clinodactyly, and sandal gap deformity that are not addressed in this document.5

Concomitant with the advancement in aneuploidy detection with soft markers was the development of improved serum screening methods to predict aneuploidy risk, including second-trimester quad screening and first-trimester screening with maternal serum analytes and nuchal translucency (NT) measurement.6,7 In 2011, the introduction of cell-free DNA (cfDNA) techniques greatly improved the ability to screen for common aneuploidies. Current guidelines from the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) state that screening (serum screening with or without NT ultrasound examination or cfDNA screening) and diagnostic testing (chorionic villus sampling or amniocentesis) for chromosomal abnormalities should be discussed and offered to all patients early in pregnancy regardless of maternal age or baseline risk.7 Historically, testing was offered only to patients considered at high risk because of maternal age or personal or family history. However, given the personal nature of prenatal testing decision-making and the inefficiency of offering testing only to patients at high risk, all patients should be offered both screening and diagnostic testing options.7

Given the high sensitivity and specificity of cfDNA for trisomies 21, 18, and 13 across all age groups, in 2020, ACOG and SMFM stated that a patient’s baseline risk should not limit screening options for chromosomal abnormalities and endorsed the option of cfDNA screening for all patients.7 The accuracy of cfDNA screening has resulted in the evolution of ultrasound-based screening for aneuploidy. Several organizations have recommendations on the role of soft markers in assessing the risk of aneuploidy, including SMFM, ACOG, the International Society of Ultrasound in Obstetrics and Gynecology, the National Institute for Health and Care Excellence, and the Society of Obstetricians and Gynaecologists of Canada.8–11 The purpose of this document is to focus specifically on the evaluation and management of isolated soft ultrasound markers for aneuploidy diagnosed in the second trimester of pregnancy. Isolated soft ultrasound marker evaluation and management are discussed both in the context of known results from serum or cfDNA screening and in patients who have not had aneuploidy screening. In this document, “isolated” is used to describe a soft marker that has been identified in the absence of any fetal structural anomaly, growth restriction, or additional soft marker following a detailed obstetrical ultrasound examination. “Serum screening methods” refers to all maternal screening strategies, including first-trimester screen, integrated screen, sequential screen, or quad screen.

What is the initial approach when an isolated soft marker is identified?

The presence of multiple soft markers or other abnormal ultrasound findings increases the risk of aneuploidy.12 Identification of a soft marker is an indication for a detailed obstetrical ultrasound examination (Current Procedural Terminology code 76811) to ensure that the finding is isolated (ie, a single marker that does not co-occur with any structural abnormality, growth restriction, or additional soft marker). The option for such evaluation should be discussed with patients. However, not all patients will desire to proceed with further evaluation, and access to trained providers varies throughout the United States and worldwide. The decision to perform a detailed examination should be made through a shared decision-making framework, incorporating patient preferences, values, and availability of resources. The discussion and patient’s decision should be documented in the medical record. In the case of multiple soft markers or structural abnormalities, the approach to evaluation should be individualized. If an isolated soft marker is confirmed, subsequent evaluation and counseling will depend on previous aneuploidy screening results; additional risk factors for aneuploidy, such as age or family history; and associations with nonaneuploid conditions (eg, cystic fibrosis or viral infection).

Traditionally, the presence or absence of specific soft markers was used to modify the probability of trisomy 21 and secondarily that of trisomy 18 for high-risk patients.13 This approach requires an accurate assessment of (1) the a priori, or pretest, risk (age-related risk at the time of delivery or age-related risk in the midtrimester of pregnancy) of the aneuploidy of interest; (2) the posttest risk based on results of a screening test, if performed; (3) validated and reproducible ultrasonographic definitions for the identification of each soft marker; and (4) accurate estimates of sensitivity and specificity to calculate the positive and negative likelihood ratios (LRs) of an isolated soft marker for a particular aneuploidy.6,12 Accepted thresholds for positive LRs are as follows: LRs from approximately 1.5 to 5 confer a small additional increase in the likelihood of the outcome; LRs between 5 and 10 confer a moderate additional increase in the likelihood of the outcome; and LRs of > 10 confer a substantial additional increase in the likelihood of the outcome.
Although LR is inherently independent of a priori risk and disease prevalence, variability in positive and negative LR estimates exists for several reasons: (1) differences in patient populations studied, (2) variability in soft marker definitions, (3) variability in detection of soft markers by ultrasound, and (4) whether or not, for any isolated soft marker, the lack of other soft markers (ie, negative LR) is incorporated into the positive LR estimate. A final risk estimate incorporating the presence or absence of an ultrasound soft marker for the aneuploidy of interest was traditionally calculated to counsel a patient on the risk of aneuploidy and risks and benefits of diagnostic testing. However, the relative importance of this approach has evolved rapidly with improved prenatal screening techniques.

The widespread introduction of cfDNA screening into current obstetrical practice has changed the relevance of a soft marker finding because the posttest probability of a common aneuploidy after negative cfDNA screening is very low. For instance, a negative cfDNA result lowers the risk of trisomy 21 by 300-fold. The residual risk of a 35-year-old woman, whose age-related risk of trisomy 21 at delivery is 1 in 356, is reduced to <1 in 50,000 after a negative cfDNA result. Although a range of positive LR exists for each soft marker, even when the highest positive LR is applied to a population that has previously had a negative cfDNA result, the risk of trisomy 21 is negligibly affected.

Among patients undergoing first-trimester NT, serum screening, or both, the DR for trisomy 21 and other aneuploidies and corresponding residual risk after a negative screening test result depends on the screening paradigm used. cfDNA is the single best screening test for the common trisomies (trisomies 21, 18, and 13) and results in the lowest residual risk of aneuploidy. The DRs for aneuploidy with commonly employed serum screening.

### TABLE 1
Isolated soft markers: Recommended management

<table>
<thead>
<tr>
<th>Soft marker</th>
<th>Aneuploidy evaluation</th>
<th>Antenatal management</th>
<th>Follow-up imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echogenic intracardiac focus</td>
<td>cfDNA or serum screen negative: none</td>
<td>Routine care</td>
<td>N/A</td>
</tr>
<tr>
<td>Echogenic bowel</td>
<td>cfDNA or serum screen negative: none</td>
<td>Evaluation for cystic fibrosis, congenital viral infection, intra-amniotic bleeding</td>
<td>Third-trimester ultrasound examination for reassessment and evaluation of growth</td>
</tr>
<tr>
<td>Choroid plexus cyst</td>
<td>cfDNA or serum screen negative: none</td>
<td>Routine care</td>
<td>N/A</td>
</tr>
<tr>
<td>Single umbilical artery</td>
<td>cfDNA or serum screen negative or no previous screening: none</td>
<td>Consideration for weekly antenatal surveillance beginning at 36 0/7 wk of gestation</td>
<td>Third-trimester ultrasound examination for evaluation of growth</td>
</tr>
<tr>
<td>Urinary tract dilation</td>
<td>cfDNA or serum screen negative: none</td>
<td>Evaluation for persistence, with frequency of evaluation dependent on initial findings</td>
<td>Third-trimester ultrasound examination to determine whether postnatal pediatric urology or nephrology follow-up is needed</td>
</tr>
<tr>
<td>Shortened humerus, femur, or both</td>
<td>cfDNA or serum screen negative: none</td>
<td>Evaluation for skeletal dysplasias</td>
<td>Third-trimester ultrasound examination for reassessment and evaluation of growth</td>
</tr>
<tr>
<td>Thickened nuchal fold</td>
<td>cfDNA negative: none</td>
<td>Routine care</td>
<td>N/A</td>
</tr>
<tr>
<td>Absent or hypoplastic nasal bone</td>
<td>cfDNA negative: none</td>
<td>Routine care</td>
<td>N/A</td>
</tr>
</tbody>
</table>

cfDNA, cell-free DNA; N/A, not applicable.

strategies are high, ranging from 81% to 99% for trisomy 21.\(^7\) Regardless of the screening strategy used, there is no one threshold value for residual risk above which additional aneuploidy evaluation is routinely recommended, as risk estimates represent a continuum and are ultimately predicated on a patient’s interpretation of risk. However, many laboratories employ a risk cutoff of 1 in 250 or 1 in 300, above which further evaluation and diagnostic testing are recommended. Because many soft markers are associated with minimal or moderate elevations in the risk of aneuploidy, the finding of an isolated soft marker in the presence of the high negative predictive value of all screening strategies is unlikely to substantially alter the risk estimate enough to warrant a recommendation for diagnostic testing.

It is important to recognize that only diagnostic testing removes residual risk for aneuploidy detection, and thus, a patient may elect diagnostic testing for any indication. However, **we do not recommend diagnostic testing for aneuploidy solely for the evaluation of an isolated soft marker following a negative serum or cfDNA screening result (GRADE 1B).** Similarly, if a pregnant person has undergone diagnostic testing and the results indicate a normal karyotype, identification of a soft marker is not meaningful concerning aneuploidy and should be reported as such.

Some pregnant people may decline any aneuploidy screening following a shared decision-making process that incorporates accurate information, accessible healthcare resources, and the patient’s clinical context, values, beliefs, and potential anxiety created by the identification and discussion of a soft marker.\(^7,16,17\) Although any fetal anatomic survey could be viewed as a screening test for aneuploidy, identification of a major structural anomaly and discussion of potential etiologies is standard of care given the likelihood of identifying a chromosomal abnormality. Identification of an isolated soft marker, in contrast, does not have a similar magnitude of association with chromosomal anomalies, and discussion of the risk of aneuploidy, albeit low, may potentially conflict with a patient’s desires and values. In addition, such counseling can generate anxiety, which may be why the patient declined screening when previously offered.\(^7\) Given the low likelihood of aneuploidy in the setting of an isolated soft marker, some providers or practices may decide that for pregnant people who have previously declined aneuploidy screening after counseling, identification of an isolated soft marker will be treated as a normal variant and neither acknowledged nor discussed, except for those associated with a need for further imaging follow-up (eg, UTD, echogenic bowel).

In contrast, other providers or practices may choose to discuss such findings with all patients and use it as an opportunity to again offer evaluation for aneuploidy or may individualize counseling based on a patient’s age-related risk for aneuploidy. Each practice should establish a standardized protocol for how the identification of an isolated soft marker will be documented and managed for patients who have previously declined aneuploidy screening. These protocols should ensure that patients are informed before the ultrasound examination of how findings will be handled to enhance shared decision-making and patient autonomy.

**What is the counseling and management regarding echogenic intracardiac focus?**

An EIF is defined as a small (< 6 mm) echogenic area in either cardiac ventricle that is as bright as the surrounding bone and visualized in at least 2 separate planes.\(^18\) EIFs may appear in either cardiac ventricle, although left-sided EIFs are more common and are thought to represent microcalcifications of papillary muscles.\(^18,20\) The pathogenesis of this finding is unclear. EIFs do not represent a structural or functional cardiac abnormality, and they are not associated with cardiac malformations in the fetus or newborn.\(^21\)–\(^23\)

EIFs are identified in 3% to 5% of karyotypically normal fetuses, and ethnic variation exists.\(^24\)–\(^27\) In the largest analysis of 7480 ethnically diverse women having amnioncentesis, the prevalence of EIF was 8.1% among Middle Eastern women, 6.9% among Asian American women, 6.7% among African American women, 3.4% among Hispanic women, and 3.3% among White women, with lower prevalence among Asian Indian and Native American women.\(^27\) Smaller studies have demonstrated a higher prevalence of EIF among women of Asian descent, with estimates up to 30%.\(^28,29\)

Since the first descriptions of EIFs as a soft marker for trisomy 21, a subsequent large body of literature has demonstrated varying positive LRs for trisomy 21, depending on the population studied (low-risk vs high-risk) and whether the EIF was isolated or in combination with other soft markers.\(^13,24,26,30\)–\(^33\) In addition, 1 meta-analysis from 2013 has demonstrated a lack of association between isolated EIF and trisomy 21, with a positive LR of 0.95.\(^34\) Overall, isolated EIFs have a positive LR ranging between 1.4 and 1.8, with a lower confidence interval extending to or lower than 1, suggesting a minimal risk.\(^32,35\)

For pregnant people with no previous aneuploidy screening and an isolated EIF, **we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for noninvasive aneuploidy screening with cfDNA or quad screen if cfDNA is unavailable or cost-prohibitive (GRADE 1B).** Although any patient may request diagnostic testing for any indication, we do not recommend diagnostic testing solely for this indication. For pregnant people with negative serum or cfDNA screening results and an isolated EIF, **we recommend no further evaluation, as this finding is a normal variant of no clinical importance with no indication for fetal echocardiography, follow-up ultrasound imaging, or postnatal evaluation (GRADE 1B).**

**What is the counseling and management regarding echogenic bowel?**

Echogenic bowel is diagnosed when the fetal bowel displays echogenicity equal to or greater than that of the surrounding fetal bone, typically the iliac wing. Transducer frequency and acoustic gain settings can influence the
diagnosis because higher frequency transducers and higher gain settings tend to exaggerate the finding. Therefore, a lower frequency transducer (≤5 MHz) with harmonic imaging turned off and set at a lower gain should be used to confirm the diagnosis. 36

Echogenic bowel is observed in up to 1.8% of second-trimester ultrasound examinations. 37–39 Echogenic bowel is often isolated, but an increased incidence of structural anomalies, particularly renal and cardiac anomalies, has been demonstrated in fetuses with echogenic bowel. 40 Although isolated echogenic bowel can be a transient or idiopathic finding in approximately 0.5% of all fetuses, it also can be associated with a wide range of pathologic conditions, such as aneuploidy, cystic fibrosis, congenital viral infection, primary gastrointestinal pathology, intra-amniotic bleeding, and fetal growth restriction (FGR). The estimated incidence of each possible etiology varies because of small sample size studies and the subjectivity in the diagnosis.

In fetuses with isolated idiopathic echogenic bowel, the primary mechanism is thought to be the accumulation of meconium. Previous studies have demonstrated the idiopathic development of echogenic bowel following invasive procedures, such as intrauterine fetal transfusions, secondary to fetal swallowing of blood from the amniotic cavity. 41 It has been demonstrated that this finding may even persist for 2 to 4 weeks following intrauterine transfusion. 42 Another study has documented subsequent identification of an echogenic bowel after amniocentesis (performed for the indication of advanced maternal age), with a strong association between echogenic bowel and blood-tinged or dark fluid at the time of amniocentesis. 43

The estimated incidence of aneuploidy in fetuses with isolated echogenic bowel ranges from 3% to 5%, with trisomy 21 being the most commonly diagnosed. 40,44–49 Other karyotypic abnormalities, such as trisomy 18, trisomy 13, monosomy X, and chromosomal mosaicism, also have been reported. 46,48 Echogenic bowel is an isolated finding in 4% to 25% of fetuses with aneuploidy. 40,50 Hypoperistalsis due to mechanical or functional bowel obstruction with subsequent dehydration of meconium is the proposed mechanism causing this finding in fetuses with abnormal karyotype. The positive LR for trisomy 21 for a fetus with isolated echogenic bowel depends on the population studied. Most positive LRs for trisomy 21 range between 6 and 8, suggesting a moderately increased risk, although 1 meta-analysis noted the positive LR for isolated echogenic bowel to be much lower at 1.65. 32–34,51

For pregnant people with no previous aneuploidy screening and isolated fetal echogenic bowel, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for noninvasive aneuploidy screening with cfDNA or quad screen if cfDNA is unavailable or cost-prohibitive (GRADE 1B). Although any patient may request diagnostic testing for any indication, we do not recommend diagnostic testing solely for this indication. For pregnant people with negative serum or cfDNA screening results and isolated fetal echogenic bowel, we recommend no further aneuploidy evaluation (GRADE 1B).

Cystic fibrosis is associated with echogenic bowel, as abnormal pancreatic enzyme secretion leads to thickened meconium, and subsequent meconium ileus is observed in some newborns with cystic fibrosis. The risk for cystic fibrosis ranges from 0% to 13% in the presence of isolated echogenic bowel. 40,46,48,52 The finding of dilated loops of bowel in addition to echogenic bowel may increase this risk to as high as 17%. 53 Parental cystic fibrosis carrier status should be determined if not previously assessed in the current or a previous pregnancy. If both parents are carriers, genetic counseling should be undertaken to discuss the risks and benefits of invasive testing for fetal genotyping. Racial and ethnic limitations of current cystic fibrosis screening panels should be considered when interpreting test results.

In addition, congenital infection has been associated with isolated echogenic bowel. Different mechanisms underlie the findings of echogenicity: (1) direct damage to the fetal intestinal wall with subsequent paralytic ileus, (2) intestinal perforation resulting in meconium peritonitis and focal calcification at the perforation sites, or (3) ascites secondary to hydrops leading to echogenicity on ultrasound. Cytomegalovirus (CMV) is the most commonly observed infection, but toxoplasmosis, rubella, herpes, varicella, and parvovirus have been reported. 36,39,40 Although most studies report a 2% to 4% incidence of congenital infection in fetuses with echogenic bowel, rates up to 10% have been reported. 39,54 In a series of 650 cases with maternal primary CMV infection, 7 fetuses with CMV infection had isolated echogenic bowel as the sole ultrasound finding. 55

Although symptomatic maternal infection is uncommon, a history should be taken to evaluate for possible timing of symptoms of CMV. CMV immunoglobulin G (IgG) and IgM titers should be drawn regardless, with IgG avidity testing as applicable. If results are suggestive of primary CMV infection (IgM positive and IgG positive with low avidity or IgG seroconversion), amniocentesis should be considered as a confirmatory test. Alternatively, if primary CMV infection is strongly suspected, amniocentesis should be recommended as the initial test to evaluate for this etiology. Amniocentesis with polymerase chain reaction for CMV DNA is the best diagnostic test for congenital CMV infection and is most sensitive when performed after 21 weeks of gestation and >6 weeks from maternal infection. Negative serologic results for both IgM and IgG rule out a congenital CMV infection. Other titer results require further evaluation, and additional recommendations for evaluation and management of antenatal CMV infection are found in SMFM Consult #39, Diagnosis and antenatal management of congenital cytomegalovirus infection. 56 Without a history of exposure or other clinical risk factors, the chance of positive results for other congenital infections, such as varicella, herpes, parvovirus, or toxoplasmosis, is very low. 57 Therefore, routine testing for these other infections may not be
useful; however, the utility of testing should be determined on the basis of the clinical scenario, differential diagnosis, and potential exposures. For fetuses with isolated echogenic bowel, we recommend evaluation for cystic fibrosis and fetal CMV infection (GRADE 1C).

Primary gastrointestinal pathology, such as bowel obstruction, atresia, and perforation, may cause an echogenic appearance of the fetal bowel. In cases of obstruction and atresia, decreased meconium fluid content is the proposed cause for the echogenicity. The presence of meconium outside the intestinal lumen likely is responsible for the echogenic appearance in cases of bowel perforation.

Finally, isolated echogenic bowel is associated with an increased risk of stillbirth, often in the second trimester of pregnancy, most fetuses with an isolated echogenic bowel have normal outcomes. The utility of antenatal fetal ultrasound examination for reassessment and evaluation of fetal growth for all fetuses with isolated echogenic bowel is reassuring, and normal fetal outcomes are likely. Normal fetal outcomes have been demonstrated in fetuses with persistent echogenic bowel as well; thus, persistent echogenicity should not be viewed as a marker for adverse outcomes. At the time of delivery, pediatric providers should be informed of the antenatal findings of echogenic bowel and a prenatal workup performed so that appropriate neonatal evaluation may be pursued.

What is the counseling and management regarding choroid plexus cyst?
A CPC is a small, fluid-filled structure within the choroid of the lateral ventricles of the fetal brain. On ultrasound, CPCs appear as echolucent cysts within the echogenic choroid. CPCs may be single or multiple, unilateral or bilateral, and most often are < 1 cm in diameter. CPCs are identified in approximately 1% to 2% of fetuses in the second trimester of pregnancy and are commonly isolated findings in fetuses with euploidy.

CPCs are associated with trisomy 18, as they are present in 30% to 50% of fetuses with this disorder. When a fetus is affected by trisomy 18, multiple structural anomalies are almost always evident, including structural heart defects, clenched hands, talipes deformity of the feet, FGR, and polyhydramnios. When a structural anomaly is present in addition to CPCs, the positive LR is 66.

In the absence of other ultrasonographic abnormalities, the likelihood of trisomy 18 with isolated CPCs is much lower. Early studies suggested that isolated CPCs conferred a 1 in 200 to 1 in 400 risk of trisomy 18. More recent studies among women with isolated CPCs suggest a range of positive LRs for trisomy 18, from 0.9 to 5.6, with most studies suggesting low risk. Based on the literature, the best estimate for the LR is < 2, suggesting a minimal risk. The presence of a CPC does not alter the risk of trisomy 21.

For pregnant people with no previous aneuploidy screening and isolated CPCs, we recommend counseling to estimate the probability of trisomy 18 and a discussion of options for noninvasive aneuploidy screening with cfDNA or quad screen if cfDNA is unavailable or cost-prohibitive (GRADE 1C). Although any patient may request diagnostic testing for any indication, we do not recommend diagnostic testing solely for this indication. For pregnant people with negative serum or cfDNA screening results and isolated CPCs, we recommend no further aneuploidy evaluation, as this finding is a normal variant of no clinical importance with no indication for follow-up ultrasound imaging or postnatal evaluation (GRADE 1C). Ultrasound characteristics of CPCs (size, complexity, laterality, and persistence) should not be used to modify risk further because these factors do not impact the likelihood of trisomy 18.

A CPC is not considered a structural or functional brain abnormality, and nearly all CPCs resolve by 28 weeks. Patients may be counseled that neurodevelopmental outcomes in children with euploidy born after a prenatal diagnosis of CPCs have not shown differences in neurocognitive ability, motor function, or behavior.

What is the counseling and management regarding a single umbilical artery?
The normal umbilical cord contains 2 arteries and 1 vein. An SUA results from atrophy or agenesis of 1 of the arteries. An SUA can be detected on a cross section of the umbilical cord during a routine second-trimester ultrasound examination. In addition, an SUA can be detected using color flow Doppler to examine the umbilical arteries in the pelvis, even at early gestational ages.

The incidence of SUA is 0.25% to 1% of all singleton pregnancies and up to 4.6% of twin gestations. An isolated SUA with no other structural or chromosomal abnormality should be distinguished from an SUA that is present with other abnormalities. Co-occurring structural abnormalities most commonly involve the cardiovascular and renal systems. With an SUA and one or multiple structural abnormalities, the frequency of associated aneuploidy ranges from 4% to 50%. A comprehensive assessment of cardiac anatomy (76811 ultrasound) should be performed, and if required cardiac views are adequately visualized and normal, fetal echocardiography is not routinely warranted. For patients with an isolated SUA, there appears to be no increased risk of aneuploidy. For fetuses with an isolated SUA, we recommend no additional evaluation for aneuploidy, regardless of whether previous aneuploidy screening results were low risk or screening was declined (GRADE 1C).

Isolated SUA has been associated in some studies with an increased risk of stillbirth and FGR, although other studies suggest that an isolated SUA does not place the fetus at increased risk of FGR. In a population-based
case-control study, SUA was associated with an increased OR of stillbirth compared with live birth (OR, 4.80; 95% confidence interval [CI], 2.67–8.62). In a cohort of fetuses with isolated SUA, the observed incidence of FGR was not higher than that expected. However, another study with a large control group of fetuses with a 3-vessel cord did demonstrate an increased risk of FGR, polyhydramnios, oligohydramnios, placental abruption, cord prolapse, and perinatal mortality after controlling for other confounders.

Given the conflicting evidence and increased risks of stillbirth, we recommend a third-trimester ultrasound examination to evaluate growth and consideration of weekly antenatal fetal surveillance beginning at 36 0/7 weeks of gestation for fetuses with an isolated SUA (GRADE 1C). At the time of delivery, the pediatric provider should be notified of the prenatal findings. Postnatal examination of infants with a prenatal diagnosis of isolated SUA revealed structural anomalies in up to 7% of fetuses in 1 study.

What is the counseling and management regarding urinary tract dilation?

Several terms have been used to describe UTD, including pyelectasis, pelviectasis, and hydronephrosis. UTD occurs in 1% to 2% of pregnancies and is most commonly a transient finding that is a normal variant. UTD may indicate renal or urinary tract pathology and may also be a marker of trisomy 21. The association between trisomy 21 and UTD has been well described in several series, and the finding of UTD confers a positive LR of 1.5, suggesting a minimal risk. For pregnant people with no previous aneuploidy screening and isolated UTD, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for noninvasive aneuploidy screening with cfDNA or quad screen if cfDNA is unavailable or cost-prohibitive (GRADE 1B). Although any patient may request diagnostic testing for any indication, we do not recommend diagnostic testing solely for this indication. For pregnant people with negative serum or cfDNA screening results and isolated UTD, we recommend no further aneuploidy evaluation (GRADE 1B).

In 2014, a consensus statement defined norms for antenatal UTD based on anterior-posterior renal pelvis diameter, with <4 mm being normal between 16 and 27 weeks of gestation and <7 mm being normal between 28 weeks of gestation and delivery. To fully assess and classify UTD, additional ultrasound features to be evaluated include the presence of calyceal dilation, parenchymal thickness and appearance, ureteral dilation, bladder abnormalities, and amniotic fluid volume. The complete evaluation of the urinary tract results in the classification of A1 (low risk) vs A2-3 (increased risk) UTD, which guides antenatal management and postnatal follow-up (Table 2). UTD between 4 and 7 mm in the second trimester of pregnancy resolves in approximately 80% of cases. Consistent with the 2014 consensus statement, for fetuses with isolated UTD A1, we recommend an ultrasound examination at ≥32 weeks of gestation to determine if postnatal pediatric urology or nephrology follow-up is needed. For fetuses with UTD A2-3, we recommend an individualized follow-up ultrasound assessment with planned postnatal follow-up (GRADE 1C).

In a minority of cases, UTD has a pathologic cause. Common pathologic causes include vesicoureteral reflux (the most common etiology), ureteropelvic junction obstruction, ureterovesical junction obstruction, multicystic dysplastic kidneys, and posterior urethral valves. Although some conditions can be diagnosed antenatally, in most

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Urinary tract dilation (UTD): Antenatal classification of findings</th>
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</thead>
<tbody>
<tr>
<td>Ultrasound findings</td>
<td>UTD A1</td>
</tr>
<tr>
<td>AP RPD, 16–27 wk of gestation</td>
<td>4 to &lt;7 mm</td>
</tr>
<tr>
<td>AP RPD, ≥28 wk of gestation</td>
<td>7 to &lt;10 mm</td>
</tr>
<tr>
<td>Calyceal dilation</td>
<td>None or central</td>
</tr>
<tr>
<td>Parenchymal thickness</td>
<td>Normal</td>
</tr>
<tr>
<td>Parenchymal appearance</td>
<td>Normal</td>
</tr>
<tr>
<td>Ureters</td>
<td>Normal</td>
</tr>
<tr>
<td>Bladder</td>
<td>Normal</td>
</tr>
<tr>
<td>Unexplained oligohydramnios</td>
<td>Absent</td>
</tr>
<tr>
<td>Prenatal follow-up</td>
<td>Third-trimester ultrasound examination at ≥32 wks of gestation</td>
</tr>
</tbody>
</table>

## Summary of recommendations

<table>
<thead>
<tr>
<th>Number</th>
<th>Recommendations</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>We do not recommend diagnostic testing for aneuploidy solely for the evaluation of an isolated soft marker following a negative serum or cfDNA screening result.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>2</td>
<td>For pregnant people with no previous aneuploidy screening and isolated echogenic intracardiac focus, echogenic bowel, UTD, or shortened humerus, femur, or both, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for noninvasive aneuploidy screening with cfDNA, or quad screen if cfDNA is unavailable or cost-prohibitive.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>3</td>
<td>For pregnant people with no previous aneuploidy screening and isolated thickened nuchal fold or isolated absent or hypoplastic nasal bone, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for noninvasive aneuploidy screening via cfDNA or quad screen if cfDNA is unavailable or cost-prohibitive or diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>4</td>
<td>For pregnant people with no previous aneuploidy screening and isolated CPCs, we recommend counseling to estimate the probability of trisomy 18 and discussion of options for noninvasive aneuploidy screening with cfDNA or quad screen if cfDNA is unavailable or cost-prohibitive.</td>
<td>1C Strong recommendation, low-quality evidence</td>
</tr>
<tr>
<td>5</td>
<td>For pregnant people with negative serum or cfDNA screening results and an isolated echogenic intracardiac focus, we recommend no further evaluation, as this finding is a normal variant of no clinical importance with no indication for fetal echocardiography, follow-up ultrasound imaging, or postnatal evaluation.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>6</td>
<td>For pregnant people with negative serum or cfDNA screening results and isolated fetal echogenic bowel, UTD, or shortened humerus, femur, or both, we recommend no further aneuploidy evaluation.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>7</td>
<td>For pregnant people with negative screening results and isolated thickened nuchal fold or absent or hypoplastic nasal bone, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for no further aneuploidy evaluation, noninvasive aneuploidy screening via cfDNA, or diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>8</td>
<td>For pregnant people with negative cfDNA screening results and isolated thickened nuchal fold or absent or hypoplastic nasal bone, we recommend no further aneuploidy evaluation.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>9</td>
<td>For pregnant people with negative serum or cfDNA screening results and isolated CPCs, we recommend no further aneuploidy evaluation, as this finding is a normal variant of no clinical importance with no indication for follow-up ultrasound imaging or postnatal evaluation.</td>
<td>1C Strong recommendation, low-quality evidence</td>
</tr>
<tr>
<td>10</td>
<td>For fetuses with isolated echogenic bowel, we recommend evaluation for cystic fibrosis and fetal CMV infection and a third-trimester ultrasound examination for reassessment and evaluation of fetal growth.</td>
<td>1C Strong recommendation, low-quality evidence</td>
</tr>
<tr>
<td>11</td>
<td>For fetuses with an isolated SUA, we recommend no additional evaluation for aneuploidy, regardless of whether previous results of aneuploidy screening were low risk or testing was declined. We recommend a third-trimester ultrasound examination to evaluate growth and consideration of weekly antenatal fetal surveillance beginning at 36 0/7 wk of gestation.</td>
<td>1C Strong recommendation, low-quality evidence</td>
</tr>
<tr>
<td>12</td>
<td>For fetuses with isolated UTD A1, we recommend an ultrasound examination at ≥32 wk of gestation to determine if postnatal pediatric urology or nephrology follow-up is needed. For fetuses with UTD A2-3, we recommend an individualized follow-up ultrasound assessment with planned postnatal follow-up.</td>
<td>1C Strong recommendation, low-quality evidence</td>
</tr>
<tr>
<td>13</td>
<td>For fetuses with isolated shortened humerus, femur, or both, we recommend a third-trimester ultrasound examination for reassessment and evaluation of growth.</td>
<td>1C Strong recommendation, low-quality evidence</td>
</tr>
</tbody>
</table>

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cfDNA, cell-free DNA; CMV, cytomegalovirus; CPC, choroid plexus cyst; SUA, single umbilical artery; UTD, urinary tract dilation.

<table>
<thead>
<tr>
<th>GRADE of recommendation</th>
<th>Clarity of risk and benefit</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A. Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risks and burdens, or vice versa.</td>
<td>Consistent evidence from well-performed RCTs, or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.</td>
<td>Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</td>
</tr>
<tr>
<td>1B. Strong recommendation, moderate-quality evidence</td>
<td>Benefits clearly outweigh risks and burdens, or vice versa.</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.</td>
<td>Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</td>
</tr>
<tr>
<td>1C. Strong recommendation, low-quality evidence</td>
<td>Benefits seem to outweigh risks and burdens, or vice versa.</td>
<td>Evidence from observational studies, unsystematic clinical experience, or RCTs with serious flaws. Any estimate of effect is uncertain.</td>
<td>Strong recommendation that applies to most patients. However, some of the evidence base supporting the recommendation is of low quality.</td>
</tr>
<tr>
<td>2A. Weak recommendation, high-quality evidence</td>
<td>Benefits are closely balanced with risks and burdens.</td>
<td>Consistent evidence from well-performed RCTs or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.</td>
<td>Weak recommendation; best action may differ depending on circumstances or patients or societal values.</td>
</tr>
<tr>
<td>2B. Weak recommendation, moderate-quality evidence</td>
<td>Benefits are closely balanced with risks and burdens; there are some uncertainties in the estimates of benefits, risks, and burdens.</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.</td>
<td>Weak recommendation; alternative approaches are likely to be better for some patients under some circumstances.</td>
</tr>
<tr>
<td>2C. Weak recommendation, low-quality evidence</td>
<td>There are uncertainties in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.</td>
<td>Evidence from observational studies, unsystematic clinical experience, or RCTs with serious flaws. Any estimate of effect is uncertain.</td>
<td>Very weak recommendation, other alternatives may be equally reasonable.</td>
</tr>
</tbody>
</table>

**Best practice**

Recommendation in which either (1) there is an enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize) or (2) recommendation to the contrary would be unethical.

**GRADE**, Grading of Recommendations Assessment, Development, and Evaluation; **RCT**, randomized controlled trial.

* Adapted Guyatt et al. 109

cases, the diagnosis is made postnatally.\textsuperscript{59} At the time of delivery, the diagnosis of UTD A1 or A2-3 should be communicated with the pediatric provider; however, resolved UTD A1 demonstrated at the third-trimester ultrasound examination requires no postnatal follow-up.\textsuperscript{89}

**What is the counseling and management regarding shortened humerus, femur, or both?**

A shortened humerus and shortened femur have been variably defined throughout the literature. For aneuploidy screening, a shortened humerus is identified when the ratio of the observed to expected humeral length (based on biparietal diameter) is \( <0.90 \).\textsuperscript{90,91} Similarly, a shortened femur is identified when the ratio of the observed femoral length to expected femoral length (based on biparietal diameter) is \(<0.92\).\textsuperscript{2,91}

With these thresholds, the singular presence of either of these markers has been associated with trisomy 21, with higher specificity for shortened humeri. For shortened humeri, the positive LR from meta-analyses ranges from 1.5 to 2.7, with the CI of the lower estimate crossing 1, suggesting a moderate risk.\textsuperscript{32,33} Racial and ethnic variation in the normal distribution for femoral length in the mid-trimester has been described in some studies, with femoral bones being shorter among Asian participants and longer among Black participants.\textsuperscript{92,93} Similar variation has not been described for midtrimester humeral lengths, and race- and ethnicity-specific definitions of foreshortened humerus, femur, or both do not improve diagnostic test characteristics for trisomy 21 detection.\textsuperscript{94,95} Parental race and ethnicity can lead to constitutionally short bones and should be considered in the differential diagnosis.

For pregnant people with no previous aneuploidy screening and isolated shortened humerus, femur, or both, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for noninvasive aneuploidy screening with cfDNA or quad screen if cfDNA is unavailable or cost-prohibitive (GRADE 1B). Although any patient may request diagnostic testing for any indication, we do not recommend diagnostic testing solely for this indication. For pregnant people with negative cfDNA or serum screening results and isolated shortened humerus, femur, or both, we recommend no further aneuploidy evaluation (GRADE 1B).

The finding of shortened humerus, femur, or both is associated with skeletal dysplasia. A thorough evaluation and measurement of all appendicular bones should be performed and compared with nomograms for bone length by gestational age. In general, many fetuses with skeletal dysplasias fall below the third percentile for bone length measurements in the second trimester of pregnancy, except for achondroplasia, which may not manifest until the third trimester of pregnancy.\textsuperscript{96}

Finally, isolated shortened humerus, femur, or both are associated with FGR.\textsuperscript{37,88} For fetuses with isolated shortened humerus, femur, or both, we recommend a third-trimester ultrasound examination for reassessment and evaluation of growth (GRADE 1C).

**What is the counseling and management regarding thickened nuchal fold?**

The nuchal fold is imaged in the transverse plane of the fetal head, angled caudally to capture the cerebellum and occipital bone, and calipers are placed between the outer edge of the skin and outer edge of the occipital bone. A thickened nuchal fold is defined as \( \geq 6 \text{mm} \) between 15 and 20 weeks of gestation.\textsuperscript{97} Thickened nuchal fold was one of the first identified ultrasound markers of trisomy 21 and is one of the most specific markers to date.\textsuperscript{98,100} After the initial report, several prospective series of consecutive amniocenteses confirmed the association between an isolated thickened nuchal fold and trisomy 21, with rare false-positive cases.\textsuperscript{1,2,100} The positive LR ranges between 11 and 23, suggesting a substantial risk.\textsuperscript{32–34} However, when identified as an isolated marker, the positive LR is estimated to be 3.8.\textsuperscript{34}

For pregnant people with no previous aneuploidy screening and isolated thickened nuchal fold, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for noninvasive aneuploidy screening via cfDNA or diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference (GRADE 1B). For pregnant people with negative serum screening results and isolated thickened nuchal fold, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for no further aneuploidy evaluation, noninvasive aneuploidy screening via cfDNA, or diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference (GRADE 1B). Given the high LR described in the literature for this marker and the variation in aneuploidy DRs across serum screening methods, the residual risk of trisomy 21 in a particular patient may increase above a threshold at which further evaluation would typically be considered. Conceptualizing this residual risk may help the patient decide whether to pursue no additional evaluation, noninvasive screening, or diagnostic testing. For pregnant people with negative cfDNA screening results and isolated thickened nuchal fold, we recommend no further aneuploidy evaluation (GRADE 1B).

Regardless of the aneuploidy evaluation pursued, serial ultrasound examinations of the evolution of the thickened nuchal fold are not indicated. Conflicting evidence exists regarding the association between a thickened nuchal fold and congenital heart disease; however, if cardiac anatomy has been adequately visualized and appears normal, no further imaging is necessary.\textsuperscript{12}

**What is the counseling and management of absent or hypoplastic nasal bone?**

The nasal bone is imaged perpendicular to the longitudinal axis of the nose, in the midsagittal plane of the fetal face.\textsuperscript{99}
A hypoplastic nasal bone in the second trimester of pregnancy is defined as a ratio against the biparietal diameter (biparietal diameter-to-nasal bone ≥10 or ≥11), by length (≤2.5 mm), by gestational age-based percentiles (<2.5th percentile), or by multiples of the median (<0.75 or ≤0.7 MoM), the latter of which has been demonstrated to have better test characteristics for the identification of trisomy 21.101,102

Absent or hypoplastic nasal bone occurs in 0.1% to 1.2% of euploid pregnancies.103,104 Ethnic variation is known to occur in some populations. Absent or hypoplastic nasal bones in the second trimester of pregnancy have been seen in 9% of the Afro-Caribbean population; however, another study has demonstrated no difference in normative values between White and Asian populations.103,105

The association between absent or hypoplastic nasal bone in the second trimester of pregnancy and trisomy 21 is well described. In many cases, these findings occur with other structural anomalies or soft markers; there are limited data on the increased risk of trisomy 21 with an isolated absent or hypoplastic nasal bone.102,106,107 In 1 meta-analysis, the positive LR of absent or hypoplastic nasal bone was 23, suggesting a high risk, although there was substantial heterogeneity in the studies included in this meta-analysis.34 When considered as an isolated marker, the positive LR is 6.6.34 The wide range of positive LRs reflects not only whether the marker was isolated but also differences based on the ethnicities of the populations included in these studies, and there are limited data to provide ethnicity-specific LRs.

For pregnant people with no previous aneuploidy screening and isolated absent or hypoplastic nasal bone, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for noninvasive aneuploidy screening through cfDNA or quad screen if cfDNA is unavailable or cost-prohibitive or diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference (GRADE 1B). For pregnant people with negative serum screening results and isolated absent or hypoplastic nasal bone, we recommend counseling to estimate the probability of trisomy 21 and a discussion of options for no further aneuploidy evaluation, noninvasive aneuploidy screening via cfDNA, or diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference (GRADE 1B). Given the high LR described in the literature for this marker and the variation in aneuploidy DRs across serum screening methods, the residual risk of trisomy 21 in a particular patient may increase above a threshold at which further evaluation would typically be considered. Conceptualizing this residual risk may help the patient decide whether to pursue no additional evaluation, noninvasive evaluation, or diagnostic testing. For pregnant people with negative cfDNA screening results and isolated absent or hypoplastic nasal bone, we recommend no further aneuploidy evaluation (GRADE 1B). In the presence of a low risk for aneuploidy, this finding is of little clinical importance and is most likely a normal variant. We do not recommend any additional antenatal ultrasound surveillance for this finding alone. Absent nasal bone can be associated with other genetic syndromes; therefore, careful evaluation of anatomy in the setting of this finding is warranted.

Conclusion

With advances in prenatal screening for fetal aneuploidy, the relative impact of soft ultrasound markers in assessing the risk for aneuploidy has decreased since their initial introduction to routine prenatal care. When an isolated soft marker is identified after negative screening results, patients may be reassured that the risks of fetal aneuploidy remain low. However, the identification of soft markers remains important to evaluate for associated conditions that are unrelated to fetal aneuploidy.

REFERENCES


13. Nyberg DA, Luthy DA, Resta RG, Nyberg BC, Williams MA. Age-adjusted ultrasound risk assessment for fetal Down’s syndrome during the


Reprints will not be available.

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