CLINICAL *INNOVATIONS*

TRANSLATING DISCOVERIES TO CARE

Autism detection advances through EEGs

Although autism can respond well to early behavioral interventions, it's typically not diagnosed until around age 5. Boston Children's researchers have taken steps toward developing early tests that could diagnose autism before symptoms even show up.

Electroencephalograms (EEGs) are inexpensive tests that could potentially be harnessed to diagnose autism based on differences in brain activity and connectivity. In a study of 65 infant siblings of children with autism (considered to be at increased risk for autism themselves), **Charles Nelson, PhD**, director of the **Labs for Cognitive Neuroscience**, found a signature pattern in EEG waves from the frontal regions of their brains. These patterns were evident as early as 6 months and appeared even in high-risk infants who didn't actually develop autism—suggesting they were born with a predisposition. In a separate study, Nelson and William Bosl, PhD, combined EEGs with machine-learning algorithms. The test had 80 percent accuracy in distinguishing between 9-month-old infants known to be at high risk for autism and controls of the same age.

> **"We could eventually come to the point where diagnostic differences are defined directly by differences in brain activity."**
>
> Frank Duffy, MD

Other investigators are analyzing EEGs for a quality known as "coherence"—a measure of connectivity between different brain regions. **Frank Duffy, MD**, led a study of 430 children with "classic" autism and 554 neurotypical controls, looking at more than 4,000 different combinations of electrode signals. The team identified 33 coherence readings that consistently distinguished the children with autism from the controls, with a sensitivity upwards of 90 percent. Using another algorithm, Duffy was able to distinguish children with classic autism from those with Asperger's syndrome. **Jurriaan Peters, MD**, also looked at EEG coherence in two groups of autistic children: 16 with classic autism and 14 whose autism is part of a genetic syndrome known as tuberous sclerosis complex. Compared with controls, both groups showed multiple redundant connections between adjacent brain areas, but fewer linking far-flung areas.

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A better IV nutrition solution for infants

Many children recovering from complex intestinal surgery or awaiting intestinal transplants are placed on intravenous feeding, called **parenteral nutrition (PN)**, until their intestines can digest solid foods. PN has revolutionized treatment for diseases such as short bowel syndrome, but unfortunately, its prolonged use often damages the liver, potentially leading to liver failure and the need for a liver transplant.

Over a decade ago, surgeon **Mark Puder, MD**, surgical resident Jenna Garza, MD, and pharmacist Kathy Gura, PharmD, discovered why PN was causing liver disease. Given to mice, the soy-based lipid used in standard PN solutions was causing fat to accumulate in the liver. They then tested Omegaven™—an omega-3-fatty-acid rich mixture made from fish oil—and found that the mice were completely free of liver injury. They went on to try Omegaven in some of their patients and saw their liver disease reverse.

Puder and colleagues now are conducting a formal clinical trial, funded by the March of Dimes and the FDA Orphan Products Division, aimed at preventing liver disease in children receiving PN.

To date, more than 150 children at Boston Children's have received Omegaven, and more than 90 percent of them are still alive. In early 2013, Puder reported that of 48 infants given Omegaven, 71 percent had normalized liver function measures—and no longer needed a transplant.

Researchers rise to the CLARITY Challenge

Whole-genome sequencing has begun moving into the clinic, sleuthing out problems, offering hope for treatments that are more effective and more personal.

Globally, however, guidelines for appropriate, clinically useful genomic sequencing are just beginning to coalesce. To begin to advance such standards, Boston Children's took a crowd-sourcing approach, launching the first **CLARITY Challenge** in 2012. The challenge tasked research groups from around the world with interpreting the genomes of three families with unexplained genetic diseases. The competition drew 23 teams, from 10 countries, and the results represent a clear victory not only for genomic medicine, but for patients everywhere.

For sixth-grader Adam Foye, who suffers from a muscle-weakening condition called centronuclear myopathy, CLARITY solved an 11-year mystery. Eight of the 23 contestants identified alterations in titin—a gene that encodes part of the contractile structure in muscles. Boston Children's researchers plan to model the titin mutation in zebrafish and test panels of drugs that might reverse it—and perhaps help children like Adam regain their muscle strength.

Guidelines for interpreting genomic data and returning results to patients are being distilled to practitioners around the world. The CLARITY 2 Challenge, involving interpretation of cancer genomes, will be announced in 2014.

As costs of genome sequencing fall further, specialists will increasingly be able to find needles by analyzing entire haystacks.

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Building a whole heart for babies born with half

Children have enormous growth and healing potential. In late 2012, members of Boston Children's departments of Cardiac Surgery and Cardiology—including **Sitaram Emani, MD**, **Wayne Tworetzky, MD, James Lock, MD**, and **Pedro del Nido, MD**—published a new strategy called **staged left ventricle recruitment (SLVR)** for rebuilding the hearts of children born with **hypoplastic left heart syndrome (HLHS)**, a lethal heart defect where the main pumping chamber of the heart does not grow normally. All children born with HLHS currently undergo a set of three surgical procedures in the days, months and first few years after birth.

> "The more blood flow we can direct into the left ventricle, the more it will grow, expand and pump in response."
>
> Sitaram M. Emani, MD

These three procedures help stabilize the heart and reconstruct it so that it can pump blood with only one ventricle. More than a decade in the making, SLVR harnesses the heart's natural regenerative potential to encourage the undeveloped left ventricle of children with HLHS to grow—giving the child a fully functional heart with additional surgeries. The approach begins in utero and relies on a combination of surgical procedures developed at Boston Children's over the past 11 years. The physicians are now seeking to refine the approach for children with closed or atretic valves.

Possibility in pediatric hand transplants

Hand transplants are a relatively recent medical advance in adults, and most are still being done under research protocols to determine their safety and efficacy over the long term. Slightly more than 50 have been performed in adults, and as of fall 2013, no transplants have been performed from a donor to a genetically different child. (One twin-to-twin transplant has been performed.)

Boston Children's experience with solid organ transplants, hand surgery and rehabilitation, along with its research capabilities, optimally position it to offer this experimental procedure to children. The **Hand Transplant Program**, kicked off in spring 2013, is currently enrolling transplant candidates over the age of 10, in good overall health, who for one or more years have been missing both hands. In addition, children who are missing one hand but are already on immunosuppression medication for a functioning solid organ transplant, or missing one hand and the other hand is poorly functioning, also will be considered.

The procedures will be conducted under a research protocol that will evaluate their safety and efficacy. Data on transplanted patients will be collected to measure the outcomes of the procedure and the patients' progress over 10 years or longer.

EAT procedure allows patients to eat normally

The **Esophageal Atresia Treatment (EAT) Program** at Boston Children's treats infants, children and young adults with esophageal and airway problems. And it is now home to one of only two hospitals in the world to offer a surgical innovation known as the Foker process to treat "long-gap" **esophageal atresia**, a congenital condition where the esophagus has a disconnection or gap that interrupts its pathway to the stomach, making oral feeding impossible.

Developed by John Foker, MD, PhD, a pediatric, general and cardiac surgeon, the EAT procedure involves placing traction sutures in each of the two ends of the esophagus and increasing tensio n on the sutures daily, pulling on them slightly until the ends of the esophagus grow close enough to be sewn together to create a continuous connection between the throat and the stomach.