Key Summary

Improving the Accuracy of Prenatal Screening with DNA Copy-Number Analysis

Letter Publication

Background

- Noninvasive prenatal screening (NIPS) that analyzes cell-free DNA (cfDNA) has improved the detection of fetal chromosomal aneuploidies.[1]
- For cfDNA-based prenatal screening, the positive predictive value (PPV) is >90% for detection of trisomy 21 (Down syndrome) but is only 64% for trisomy 18 (Edwards syndrome) and 44% for trisomy 13 (Patau syndrome).[2,3]
- The lower PPVs for trisomies 18 and 13 are caused by a combination of factors: lower prevalence of the disorders, technical limitations, and biological variation.[1]
- Maternal duplications are an example of biological variation that can cause false-positive NIPS results.[1] Incorporating detection of maternal duplications as part of NIPS can help avoid false-positive results.
- **Objective:** In this letter, the authors retrospectively evaluated the impact of accounting for maternal duplications on the PPVs of cfDNA-based prenatal screening for trisomies 21, 18, and 13.

Methods

- The authors analyzed cfDNA results from ~30,000 pregnant women undergoing prenatal screening using whole-genome shotgun sequencing (QNatal® Advanced) at Quest Diagnostics.
- For cases with elevated Z scores indicating an aneuploidy, a karyogram (graphical representation of the Z-score) of the affected chromosome was examined before finalizing results.
- Maternal duplications were distinguished from true-positive fetal duplications by the pattern of Z score: maternal duplications show markedly higher Z scores in a small fraction of the chromosome, whereas true-positive cases show mildly increased Z-scores over the entire chromosome.

Results

- A substantial proportion of samples with elevated Z scores in fact had maternal duplications, which would have been reported as fetal aneuploidies without karyogram analysis:
  - Chromosome 21: 12 out of 313
  - Chromosome 18: 21 out of 106
  - Chromosome 13: 28 out of 93
- Microarray analysis was ordered for 14 cases and confirmed the maternal duplication in all of them.
- Excluding maternal duplications allowed markedly higher PPVs than would have been achieved without such exclusion:
  - Chromosome 21: 4% higher (98% vs 94%)
  - Chromosome 18: 20% higher (92% vs 72%)
  - Chromosome 13: 30% higher (69% vs 39%)

Conclusions

- Identifying maternal duplications in cfDNA-based NIPS substantially improves PPVs for trisomies 21, 18, and 13.
- The use of karyograms for data visualization prevents the reporting of some false-positive results to patients and may help avoid unnecessary invasive procedures.

Letter published in the *New England Journal of Medicine*

Authors
Charles M Strom, Megan D Maxwell, Renius Owen

Affiliation
Quest Diagnostics Nichols Institute, San Juan Capistrano, CA

Citation
Strom CM, Maxwell MD, Owen R. *N Engl J Med*. 2017 Jan 12;376:188-189.

Webpage
http://www.nejm.org/doi/full/10.1056/NEJMc1604205

References

1. Snyder MW, Simmons LE, Kitzman JO, et al. *N Engl J Med.* 2015;372:1639-1645.
2. Bianchi DW, Parker RL, Wentworth J, et al. *N Engl J Med.* 2014;370:799-808.
3. Wang JC, Sahoo T, Schonberg S, et al. *Genet Med.* 2015;17:234-236.

QuestDiagnostics.com