

ISUOG updated consensus statement on the impact of cfDNA aneuploidy testing on screening policies and prenatal ultrasound practice

The widespread use of fetal cell-free DNA (cfDNA)-based techniques to screen for trisomy 21 and other aneuploidies has expanded greatly the range of prenatal tests available over the last few years. cfDNA tests are being incorporated rapidly into prenatal care, thus changing the traditional approach to prenatal screening and diagnosis. However, although cfDNA techniques are highly efficient, their role and performance must be considered alongside and combined with other screening modalities. The role of prenatal ultrasound, in particular, needs to be reaffirmed as cfDNA testing becomes more widely available.

It is important to emphasize that the main goal of prenatal screening is to provide accurate information that will facilitate the delivery of optimized antenatal care, with the best possible outcome for both mother and fetus. Women should be informed about the prevalence and the clinical manifestation of the disease of interest and about prenatal screening performance (detection rate, false-positive rate, positive predictive value in the general population, failure rate) by appropriately trained health professionals, allowing them to make an informed decision. It is the parent's choice to undergo such procedures, and their wishes should be determined and respected.

This consensus statement constitutes a revised and updated version of the previously published ISUOG consensus statement on the impact of non-invasive prenatal testing (NIPT) on prenatal ultrasound practice¹; updates will be produced on a regular basis.

- All women should be offered a first-trimester ultrasound scan according to ISUOG guidelines², regardless of their intention to undergo cfDNA testing.

- If the woman has had a negative cfDNA test result, nuchal translucency (NT) thickness should still be measured and reported as a raw value and centile. The management of increased NT with a normal cfDNA test result is currently based on local guidelines. However, it is not necessary to compute first-trimester risk estimates for trisomies 21, 18 and 13 based on NT measurements and maternal biochemistry in a woman known to have a normal cfDNA result. Accordingly, soft markers for trisomy 21 should not be assessed in

women with a normal cfDNA test result due to their high false-positive rate and poor positive predictive value.

- If the woman has not had a cfDNA test, pretest counseling is essential. Various options regarding screening or testing for trisomy 21 and, to a lesser extent, trisomies 18 and 13 should be explained clearly, including information on the expected test performance, potential adverse effects, and pros and cons of each option. Following a normal first-trimester scan, as defined by ISUOG guidelines², three options might be considered for women who wish to have further risk assessment:

- (1) Screening strategies based on individual risk calculated from maternal age and NT measurement and/or maternal serum markers and/or other ultrasound markers in the first trimester (defined by the conventional crown–rump length range of 45–84 mm). Following such screening, women can be offered a choice, according to their calculated individual risk, of having no further testing, cfDNA testing or invasive testing. Cut-offs, defining two (low/high risk) or three (low/intermediate/high risk) groups, should be defined on a local/national basis and will be affected by public health priorities and available resources. Offering cfDNA testing should always be balanced with the potential and risk of conventional karyotyping, with or without microarray analysis, following invasive sampling. More importantly, the role of cfDNA testing as an alternative to standard invasive testing in women considered to be at very high risk after combined screening ($> 1:10$) but with no ultrasound anomaly should be evaluated in prospective studies. Expert opinion currently suggests that cfDNA testing should not replace routinely invasive testing in this group, based on the fact that, in this population, only 70% of the chromosomal abnormalities are trisomy 21, 18 or 13, and that chromosomal microarray analysis, if offered, is able to detect a large number of additional anomalies.

(2) cfDNA testing as a first-line screening test.

Most current guidelines endorse cfDNA testing only for high- or intermediate-risk populations, for which comprehensive data exist. Experience in low-risk populations is increasing, apparently confirming the high detection rates published for high-risk populations. However, testing in low-risk women may impact on the quality of both pretest counseling and subsequent ultrasound screening. In particular, cfDNA testing should not replace first-trimester ultrasound and should not be offered when an ultrasound anomaly or markedly increased NT is detected. Using cfDNA in low-risk patients might be endorsed as a widely available option only when more data emerge and cfDNA costs decrease.

(3) Invasive testing based on a woman's preference or background risk (maternal age, previous history, fetal ultrasound anomaly) with no further individual risk calculation.

An invasive test might be discussed in light of the recently reported reduction in the risk of invasive procedures^{3,4}, as well as the increase in cytogenetic resolution provided by microarray techniques. However, the cost of this option is not usually covered by most national insurance policies and it should not be recommended beyond the context of clinical trials and until sufficient peer-reviewed data and validation studies have been published.

- cfDNA test results should always be interpreted and explained individually in relation to the *a-priori* risk and the fetal fraction.
- In the presence of a fetal structural anomaly, the indications for fetal karyotyping and/or microarray testing should not be modified by a previously normal cfDNA test result.
- In the case of a failed cfDNA test, the patient should be informed about the increased risk of anomalies as well as alternative screening and testing strategies.
- cfDNA testing is not diagnostic, and confirmatory invasive testing is required in the presence of an abnormal result. Whenever there is discordance between an abnormal cfDNA test result and a normal ultrasound examination, amniocentesis rather than chorionic villus sampling should be performed.
- Accuracy of cfDNA testing in twin pregnancies should be investigated further.
- Variations in cfDNA test performance by different providers should be investigated further.

- It is becoming technically feasible to test non-invasively, not only for trisomies but also for other genetic syndromes. Both healthcare providers and women should be clearly aware of the tests being performed and of their performance, as having multiple tests increases the overall false-positive rate and failure rate. The detection rate for microdeletions has yet to be established and most national guidelines currently do not support testing for microdeletions on cfDNA. Screening for microdeletions also raises complex issues regarding pretest and post-test counseling.
- Prospective, publicly funded studies assessing the cost-effectiveness of various screening strategies should be performed as a matter of urgency.

Writing group

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