Highlights of This Issue

Analysis of fetal DNA from maternal circulation. Almost ready for prime time?

For decades, tantalizing reports have regularly surfaced reporting an ability to non-invasively analyze fetal material in maternal plasma. The need for such techniques can hardly be overestimated but their feasibility and reproducibility have only recently begun to be documented.

A major step in the realization of such strategies is reported this month by Palomaki et al (page 913) detailing the use of next generation sequencing (NGS) of enriched fetal DNA from maternal plasma to detect Down Syndrome in an international clinical validation study.

The investigators performed a blinded, nested case/control study within a cohort of 4,664 pregnancies at high risk for Down syndrome. Fetal karyotyping was compared to an internally-validated, laboratory developed test based on NGS in 212 Down syndrome and 1,484 matched euploid pregnancies. Primary testing occurred at a CLIA-certified commercial laboratory, with cross validation by a CLIA-certified university laboratory.

The authors achieved a detection rate of 98.6% (209/212) and a false positive rate of 0.20% (3/1,471). Adjusting chromosome 21 counts for GC base content reduced errors to one false negative with no false positives.

Thus, when applied to high risk pregnancies, measuring maternal plasma

DNA in this study detected nearly all cases of Down syndrome with a very low false positive rate. Replication and implementation of this approach could substantially reduce the need for invasive diagnostic procedures and attendant procedure-related fetal losses. Ultimately, it could prove highly generalizable, eventually allowing detailed genetic diagnostic studies of fetuses without invasive procedures. Implementation issues still need to be addressed, but we may be nearing the day when introduction of such testing can be offered on a clinical basis.

Competencies for the Physician Medical Geneticist in the 21st Century

The field of medical genetics is in a period of considerable flux. New knowledge promises to broaden the impact of our field considerably and new technologies promise to inform carrier screening programs, newborn screening, testing for adult-onset disorders and pharmacogenomics. Moreover, with emergent treatments for many genetic disorders, we may be finally moving away from the day when only a small minority of genetic diseases are treatable. In such a dynamic setting it can be difficult to define just what a medical geneticist should know. Thus, a contribution this month by Korf, Irons and Watson (page 911) discussing competencies for the 21st century medical geneticist should be of great interest to *GIM*'s readership.

News Briefs

Be a Trailblazer! Get a Medical Test!

In a predictable development, 23andMe is now marketing whole exome sequencing directly to consumers (https://www.23andme.com/exome/), with a come-on that promises that by doing so you can "be a trailblazer". Self-styled "early adopters" can enter a pilot program on a first come, first served basis to have their exome sequenced for $999. "Winners" will receive their raw data (50 million bases at 80X coverage) but no interpretation at present.

Technically savvy companies like Google, and its spin-off, 23andMe, have undeniable potential to contribute in meaningful ways to healthcare. But as a practicing physician, I find the unrelenting conflation of entertainment with medical testing by many DTC companies concerning. While previous offers have focused on largely trivial SNP array analysis, the stakes are now higher with whole exome sequencing. Such analysis is undeniably a real medical test with potential to divulge important medical information (some welcome and some not) and is guaranteed to yield myriad false positives and false negatives. In my opinion, such tests should be regulated as are other medical tests that have the power to help, harm or confuse. Appealing to the public's desire to be "trailblazers" seems a fine marketing strategy for snack chips and skateboards. But it seems woefully inappropriate as an inducement to engage in new forms of medical testing.

Highlights of the *AJHG* Retinoic Acid Metabolism and Craniosynostosis

Laue et al. extend our knowledge of human embryogeneis in this month's *AJHG*, demonstrating that genetic defects in localized degradation of retinoic acid result in craniosynostosis and multiple skeletal anomalies.

Excess exogenous retinoic acid (RA) has long been documented to have teratogenic effects in the limb and craniofacial skeleton. However, a physiological role for RA during suture closure has not been previously demonstrated. Lune et al. present evidence that genetically based alterations in RA signaling interfere with human development, identifying mutations in the gene encoding the RA degrading enzyme CYP26B1 that lead to skeletal and craniofacial anomalies.

Analyses of murine embryos exposed to a chemical inhibitor of Cyp26 enzymes and zebrafish lines with mutations in *cyp26b1* suggest that the endochondral bone fusions are due to unrestricted chondrogenesis at the presumptive sites of joint formation within cartilaginous templates, while craniosynostosis is induced by a defect in osteoblastic differentiation. This work reveals a physiological role for RA in partitioning skeletal elements and in the maintenance of cranial suture patency.