

Care4Rare: A National Rare Disease Team Led from CHEO

By Mike Foster

The use of next-generation sequencing to pinpoint the genetic mutations behind rare diseases is one of the great success stories of Care4Rare. In its 4th year, the nation-wide network of doctors, scientists and clinical researchers is dedicated to improving the diagnosis and treatment of rare diseases. The challenge is great; 7000 rare diseases with more than half not yet understood and only 200 therapies available. However, with novel DNA technology, researchers at CHEO can look through an individual's entire genetic code of 22,000 genes and spot things that don't belong. The hunt itself is like finding a single typo in four copies of Leo Tolstoy's epic novel War and Peace.

As such, Care4Rare is making tremendous progress in equipping families with answers when their children present with mysterious symptoms. Answers matter because the questions pile up for families impacted by rare disease; many make repeat visits to the hospital, see multiple specialists at a time, and their children undergo a litany of tests like muscle biopsies and MRI scans before the answer is clear.

Since 2011, the extended team of 80 physicians and 50 scientists from 21 sites led out of the CHEO Research Institute has studied more than 1000 rare diseases and 5000 patients. Families have participated from Canada and around the world. Care4Rare has achieved a molecular diagnosis for more than 40% of these families, truly a signal achievement when one considers that many have gone years without a diagnosis.

En route to these diagnoses, Care4Rare has discovered mutations in 135 genes never previously associated with a rare disease – a globally recognized accomplishment. Each new discovery also adds to the worldwide body of scientific knowledge. The next person with similar symptoms and genetic mutations can avoid a lengthy diagnostic journey; the net result is the potential to save millions of health care dollars.

Not only is Care4Rare recognized internationally as a world leader in advancing the cause of rare diseases but founder Dr. Kym Boycott, a clinical geneticist and senior scientist at CHEO, also finds time to make a rare disease international impact in other ways, chairing the Diagnostics Committee of the EU-based International Rare Disease Research Consortium. She has also worked to address the fact that, around the globe, rare disease patient information has been siloed and fragmented across many different clinical laboratories and disease-specific organizations, making final diagnoses difficult. Working with University of Toronto scientist Dr. Michael Brudno, Dr. Boycott helped to establish Matchmaker Exchange, a database sharing rare disease patient clinical and genomic information from around the world, shedding light on previously undiagnosed patients in Canada and countries everywhere, working towards the international goal of diagnosing most rare genetic diseases by 2020.

The use of precision medicine, sometimes called personalized medicine, to diagnose rare diseases also lays the groundwork for using genomic sequencing in routine medical care. "Our comprehension of the genome with mechanistic detail is currently having an impact and, ultimately, shall make a huge difference. Rare disease is a *de facto* beta test for precision medicine, improving our understanding of how to incorporate DNA sequencing in clinical care," says Dr. Alex MacKenzie, senior scientist at CHEO and co-founder of the Care4Rare program.

In addition to making diagnoses, Care4Rare has also taken up the challenge of developing effective therapies for rare diseases. Today, there are only around 500 known therapies for some 3,500 genetic diseases across the world. As even more genes responsible for rare diseases are identified, the work to find novel therapies and advance treatment plans shall only grow.

Care4Rare is examining whether drugs approved for other conditions might have an impact on rare disease genes. Around 10 promising drug-gene combinations are being evaluated in the CHEO laboratory including:

- A phase one clinical trial of the drug Celecoxib, an anti-inflammatory drug typically used to treat pain or inflammation, on patients with spinal muscular atrophy (SMA);
- A pre-clinical trial using zebrafish to evaluate a new therapy for a lysine degradation disorder that causes epilepsy;
- A pre-clinical trial using mice to evaluate a new therapy to treat a genetic form of aortic aneurysms, a weakness in the walls of the heart, in partnership with Johns Hopkins University.

It is clear Care4Rare is building an evidence-based approach to diagnosing rare disease and finding new therapies. Care4Rare has also altered the perception of rare diseases – ironically, not so rare after all. Far from just affecting a tiny minority, 500,000 Canadian children are affected by rare diseases. These kids are affected for a lifetime, witnessed by the many adults we see in CHEO's genetic clinic.

CHEO researchers have put a stake in the ground to advance this field of study, and because of our proven results and excellence we are making a real impact for children and families with rare disease. It's something we can all be truly proud of as we celebrate **International Rare Disease Day today**.