Reviewer’s report

Title: Noninvasive Fetal Trisomy Test (NIFTY) An Advanced Noninvasive Prenatal Diagnosis Methodology for Fetal Autosomal and Heterosomal Aneuploidies

Version: 3 Date: 24 March 2012

Reviewer: Ida Vogel

Reviewer’s report:

I am not sure I am the most competent reviewer for this study, as I am a clinician. I would recommend to supplement with a statistician or bioinformatics person as the purpose is to compare different mathematical models.

This is a well conducted study of a new interesting technique and of very high clinical relevance. The study is well performed, but small.

1. Is the question posed original, important and well defined?
Yes. The aim is to compare different data approaches in designing the most optimal tests for fetal aneuploidies using ffDNA.

2. Are the data sound and well controlled?
The study is really too small to compare with previous samples and data preparations. However, with this very novel and expensive technique on rare outcomes, it is a large dataset.

3. Is the interpretation (discussion and conclusion) well balanced and supported by the data?
Data interpretation seem solid and well performed. I feel convinced by the data that GC correction and internal chromosome control are both superior to standard z-score. I am however not convinced that these 2 methods differ. I miss information about gestational age of sampling and a more clinical approach in data interpretation regarding false-positive false negative tests. What about mosaics? It is not labelled X0 – it is only labelled 45,X or plainly X.

4. Are the methods appropriate and well described, and are sufficient details provided to allow others to evaluate and/or replicate the work?
You definitely need an additional reviewer with statistical expertise.

5. What are the strengths and weaknesses of the methods?
The main problem is the sample size. Also, the publication reads very difficultly for a clinician and especially the additional methods section was beyond my capabilities.

6. Can the writing, organization, tables and figures be improved?
The paper is long and especially the figures need trimming. The tables are relevant and read well, but should for all sensitivities and specificities be altered from percentages to absolute numbers, as numbers are very small. (Table 2)

7. When revisions are requested.
Small justifications and a statistical review and the paper should be accepted for publication. You cannot say that detection rate goes from 75% to 100% detection rate by eliminating a mosaic case, and thereby going from 4 to 3 cases!!!. Please be more moderate in the way sensitivity and specificity are addressed with these very small numbers. 99,9% is not a relevant way to describe 3 cases! Time is important in this very competitive area.

8. Are there any ethical or competing interests issues you would like to raise?
Se above regarding false negative etc

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
'I declare that I have no competing interests'