JUNE 2017 IMPACT REPORT

CAUSES CLINIC

FUNDED BY

MINING FOR MIRACLES

BC Children's Hospital

THANK YOU FOR HELPING KIDS SHINE

The CAUSES Research Clinic at BC Children's Hospital is creating new hope for children living with complex, undiagnosed medical conditions. It provides advanced DNA testing, clinical interpretation, genetic counselling, and personalized recommendations for treatment in cases where a causal diagnosis is made. For many families, the experience has been life-changing.

A single DNA test can help to diagnose more than 7,000 known rare genetic disorders. As part of its three-year initiative, CAUSES will provide genome-wide sequencing for at least 500 children living with suspected genetic disorders. The clinic has already provided more than one hundred families with answers, which has resulted in fewer invasive tests and procedures and better treatment options.

CAUSES opened its doors in June 2015. Since that time, more than 800 children have been referred to the clinic; 350 families have been evaluated and 315 of those families have been sequenced. So far, clinicians have provided results to 209 families, with answers discovered in 46 per cent of those cases—a diagnostic hit rate considerably higher than other genomic sequencing initiatives.

The CAUSES team—clinical geneticists, pediatric subspecialists, genetic counsellors, bioinformaticians, molecular geneticists, laboratory scientists, health economics researchers and support staff—work collaboratively to make the clinic a success. They, along with the referring physicians, carefully evaluate each child and their family to provide them with the best care possible.

In addition to identifying conditions for children whose illnesses have previously gone undiagnosed, clinicians also hope to provide enough evidence to British Columbia's Ministry of Health for it to support genome-wide sequencing as a clinical service for those who need it.

“Through the CAUSES clinic, we were able to find an answer and diagnosis for Gabby after 11 years of searching. Thanks to Mining for Miracles for helping our family.”

– Frances Braile, Gabby’s mom

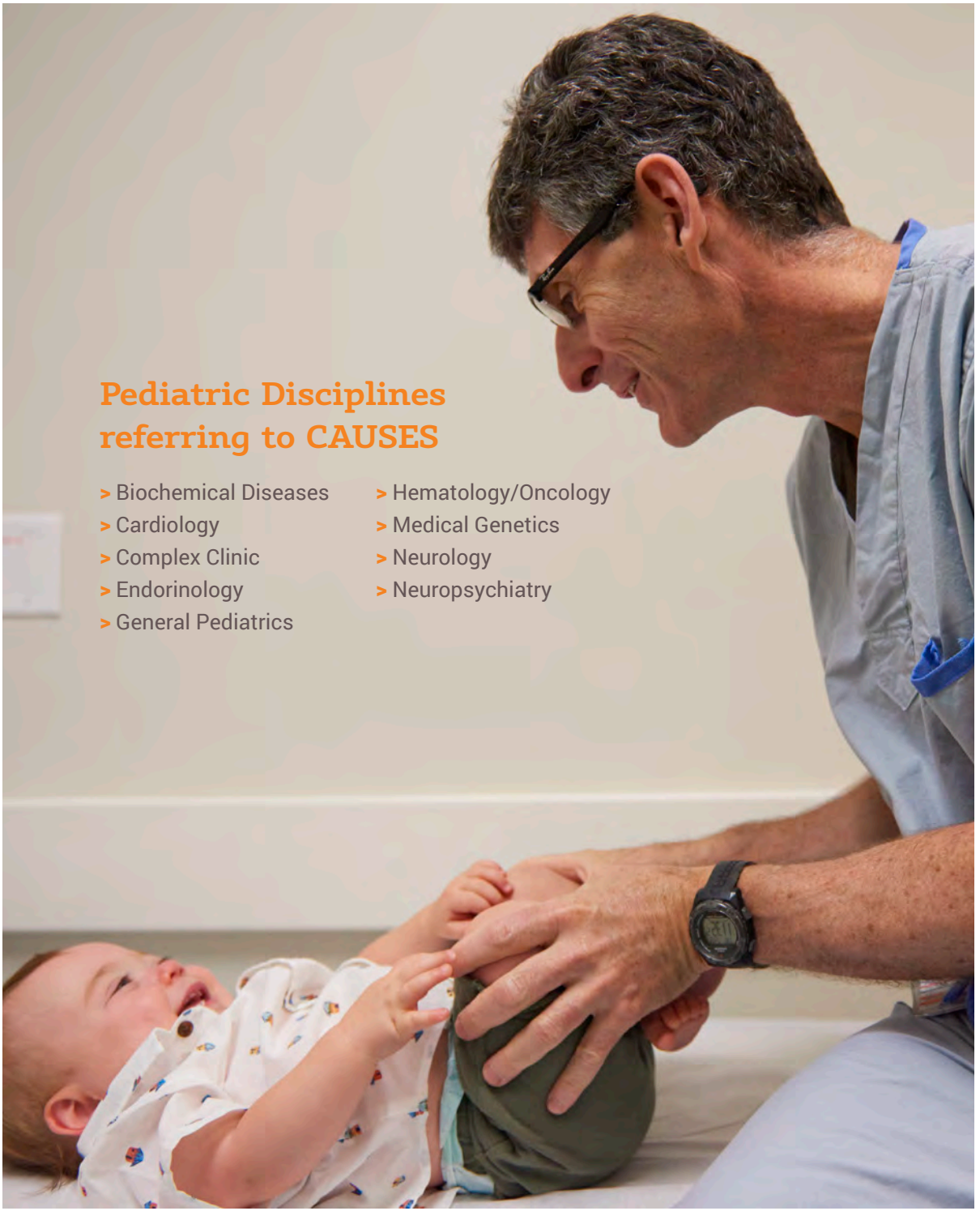
MINING FOR MIRACLES

The CAUSES team is extremely grateful to BC's mining community for its generosity. Mining for Miracles, a longstanding fundraising campaign in support of BC Children's Hospital, donated a total of $3-million in 2015 and 2016 for the development and implementation of the clinic.

This major commitment is just one way Mining for Miracles is helping to keep BC Children's Hospital at the forefront of pediatric care excellence. Every year volunteers work together, through a variety of fundraising initiatives, to make a positive impact on the health of sick children and their families. Since 1988, Mining for Miracles has donated more than $28 million to the hospital.

The CAUSES Research Clinic is supported by the Provincial Health Services Authority (PHSA), University of British Columbia, BC Children's Hospital Research Institute (BCHRI) and the Provincial Program of Medical Genetics at BC Children's and BC Women's Hospital. Genome BC has also agreed to support CAUSES.

CAUSES Team (L-R) Christele du Souich, Dr. Jan Friedman, Dr. Anna Lehman, Dr. Jill Mwenifumbo, Dr. Nick Dragojlovic, Simone Race and Dr. Alison Elliott. Missing from photo: Shelin Adam, Dr. Larry Lynd, Dr. Tanya Nelson, Dr. Clara van Karnebeek



Pediatric Disciplines referring to CAUSES

- > Biochemical Diseases
- > Cardiology
- > Complex Clinic
- > Endorinology
- > General Pediatrics
- > Hematology/Oncology
- > Medical Genetics
- > Neurology
- > Neuropsychiatry

WHAT IS CAUSES?

CAUSES (Clinical Assessment of the Utility of Sequencing and Evaluation as a Service) is a translational research program at BC Children's Hospital.

Within a three-year period, at least 500 children and their family members will undergo genome-wide sequencing at the clinic. In addition to identifying illnesses in these children that would have previously gone undiagnosed, clinicians plan to illustrate the importance of genome-wide sequencing as the provincially-funded standard of care.

Who does it help?

An average of 10 patients are referred to CAUSES every week. Since June 2015, more than 850 referrals have been received.

The majority of patients referred are dealing with extremely rare disorders of which the genetic cause is unknown. Many live with severe intellectual disabilities or impairments—either in isolation or in addition to other medical problems such as heart defects. In many cases, patients lack identifying features, which can be associated with specific disorders.

What happens at the clinic?

The first step is a referral from the child's doctor. Based on the information provided, a team of clinicians, which includes geneticists, pediatric subspecialists and genetic counsellors, will assess whether the child meets the criteria needed for a genomics consultation.

The Genomic Consultation Service helps to identify the most appropriate course of action for each patient, which may include single gene test, multi-gene panel, referral to Medical Genetics or genome-wide sequencing.

The family is asked to carefully review the process to determine if CAUSES is right for them. Genome-wide sequencing involves studying trios (the affected child and both biological parents), therefore all three must be available to participate. Once a family consents, clinicians will then carefully review the patient's medical records and the family is put forth for genetic counselling.

What is genetic counselling?

Genetic counselling plays an integral role in helping young patients and their families understand all options presented to them throughout the genetic testing process.

All processes and their findings are explained to the family in an unbiased manner. It is up to the patient and their families to decide if they want to proceed, what tests they will undergo and what genetic information they will receive once the results are available. Regardless of positive or negative results, patients and their family are advised of all their options including further testing and/or avenues for treatment should a diagnosis be made. A diagnosis allows for access to available resources and community support.

How does genome-wide sequencing and genetic counselling improve child health?

Genome-wide sequencing reduces the number of invasive tests — biopsies, single gene tests, biochemical tests and MRI scans — children may have had to endure to diagnose their condition. It also helps to prevent medical complications.

Genetic counselling helps patients understand their DNA results and provides personal treatment options for those who receive a diagnosis. The sooner a child has access to the right treatment, the more likely they will be able to resume an active, healthy life. The cost-effective service often results in significant savings for both the families and the health care system.

Genetic counselling helps patients understand their DNA results and provides personal treatment options for those who receive a diagnosis.

GRIFFIN’S STORY

Angela and Mike Wilson realized their son, Griffin, was different from most when he was around two years old.

Griffin didn't achieve life's usual milestones — talking, walking and eating — the same way the Wilsons' other sons did. Low muscle tone inhibited his speech and affected his balance, preventing him from walking with a normal gait. He had difficulty eating. Griffin also developed facial features that made him look different from other members of his family; his head was abnormally small and his eyes sloped downward. Though the young boy underwent a series of genetic tests, his doctors were no closer to finding out what was wrong with him.

By the time Griffin entered kindergarten, both his physical and intellectual development were significantly delayed. He still couldn't talk, and his parents didn't know why. It wasn't until their doctor told them about CAUSES that they finally began to understand what was going on with their youngest son.

Through the clinic, Griffin was diagnosed with Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia. Though the rare developmental illness affects many areas of the body, it is mostly characterized by dysmorphic facial features, skeletal abnormalities and stunted growth. Patients also have a greater risk of developing cardiac disease and malignancy.

Angela says finally understanding Griffin's condition was a huge relief.

"When [the doctors] said he was prone to leukemia and may have trouble fighting cancer tumours — my heart sank," recalls Angela. "But, I felt better once I realized we can be proactive with his treatments."

Today, seven-year-old Griffin is a gentle, happy little soul. Angela describes him as a smiley, cuddly child who likes books and building toys. He has many friends and is learning sign language to communicate.

While his future remains uncertain, Griffin's parents are grateful for the knowledge the CAUSES clinic has provided them.

"My family is so appreciative of this research project as it has impacted our lives in such a strong, positive way," says Angela. "I would love to thank each and every one involved."

TELEHEALTH

Geographic location, along with the time and cost associated with travel, can be limiting factors for families seeking answers from CAUSES. Telehealth, or Telemedicine, has become an important part of the process by providing families with an affordable option.

Families living outside the Lower Mainland can access pre-test genetic counselling via videoconferencing over a secure connection. The service is also used for discussing post-test genetic counselling results with both families and their referring physicians.

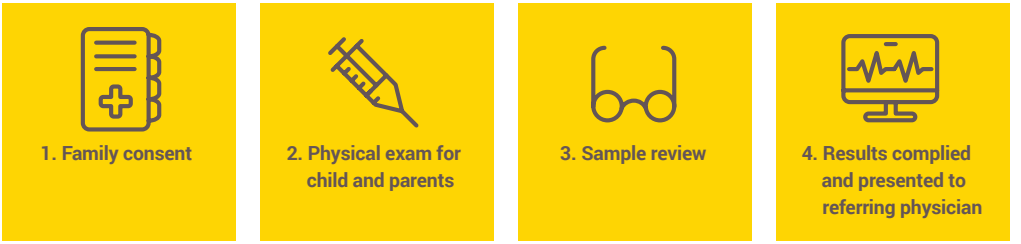
Families residing in all five health authorities in British Columbia — some in remote areas of the province — are now using this option. Approximately 18 per cent of families who have participated in pre-test genetic counselling have done so via Telehealth.

SEQUENCING & BIOINFORMATICS

The genome-wide sequencing process begins once the family consents to be part of the CAUSES Research Clinic. Clinicians perform a brief physical exam on the child and all three members of the trio (child and both parents) will have their blood drawn and sent to a sequencing provider for DNA testing.

Bioinformatic experts then work through a massive amount of genetic data. On average, six patients' samples are reviewed a week; the testing is often completed in batch samples. Clinicians compile the results, including any possible causal genomic factors of the child's condition, into a list and present it to the referring physician for discussion.

Genome-wide sequencing process



DIAGNOSTIC HIT RATE, ANSWERS FOR FAMILIES

CAUSES has been successful in its goal of providing answers for young patients whose rare genetic conditions have previously gone undiagnosed.

As of June 2017, at least 315 patients have been sequenced; bioinformatics and clinical interpretation has been completed in 209 of those cases. Clinicians have established a definite or probable genetic cause, referred to as diagnostic hit rate, in approximately 46 per cent of those children. This is particularly impressive as most comparable studies have a diagnostic hit rate of about 25 per cent.

Since June 2015

315 patients have been sequenced

209
Results provided

46%
Diagnostic hit rate

RESEARCH & TRANSLATION OF KNOWLEDGE

Dr. Alison Elliott, Project Lead, Dr. Jan Friedman, Director of CAUSES and the CAUSES research team are actively seeking ways to share their progress and knowledge with others.

A few recent opportunities include:

- Dr. Elliott presented five abstracts (Diagnostic Hit Rate, Telehealth, Genomic Consultation Services, Genetic Counselling Research and Health Economics) at the 2016 American Society of Human Genetics annual meeting in Vancouver.
- Dr. Elliott, Dr. Friedman and members of the CAUSES team spoke at genomic workshops at SickKids Hospital in Toronto.
- Three recent CAUSES publications in the American Journal of Human Genetics include; Loss-of-Function and Gain-of-Function Mutations in KCNQ5 Cause Intellectual Disability or Epileptic Encephalopathy. De Novo Mutations in EBF3 Cause a Neurodevelopmental Syndrome. Mutations in the Chromatin Regulator Gene BRPF1 Cause Syndromic Intellectual Disability and Deficient Histone Acetylation.
- Dr. Nick Dragojlovic and team have presented at a number of meetings on the health economics of CAUSES.

By expanding their reputation and promoting their findings, they, along with other CAUSES clinicians and researchers, hope to provide enough evidence to justify provincial funding for genome-wide sequencing as a regular clinical service for patients with severe undiagnosed suspected genetic diseases.

FUTURE OF THE CAUSES CLINIC

Currently, genome-wide sequencing is not routinely available as a clinical option in British Columbia. The CAUSES team is looking to change that.

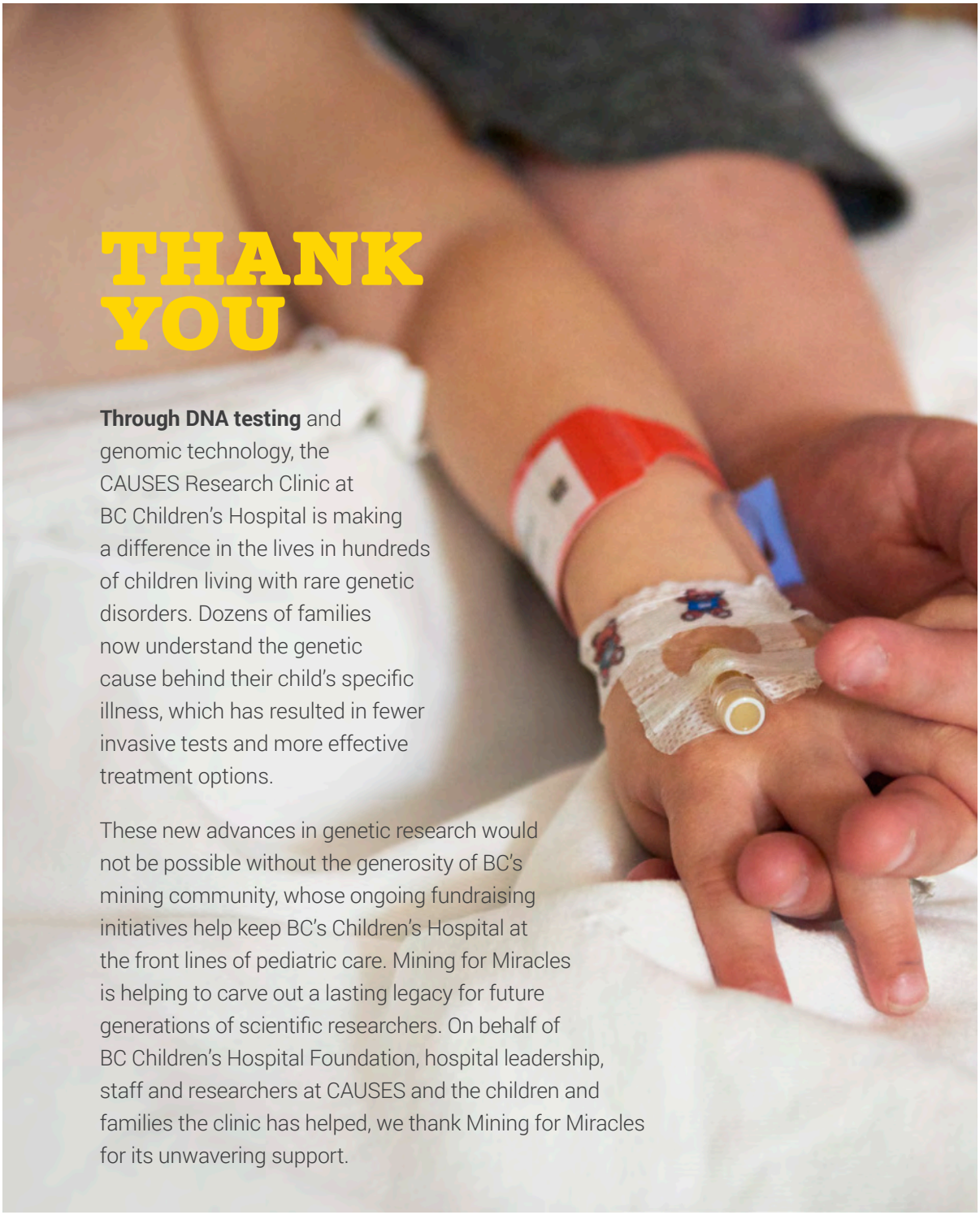
Thanks to Mining for Miracles, the clinic was initially funded as a three-year research pilot project. However, Dr. Elliott and her team feel so strongly about its potential to transform patients' lives that they are actively gathering evidence to prove genome-wide sequencing should be clinically available to all children who need it.

The Ministry of Health has taken notice of the clinic's progress and the results obtained. The dialogue regarding making genome-wide sequencing a provincially-funded diagnostic service is currently ongoing.

"CAUSES is a hallmark translational program that proves, on many levels, how [genome-wide sequencing] should work as a comprehensive program. My goal is for this program to be funded by BC's Ministry of Health for patients for whom sequencing is indicated.

This clinical option needs to be available for BC kids and their families because it gives them answers."

– Dr. Alison Elliott, Project Lead at CAUSES Research Clinic at BC Children's Hospital.



THANK YOU

Through DNA testing and genomic technology, the CAUSES Research Clinic at BC Children's Hospital is making a difference in the lives in hundreds of children living with rare genetic disorders. Dozens of families now understand the genetic cause behind their child's specific illness, which has resulted in fewer invasive tests and more effective treatment options.

These new advances in genetic research would not be possible without the generosity of BC's mining community, whose ongoing fundraising initiatives help keep BC's Children's Hospital at the front lines of pediatric care. Mining for Miracles is helping to carve out a lasting legacy for future generations of scientific researchers. On behalf of BC Children's Hospital Foundation, hospital leadership, staff and researchers at CAUSES and the children and families the clinic has helped, we thank Mining for Miracles for its unwavering support.