Little Livers, Big Challenges:

What Every APP Should Know About Pediatric Cholestasis and Genetic Testing

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Neonatal cholestasis is a clinically rare but complex condition. Its causes are diverse but broadly classified as obstructive or non-obstructive (including metabolic, genetic, and infectious causes). Once direct hyperbilirubinemia is noted in an infant, rapid differentiation of biliary atresia (BA) from other causes of pediatric cholestatic disease is necessary due to the time sensitivity of surgical intervention, specifically Kasai portoenterostomy (KPE). If left untreated, BA progresses rapidly to cirrhosis and liver failure. With advances in imaging, new serum biomarkers such as matrix metalloproteinase-7 (MMP7), and more accessible genetic testing, the workup for BA looks different from what it did years ago. The significance of genetic testing is highlighted here; if a pathogenic or likely pathogenic variant is identified early in the patient's course, clinicians may be able to confidently limit further diagnostic evaluation and interventions for BA. However, interpretation of genetic testing results can be incredibly complicated for providers.

Targeted gene panel analysis for patients with cholestasis involves sequencing several selected cholestasis-associated genes. With new pathogenic variants frequently identified, even experienced providers may be uncertain about indeterminate results. So, what do providers do when genetic testing is indicated and the results are not the proverbial "slam dunk" diagnosis? Providers must navigate unclear genetic results while trying to build trust with patients and their families, who often find reassurance in a diagnosis supported by genetic confirmation. The world of genetics is rapidly evolving as we continue to learn more about additional pathogenic gene variants and results identified as a variant of uncertain significance (VUS) may become clinically significant in the near future. Partnerships with our genetic counselors, physicians, and teams will improve confidence in the utility of genetic testing for patients with cholestasis. However, the demand for genomic testing has outpaced growth in the workforce, and patient access remains a national issue.

The most common genetic diagnoses related to pediatric cholestatic liver disease are Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC). Diagnosis was previously made primarily through clinical assessment and workup; however, gene sequencing is now much more common and is considered the "gold standard." Still, recent data show small subsets of patients with each condition who are diagnosed on the basis of clinical presentation without genetic confirmation.

As with any new diagnosis, families hope to understand what their child's clinical course may look like. This can be incredibly challenging with diagnoses of BA, ALGS, and PFIC in young children, as clinical courses are highly variable. During the first year of life, we traditionally focus on formulas high in medium-chain triglycerides (MCTs) (or expressed human milk with MCT fortification, if needed), fat-soluble vitamin levels and supplementation, growth and development monitoring, and, for ALGS and PFIC more specifically, pruritus management. We also ensure that all other appropriate subspecialists are involved in the patient's care. Partnering with pediatrician colleagues to co-manage these children is crucial to reduce the burden of visits on families and increase patient safety by ensuring that subspecialty and primary care management goals are aligned. For example, if a patient with BA who has undergone surgical intervention presents to the pediatrician with a fever, the pediatric hepatologist should be notified to rule out cholangitis rather than assume the more common viral-induced fever. This relationship is pivotal to patient success.

This same collaboration is needed during the transition from pediatric subspecialty care to adult care. As we work with our adolescent patients to take a more active role in their health care decisions and medical management, transition-of-care clinics have been shown to benefit young adult patients, which includes better health outcomes, enhanced self-advocacy, and improved continuity of care. However, transition-of-care clinics within hepatology are not standard practice at all institutions, even as many pediatric patients with complex liver disease are living into adulthood. The rapidly evolving research in genetics and continued advancements in medical management and therapies for pediatric cholestatic disease will continue to change the way we care for our patients. Our simplest next step as a medical community is to ensure appropriate and safe transitions from pediatric to adult care for our patients.