



# The role of ultrasound in women who undergo cell-free DNA screening

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The practice of medicine continues to evolve, and individual circumstances will vary. This publication reflects information available at the time of its submission for publication and is neither designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.

The introduction of cell-free DNA screening for aneuploidy into obstetric practice in 2011 revolutionized the strategies utilized for prenatal testing. The purpose of this document is to review the current data on the role of ultrasound in women who have undergone or are considering cell-free DNA screening. The following are Society for Maternal-Fetal Medicine recommendations: (1) in women who have already received a negative cell-free DNA screening result, ultrasound at 11–14 weeks of gestation solely for the purpose of nuchal translucency measurement (Current Procedural Terminology code 76813) is not recommended (GRADE 1B); (2) diagnostic testing should not be recommended to patients solely for the indication of an isolated soft marker in the setting of a negative cell-free DNA screen (GRADE 2B); (3) in women with an isolated soft marker that has no other clinical implications (ie, choroid plexus cyst or echogenic intracardiac focus) and a negative cell-free DNA screen, we recommend describing the finding as not clinically significant or as a normal variant (GRADE 2B); (4) in women with an isolated soft marker without other clinical implications (ie, choroid plexus cyst or echogenic intracardiac focus) and a negative first- or second-trimester screening result, we recommend describing the finding as not clinically significant or as a normal variant (GRADE 2B); (5) all women in whom a structural abnormality is identified by ultrasound should be offered diagnostic testing with chromosomal microarray (GRADE 1A); and (6) routine screening for microdeletions with cell-free DNA is not recommended (GRADE 1B).

**Key words:** aneuploidy assessment, aneuploidy screening, cell-free DNA screening, nuchal translucency measurement, serum markers, ultrasound

The introduction of cell-free DNA (cfDNA) screening for aneuploidy into obstetric practice in 2011 revolutionized the strategies utilized for prenatal testing. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) both recommend that all women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders.<sup>1</sup>

The most recent guidance addressing this issue suggests that traditional screening with serum markers and nuchal translucency measurement remains the most appropriate

option for low-risk patients,<sup>2,3</sup> while in women at higher risk for common aneuploidies, cfDNA screening may be more accurate for detecting these aneuploidies. In addition, SMFM has stated that because of the ethics of patient autonomy, after appropriate genetic counseling regarding the benefits and limitations of cfDNA screening, this option should be available to women who request additional testing beyond what is currently recommended by professional societies.<sup>4</sup>

The number of different screening and testing options has left many obstetric care providers with questions about how to incorporate cfDNA screening into traditional approaches to screening. The purpose of this document is to review the current data on the role of ultrasound in women who have undergone or are considering cfDNA screening, acknowledging that prospective evidence is limited.

### What is the role of nuchal translucency measurement in women who plan to have, or have already had, cfDNA screening and received a negative or low-risk result?

With the introduction and increasing use of cfDNA screening, the question has arisen as to the value of first-trimester nuchal translucency (NT) ultrasound evaluation in patients who have chosen cfDNA instead of traditional aneuploidy screening. While cfDNA screening is very accurate for trisomies 21, 18, and 13 and potentially some sex chromosome aneuploidies, these tests do not provide information on other chromosomal aberrations that might be identified with conventional first- and second-trimester screening or the more comprehensive genetic information provided by diagnostic testing.<sup>3</sup>

While the precise measurement of the NT is not required for aneuploidy risk estimation when cfDNA screening is performed, such assessment prior to cfDNA screening, especially in a higher-risk population, affords women in whom an enlarged NT is identified the option to proceed directly to diagnostic testing. While an enlarged NT has been associated with other aneuploidies, it has limited utility in the detection of chromosomal abnormalities other than trisomies 21, 18, and 13 because of their overall lower prevalence as well as lower sensitivity for these other conditions.<sup>5</sup>

An increased NT has been associated with structural anomalies, neuromuscular disorders, and a variety of other genetic conditions. It has been noted that imaging the fetus at 11–14 weeks of gestation (first-trimester ultrasound [Current Procedural Terminology] [CPT] code 76801) provides an early opportunity to evaluate the pregnancy and to potentially identify a fetus at risk for additional genetic or structural abnormalities.

One study reported on 1739 patients who had an ultrasound at 11–14 weeks of gestation in the setting of a negative cfDNA screening result.<sup>6</sup> The authors reported that a variety of findings were identified in 60 women who underwent first-trimester NT assessment (3.5%), including 13 women with unrecognized twins (0.7%) and 10 with an unrecognized fetal demise (0.6%). This group, however, also included 26 fetuses (43%) with an NT measuring 3–4 mm but a normal anatomic scan in the second trimester and that were normal at birth. A total of 11 fetuses were found to have either a structural anomaly or a cystic hygroma (0.6% or 1 of 155). Of the 7 structural anomalies diagnosed, one (pleural effusion and NT of 4.5 mm) resulted in a normal fetus at birth and in 6 the women chose pregnancy termination. Therefore, in this study, following negative cfDNA results, abnormal ultrasound findings were identified in 1 in 28 women, and a fetal anomaly was identified in 1 in 290.

Another large study (n = 5306) evaluated the role of cfDNA screening and first-trimester NT assessment in the detection of chromosomal abnormalities in a high-risk cohort referred for chorionic villus sampling (CVS).<sup>7</sup> The prevalence of chromosome abnormalities was 19% in this cohort, and it

was estimated that a cfDNA screen would have detected 88.9% of these. The addition of first-trimester NT assessment would have increased the detection of chromosomal abnormalities to 94.8% if CVS was performed on the 21.7% of cases with an NT  $\geq 3.0$  mm (Table 1). In other words, adding the first-trimester NT measurement increased the detection rate of chromosome abnormalities by 6% over the detection rate that would have been achieved with cfDNA screening alone, but this resulted in an increase in the rate of CVS from 2% to 22%.

Using cfDNA screening as the primary evaluation strategy, the residual risk of a significant chromosomal abnormality after a negative cfDNA screen result was 2.5%. In contrast, using cfDNA screening alone for those with an NT  $< 3.0$  mm and CVS for women with an NT of 3.0 mm or higher resulted in a residual risk of a significant chromosome abnormality of 1% in this high-risk cohort.

The current ACOG and SMFM guidance states that nuchal translucency measurement for aneuploidy risk is not necessary at the time of cfDNA screening in the first trimester. However, ultrasound examination is useful to confirm viability, to confirm the number of fetuses and the presence of an empty gestational sac, to assign gestational age, and to identify some major fetal anomalies for patients who may choose to have cfDNA screening.

Patients who choose serum integrated screening may be offered first-trimester ultrasonography for gestational dating, even if an NT measurement is unavailable or cannot be obtained. If an enlarged NT, an obvious anomaly, or a cystic hygroma is identified on ultrasonography, the woman should be offered genetic counseling and diagnostic testing for aneuploidy as well as follow-up ultrasonography for fetal structural abnormalities.<sup>1</sup>

Therefore, in women who are considering having cfDNA screening, first-trimester NT assessment may provide some benefit in helping them to choose between screening and diagnostic testing. In women who have already had a negative cfDNA screen, first-trimester NT screening may slightly reduce the residual risk of significant chromosome abnormalities. However, further research is needed to determine the optimal approach. In women with a negative cfDNA screen, first-trimester NT measurement is of limited additional benefit as a screening test for aneuploidy or structural abnormalities. This is due to the fact that the detection rate for trisomies 21, 18, and 13 by cfDNA is sufficiently high that if the result is negative/low risk, the NT measurement provides little additional information.<sup>1</sup>

**In women who have already received a negative cfDNA screen, ultrasound at 11–14 weeks of gestation solely for the purpose of NT measurement (CPT code 76813) is not recommended (GRADE 1B).** The detection of some anomalies is possible as early as 11–14 weeks of gestation; however, the use of ultrasonography to screen for major structural abnormalities in the first trimester should not replace screening of fetal anatomy in the second trimester.<sup>8</sup>

### Should the presence of soft markers of aneuploidy be reported in women who have already had cfDNA screening?

The concept of soft markers was introduced in an era pre-dating methods of screening for Down syndrome other than maternal age, when the detection rate for Down syndrome was only 20–30%. This approach was promoted as a means to detect aneuploidy in otherwise low-risk women who had no other screening options.<sup>9</sup>

Because the sensitivity of cfDNA screening for Down syndrome approaches 99%, the residual risk for Down syndrome is exceedingly low in patients who have had a negative cfDNA screen. In one study, the negative likelihood ratio was calculated as 1 of 148 for Down syndrome with a negative cfDNA screen.<sup>10</sup> Therefore, for a 38-year-old woman, whose age-based risk of Down syndrome is about 1 in 100, her risk after a negative cfDNA screen is now approximately 1 in 14,800.

Given the low a priori risk, the presence of an isolated soft marker is unlikely to add to the detection of Down syndrome to any measurable degree. Recommending diagnostic testing in women when a soft marker is identified would, however, result in a substantial increased number of diagnostic tests.

**Therefore, diagnostic testing should not be recommended to patients solely for the indication of an isolated soft marker in the setting of a negative cfDNA screen (GRADE 2B) (Table 2).**

Because the residual risk for Down syndrome in a woman with a negative cfDNA screen is so low, when an isolated soft marker is noted on second-trimester ultrasound examination, the sonologist may either choose to state that it is a normal variant or likely of no clinical significance. **In women with an isolated soft marker that has no other clinical implications (ie, choroid plexus cyst or echogenic intracardiac focus) and a negative cfDNA screen, we recommend describing the finding as not clinically significant or as a normal variant (GRADE 2B).**

When more than 1 marker is found, the likelihood of aneuploidy is higher than in the presence of an isolated marker, but the actual magnitude of the increase depends on the specific markers involved. Because of these complexities and the limitations of prenatal ultrasound in the setting of a negative cfDNA screen with multiple soft markers, genetic counseling should include consideration for diagnostic testing. Prenatal risk assessment for aneuploidy and/or chromosomal abnormalities based on soft markers should be limited to individuals and centers with training and/or experience in prenatal diagnosis.<sup>8</sup>

Some soft markers (eg, choroid plexus cysts and echogenic intracardiac foci) have minimal clinical significance in the absence of a higher pretest risk of fetal aneuploidy. However, other sonographic soft markers, such as mild pyelectasis and echogenic bowel, may indicate a fetal abnormality other than aneuploidy (Table 2). Even if cfDNA screening has been performed, such cases require additional prenatal or postnatal evaluation.

**TABLE 1**

**Detection rate of significant chromosomal abnormalities in a high-risk cohort<sup>a</sup> referred for first-trimester diagnostic testing: comparison of cfDNA only with cfDNA plus NT and diagnostic testing for those above a NT threshold**

Variable	cfDNA only	cfDNA plus NT; CVS for NT $\geq 3.0$ mm
Detection rate of all chromosomal abnormalities	88.9%	94.8%
Screen-positive/ CVS rate	2.0%	21.7%
Residual risk of significant chromosome abnormality	2.5%	1.00%

cfDNA, cell-free DNA screening; CVS, chorionic villus sampling; NT, nuchal translucency.

<sup>a</sup> High risk is defined as any of the following: increased NT with or without biochemistry, structural anomalies, advanced maternal age/anxiety, or family history.

Data from Khalil et al.<sup>7</sup>

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### When soft markers of aneuploidy are detected in an otherwise low-risk woman, should cfDNA screening be offered?

In general, isolated soft markers have limited utility in the detection of aneuploidy in low-risk patients. In women who have already had traditional aneuploidy screening with normal results, the risk of trisomy 21 typically remains low,

**TABLE 2**

**Management of second-trimester isolated ultrasound findings in setting of negative cfDNA screen<sup>a</sup>**

Do not report or report as normal variant

- Echogenic intracardiac focus
- Choroid plexus cyst
- Sandal gap toe
- Clinodactyly

Evaluate as per routine clinical indications but do not consider as a soft marker for aneuploidy

- Pyelectasis
- Single umbilical artery
- Ventriculomegaly
- Echogenic bowel
- Thick nuchal fold
- Hypoplastic nasal bone
- Shortened humerus or femur

cfDNA, cell-free DNA screening.

<sup>a</sup> Classification is based on the fact that the risk of Down syndrome remains very low, even after identification of isolated soft marker in a woman who has had negative cfDNA screen.

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even in the presence of an isolated soft marker, given the low a priori risk and the relatively low positive likelihood ratios for the soft markers.<sup>11</sup>

Although the addition of negative cfDNA screening could potentially alleviate patient anxiety, it has been reported that even with normal diagnostic testing, the presence of soft markers is still anxiety provoking, and many patients are not completely reassured by normal results on diagnostic testing.<sup>12</sup> Presumably, negative results on cfDNA screening would likewise not completely alleviate anxiety. Therefore, providers should carefully consider a consistent approach to such findings.

In a woman who has an identified isolated soft marker on a second-trimester ultrasound in the setting of a negative serum screen, a reasonable approach is to consider the presence of the isolated soft marker as a normal variant. **In women with an isolated soft marker without other clinical implications (ie, choroid plexus cyst or echogenic intracardiac focus) and a negative first- or second-trimester screening result, we recommend describing the finding as not clinically significant or as a normal variant (GRADE 2B).**

In an effort to achieve further reassurance (without the risks of diagnostic testing), cfDNA screening may be made available to these patients; however, they should be counseled that their risk of aneuploidy is low based on their initial screening result and the amount of additional risk reduction with a negative cfDNA screening result is unclear.

### Should cfDNA screening be offered to women when structural fetal anomalies are detected?

The presence of fetal structural abnormalities significantly increases the risk that a fetal chromosomal abnormality or a copy number variant detectable by microarray is present.<sup>13</sup> While those aneuploidies detectable by cfDNA screening make up a significant proportion of such abnormalities, a substantial number of structurally abnormal fetuses have chromosomal abnormalities that are not detectable by cfDNA screening.

One study reported on 290 patients with an abnormal fetal ultrasound who underwent cfDNA screening.<sup>14</sup> In this cohort, 32 of 290 (11%) had chromosomal abnormalities not detected by cfDNA screening. However, 13 were sex chromosomal aneuploidies, likely to be detected by most current cfDNA screening platforms. Nevertheless, the residual risk that an aneuploidy was present following a negative cfDNA screen was 1 in 15.

In addition, it is recognized that diagnostic testing with chromosomal microarray will detect genetic abnormalities in 6–7% of structurally abnormal fetuses despite a normal karyotype.<sup>13,15</sup> For this reason, **we recommend that all women in whom a structural abnormality is identified by ultrasound be offered diagnostic testing with chromosomal microarray<sup>16,17</sup> (GRADE 1A).**

Women who decline diagnostic testing may request cfDNA screening as an alternative. If this approach is chosen, women should be counseled that there is a substantial risk that a chromosomal abnormality other than trisomy 21, 18, and 13 is present in the fetus that will not be detected by cfDNA screening.

In the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development-sponsored microarray study, 552 clinically significant chromosome abnormalities were detected in the women who were tested. Of these, 374 (approximately 68%) would have been potentially detected by cfDNA, whereas 32% would not have been detected.<sup>13</sup>

Because the prevalence of chromosome abnormalities is higher in the setting of a structural anomaly, the residual risk for a chromosome abnormality following negative cfDNA screens is likely even higher if a structural anomaly has been identified. While some expanded cfDNA screening panels have been reported to detect a select few targeted microdeletions, and one panel offers evaluation of all chromosomes at a resolution of 7 megabases (similar to that of

### Summary of recommendations

	Recommendations	GRADE
1	In women who have already received a negative cfDNA screening result, ultrasound at 11–14 weeks of gestation solely for the purpose of NT measurement (CPT code 76813) is not recommended.	1B Strong recommendation, moderate-quality evidence
2	Diagnostic testing should not be recommended to patients solely for the indication of an isolated soft marker in the setting of a negative cfDNA screen.	1B Strong recommendation, moderate-quality evidence
3	In women with an isolated soft marker that has no other clinical implications (ie, choroid plexus cyst or echogenic intracardiac focus) and a negative cfDNA screen, we recommend describing the finding as not clinically significant or as a normal variant.	2B Weak recommendation, moderate-quality evidence
4	In women with an isolated soft marker without other clinical implications (ie, choroid plexus cyst or echogenic intracardiac focus) and a negative first- or second-trimester screening result, we recommend describing the finding as not clinically significant or as a normal variant.	2B Weak recommendation, moderate-quality evidence
5	We recommend that all women in whom a structural abnormality is identified by ultrasound be offered diagnostic testing with chromosomal microarray.	1A Strong recommendation, high-quality evidence
6	Routine screening for microdeletions with cfDNA is not recommended.	1B Strong recommendation, moderate-quality evidence



## Guidelines

The content of this document reflects the national and international guidelines related to the use of ultrasound in women who have undergone or who are considering cfDNA screening.<sup>1-4,8,16,17,19-21</sup>

Organization	Title	Year of publication
ACOG and SMFM <sup>16</sup>	Committee opinion 682, Microarrays and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology	2016
SMFM <sup>17</sup>	Consult Series 41, The use of chromosomal microarray for prenatal diagnosis	2016
ACOG and SMFM <sup>1</sup>	Practice bulletin 163, Screening for fetal aneuploidy	2016
ACOG <sup>8</sup>	Practice bulletin 175, Ultrasound in pregnancy	2016
American College of Medical Genetics and Genomics <sup>19</sup>	Statement, Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics	2016
National Society of Genetic Counselors <sup>20</sup>	Prenatal cell-free DNA screening	2016
SMFM <sup>3</sup>	Consult Series ##36, Prenatal aneuploidy screening using cell-free DNA	2015
ACOG and SMFM <sup>2</sup>	Committee opinion 640, Cell-free DNA screening for fetal aneuploidy	2015
SMFM <sup>4</sup>	SMFM statement: clarification of recommendations regarding cell-free DNA aneuploidy screening	2015
International Society of Ultrasound in Obstetrics and Gynecology <sup>21</sup>	Consensus statement on the impact of noninvasive prenatal testing on prenatal ultrasound practice	2014

conventional karyotype), the detection and false-positive rates of such panels have not been studied in prospective clinical trials.<sup>18</sup>

In addition, such panels are able to detect only a very small percentage of the total number of copy number variants that can be identified with chromosomal microarray. For this reason, routine **screening for microdeletions with cfDNA is not recommended (GRADE 1B)**.

Finally, it is recommended that pregnancy management not be altered solely based on the results of cfDNA screening because false-positive and false-negative results are possible. For women who decline diagnostic testing in the setting of fetal structural abnormalities, pregnancy management should depend on the entire clinical scenario

including the specific abnormalities present, the gestational age, and the preferences of the woman as well as the results of the cfDNA screen. ■

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