Foreword

Advances in Pediatric Genetic Testing

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In recent years clinical laboratory genetics has experienced sweeping changes spurred largely by availability of novel genomic technologies. While single analyte testing of individual genes remains the cornerstone of familial and simple mendelian genetics, the increasing use of new tools in the laboratory genetics armamentarium has allowed for characterization of a growing number of disease causing genes and development of expanded testing platforms with improved clinical utility compared with more classic approaches. The increasing utility of genetic testing coupled with decreasing costs, improved throughput, and refinement of molecular, cytogenomic, biochemical, and epigenetic technologies is driving forward a paradigm shift in laboratory genetic practices. This shift is most apparent in an increasing trend away from single gene analysis to the development of tests that enable analysis of multiple genes or pathways simultaneously but is also apparent in the application of novel testing modalities to the assessment of both mendelian genetic disorders and multifactorial traits. This issue is inspired by this paradigm shift and is particularly focused on those advances in laboratory genetic testing that have had an important impact on pediatric genetic testing.

For heterogeneous phenotypes, sequential analysis of associated genes within the differential diagnosis list can be prohibitively costly, require numerous blood draws, and evoke considerable anxiety for patients who require repeated testing along their “diagnostic odyssey.” A recurrent theme in this issue is the potential of genetic testing advancements to minimize this diagnostic odyssey by increasing test sensitivity and/or expanding the range of potentially pathogenic variants that can be detected in a single assay. The development of gene panel tests, for example, provides important advantages over single gene test by enabling simultaneous assessment of genes that contribute to a group of disorders having a common phenotype (i.e., ataxia, cardiomyopathy, or hereditary cancer gene mutation panels) or a common molecular etiology (i.e., fatty acid oxidation defects or rasopathies gene mutation panels). In this issue, ciliopathies are

reviewed as a useful example of how gene mutation panels can improve utility of genetic testing. More than 120 ciliopathy-associated genes have been identified, which can create unique challenges in developing molecular genetic tests for this group.¹ Given phenotypic overlap and variable expressivity among different ciliopathy-associated conditions, inclusion of all the known ciliopathy genes on a single mutation panel allows for interrogation of a larger set of relevant targets, thus enabling detection of novel genotype-phenotype associations and anticipated increases in the diagnostic yield of the test.

Genomic tools such as chromosomal microarray and exome sequencing are also being increasingly used to investigate individuals with suspected genetic conditions, as neither method requires prior knowledge of which gene to target for testing and therefore has a greater capacity for detecting well-characterized and novel variants that may not have been previously associated with the observed phenotype(s). The adoption of chromosomal microarray technologies into mainstream practice for the diagnosis of pediatric congenital and developmental disorders has had a profound effect on clinical genetics by enabling increasing characterization of novel microdeletion/microduplication syndromes (reviewed in Rosenfeld and Patel²), but also by expanding our understanding of the molecular pathogenesis contributing to a range of pediatric genetic conditions. Increasing application of chromosomal microarray testing has also highlighted important genetic counseling challenges, particularly about reduced penetrance and variable expressivity of a subset of recurrent copy number variants, identification of “incidental” findings that may be unrelated to the original medical concern, and identification of variants of uncertain clinical relevance (reviewed in Rosenfeld and Patel²). Many of the benefits and challenges of chromosomal microarray testing will also apply to the growing use of exome and whole genome analysis in clinical practice. These genomic platforms are enabling characterization of an increasing volume of new genetic syndromes and have facilitated characterization of

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expanded phenotype spectrums of several syndromes beyond those predicted by single gene testing. Although new genomic tools have the potential to identify the genetic basis in a large subset of patients with otherwise negative genetic testing, issues related to incidental findings and variants of unknown clinical relevance remain relevant with these methodologies and are further compounded by limited understanding of the functions and normal variation in many of the protein-coding genes across the genome.

Beyond genomics and microarray, this issue also highlights important advances in other areas of laboratory genetics that have significantly impacted pediatric genetic testing in recent years, including rapid expansion of newborn screening programs in many countries. Many newborn screening programs worldwide arose out of efforts to detect neonates with increased risk of intellectual disability related to phenylketonuria so that timely treatment could be initiated to mitigate negative affects of the condition. Tandem mass spectrometry and other applications have further enabled expansion of these programs to permit screening of additional treatable conditions, thus reducing morbidity and mortality in affected children. Lysosomal storage enzyme testing represents one of the most recent applications that have been modified for newborn screening. While newborn screening for lysosomal storage disease enables identification of children that would benefit from enzyme replacement therapies, this issue also highlights differences between localities in application of new population screening protocols and discusses some of the ethical considerations related to presymptomatic newborn testing of disorders with possible adult-onset phenotypes (reviewed in Peake and Bodamer³).

Another rapidly growing area of pediatric genetics highlighted by this issue is testing for imprinting and epigenetic disorders. Our understanding about imprinting disorders stems largely from characterization of a handful of conditions, including Prader-Willi, Angelman, and Beckwith-Wiedemann syndromes, among others. Testing for these syndromes has been available for several years and remains an important example of how technological advancements can improve testing of groups of similar diseases and of specific disorders.⁴ Imprinting disorders offer unique challenges for genetic testing given a requirement for differ-

entiating between maternally and paternally inherited alleles. The review about imprinting in this issue highlights how technological advances have been applied to genetic testing of imprinting disorders but also emphasizes the importance of classic approaches for detection of the full range of pathogenic variants that can contribute to this class of disorders.⁴ Beyond imprinting, aberrant epigenetic modification is emerging as an important etiology for a growing spectrum of conditions.⁵ Similar to chromosomal microarray and clinical exomes, many of the tools used to investigate imprinting disorders may be applied to whole epigenome testing, thus having the potential to yield new tools for diagnostic testing in the pediatric setting. The review by Schaenkel et al, in this issue, provides an overview of the growing body of evidence supporting a role of epigenetics in a broad range of pediatric conditions and how whole genome methylation testing may provide a practical benefit for the diagnosis of these conditions.⁵

While this issue highlights several advances in pediatric genetic testing, continued development of genomics technologies will no doubt lead to further expansion of the relevant tools in the genetic testing armamentarium. Continued growth in this field is critical to further match our growing understanding of genetics and epigenetics in health and disease, aid timely diagnosis of genetic conditions, and identify individuals who may benefit from targeted therapies.

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