Highlights of This Issue

New Technology vs. Old Technology

Approximately 15-20% of recognized pregnancies end in spontaneous abortion before 20 weeks gestation and recurrent pregnancy loss (RPL) affects approximately 5% of couples. The major factors contributing to pregnancy loss are chromosomal in origin and investigation of the etiology can be critical for planning future pregnancies and providing optimal medical care. This month's issue of *GIM* features an article by Caramins et al. (page 46) which evaluates the sensitivity and specificity, as well as the advantages and limitations of multiplex ligation-dependent amplification (MLPA) compared with conventional karyotype analysis in the investigation of RPL. In their study, the investigators analyzed 284 products of conception by both conventional karyotyping and MLPA. MLPA enabled diagnosis in an additional 16.5% of patients but comes at a cost of a higher false positive rate and an inability to characterize structural rearrangements. The calculated performance characteristics of MLPA in their cohort yielded a sensitivity of 86.9% and specificity of 92.4%. The authors conclude that the advantages of molecular methodologies such as MLPA, including lower failure rates, faster turnaround times and lower cost must be coupled with adequate counseling, family follow-up and explicit recognition of the limitations inherent to such techniques.

Evidence and Clotting Disorders

As any reader of *GIM* knows, we are enthusiastic advocates for evidence-based medicine and are thus strong supporters of the EGAPP working group products. We're delighted this month to publish another EGAPP report (page 74), this time regarding the common and often complex issue of genetic predisposition to venous thromboembolism, specifically Factor V Leiden (*FVL*) and prothrombin 20210G>A (*PT*). The EGAPP working group found adequate evidence to recommend against routine testing for *FVL* in several circumstances, including adults with idiopathic venous thromboembolism and asymptomatic adult family members of such patients with an *FVL* or *PT* mutation, for the purposes of considering primary prophylactic anti-coagulation. The authors deemed the evidence was insufficient to determine whether *FVL* or *PT* testing might have clinical utility in some circumstances, such as for identifying homozygosity.

The EGAPP results once again illustrate that we must be cautious in prematurely embracing a given test or intervention, as it must always be remembered that harm can result even from the best of intentions in medicine. In this case, that harm is manifested by the potential for unnecessary long-term use of anti-coagulants which, in and of themselves, have significant risks.

News Briefs

Genetics and Scoliosis Prognosis

While many applications of GWAS data in the clinical world have fallen considerably short of our hopes, our orthopedic brethren have revealed a glimmer of real promise for the use of such data in grappling with a difficult clinical problem. When a child is diagnosed with mild adolescent idiopathic scoliosis (AIS) it can be difficult to know how to treat them. In this study, published in *Spine* [35:25;E1455-E1464], logistic regression was used to develop an algorithm to predict spinal curve progression by analysis of genotypes for 52 SNPs and the degree of a patients' presenting spinal curve. In a retrospective study, the investigators examined three cohorts with known AIS outcomes and calculated an AIS prognostic test score which could range from 1 - 200. Those achieving low risk scores had negative-predictive values of 100, 99 and 97% respectively in the tested populations. By using specific cut off scores the investigators could identify 75% of patients as low risk (<1% risk of progression to a surgical curve), 24% as intermediate risk and 1% as high risk. Clearly the most promising utility of this test, given the high negative-predictive values, would appear to be when a negative score is achieved. Two caveats to this potentially very useful study should be kept in mind: since the sample was retrospective ongoing studies should focus on prospective cohorts, and secondly, the investigators (as they divulge upfront in the paper) are employed by a firm which markets this test.

Highlights of the *AJHG*

The AJHG publish a report this month entitled "A Proposed Clinical Scoring System for Selection of Patients for *PTEN* Mutation Testing Based on Prospective Cohort Analysis of 3,042 Probands" which should help clinicians struggling with the decision of whether to test patients for *PTEN* mutations. The disorders of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome, both of which result from *PTEN* mutations, are challenging in part due to the non-specific nature of some of their features. For example, in adults with Cowden syndrome, breast, thyroid and uterine cancer are all features of the disorder but are, or course, also common in the general population. Likewise, in the pediatric population, *PTEN* mutations are associated with developmental delay but this too is an extremely non-specific finding. In this report, Tan et al. conducted a multi-center prospective cohort study with molecular analysis in order to develop an optimized clinical practice model to estimate pre-test probability of discovering a germline *PTEN* mutation in adult and pediatric patients. The authors succeeded in determining highly sensitive criteria (which differ between adults and children) for *PTEN* testing. This work should help guide both testing and the interpretation of negative sequencing results.