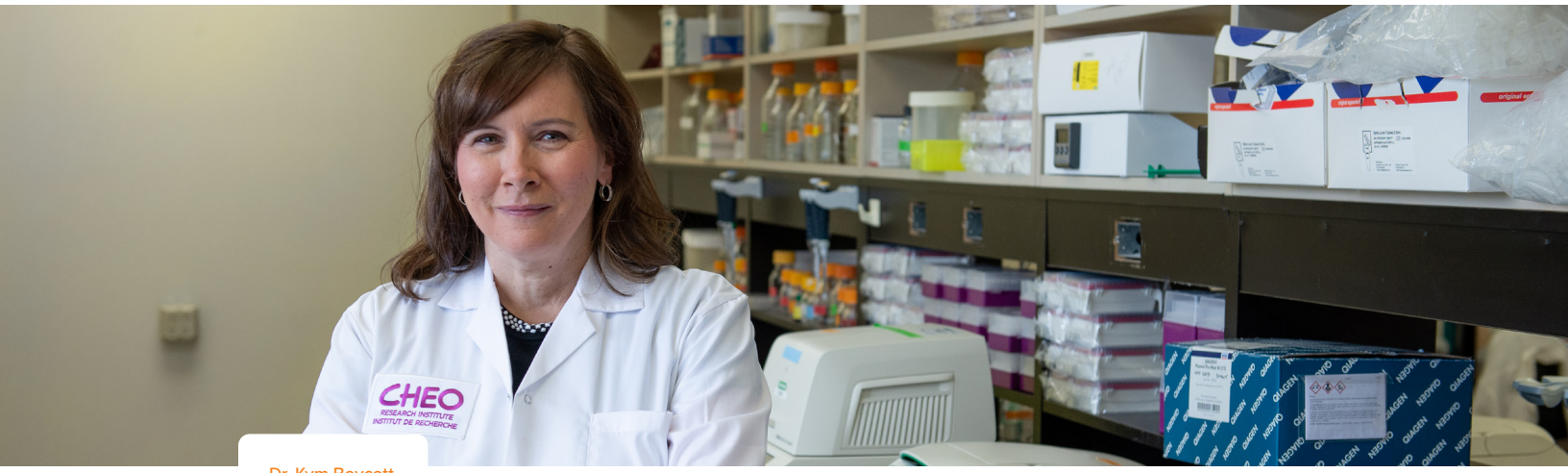
ADVANCING THE DIAGNOSIS OF RARE GENETIC DISEASES

Care4Rare Canada is a consortium of 20 Canadian clinical and research sites, led by Dr. Kym Boycott, a geneticist at the Children's Hospital of Eastern Ontario (CHEO) and senior scientist at CHEO Research Institute. Care4Rare is a 10-year research program which helps people — mainly children — who have rare genetic conditions, by identifying the precise DNA change or genetic variation responsible for the individual's symptoms. With this information, clinicians can make an accurate diagnosis that can help families understand their condition and access the resources they need.

While each rare disease is by itself uncommon, and therefore not well understood, more than 7,000 such diseases have been identified, together affecting at least 1 million Canadians. People with a rare disease spend on average 7 years consulting multiple specialists and undergoing many tests before their condition is diagnosed. However, many will remain undiagnosed following clinical investigations. Care4Rare grew out of a need for a personalized approach for these individuals. Over the past 10 years, Care4Rare has offered families with rare disease emerging genetic technologies which has led to the discovery of over 125 novel disease-causing genes.

To make these breakthroughs, the consortium had to overcome a major obstacle — siloing of data. "If you sequence any individual's genome, you might find several thousand variants," says Dr. Boycott.



Dr. Kym Boycott

Photos courtesy of Children's Hospital of Eastern Ontario

"How do you know which of these variants is the key to the disease? One of the tools at our disposal is to compare one family's data with that of others to see if they have similar symptoms and genetic profiles. But with only one or two cases of any given rare disease, this means going outside of your institution to find additional families."

Enter HPC4Health, a partnership between SickKids and the Princess Margaret Cancer Centre at University Health Network that provides clinical researchers with secure computing services, while

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satisfying personal health information privacy requirements. HPC4Health supplies Care4Rare with storage for its extensive research data (anywhere from 54 to 425 GB per family), made accessible to consortium members through a platform called Genomics4RD, developed in collaboration with the Centre for Computational Medicine at SickKids.

Genomics4RD, launched in 2019, is the first pan-Canadian rare disease data repository and analysis platform. It is hosted on the advanced research computing cluster at HPC4Health and provides centralized access to harmonized data from thousands of rare disease families. Storage, authorization and access procedures were developed in collaboration with policy experts and stakeholders to ensure data stewardship.

Using Genomics4RD, approved researchers can compare cases to facilitate diagnoses. For example, Care4Rare recently identified a novel disease gene and linked it to a rare form of spastic paraplegia. The team was suspicious about the gene in a French-Canadian family and queried Genomics4RD. They discovered a second family with overlapping symptoms and variants in the same gene. This resulted in a diagnosis for both families and allowed the team to validate the connection between the gene and the disease as well as identify several additional families with this disease in other countries (Lemire et al., 2022; PMID: 34587489).

“Data-sharing is critical in rare disease research,” Dr. Boycott says. “A clinician might see only one person in their lifetime with a specific rare disease. Unless we share our knowledge with other researchers, we simply don’t have enough data to provide answers for these families.” Genomics4RD is working towards identifying additional ways to link this Canadian resource to international rare disease databases, continuing their global effort to solve all rare diseases.