Title: **Diagnostic opportunities for rare diseases in the era of next-generation sequencing**

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Dr. Sawyer completed her BSc. at the University of Alberta in honours Genetics, and then went on to complete a PhD. in Genomics at the Karolinksa Institute in Stockholm, Sweden. From there she returned to Canada for medical school at the University of Calgary where she earned her M.D. and completed her residency training in Medical Genetics. Following this she moved to Ottawa for a one year clinical and research fellowship in Neurogenetics and Exome sequencing with Dr. Kym Boycott. She is now working as a clinical geneticist at the Children's Hospital of Eastern Ontario in the pediatric cancer genetics clinic and general genetics clinic. She is also pursuing her research interests in translating next generation sequencing technologies into clinical practice for the identification of genes in rare pediatric onset disorders.

Abstract: An accurate diagnosis is an integral component of patient care for children with rare genetic diseases. A definitive diagnosis can improve disease management, permit appropriate access to resources, provide accurate recurrence risk counseling and imparts important psychosocial benefits. Unfortunately, for many children, a diagnosis is difficult to achieve; as many as half of affected children with a rare genetic disease are never given a molecular diagnosis. As a result, many pediatric patients embark on diagnostic odyssey; a long and expensive undertaking that can span decades. Next-generation sequencing (NGS) has the potential to dramatically improve diagnostic rates for children with rare diseases while at the same time shortening the length of the diagnostic odyssey for patients. The Finding of Rare Disease GEnes (FORGE) Canada project, was a nation-wide effort to identify mutations in disease genes for childhood disorders using whole-exome sequencing (WES). We set out to determine the diagnostic utility of exome sequencing in pediatric patients with rare diseases without a molecular diagnosis after standard-of-care assessment in Canada. In total, 95 mutations in known disease genes provided a diagnosis for 130 children with rare diseases from across Canada, representing 36% of the cohort studied. Our analysis showed that the disease gene was not identified after standard-of-care assessment for several key reasons including genetic heterogeneity associated with the clinical diagnosis and atypical presentation of known, clinically recognizable diseases. Of the 130 children who were given a molecular diagnosis, six patients had disorders for which knowing the genetic basis lead to a specific treatment or targeted therapy, resulting in a change in a dramatic change in management. Our findings demonstrate that genomic sequencing is a powerful tool to diagnose children with rare diseases and addresses an important clinical need. Canada is building on the success of this experience to develop a national framework for clinical genomic sequencing.