TED ROGERS CENTRE
FOR HEART RESEARCH

FULFILLING THE PROMISE

THE TED ROGERS CENTRE FOR HEART RESEARCH 2020 IMPACT REPORT



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The Ted Rogers Centre for Heart Research was designed with a unique architecture that gave us the capacity and resources to not only issue bold promises, but to deliver on them. Our teams are laser-focused on finding answers to complex challenges that will, in turn, change the fortunes of Canadians with—or at risk of—heart failure.

—Dr. Mansoor Husain, Executive Director,
Ted Rogers Centre for Heart Research.



FROM THE DIRECTOR

The Ted Rogers Centre for Heart Research's fifth year of operations was a time of resiliency in the face of a pandemic, self-reflection in the form of a major international review, and rising impact in the opening of new discoveries, innovations and partnerships.

It was also the time to transform the way we bring you our annual update. This year, we've curated new stories of transformation and impact from all areas of our Centre. Please consider this not a comprehensive account of our efforts, but a collection of intersecting highlights. While the milestones and financials will follow in a second document, this selection of discoveries and accomplishments is handpicked by our program leads and chairs to demonstrate the translational influence of our collaborative efforts.

This comes on the heels of our five-year external review, a critical juncture for the Centre as we presented our successes and challenges in full transparency to a group of esteemed international scientific experts. This exercise forced all our teams to analyze each step taken since 2015, encompassing everything we have learned along the way. I am pleased to report that the review panel believes we are meeting—and, in many areas, exceeding—the lofty levels of achievement we have set for ourselves.

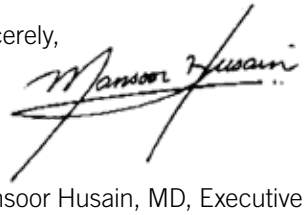
This Centre was designed with a unique architecture that gave us the capacity and resources to not only issue bold promises, but to deliver on them. Our teams are laser-focused on finding answers to complex challenges that will, in turn, change the fortunes of Canadians with—or at risk of—heart failure.

These pages reveal some of those answers: a world-first model to identify children at risk of sudden cardiac death; proving that heart-on-a-chip technology truly works; a "calculator" that can predict risk of future heart damage before a breast cancer patient begins treatment; genomic clues that guide precision medication use for each person; the role of immune cells inside our heart; and more.

Then, of course, there is COVID-19. I am proud of how our many clinical and research programs were able to pull through—and continue to pull through—this enormous challenge. There is no timelier demonstration of the Centre's impact than how our heart failure remote management system was used by Canada's largest hospital to pivot safely toward virtual care amidst a pandemic—even among patients who have such serious health issues as heart failure.

On behalf of our clinicians, scientists, staff and students: thank you for the gift of these first five years. We look forward to realizing so much more to come.

Sincerely,



Mansoor Husain, MD, Executive Director,
Ted Rogers Centre for Heart Research.

1. CLINICAL INNOVATIONS

MEDLY, PROVEN TO REDUCE HEART FAILURE HOSPITALIZATIONS, IS POISED FOR MAJOR GROWTH

Funded by the Ted Rogers Centre for Heart Research and developed by UHN eHealth Innovation, Medly—a heart failure remote management program 10 years in the making —launched at the Peter Munk Cardiac Centre (PMCC) in 2016. Within one year, it was being used by all cardiologists in the heart function clinic and soon became standard of care. Earlier this year, a new study demonstrated Medly's role in reducing rehospitalizations for heart failure by 50 per cent, and hospital stays for any reason by 24 per cent, over six months.

Now, Medly is poised for major growth after being licensed by Health Canada as a class-2 medical device and demonstrating its versatility during the COVID-19 pandemic by keeping patients safe at home.

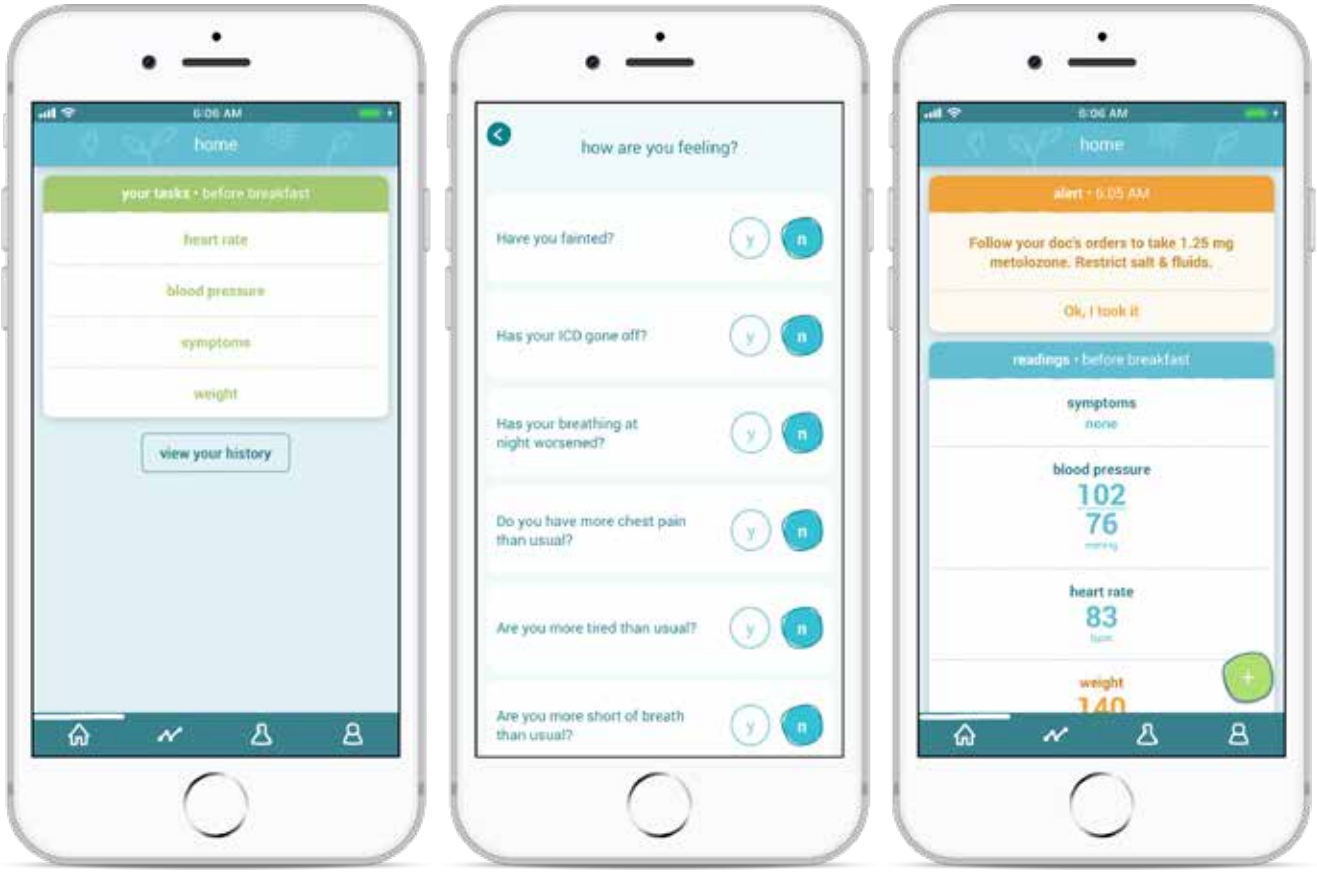
"Medly represents a groundbreaking change in terms of our ability to manage patients with heart failure in between their episodes of care, and critically, to keep patients out of hospital," says Dr. Heather Ross, Ted Rogers Centre Scientific Lead at UHN and Head of Cardiology at the Peter Munk Cardiac Centre.

"Its unique algorithm allows patients to receive real-time feedback on self-care, enables clinicians to adjust medications remotely, and alerts our team if there are any urgent issues or important concerns that require follow-up."

With more than one million Canadians living with heart failure, and at least 300,000 in Ontario, Medly has the potential to profoundly impact Canada's health-care system. Now endorsed by CorHealth Ontario, more than a dozen hospitals are ready to adopt Medly, pending funding.

Patients use Medly to monitor their heart failure symptoms, receive personalized support, and maintain direct contact with their care team from the comfort of their home.




6:06 AM
home
your tasks • before breakfast
heart rate
blood pressure
symptoms
weight
view your history
how are you feeling?
Have you fainted?
Has your ICD gone off?
Has your breathing at night worsened?
Do you have more chest pain than usual?
Are you more tired than usual?
Are you more short of breath than usual?
y
n
6:06 AM
home
alert • 6:05 AM
Follow your doc's orders to take 1.25 mg metolozone. Restrict salt & fluids.
Ok, I took it
readings • before breakfast
symptoms
none
blood pressure
102
76
heart rate
83
weight

Fast-tracking specialized care to patients

Medly's main objective is to keep stable patients stable by flagging deteriorations and symptoms early to help mitigate issues and prevent hospitalizations.

Its sophisticated algorithm sets Medly apart from other telemonitoring systems, serving as an expert triage system enabling clinicians to care for more patients remotely. With other telemonitoring programs, one nurse can remotely monitor 50-70 patients; with Medly, that number rises to 400.

Medly's intuitive design allows clinicians to seamlessly adopt the technology into their existing workflow while collecting meaningful data from patients. For patients, it is easy to use, a routine part of their daily life.

"They treat it like a prescription from the cardiologist," says nurse Mary O'Sullivan, adding that it's so simple to use that she even taught it to a 94-year-old man who had never used a cellphone.

Each morning, patients record their weight, blood pressure, heart rate and symptoms—data filtered by the algorithm, which then sends an actionable message to the patient. If Medly detects one's status is deteriorating, an alert is sent to the dashboard monitored by nurses like Mary.

In addition to shortness of breath and swollen ankles, even small changes in heart rate, weight and blood pressure can be red flags. Ideally, patients are educated in how to monitor symptoms and doctors can adjust their medications as necessary, sending information to a nearby pharmacy.

"Medly provides rapid access to specialized care that patients would otherwise have to go through regular health-care system channels to receive," Mary says.

Medly, in use since 2016 and continually studied, tested and updated since then, was launched at UHN's Toronto Western Hospital in January 2020. By November there were 710 active users on Medly, and more than 1,000 patients have used it to date.

> **Medly represents a groundbreaking change in terms of our ability to manage patients with heart failure.**
>
> —Dr. Heather Ross, Ted Rogers Centre for Heart Research Scientific Lead at UHN

COVID-19 puts Medly to the test

In spring of 2020, the COVID-19 pandemic hit Ontario. During this time, Medly helped to transform patient care and keep patients with heart failure safe. As UHN relied on virtual care programs to reduce hospital visits, Medly was put to the test.

"Nurses were diverted to our team and, despite having no experience with Medly, were able to seamlessly join and start monitoring patients within days," says Patrick Ware, implementation science lead at UHN's eHealth Innovation.

"Whereas before we onboarded new patients in an outpatient visit, we were able to start them on Medly remotely, which was a big step. For cardiologists who can't see patients in person, accessing this snapshot of their condition was a vital supplement to virtual visits."

Heart failure medications must be regularly assessed and adjusted so patients get the maximum dose without adverse effects. The team had been testing Medly's ability to do this remotely and, on the back of promising early results, they began remote medication titration as part of standard of care during COVID-19.

> **We were able to seamlessly join and start monitoring patients within days.**
>
> — Patrick Ware, implementation science lead at UHN's eHealth Innovation

The future is bright

Because it is built to scale, Medly is set up to be deeply valuable not only in Canada but internationally. Medly is both advanced technology and a structured program with defined roles for nurses, cardiologists, patients, process and more.

"It is designed to be a turnkey solution that can be easily adapted by any clinic, whatever their unique workflows and needs may be," Patrick says, adding that it can now simply be added to a patient's own smartphone.

By October 2020, Medly was used to support over 700 active patients at UHN. The program is also deployed at Toronto's Sunnybrook and Mount Sinai hospitals with operational plans on the horizon. The Medly team is working with Ted Rogers Centre partner SickKids to adapt it for children with heart disease, and Medly is being considered in ways to manage heart failure among Indigenous communities in northern Ontario. Researchers are also looking into ways Medly can serve patients with heart failure's key comorbidities: diabetes, kidney disease and hypertension. And a grant application has been filed to have Medly deployed in four countries in Europe.

"This coming year we're expecting significant growth for Medly and we are excited to see what's in store," says Dr. Ross.

2. PRECISION MEDICINE

NEW TOOL TO HELP DOCTORS PREVENT SUDDEN CARDIAC DEATH IN CHILDREN

In a study published this past spring in *Circulation*, Ted Rogers Centre for Heart Research scientists showed that a new approach developed at SickKids can successfully identify pediatric cardiomyopathy patients who are at high risk for sudden cardiac death.

This risk prediction "calculator" was tested and validated in over 850 children with hypertrophic cardiomyopathy (HCM) at over 20 of the world's leading children's hospitals. It proved to be over 70 per cent accurate in identifying children who are at greater risk of this tragic outcome.

When to use an ICD

HCM is a genetic disease that causes thick, stiff heart muscle and is a leading cause of sudden cardiac death in adolescents and young adults. To prevent these outcomes, and to stop the dangerously fast heartbeats associated with HCM, doctors use implantable cardioverter-defibrillator (ICD) devices.

However, until recently, doctors had no way to accurately identify children at a heightened risk of sudden death and in need of an ICD. This has both resulted in tragic, unnecessary deaths as well as devices implanted in children who don't need them, exposing them to complications.

"In pediatric heart failure, there is a huge gap in knowledge that has interfered with our ability to prevent these outcomes, while resulting in an unnecessary use of ICDs," says Dr. Seema Mital, Ted Rogers Centre Scientific Lead at SickKids and lead of the Cardiac Precision Medicine Program.

"Our risk model is the first to be validated in a pediatric population, and is driven by factors unique to child patients. It is a much-needed precision strategy to prevent sudden cardiac death and make informed decisions on the use of ICDs."

> **"Our risk model is the first to be validated in a pediatric population, and is driven by factors unique to child patients.**
>
> —Dr. Seema Mital, Ted Rogers Scientific Lead at SickKids





Data-driven decisions for each individual child

The decision to implant an ICD in a young patient requires a complex discussion between physicians and families. To that end, this calculator provides an individual risk score rather than more arbitrary "high" and "low" risk categories. It does so by combining many risk factors—for example, a child's age, medical history, family history, genetic information, and measurements from diagnostic tests such as echocardiogram.

"Instead of a one-size-fits-all approach, the tool can help people make decisions based on their individual risk tolerance," says Dr. Mital. "Each family can debate risks and benefits of an ICD placement with their doctors, and take a fully informed approach to their child's treatment."

For greatest impact, the calculator will be embedded as a digital tool in hospital electronic medical records, combining clinical, physiological, environmental and lifestyle data from each patient to generate a risk score that physicians and families can trust. This will also allow health-care teams to document patient progress over time, potentially revealing important new clinical clues.

After a pilot phase at SickKids, the calculator will be ready to use at any centre with a health record system, providing physicians greater precision in helping to save the lives of children with heart failure.



Each family can debate risks and benefits of an ICD placement with their doctors, and take a fully informed approach to their child's treatment.

—Dr. Seema Mital

Further into the Cardiac Precision Medicine Program

Since inception, this program has targeted whole genome sequencing, stem cell science and gene editing to discover and design precision approaches to cardiomyopathy and congenital heart disease. These are the leading causes of heart failure and mortality in children with heart disease.

The team has now sequenced 377 families with cardiomyopathy and over 1,152 families with congenital heart disease. Nearly 10,000 patients have been enrolled through the program in the SickKids Heart Centre Biobank, Canada's largest pediatric heart disease biobank—funded by the Ted Rogers Centre. Genome sequencing of over 300 cardiomyopathy cases from the biobank helped identify the genetic cause in twice as many families as using conventional genetic testing.

These findings are being returned to families in real time so that other family members can be screened for their risk of developing the disease and allow timely interventions to prevent complications. In year-5, through a Return of Results Committee, the team was among the first in the world to publish a study a practical roadmap for returning new genomic research results to families with heart disease.

3.
IMMUNOLOGY

STUDY FINDS THAT BODY REPROGRAMS IMMUNE CELLS TO HANDLE HIGH BLOOD PRESSURE

Hypertension can result in many health problems—from fibrosis to heart failure to a more severe case of COVID-19. In response to high blood pressure, heart cells swell in size with every beat, minimizing stress on blood vessel walls.

It's one of the world's most prevalent and burdensome health problems. Nearly 1 in 4 Canadians have high blood pressure, which is often linked to lifestyle (lack of exercise, poor diet), obesity, and diabetes.

Despite the use of medications that help control the condition, hypertension remains a leading risk factor for cardiovascular-related death.

While the disease has been well-studied from a physiological perspective, nobody had used modern technology to see if and how immune cells play a role in how hypertension develops, or what patient outcomes may be.

That is, until researchers in the lab of Dr. Slava Epelman—the first Loretta Rogers Chair in Immunobioengineering—addressed the question in a new study with the potential to change how we prevent heart failure in at-risk patients.



Dr. Slava Epelman, first Loretta Rogers Chair in Immunobioengineering

Target: resident cardiac macrophages

Inside the heart, the most abundant immune cells are called resident cardiac macrophages (RCMs), which are there from birth. In 2014, Dr. Epelman published an important study that shifted our understanding of RCMs in the heart, proving they come from many different sources in the body. His lab is a global leader in studying cardiovascular disease through the lens of immunology.

"We were especially interested because we had found clear evidence that resident cardiac macrophages are key to the heart's function," says Rysa Zaman, a Ted Rogers Centre researcher in the Epelman lab. "We were the first to use genetic mapping tools to investigate the role of these immune cells in hypertension."

The team was surprised to discover that the number of RCMs increases under the stress of high blood pressure – suggesting they have a positive benefit in the heart. (This is in stark contrast to a heart attack, where RCMs die in large numbers.)

The researchers also found that when they depleted RCMs in hypertensive mice, it led to immediate heart failure with signs of fibrosis and other dangerous conditions.

"This was very unexpected," Rysa says. "By removing this immune cell, we realized the heart can't compensate for hypertension. It was remarkable to learn that these macrophages have such a non-immune-related function."



We were the first to use genetic mapping tools to investigate the role of these immune cells in hypertension.

— Rysa Zaman, Ted Rogers Centre researcher

Unique, breakthrough finding

Using RNA sequencing, the team found that the body responds to hypertension by reprogramming RCMs to divert from typical immune functions to instead help repair damage and enable the heart to grow.

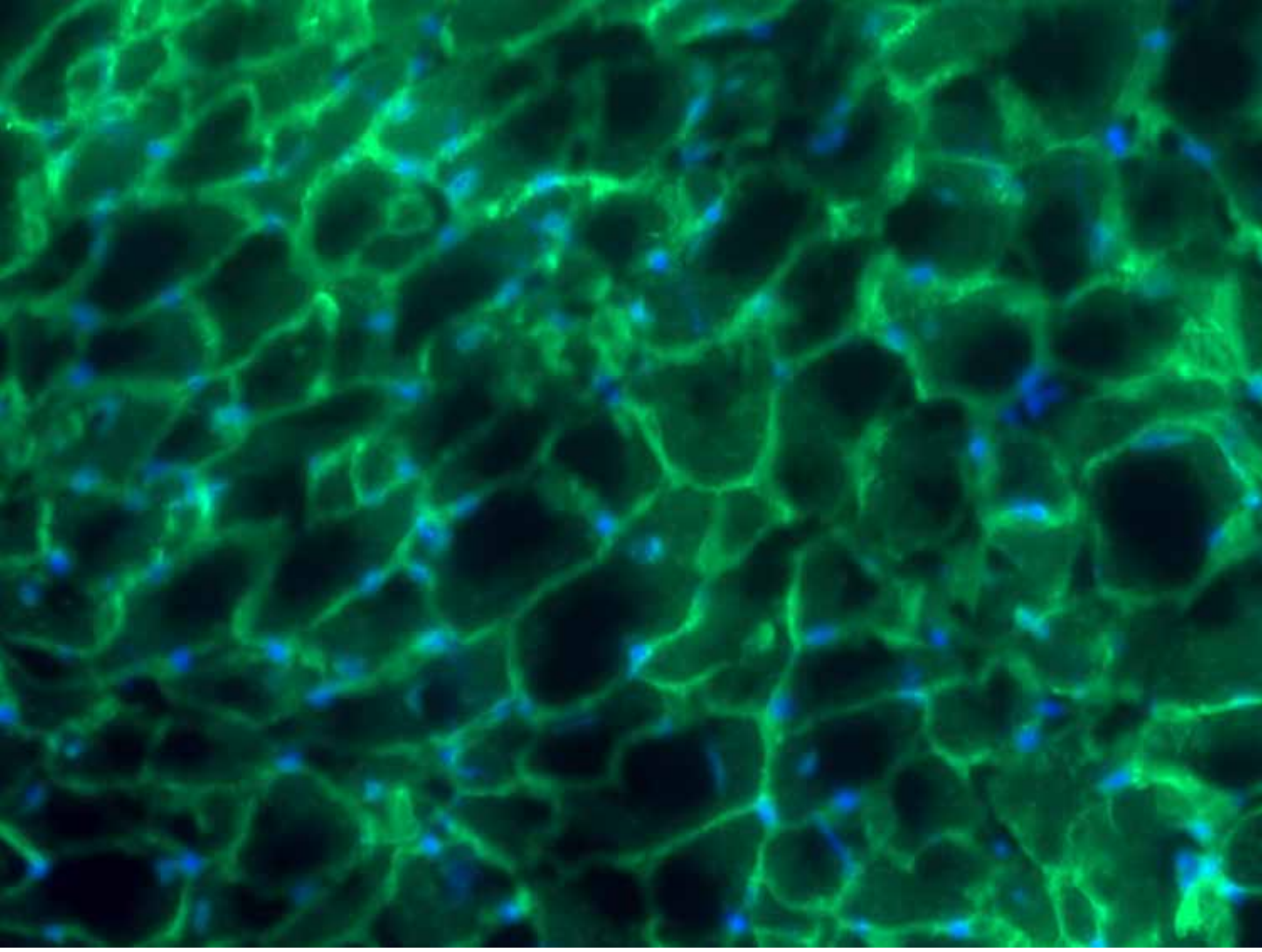
"This is very unique, as we don't associate immune cells with muscle growth," Rysa says. "Yet during hypertension, resident cardiac macrophages restructure and actually dictate the heart's growth to withstand high blood pressure."

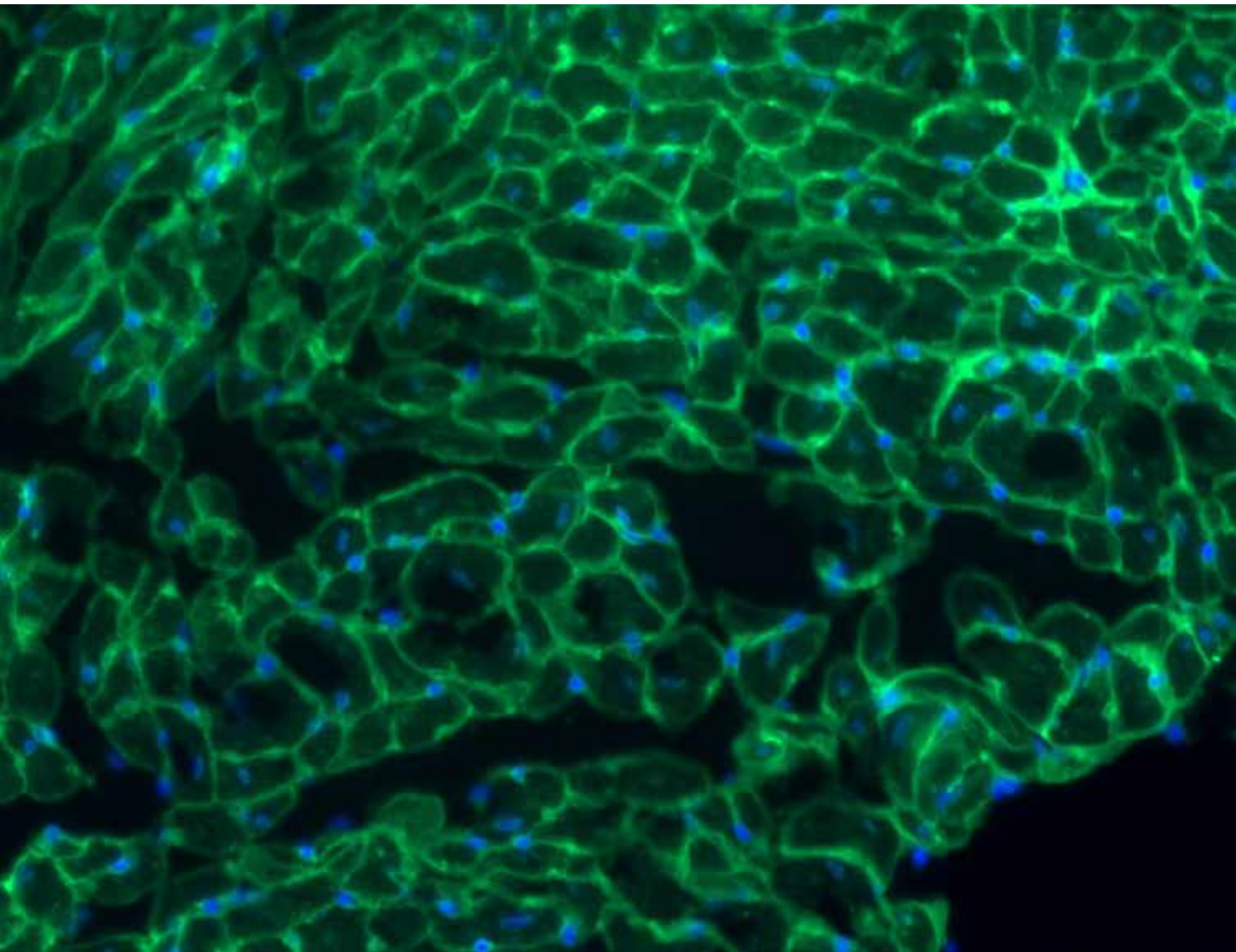
In a major breakthrough, Dr. Epelman's team uncovered the precise substance created by these macrophages to perform this function. The study is yet to be published, but this finding may open the door to novel stem cell approaches and potential therapies—particularly for people who develop high blood pressure and who may be at risk of heart failure because a past cardiac event wiped out their RCMs.

The study is set to be published soon in *Immunity*, the top journal in this field.

"This is fascinating new work that aligns with a key focus of this Chair, which is to perform computational analyses on the immunological response to better understand heart failure," Dr. Epelman says.

At top, heart cells in mice grow larger so that the heart can compensate for the pressure of hypertension. At bottom, with macrophages depleted, they do not enlarge. This shows the immune cells' role in protecting against heart damage.





4.
TYPE 2 DIABETES

A DIABETES-HEART FAILURE CONNECTION EMERGES AS TED ROGERS CENTRE GROWS

One in three Canadians lives with diabetes or prediabetes, an epidemic with a key complication: it is a leading cause of heart failure. This toxic connection, long underappreciated, carries dire consequences for patients.

Dr. Mansoor Husain, executive director of the Ted Rogers Centre for Heart Research, has been a leader in this area of research for over a decade. His work has uncovered key molecular insights into how diabetes and its treatments link to heart failure.

In 2014—coincidentally the same year the Ted Rogers Centre formed—two of the most important papers in decades on the management of diabetes were published.

The papers focused on two drug classes, SGLT-2 inhibitors and GLP-1 receptor agonists, which were also key subjects of study by members of the Husain lab. This coincidence would cement Dr. Husain, and the Ted Rogers Centre for Heart Research, as important members of Toronto's world-leading diabetes research efforts.

Those studies demonstrated that SGLT-2 inhibitors and GLP-1 receptor agonists appear to protect the heart from adverse events—and so now are used as cardiovascular treatments, regardless of whether or not a patient has diabetes.

Dr. Husain's leadership of the Centre at a time where seminal research on diabetes and heart failure was entering a new phase offered the opportunity to help broaden clinical knowledge around the mechanisms of diabetes and what role they play in the onset of heart failure.

Key recent studies with eye-opening results

The relationship between diabetes, diabetes drugs and heart failure has been a recurring theme of the Ted Rogers Centre's annual symposium, which has attracted world-leading experts in the field. Interest in this area has been further fueled by an emerging consensus that type 2 diabetes is actually a form of heart disease.

While the Centre has no official diabetes theme, Dr. Husain's unique expertise and role as a clinician-scientist focused on cardiovascular outcomes of diabetes folds this important area into the Centre's mission.

To that end, Dr. Husain was also involved in a landmark study published in the *New England Journal of Medicine* in 2019. The PIONEER-6 study proved that the first GLP-1 receptor agonist to be taken in pill form (all had previously been injected) was not only safe for the heart—but, in a small sample size, appeared to reduce deaths in the high-risk diabetic patients who took it.

Meanwhile, the Husain lab published two more key studies that year. One, led by PhD and MD student Luke Dingwell, studied the intersection of immunology and blood pressure control, both key factors in heart failure.

This early research, published in the field-leading journal *Hypertension*, determined that the kidney appears to be a main effector organ for blood pressure control through specialized immune cells known as B cells. This may open the door to an entirely new therapeutic approach to hypertension and heart failure.

Another, led by postdoctoral researcher Ahsan Siraj, found that fragments of the GLP-1 protein reduced signs of heart failure and preserved heart function in mice that had experienced a heart attack. This naturally occurring protein in the body appears to protect the heart, irrespective of diabetes. This high-profile paper was published in the *Journal of Clinical Investigation*.

As the Centre's diverse, multidisciplinary teams fulfil their clinical and research missions, the Husain lab works in concert to unearth promising metabolic discoveries, and further our critical understanding of diabetes as it relates to the heart.



Ahsan Siraj, postdoctoral researcher funded by the Ted Rogers Centre for Heart Research

5. PATIENT OUTCOMES

INVESTIGATING THE USE OF CARDIAC IMAGING FOR HEART FAILURE

Cardiac imaging is an essential tool in making clinical decisions for patients with heart failure. Yet, largely because it can be expensive and time-consuming, its use is contentious.

In fact, there is a broad international movement to reduce potentially unnecessary tests, treatments and procedures—including cardiac imaging—called "Choosing Wisely", which launched in 2014. Choosing Wisely's Canadian arm cites research that says 30 per cent of tests and procedures in Canada—including cardiac imaging—are potentially unnecessary, consuming time and resources with little added value for patients and possibly exposing them to possible harm, stress and more procedures to investigate false positives.

Nevertheless, most clinicians today cannot properly manage a patient with heart failure without techniques such as an echocardiogram (echo), which uses ultrasound to image how the heart muscle and valves are working.

"Understanding the right rate of imaging is a critical research area, because finding heart failure early is very important: you can start a patient on drugs to improve or normalize heart function, or even delay disease onset," says Dr. Douglas Lee, Ted Rogers Chair in Heart Function Outcomes.

"Historically, it's been difficult to actually prove the benefits of cardiac imaging, with some studies suggesting, for instance, that echo has no impact on survival. In the face of this uncertainty, we explore this research area purposefully, because answers here have major implications on patient care."



Cardiac imaging like echo is widely used, but misperceptions abound as to whether it impacts actual patient outcomes. Our research provides definitive new answers.

Uncovering a 'misguided concern' over imaging

In 2019, a study led by Dr. Lee sought to understand how cardiac imaging is actually used in clinical practice as it relates to patients with heart failure. Using a rich source of Ontario data, investigators found that while the use of such imaging rises each year, echocardiography remains the most popular option, less costly than CT, MRI and PET scans.

"As patients live longer with heart failure, it's likely that we are seeing increased imaging used to manage people who develop complex and more advanced disease," says Juarez Braga, a Ted Rogers Centre for Heart Research doctoral fellow and first author of the study.

"Meanwhile, the study shows that clinicians favour more established techniques and seldom use more modern, expensive imaging technology such as MRIs and CT scans."

Dr. Lee's research cuts through the noise and brings clarity to the issue of echo's impact on the health-care system. This study shows that echocardiography was in fact responsible for more than half of all imaging expenses in Ontario—while MRIs, and CT and PET scans accounted for less than five per cent.

"This indicates a misguided concern about the excessive use of modern, more expensive technologies," Juarez says.

> **"This important work shows that echocardiography has tremendous prognostic impact in an array of real-world settings.**
>
> —Dr. Douglas Lee, Ted Rogers Chair in Heart Function Outcomes

Echo proven to have 'tremendous' prognostic impact

In a recent study in collaboration with multiple hospitals, Dr. Lee's team focused on echo's value in assessing a patient's left ventricular function. Scientists had never before studied how well an echo can measure ejection fraction and predict risk for mortality or heart failure hospitalization in a broad range of cardiac and non-cardiac patients.

The study looked at varying measurements of left ventricular ejection fraction and how it affects patients with reduced pumping ability in the left ventricle.

Researchers merged 40,000 echo studies from UHN, St. Michael's Hospital and London Health Sciences Centre, and linked it to data from the Institute for Clinical Evaluative Science (ICES, where Dr. Lee leads cardiovascular research).

The study found that echo imaging did predict those at greater risk of cardiovascular and all-cause death, as well as hospitalization.

"This important work shows that echocardiography has tremendous prognostic impact in an array of real-world settings," says Dr. Lee.

"Whether in hospital or in ambulatory care, echo measurements of left ventricular ejection fraction had a huge impact on heart failure outcomes."

A Ted Rogers Centre for Heart Research study showed echo imaging can predict the risk of cardiovascular and all-cause death.

Uncovering important marker for coronary artery disease

Dr. Lee led another important study on cardiovascular imaging in year-four of the Ted Rogers Centre. With collaborators, he targeted "myocardial perfusion imaging" (MPI), which is used to detect "transient ischemic dilation" of the left ventricle—an important marker for coronary artery disease.

"The problem is that we don't really know how effectively transient ischemic dilation, observed on MPI, predicts outcomes, and how well it identifies those at higher risk for severe coronary artery disease," Dr. Lee says.

The team's literature review analyzed 31 studies involving 11,000 patients. They discovered that abnormal MPI measurements of transient ischemic dilation were directly linked to higher cardiac event rates and was indicative of multivessel coronary disease, which often precedes heart failure. The team's paper was translated into four languages.

"Our work in demonstrating the value of cardiac imaging is absolutely crucial for people with heart failure to get the specific care they need to achieve better outcomes," says Dr. Lee.

"Our team is uniquely positioned within the Ted Rogers Centre, the Peter Munk Cardiac Centre and ICES to analyze vast amounts of patient data to solve the questions that have lingered throughout the decades."

> **Our work in demonstrating the value of cardiac imaging is absolutely crucial for people with heart failure to get the specific care they need.**
>
> — Dr. Douglas Lee

6.
GENOMICS

WITH A REMARKABLE FAMILY HISTORY COMES THE CHANCE TO SAVE LIVES

When Katie Shea went to be screened at the Heart Function Clinic at the Peter Munk Cardiac Centre in the fall of 2018, she knew that, due to her family history, she was at risk of developing dilated cardiomyopathy (DCM). To help her clinicians, she brought a colour-coded family tree.

"I had highlighted in red my relatives who had been diagnosed with cardiomyopathy," Katie says. "I didn't anticipate any findings in my tests as all previous diagnoses had been made after the age of 50."

There, at the age of 41, Katie became the first of her generation to be diagnosed with DCM, which can cause heart failure.

"I was really tired at the time, but I'm the mother of three young children," she says. "It was a huge shock. Everything changed that day."

As a nutritionist, retired dancer, non-smoker and non-drinker, Katie lived a healthy lifestyle. The cause of her heart disease seemed locked in her DNA. In 1995, Katie's grandmother's brother died of DCM in his early 60s. In 2000, her grandfather died suddenly in his early 70s—an autopsy suggested it was cardiomyopathy.

In 2004, Katie's father was screened and diagnosed with DCM at age 52; five years later, he nearly died of sudden cardiac arrest at his workplace. Katie's father is the eldest of seven siblings, among whom a brother and identical twin sisters have also been diagnosed. Two of Katie's fathers first cousins also have DCM.

Even one relative sharing her diagnosis would be enough to prompt a genetic exploration in her family—Katie's had many.



Katie Shea's diagnosis of dilated cardiomyopathy was a turning point in her family's history with the disease. Her children (left to right), Linden, Sutton and Paisley are now screened regularly at SickKids.

Finding answers at the Cardiac Genome Clinic

Katie underwent standard clinical genetic testing for 50 genes known to be related to heart disease, all of which were normal—unsurprising, as the diagnostic rate for these tests is only between 30 and 50 per cent.

Katie and her siblings were all "gene-elusive." says Dr. Heather Ross, Ted Rogers Centre Scientific Lead at UHN. From the Peter Munk Cardiac Centre, Dr. Ross connected Katie's family to the the Ted Rogers Centre's Cardiac Genome Clinic at SickKids—a leading program in Canada that uses whole genome sequencing (WGS) to hunt for clues to heart failure.

"This hypothesis-free method allows us to take a deep dive into the genome, searching for any possible genetic variant that could be causing disease," says Eriskay Liston, a Ted Rogers Centre genetic counsellor who first brought Katie into the program.

Katie has three young children of her own and seven more nieces and nephews, so with all signs pointing to a hereditary cause of the disease, she was keen to join the Cardiac Genome Clinic to find some answers.

"Knowledge is power," says Katie. "I hope that we identify the genetic cause and determine if any of our children carry that gene, long before they are ever diagnosed. It's an opportunity to use my genetic profile, and that of several first-degree relatives, to be proactive and to provide new information to researchers studying dilated cardiomyopathy."

All ten of the Shea children are now being screened by SickKids cardiologists as a proactive measure while the genomic team searches for answers.

Katie also contributes tissue samples to the Peter Munk Cardiac Centre Cardiovascular Biobank and her children's saliva samples to the SickKids Cardiovascular Biobank – both of which are supported by the Ted Rogers Centre. (Katie is also among the first 100 patients to be monitored with Medly, a remote patient management system developed at the Ted Rogers Centre for Heart Research.



"Knowledge is power," says Katie Shea, who is enrolled in multiple Ted Rogers Centre programs. "I hope that we identify the genetic cause and determine if any of our children carry that gene, long before they are ever diagnosed." Pictured here are her three children and seven nieces and nephews.

Determining the optimal drugs for each patient

Whole genome sequencing can also provide other information relevant to someone's overall health, including "pharmacogenomics"—how genes affect a person's response to drugs. By studying our genomic makeup, researchers can discover genetic variants that determine what medications, including dosage, are safest and most effective for each person.

"This is critical to precision medicine because if someone is at risk of a heart issue in the future, we can find out today what the right therapy will be," says Eriskay. "This in turn helps avoid possibly catastrophic side effects while making that patient's life and treatment easier."

To this end, the Cardiac Genome Clinic team explores each person's genome, hunting for specific genes that are known to influence the speed at which the body metabolizes certain medications. This technology doesn't yet exist in Canadian clinics, but those in the clinic's research program benefit now from this innovation.

About 95 percent of all families in the program have had pharmacogenetic findings returned, with direct implications on their current and future medications.

For Katie, the team found a variant that increases the function of a metabolizing enzyme involved in activating the antiplatelet drug, clopidogrel. This drug can be effective, if needed, but with this variant, Katie would be at a greater risk of bleeding.

This same enzyme also helps breaks down other medications, and since she is a fast metabolizer, standard doses may be ineffective. Such intel will help define a precision strategy for her future care.

95 percent of all families in the program have had pharmacogenetic findings returned with direct implications on their medications.

No families left behind

Eriskay says that, because someone's WGS data don't change, it is always possible to search for new answers.

"We can easily re-interrogate a person's data every few months should we learn more about the genomic links to heart function," she says. "Whole genome sequencing allows us to go back and look again, with little to no burden on the families. For Katie, we can potentially find a new diagnosis the next time we look. Within a year, the story could change from not having found any clues to pinpointing the responsible gene."

Eriskay notes that, while it take resources to re-interrogate data, the Cardiac Genome Clinic is funded for 10 years by the Ted Rogers Centre, meaning that the 300 families sequenced thus far have longer windows of opportunity. Those with a strong family history with DCM such as the Sheas will be reassessed more regularly because of the ground-breaking potential to identify a new gene that causes the condition..

It is expected that, within five years, WGS will be a routine aspect of clinic care. The Cardiac Genome Clinic is helping to pave that road by demonstrating the value of this technology, and how to incorporate it safely and strategically into patient care.

> **I am so grateful for the care that my family and I have received. You can never repay that.**
>
> —Katie Shea

From diagnosis to determination

For Katie, the shock and sadness of her diagnosis have given way to gratitude and empowerment.

"I am so grateful for the care that my family and I have received—everyone at the hospitals has supported and protected us. You can never repay that."

Katie is now active in the heart failure community, volunteering to participate in projects she hopes will generate better outcomes for others with heart failure. She has raised more than $30,000 to help foster earlier diagnoses, better treatments, and ultimately a cure for the disease that has had such a significant impact on her family.

7.
PREVENTING CARDIOTOXICITY

CALCULATING RISKS TO SAVE MORE LIVES

In December 2018, nine months after retiring as an elementary school librarian, Luanne Teall was diagnosed with breast cancer.

The following month, on the day she was to begin chemo, Luanne was told she had an underlying heart issue that would impact her treatment.

With low ejection fraction, Luanne's heart wasn't functioning at a normal level, so doctors opted to perform a lumpectomy first, and told Luanne that her weak heart may make her ineligible for the potentially life-saving breast-cancer drug Herceptin.

Luanne connected with Dr. Husam Abdel-Qadir, a clinician-scientist in the Ted Rogers Centre Cardiotoxicity Prevention Program. Dr. Abdel-Qadir, she learned, had for years been studying the cardiac impact of breast cancer treatment on postmenopausal women.

Dr. Abdel-Qadir welcomed Luanne, who lives in Kitchener Ontario, to Women's College Hospital where, after reviewing her echo results, he prescribed her heart medications that would quickly improve her heart's pumping ability. Once it reached normal levels, Dr. Abdel-Qadir assured Luanne's oncology team that it was safe to begin Herceptin and kept in touch with her progress and care from Toronto.

"Lives can change in moments, right?" says Luanne. "I had no idea there was any correlation between chemotherapy and heart damage.

Without Husam's involvement it's likely I wouldn't have been treated with Herceptin, which has the best survival rates. I feel blessed to have been able to access this level of expert care."

Luanne Teall with her grandchildren. The Ted Rogers Centre's unique cardiotoxicity 'risk calculator' helped ensure Luanne could safely receive Herceptin to treat her breast cancer.



A new prediction model in the fight against cancer

Dr. Abdel-Qadir was confident that the benefits of Luanne's cancer treatment far outweighed any risks thanks to a "calculator" that he created at the Ted Rogers Centre for Heart Research, which predicts each person's risk of suffering a major cardiovascular event within one decade.

This innovation was validated in a December 2019 study in the European Heart Journal, in which researchers analyzed how 90,000 Ontario women with early-stage breast cancer progressed over 10 years. Using population data, researchers tracked patients who developed a serious heart problem, how long it took to develop, and what risk factors each person had, while weighing that against the competing risk of dying from cancer.

Using a statistical model, they distilled the data into a "risk score" that is easy to interpret by any clinician, in any location. It works by assigning points on risk factors such as age, blood pressure, presence of diabetes or kidney disease, and any existing heart issues. This data then projects a woman's risk of having a cardiovascular event, or dying due to one, five and 10 years after chemotherapy.

"To actually quantify the risk for these women is new, and it expands the conversation to the overall questions of heart health," says Dr. Abdel-Qadir. "Before cancer treatment even begins, this tool can help inform treatment decisions that are tailored to each patient."

Treating the cancer must be prioritized wherever possible. Through this model, women at lower risk of serious future heart problems are empowered to get necessary cancer therapy while working to mitigate any potential adverse effects. At the same time, the calculator can help identify the few women whose risk of heart disease may be so high that cancer treatment should be modified.

"I see rising interest among oncologists, who care about their patient's entire health because they want to provide the best care possible to the whole person," says Dr. Abel-Qadir. "And breast cancer patients themselves are increasingly asking to be referred to our Centre to be evaluated."



Before cancer treatment even begins, this tool can help inform treatment decisions that are tailored to each patient.

— Dr. Husam Abdel-Qadir, clinician-scientist in the Ted Rogers Centre cardiotoxicity prevention program

Canada's largest cardiotoxicity prevention program

Led by Dr. Dinesh Thavendiranathan, (Dr. Abdel-Qadir's mentor), the Centre's cardiotoxicity prevention program is the largest of its kind in Canada, caring for more than 1,500 patients each year at the Peter Munk Cardiac Centre—up from 200 when the clinic began in 2014.

Providing care to more than 1,500 cancer patients each year.

The program has also broadened in scope to focus on new, poorly understood areas of medicine. That includes one of the world's first clinics for patients with clonal hematopoiesis—a phenomenon involving mutated cells once tied to cancer (leukemia) that is now understood to be more closely related to heart disease.

The program also focuses on cardiac amyloidosis, caused by abnormal protein deposits in the heart tissue, which disrupt the heart's function. While the team seeks new therapies for these patients, they are integrating them into ongoing clinical trials in Toronto, led by Dr. Diego Delgado.

The aligned research program has produced some of the world's most important cardiotoxicity studies. Researchers have secured several grants to unearth new blood biomarkers that could help stratify cardiovascular risk for those set to undergo cancer therapy; while seeking to add machine learning approaches to further refine each individual's risk factors.

Over the past two years, the Ted Rogers Centre for Heart Research cardiotoxicity prevention team has published many impactful papers, including those that identified:

- Heart disease as a major cause of death in breast cancer survivors over 65 with cardiovascular risk factors
- A risk of heart attacks in women with early breast cancer treated with different types of therapy
- A mismatch between a person's cardiovascular risk and how cardiac imaging is used to assess them
- Hospitalizations for heart failure are often caused by preventable risk factors
- A higher risk of heart failure among childhood cancer survivors

Looking ahead, Dr. Thavendiranathan and Dr. Delgado are overseeing four major trials whose results will better inform the management of cancer survivors when it comes to their heart health.

8. DISCOVERY SCIENCE

TED ROGERS CENTRE COLLABORATION GETS TO THE HEART OF CARDIAC FIBROSIS

A leading cause of heart disease is fibrosis, where scar tissue forms on the heart muscle after a cardiac injury such as a heart attack. Fibrosis is one of the greatest underlying triggers of heart failure, but how it develops in heart cells has long puzzled scientists.

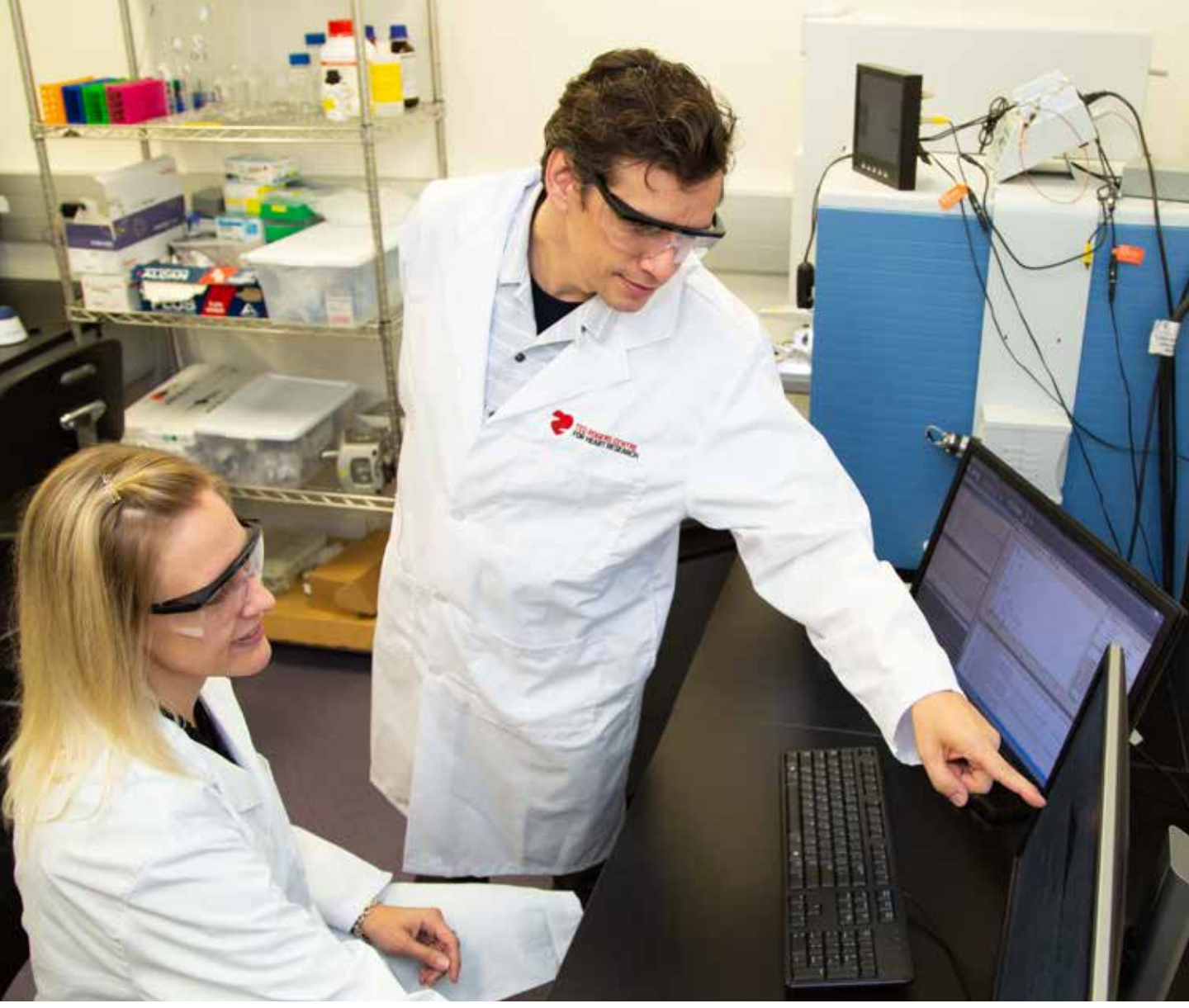
A key problem is the inability to study actual human tissue samples, which must be carefully collected, processed and stored. In 2020, however, a new Ted Rogers Centre study featured a rare approach using advanced technologies to uncover new answers on the molecular nature of cardiac fibrosis.

The study is built on a collaboration made possible through the Centre's network of clinicians and multidisciplinary scientists, and funded by its Translational Biology and Engineering Program (TBEP).

The team is led by investigator Anthony Gramolini as well as Milica Radisic, Canada Research Chair in Functional Cardiovascular Tissue Engineering at U of T, and Andrew Emili, director of the Center for Network Systems Biology at Boston University. Their novel approach to cardiac fibrosis emerged from discussions between the lab and several cardiologists—doors that had been opened by the Ted Rogers Centre.

Top: Meghan McFadden, mass spectrometry expert, and Anthony Gramolini, principal investigator.

Bottom: Milica Radisic, Canada Research Chair in Functional Cardiovascular Tissue Engineering.





Mapping answers using human tissue and organ-on-a-chip

Proteins carry the load inside heart cells, and how they develop is key to understanding where disease begins. This study is believed to be the first ever to combine the fields of phosphoproteomics, mass spectrometry and computational analysis to uncover differences in how proteins signal inside healthy and diseased hearts.

The result is a map of signaling pathways that reveals where changes happen during cadiac fibrosis—and new areas to target therapy. The team identified a new compound that works to prevent fibrosis in the human heart, and now they are in discussions with a corporate partner to translate the discovery for clinical use.

Uros Kuzmanov, Ted Rogers Centre researcher and first author of the study, says what makes their approach unique is that they compared three distinct samples in creating that map: a mouse model, an organ-on-a-chip model (called the Biowire), and human tissue samples obtained from the Peter Munk Cardiac Centre biobank, directed by Dr. Phyllis Billia and funded by the Ted Rogers Centre.

The study also discovered remarkable similarities between a fibrotic heart-on-a-chip and actual diseased human hearts—similarities that can't be captured in a standard mouse model.

"This was the first phosphoproteomics ever used in a heart-on-a-chip model, and the Biowire proved to closely mimic what's going on in actual patients," Kuzmanov says. "This verifies that it can be used to help identify new therapies for cardiac fibrosis."

"This project not only validates the heart-on-a-chip's high value in heart disease research but delivers new insights.

—Anthony Gramolini, principal investigator at the Centre's Translational Biology and Engineering Program

Unique collaboration moves the field forward

This study required close collaboration between doctors, surgeons, bioengineers, as well as systems biology and bioinformatics experts.

The team overcame difficulties in studying patient tissue at a molecular level by ensuring the human samples were meticulously collected, transported, and stored in a way that ensured their molecular makeup would not alter on its way to the lab.

"This project not only validates the heart-on-a-chip's high value in heart disease research, but also delivers new insights into the field, and provides new testable therapeutic approaches," says Anthony Gramolini.

"We are very excited about the potential to exploit these systems, not only for cardiac fibrosis, but also for other cardiomyopathies as well."

Fibrosis has been a key target for TBEP, which has provided more than $2 million for grants, equipment and salary support in this area. TBEP has also partnered with the U of T Faculty of Dentistry and St. Michael's Hospital to launch a Toronto-based Global Fibrosis Network. Overall, TBEP labs have generated a pipeline of projects in cardiac fibrosis, repair and regeneration, and HF comorbidities.

Previously disparate teams now pursue new ideas in concert, providing a foundation for the Ted Rogers Centre community to study the mechanisms of heart failure via pre-clinical model systems, proteomics, imaging, biomaterials, and bioengineering-expertise.

Using advanced technologies to uncover the molecular nature of cardiac fibrosis.



Trainees performing collaborative experiments in TBEP's expansive wet lab space.

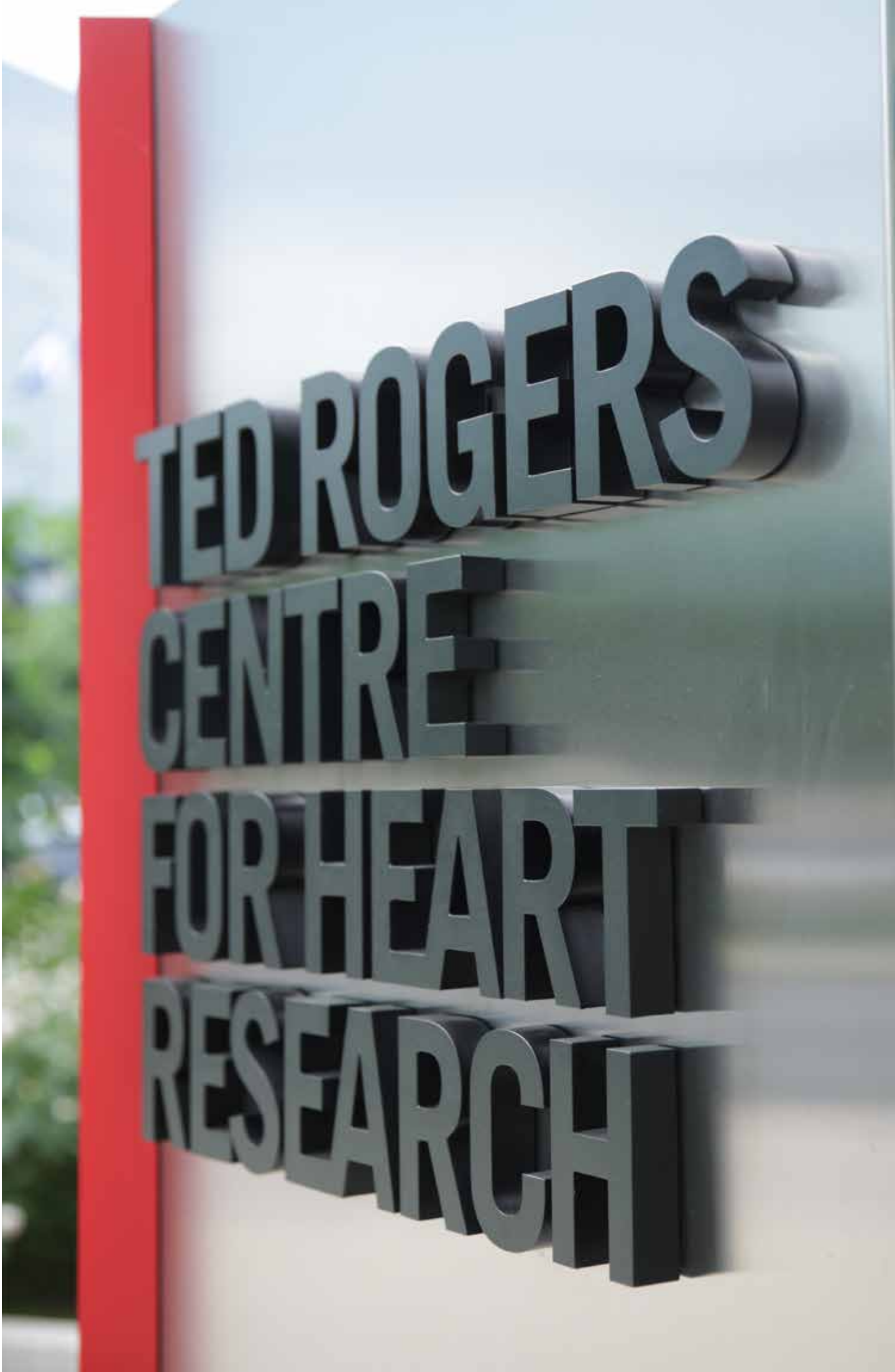
THANK YOU

In five short years, the Ted Rogers Centre for Heart Research has accelerated research and clinical care in nearly every area related to heart failure, with lasting impact on the health of well-being of people with heart failure and those who care for them.

Whether it's reducing hospitalizations through Medly, tailoring heart failure medications to match the genetic fingerprints of our patients, developing a Digital Cardiovascular Health Platform, or helping cancer patients better understand the risks of certain medications to their heart, the Ted Rogers Centre has already had an extraordinary impact on the lives of patients and their families.

And now, amid the current global pandemic, the Ted Rogers Centre continues its important work—including keeping vulnerable patients safe at home.

These remarkable stories of discovery, innovation and care could not have been written without your transformative generosity. Thank you for supporting the Ted Rogers Centre for Heart Research. We look forward to working with as we continue to fulfill the promise of a healthy heart for many years to come.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