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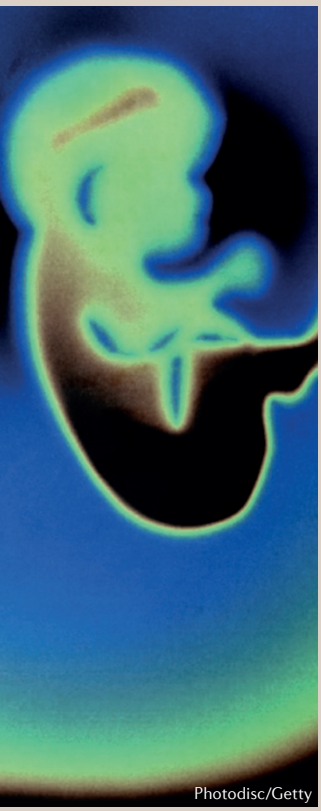
GENETIC TESTING

cfDNA screening for trisomy 21 tested in unselected pregnancies



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A new prospective study provides further evaluation of the potential use of cell-free DNA (cfDNA) screening for trisomy 21 (Down syndrome) as a primary screening method among unselected pregnancies in the general population.

Non-invasive testing for trisomy 21 based on analysis of cfDNA in maternal plasma was introduced in 2011. Although studies have shown that cfDNA screening methods offer high specificity and sensitivity in the detection of trisomy 21, most of these studies were conducted in women at high risk due to increased age or because previous standard screening gave a high-risk result.

Among the first to address the performance of these tests in the general population, Bianchi *et al.* reported in 2014 the results of a prospective study including 1,914 women from 21 centres in the United States. They demonstrated a lower false-positive rate for cfDNA testing using massively parallel sequencing than for standard screening measures for the detection of trisomy 21. However, the small sample size limited the ability to precisely estimate sensitivity and positive predictive value from this study.

Norton *et al.* now report a blinded, prospective study as part of the Noninvasive Examination of Trisomy (NEXT) study to compare the performance of cfDNA screening using targeted sequencing to standard measures for detecting trisomy 21 in unselected pregnancies in the general population. For 15,841 women presenting for first-trimester aneuploidy screening at 35 centres participating in this study from across the United States, Canada and Europe, the authors performed both cfDNA and standard screening, based on fetal ultrasonographic measurement of nuchal translucency and biochemical analyses of maternal serum.

Norton *et al.* confirm the high detection rate for cfDNA screening, identifying all 38 of the cases present among those with a returned cfDNA result, compared to 78.9% detected by standard screening. They report a positive predictive value of 80.9% (95% confidence interval 66.7–90.9%) for cfDNA screening, compared to 3.4% (2.3–4.8%) for standard screening. The false-positive rate for cfDNA screening was considered low at 0.06%, in comparison to 5.4% for standard screening. Although promising, these results still signal the need for further diagnostic testing to confirm a positive cfDNA result, as 9 of the 47 positive cfDNA results were false positives.

Another limitation is the 'no-call' rate, as no cfDNA result was returned for ~3% of women in this study, many because of a low proportion of cfDNA in the maternal plasma. The authors found a higher proportion of confirmed chromosomal abnormalities among the no-call cases, including 3 cases of trisomy 21, raising the question of how to continue to screen these cases if cfDNA testing was implemented as the primary screening method.

Further studies are also needed to compare other cfDNA screening methods, in particular as the targeted sequencing-based approach used in the current study shows a higher no-call rate than other cfDNA screening methods and may differ in other aspects of test performance.

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ORIGINAL RESEARCH PAPERS Bianchi, D. W. DNA Sequencing versus standard prenatal aneuploidy screening. *N. Engl. J. Med.* **370**, 799–808 (2014) | Norton, M. E. Cell-free DNA analysis for noninvasive examination of trisomy. *N. Engl. J. Med.* **372**, 1589–1597 (2015)