2018

INNOVATION REPORT

Clinic *for* Special Children

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Our Vision

We envision the Clinic for Special Children as a MEDICAL HOME

for predominately Amish and Mennonite children and adults who are born with genetic predispositions to disability, chronic disease or untimely death. We continually strive to integrate advanced scientific tools and concepts into clinical practice so that genetically vulnerable people have access to the most timely, affordable, and effective healthcare. The Clinic for Special Children represents an innovative and holistic approach to modern medical care that can inform the practice of genomic medicine in other settings. We seek opportunities for education and collaboration that promote the well-being of genetically disadvantaged, underserved individuals throughout the world, and we are dedicated to training the young clinicians and scientists who will care for these individuals now and into the future.

GENERAL STATS

18 *staff members*

2 *gene therapy trials*

Unique Medical Insights From A
Unique Community

It's with great excitement that we introduce the Clinic for Special Children's (CSC) first annual innovation report. For 30 years, CSC has been on the cutting-edge of genomic research and 2018 proved to be one of the most progressive in our long history. We established a new Research Operations Department, added Next Generation Sequencing technology to our laboratory services, established an extensive Spinal Muscular Atrophy (SMA) carrier testing program, continued our involvement in gene therapy trials, and published six peer-reviewed publications with broad relevance.

The expansion and advancement of carrier testing in Plain communities has been one of the largest goals for our research team. In late 2018, we launched our Plain Insight Panel™, a Next Generation Sequencing test that allows us to gain insight into carrier status for Plain couples. The panel includes over 1,300 genetic variants, with significance placed on those that are known to cause disease. We also launched the SMA Prevention Readiness Program, that allows us to carrier test over 2,000 Plain individuals for their SMA carrier status and provide counseling to those couples who are identified as carriers.

As we look ahead to 2019, we will be commemorating the Clinic's 30th anniversary - a milestone that couldn't have been achieved without your support. On behalf of our staff and board, we thank everyone who has supported the work of the Clinic for Special Children.

Erik G. Puffenberger, PhD
Laboratory Director

Karlla W. Brigatti, MS, LCGC
Research Operations Director

Published Papers

This year, 7 CSC staff members contributed to original research published in

JOURNAL OF PEDIATRIC ORTHOPAEDICS

The report identified an alternative method to deliver nusinersen to patients with Spinal Muscular Atrophy (SMA) using a subcutaneous intrathecal catheter system (SIC) configured by connecting an intrathecal catheter to an implantable infusion port. SMA is a devastating genetic disease that leads to progressive degeneration of motor neurons that control movement, swallowing, and breathing. It is the leading genetic cause of infant death worldwide. Nusinersen is the first FDA approved therapy for SMA but must be administered into the cerebrospinal fluid by repeat lumbar puncture every 4 months of life. Unfortunately, the majority of surviving SMA patients have skeletal deformities or spinal hardware that make it difficult to safely and reliably access the cerebrospinal fluid. Ten SMA patients underwent implantation of the catheter devise and received nusinersen dosing through the SIC. The study is an ongoing research initiative.

READ THE ARTICLE ONLINE AT:

https://bit.ly/2wBOHFc

RESEARCH & DEVELOPMENT STATS

42 **NEW** *disease-causing genetic variants*

6 *peer-reviewed publications*

SMA Prevention Readiness Program

SPINAL MUSCULAR ATROPHY (SMA), is a progressive genetic condition affecting motor nerve cells (neurons) in the spinal cord and brainstem. These cells control breathing, eating, and movement. SMA is a recessive disorder such that both parents must carry the genetic variant of SMA in order to have an affected child together. SMA is the most common genetic cause of infant death worldwide and is found in all people of the world, including members of the Plain communities. One in 2,800 Mennonite and 1 in 250 Hutterite babies are born with SMA with 1 out of every 25 Mennonites being a carrier for SMA. However, recent targeted therapies have changed the course of this condition and improved quality of life for affected individuals everywhere. Studies have shown that the earlier these treatments are given, the better they work.

The SMA Prevention Readiness Program was launched in October of 2018, with the goal to identify individuals and couples who are carriers for this condition, to present therapeutic options to at-risk couples should they have an affected child, and to ensure that any newborn with SMA in the Plain community is diagnosed within the first few days of life, before the onset of symptoms. The program is able to provide carrier testing **free of charge** to couples and our team travels to various states, like Ohio, to reduce the barriers for testing. The program is structured in three steps: Patient Education, Carrier Testing and Personalized Counseling.

The first step, Patient Education, ensures that Plain couples know the importance of starting treatment before a child exhibits any symptoms. During this step, couples are also introduced to the two targeted treatments currently available for SMA, SPINRAZA® (also called nusinersen) and gene therapy.

Next, carrier testing is completed, free of charge, via a simple blood test which is performed at the Clinic for Special Children's (CSC) in-house laboratory. CSC will have results within a few weeks for couples that are tested. Lastly, if a couple is identified as carriers of SMA, a Clinic staff member will follow up with the couple to discuss the results and treatment options so they can think about their choices should they have an affected baby.

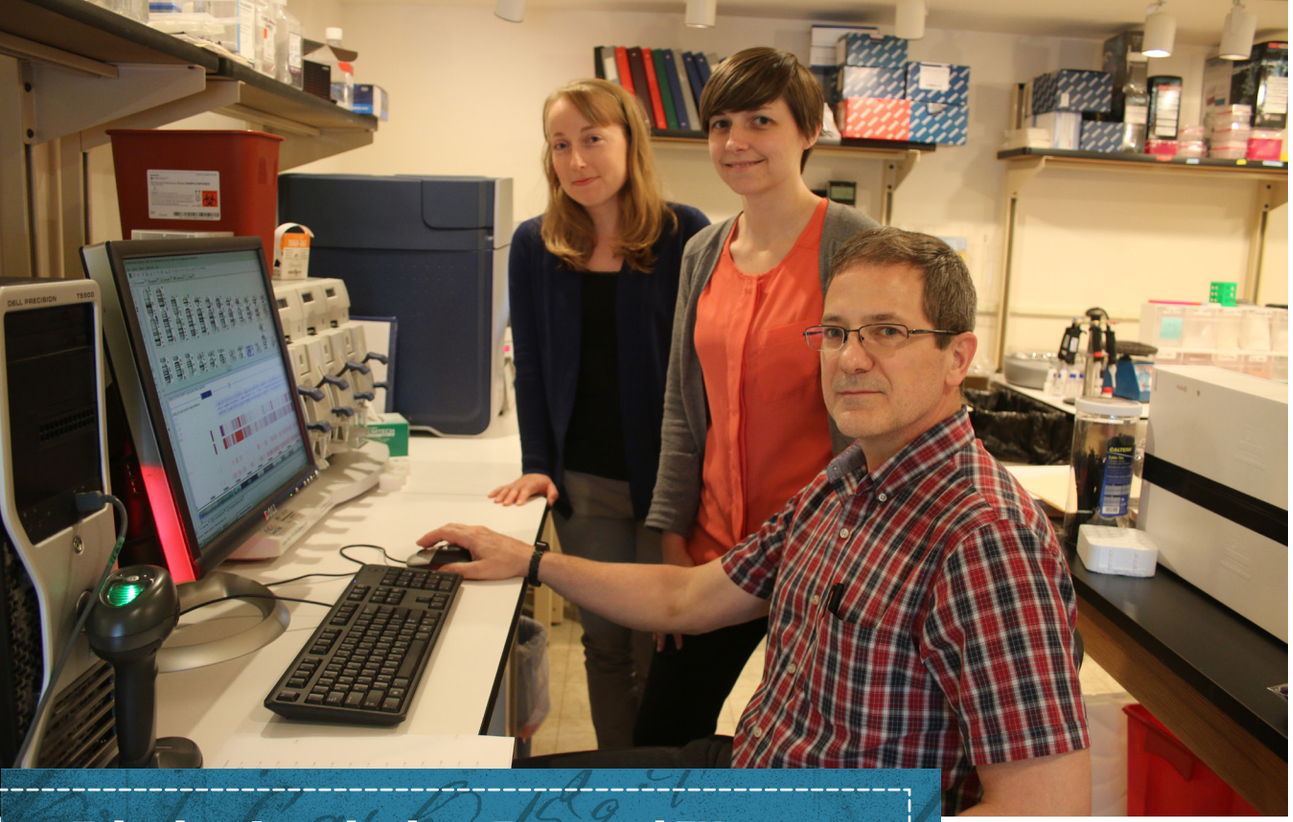
If a baby is born with SMA, CSC can test cord blood at birth with a result in a few hours so parents can begin treatment immediately, if they choose. Over 300 couples of Plain descent have been tested through the SMA Prevention Readiness Program in the few months since the program began.

The SMA Prevention Readiness Program team is comprised of Karlla W. Brigatti, Research Operations Director, Millie Young, RNC, Research Nurse, and Lauren E. Bowser, Research Fellow.

The SMA Prevention Readiness Team (L-R):
Lauren E. Bowser, Millie Young, RNC, and Karlla W. Brigatti, MS, LCGC

SMA PREVENTION READINESS PROGRAM *STATS*

1,300 *carrier tests performed*	**3** *team members*	**$0** *cost for patients*



Plain Insight Panel™

Next Generation Sequencing

Over the Clinic's 30-year history, over 300 genetic variants associated with disease have been identified. The majority of these conditions are recessive and are not included on the Pennsylvania State Newborn Screen. In response, the Clinic for Special Children team developed a genetic test that identifies carriers for genetic conditions found in the Plain community. For many conditions, scientific advances make treatment possible, but early detection is necessary so that the best possible health outcomes can be achieved.

About two years ago, Dr. Puffenberger teamed up with Drs. Erin Crowgey and Anders Kolb from Nemours Alfred I. duPont Hospital for Children in Wilmington, DE and ArcherDX in Boulder, CO to design a Next Generation Sequencing (NGS) panel to perform carrier testing in the Plain populations of Lancaster County, PA. The first version of the panel contained 203 known mutations. Initial testing of 48 individuals previously tested through and alternative method revealed complete concordance between the new panel and other NGS technologies.

After testing the initial panel, CSC reached out to the members of the Plain Community Health Consortium to solicit additional variants in their local populations. Clinics in Ohio, Indiana, Wisconsin, and Canada provided an additional 66 known mutations, and the extensive curation of CSC's exome database, increased the panel size to over 1,300 variants. The panel now has applicability to multiple Plain communities in North America. In 2018, CSC purchased a MiniSeq, which allowed the panel to be run internally. The machine was a $50,000 investment in genetic technology for Plain communities.

The new panel, aptly named the Plain Insight Panel™, will allow the Clinic for Special Children's research and clinical teams to predict which couples are at risk for having children with genetic diseases. Dr. Erik G. Puffenberger explains the importance of having the panel, "Having this capability in-house will greatly reduce overhead and reagent costs, and allow us to tweak the protocol so that we can run the test more cheaply and rapidly, passing on the cost savings to our patients." As new genetic conditions are identified in the community, they can be rapidly and easily added to the panel identify carriers.

While each assay test costs about $400-$500 to run, we hope to charge our patients $99 for this service through support from individuals and foundations.

THE PLAIN INSIGHT PANEL™ *AT A GLANCE*

265 *targeted tests for Plain populations*

6 *collaborators*

1,308 *mutations in Plain Insight Panel™*

$50,000 *cost of MiniSeq sequencer*

Gene Therapy

WHAT IS GENE REPLACEMENT THERAPY?

In its 30-year history, the Clinic for Special Children team has identified the genetic cause of many disorders that affect the patients we serve. Understanding the genetic basis for rare disease has been a key element to finding new therapies and treatments to improve quality of life for these patients. Until recently, therapies targeted the symptoms or features of a disorder without correcting the underlying genetic error of that condition.

Gene replacement therapy (GRT) has the goal to deliver a new copy of the nonworking gene into the appropriate cells of the body, producing the proper protein and therefore correcting the disease; in some cases, it can potentially prevent symptoms of the disease from manifesting if given early enough in the disease process. The gene-delivery system is called a vector, generally a modified virus. The majority of GRT programs use the adeno-associated virus (known as an AAV) as the vector because it is small and does not make people sick. Different types of AAV viruses target different tissues in the body, so the type of AAV selected is based on where in the body that new gene needs to work best, such as the nervous system, liver, heart, and muscle. The viral genetic material is removed and replaced with the working gene of interest and then administered as a one-time infusion or injection. After delivering the novel gene, the viral shell is then broken down and shed from the body. At present, most patients who receive GRT cannot be redosed with the same therapy, as they develop an immune response that renders subsequent dosing ineffective.

Given the novelty of this approach, the scientific community is still learning about the durability of therapeutic effect, long-term safety, and redosing paradigms. In 2017 the FDA approved Luxterna, a GRT for Leber's congenital amaurosis, a rare type of blindness. Over 200 studies in various conditions are ongoing, have been completed, or are under FDA review for approval. The Clinic for Special Children is one of only a few sites around the world for two clinical trials in GRT: the first for patients with Crigler-Najjar syndrome (CN1), and another for presymptomatic infants with spinal muscular atrophy (SMA). We are actively working on a pipeline to develop GRT options for patients in a host of different conditions, beginning with the natural history studies that inform study design. These efforts are in concert with other academic and industry collaborators and would not be possible without the partnership with our patients and their families. Gene replacement therapy is an exciting new frontier in personalized treatments for rare genetic conditions, and the Clinic for Special Children is primed to explore this therapeutic avenue.

A CLINICAL SITE

The Clinic for Special Children is a clinical site for the AveXis Phase 3 Trial of AVXS-101 in Pre-Symptomatic SMA Types 1, 2 and 3 (SPRINT). "Treating SMA as early as possible is critically important in order to rescue motor neurons before they are permanently lost. SPRINT enables us to understand how intervening in pre-symptomatic infants with AVXS-101 may impact clinical outcomes, including milestone development such as functional sitting, standing without support and walking," said Dr. Sukumar Nagendran, Chief Medical Officer of AveXis. "In addition to our ongoing studies in SMA Types 1 and 2, SPRINT adds to our development program as we continue toward the goal of making AVXS-101 available to the SMA community."

(L-R): Ashlin Rodrigues, Erik Puffenberger, KaLynn Loeven, Emily Seitz, Keturah Beiler, Yalonda Kosek, Kevin Strauss, Karlla Brigatti, Christine Hendrickson, Candace Kendig, Millie Young, Vincent Carson, Julia Martin, Lauren Bowser, Kelly Cullen, and Adam Heaps.
(Not Pictured: Lavina King, Donna Robinson)

Clinic *for* Special Children

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