Genetic Testing Registry Public Meeting
Tuesday, November 2, 2010

I would like to briefly describe a large genetic testing collaboration and database project that may be a useful model for the Genetic Testing Registry. The ISCA, or International Standards for Cytogenomic Arrays was initiated in 2007 and now includes over 145 clinical cytogenetics testing laboratories performing whole genome cytogenetic microarray analysis. Three international workshops have been held bringing together experts and stakeholders in clinical genetics, genetic counseling, clinical genetic testing, genomics, bioinformatics and patient advocacy groups, to discuss the goals of the Consortium.

The first work product from the Consortium was a Consensus Statement in the May issue of the American Journal of Human Genetics recommending that Chromosomal microarrays should be the first tier test in the genetic evaluation of any child with unexplained developmental disabilities—replacing the previous gold standard of G-banded karyotype in this postnatal setting. This same recommendation has now been endorsed by the American College of Medical Genetics in an updated Practice Guideline posted on their website in September.

The goals of the Consortium are to

1) to develop standards for genotypic and phenotypic data associated with cytogenetic arrays

2) develop standards for the appropriate clinical indications for testing and for interpretation of CNV results
3) contribute CNV and phenotype data to a central, freely available database at NCBI/NIH, utilizing dbGaP and dbVar. The database currently contains data from about 20,000 clinical array tests, with a goal of 200,000 within two years.
4) develop data analysis and curation methods to create new knowledge regarding the functional and clinical significance of CNVs in the human genome; thus creating a “Learning CNV Database and Registry” that will continue to improve patient care by improving our diagnostic, prognostic and therapeutic approaches to patients with specific CNVs.

About 20% of children with unexplained developmental disabilities are found to have a single, pathogenic CNV responsible for their condition. In a significant subset of these children, a deletion is found to include genes with known disease association, such as deletion of a tumor suppressor gene (like p53, retinoblastoma, VHL, other) that prompts life-saving or clinically significant medical management decisions and referrals. This leads to the somewhat ironic situation that children with developmental disabilities, often disadvantaged in terms of access to critical medical resources and care, are now among the first beneficiaries of truly personalized, predictive medicine as a consequence of their whole genome genetic test result. The next challenge will be to integrate this whole genome data into electronic health records in a seamless and useful way, a project I hope to address in my new role at Geisinger Health System with their advanced EHR. This also overlaps with the goals of the eMERGE Network funded

by the National Human Genome Research Institute to integrate genomics data and EHR data for high-throughput genomics research.

In the near future, significantly more genomic data will be generated during the course of routine patient care than through large-scale genomics research projects.
The lessons learned from routine clinical testing by whole genome cytogenomic arrays may be a useful model for other whole genome technologies such as exome sequencing or whole genome sequencing, in developing methods for data submission from routine clinical lab testing and development of a Learning Database and Registry that creates new knowledge regarding the functional and clinical significance of sequence variation in the context of phenotypic information on very large datasets from patient and normal populations.

In summary, our experience in setting up a voluntary database and registry for whole genome cytogenetic array testing in clinical labs indicate that:

1) clinical labs and clinicians are happy to submit patient data to a central, freely available “Learning Database/Registry” with information provided regarding IRB protocols and if data submission does not interfere with busy clinical workflows
2) Industry partners are eager to support educational activities and to develop software tools that allow clinicians and clinical laboratories to collect and submit phenotype and genotype data to a central database in a seamless, single click way

3) Data analysis and curation remains challenging, but is an opportunity for significant new knowledge generation that will rapidly contribute to improved patient care through a Learning Database/Registry.

The Genetic Testing Registry can play a major role in promoting data sharing and collaboration among the large network of clinical genetics testing labs to accelerate our understanding of the functional and clinical significance of sequence and structural genetic variation in the human genome and rapidly translating that knowledge to improve patient care.