Expanding non-invasive prenatal testing (NIPT) beyond chromosomes 21, 18, 13, X and Y

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Objective
Non-invasive prenatal testing (NIPT) can potentially detect additional chromosome abnormalities beyond chromosomes 21, 18, 13, X and Y. For example, NIPT could be applied to the detection of all abnormalities larger than one chromosome band (approximately 5Mb). I will summarize population cytogenetic data from newborns, amniocenteses, and chorionic villus samples (CVS) that provides an estimate of the frequency of these additional abnormalities. The likely associated incremental increase in the false-positive rate that can be expected due to confined placental mosaicism (CPM) will also be assessed.

Methods
Published data from cytogenetic studies on consecutive newborns, amniocenteses and CVS were reviewed to establish the frequencies of chromosome imbalances, excluding those involving chromosomes 21, 18, 13, X and Y. To estimate the likely NIPT incremental false-positive rate due to CPM, it was assumed that this rate would be equivalent to the rate of those cytogenetic abnormalities that are limited to the placenta and detectable through conventional cytogenetics. This rate was derived from a large set of CVS studies in which both cytotrophoblasts and mesenchyme were analyzed and where mosaic cases were re-evaluated at amniocentesis.

Results
Cytogenetic studies on newborns indicate that additional imbalances (mosaic and non-mosaic unbalanced translocations, insertions, deletions, ring chromosomes, rare autosomal trisomies, triploidy and marker chromosomes) will be present in less than 1/1,000 livebirths. These same types of abnormality are present in 1.67/1,000 amniocenteses and 12.3/1,000 CVS from advanced maternal age women. In CVS, most of the abnormalities are mosaic or non-mosaic rare autosomal trisomies that are hardly ever seen in newborns. The detection rate for mosaic abnormalities through cytotrophoblast analysis (truth based on an abnormal karyotype at amniocentesis) is 55% and the false-positive rate (due to confined placental mosaicism) is 0.6%.

Conclusion
The expansion of NIPT with a resolution comparable to karyotyping would identify additional rare clinically significant imbalances, notably unbalanced translocations. However, the incremental test-positive rate is expected to be >0.6%, primarily due to the identification of rare autosomal trisomies most of which would represent CPM. Genetic counseling is complex when NIPT is expanded to include all abnormalities greater than one chromosome band.