The growing use of cell-free DNA (cfDNA) screening has drawn attention to the need for informed decision-making for prenatal screening and testing. Concerns include the influence of commercial marketing and hype around cfDNA products, the increasing amount of information that pregnant women/couples are expected to absorb during the prenatal period, and the history of routinization of prenatal screening and testing in prenatal care.¹

Some providers believe that signed informed consent is less imperative in cfDNA screening because it requires only a blood draw.² However, as a genetic test, the information load of cfDNA screening is significant and promises to become even heavier as testing expands to more conditions and broader populations.³ Although informed decision-making is a process rather than a single document, written information helps patients assimilate information at their own pace and signing a document provides them an opportunity to reflect upon and exercise choice. In order to better understand how women and families are making decisions about cfDNA screening, we assessed informed consent documents provided to patients.⁴

Informed consent documents
We collected informed consent documents (IC) between March and December of 2014 through our professional contacts with individual clinics or clinicians (n=21), internet searches (n=69), and by a request posted to an email list for prenatal genetic counselors (n=3). Once we eliminated duplicates and documents that did not meet our criteria (e.g., advertising brochures without a consent statement for patients to sign, documents we could not analyze because they did not contain substantial text in English), we had 32 documents that were clearly intended to be used for patient informed consent. Approximately half were from the US, and the rest were from 10 other countries. Dates on documents, when available, ranged from 2012 (no month identified) to October 2014. We assessed the reading level of each one using the Flesch-Kincaid grade level, and coded all the text directed to patients using a codebook our team developed.

• Commercial versus Non-Commercial IC: Of the 32 IC, we categorized 22 as “Commercial IC” (produced by a commercial laboratory) and 10 as “Non-Commercial IC” (produced by a local clinic or health care system). Commercial IC were typically longer and written at a more difficult reading level than Non-Commercial IC, and less often stated clearly that cfDNA only screens for certain conditions. Commercial IC often devoted space to information about sample retention/use, which is regulated in some legal jurisdictions.

• IC formats: About one-third of IC had patient informed consent materials combined with a laboratory order form. We found this format in both Commercial IC and Non-Commercial IC. Typically this format would be a single document with a laboratory order form on the front, and more detailed patient information on the back. These would often include significant text in small print, and sometimes interspersed text directed at patients.
with instructions for the ordering clinicians. It was also unclear whether patients would be able to keep a copy of this information. Of the 32 IC, only two specifically directed patients to take a copy home.

- **Information about screened conditions and counseling**: Nearly all IC listed the conditions screened, but only about half included any phenotypic descriptions of any of the conditions, and very few included any information about quality of life or other issues. Over half of all IC recommended or suggested post-test genetic counseling (usually, specifically for positive results), but few mentioned other supports or psychosocial considerations.

- **Information about test complications**: Though most recommended confirmatory testing for positive results, somewhat fewer clearly stated that results could be incorrect. A few mentioned that testing could uncover incidental genetic findings about a parent (and none indicated whether this information would be reported). None mentioned that testing may reveal tumors or cancer in the mother.

**Our Recommendations**

To assure that women and families have an opportunity to carefully consider their options, we recommend that written, well-informed consent should be sought before performing cfDNA screening.

To support laboratories and clinics offering these documents, we propose the following recommendations for the basic elements of written informed consent documents for cfDNA screening:

1. Offer a free-standing consent/information document and encourage the patient to take a copy home.
2. Make it easy to read: Write in plain language, aimed at 9th grade or below, minimum 12-point font, avoid all-caps or italics, and include plenty of white space.
3. Simply state risks and benefits of the test. Clearly state that cfDNA is not diagnostic, there can be errors, and positive results should be confirmed.
4. Clearly state that cfDNA screening is optional and there are alternatives.
5. Explain the conditions screened, including phenotype, quality of life, and variability. This information might be in a separate pamphlet that accompanies the form, but shouldn’t only be available online since not all patients have easy access to the internet.
6. Recommend genetic counseling for positive results.
7. Include a simple consent statement (with or without a requirement for patient signature), not combined with legal or financial agreements.
8. Include contact information for further questions.

Based on our findings and on normative principles for informed consent, these recommendations can help smooth clinical implementation of cfDNA screening, and help ensure that women and families receive the accurate, balanced, and relevant information they need for prenatal decision-making.

For more information, access our original article on this topic at https://www.ncbi.nlm.nih.gov/pubmed/27699200.

**References**

Due to the heightened rates of spontaneous preterm birth (SPTB) associated with twin pregnancies, researchers are investigating methods to predict, and potentially treat, at-risk twin pregnancies. It is agreed among experts that proper identification of those at increased risk of preterm birth will lead to better understanding of the pathophysiology and eventually to the development of appropriate treatment. The Society for Maternal Fetal Medicine, however, recommends against routine cervical length (CL) screening in multiple pregnancies at mid-gestation as the etiology of SPTB in these women is assumed to be uterine over distention, not cervical insufficiency. Conversely, SMFM’s position on serial cervical lengths in twins has yet to be established. Here we will review three articles that address the utility of serial CL measurements in twin pregnancies to identify those at risk for SPTB.

Melamed, et al, presented two retrospective chart reviews of 441 women with twin pregnancies who underwent serial CL measurements from 18 to 32 weeks, with the goal of creating an algorithm for better SPTB prediction. In the first study, women were evaluated four times during the 14-week time period. Each subject’s serial CL measurements were then analyzed stepwise and placed in a “positive” or “negative” group, with “positive” indicating CL less than the 10th percentile for gestational age. With each subsequent measurement after the initial screen, however, the area under the curve (AUC) for prediction accuracy of SPTB improved. With a single measurement at mid-gestation, the prediction accuracy was only 0.613, but when four serial measurements were looked at longitudinally, the accuracy improved to 0.917 and showed potential benefit of serial CL measurements prediction of SPTB.

Melamed, et al, conducted a second retrospective study in which women with twin pregnancies were followed with serial CL measurements every two to three weeks from 14 to 32 weeks of gestation, with an average of six measurements per patient. Their objective was to define distinct patterns of change in CL over time and to better understand the association with rates of SPTB. The study identified four patterns of change: stable cervix (pattern I), early and rapid shortening (pattern II), late shortening (pattern III), and early shortening with plateau (pattern IV) each of which could be determined by 26 to 28 weeks of gestation. The rate of SPTB at <36, <34, and <32 weeks was significantly different among the 4 groups: lowest in pattern I, highest in pattern II, and intermediate in patterns III and IV. They also found that subjects with pattern II were at >10 times greater hazard for SPTB <34 weeks, and women with pattern III were at >2 times greater hazard for PTB, while women with patterns I and IV were not at greater hazard for PTB <34 weeks. These investigators concluded that pattern of change in serial CL measurements may aid in counseling women about their SPTB risk.

Moroz, et al, conducted a retrospective cohort study of women with diamniotic twin pregnancies who underwent CL screening at 18 and 22 weeks of gestation to determine whether the rate of change in CL was associated with SPTB. Rate of change was determined by dividing the difference in transvaginal cervical length (TVCL) at 22 and 18 weeks by the number of days between measurements and multiplying by 7, giving units of change as centimeters per week (cm/wk). They studied rates of SPTB at <35 and <32 weeks of gestation. In their cohort of patients, the mean decrease in CL between 18 and 22 weeks was -0.13 cm/wk. For those women with SPTB <35 weeks, the rate of change was -0.21 cm/wk, compared to those with delivery >35 weeks (-0.10 cm/wk). For those women with SPTB <32 weeks, the rate of change was -0.31 cm/wk, compared to -0.11 cm/wk for those who delivered > 32 weeks. Overall they found that for every -1 cm/wk change in TVCL, the odds of SPTB increased by 5.75. One quarter (25%) of subjects with TVCL -0.2 cm/wk experienced SPTB <35 weeks; this threshold, defined as rapid change in TVCL, confers 3.45 times greater odds of SPTB compared to women with a rate less than -0.2 cm/wk. These investigators concluded that serial TVCL could help clinicians identify patients who are at increased risk for SPTB prior to the onset of viability.
Although this research is innovative and compelling, the additional costs, stress, and resource utilization may not be outweighed by the potential benefits associated with prediction. Because interventions for SPTB prevention also have not consistently shown efficacy in randomized trials, there remains inadequate data to justify routine serial screening in twins, and - at this time - it is not recommended by SMFM.


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**MEASURING MULTIPLE COMPONENTS OF PROFICIENCY WITH FETAL MONITORING**

Conventional examinations that focus on fetal heart rate monitoring only assess practitioner knowledge. The PQF FMC exam, however, assesses judgment, or how the practitioner would apply their knowledge in the face of uncertainty. Sound clinical judgment is an essential skill required to integrate the FHR tracing with the other pieces of the clinical picture. FMC data has shown that individual physicians and nurses (blue dots) can demonstrate discrepant degrees of knowledge and judgment. The diversity among individual provider's knowledge and judgment scores demonstrates the value of a fetal monitoring examination that assesses both measures.
For some NTQR participants, Epidemiology Monitoring reveals a nuchal translucency (NT) measurement slope below the 5th percentile. A low slope means that NT measurements are not increasing as the crown-rump length (CRL) increases as would be expected.

A low slope may be caused by inaccurate CRL measurements. Although NTQR does not credential or monitor CRL measurements, this value is very important in risk assessment.

As a reminder, an acceptable CRL measurement has the following characteristics:

- The fetus is seen in a mid-sagittal plane
- The fetal neck is in a neutral position, neither hyperextended or flexed with the chin on the chest.
- The image magnification is such that the fetus occupies more than 50% of the images.
- The measurement is made from the crown to rump, not to the posterior thigh, distal spine, or other location.

A “low slope” may also be caused by over-reporting of a specific NT measurement. This may occur when the NT appears to be small and the imager uses a favored NT value. An NT value may also be overrepresented across CRLs if the machine calipers stick on one number.

In order to ensure that NT slope increases across gestational age as expected, it is important to optimize not only NT measurement and reporting, but also CRL measurement!
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- Review of testing approaches
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FOR PATIENTS

- Explanation of carrier screening
- Description of testing approaches
- Factors to consider to facilitate decision making
- Discussion planner

CARRIER SCREENING MODULES NOW AVAILABLE

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