PRECISION MEDICINE

One size does not fit all

What if your health care could be tailored to your own biology and lifestyle? That's precision medicine. Through the development of a massive data 'lake,' the Peter Munk Cardiac Centre is aggregating the health information of thousands of patients across Ontario and taking the first step in making precision cardiac medicine a reality

Mirjam Guesgen

Dr. Barry Rubin has a vision.

The Medical Director and Chair of the Peter Munk Cardiac Centre imagines a day when a patient comes in, has an oral swab taken and has their entire genome sequenced in an hour. That, together with data about their lifestyle, weight and blood pressure, is integrated into a complete patient profile, along with all of their imaging studies, such as ultrasounds and CT scans. The profile is then used to create a personalized treatment plan, and a computer algorithm automatically predicts treatment success and chances of readmission.

It may sound too good to be true, but Dr. Rubin says it's coming.

"It will be totally different," he says of patient care in the future. "In 10 years, I think we'll be unrecognizable in [comparison to] our current approach."

Dr. Rubin's vision is part of a wider initiative at the Peter Munk Cardiac Centre – one based on the principle of precision medicine. It's an approach that can be described as: the right treatment for the right patient at the right time.

Instead of a "one-treatment-fits-all" approach – the current standard in medicine – precision medicine looks to break up the wider population into smaller subgroups based on characteristics such as the genetic or molecular mechanisms underlying the disease, the patient's lifestyle or the patient's unique physiology.

Then, instead of basing treatment on the average results of a randomized controlled trial, which targets that wider population, treatment is personalized to each subpopulation of patients.

"Currently, if two people come to the hospital – same age, same sex, same risk factors – and have narrowed heart arteries, we tend to treat them the same. But the cause of the narrowed heart arteries or the optimal treatment may be totally different," Dr. Rubin explains. "Everybody gets grouped the same, but the diseases aren't likely the same."

The precision medicine approach has been applied primarily in the field of oncology, but Dr. Rubin and others at the Peter Munk Cardiac Centre see heart disease as its next frontier. As part of the strategic vision for the centre, doctors and data scientists are coming together to realize the possibility of one day providing individualized care for their patients. Their efforts will not only mean a better match between patient and treatment, but also the potential to detect problems before they arise or even redefine particular diseases altogether.

CREATING A 'LAKE' OF DATA

Big data and artificial intelligence (AI) are the scalpel and stent in precision medicine.

The combination of complex AI algorithms and massive amounts of data can reveal subpopulations of individuals with a particular gene or molecular pathway. In cardiology, having genetic sequence data, heart ultrasounds, X-rays, blood work, tissue samples, treatment outcomes and lifestyle information for every patient is crucial. To see any trends requires thousands upon thousands of patients. The spreadsheet quickly fills up.

"That information for just one person generates a lot of data, so imagine doing that for every one of the 163,000 people we see every year," Dr. Rubin says.

For that reason, much of the effort in bringing precision medicine to cardiology has focused on developing a way to bring all available data for many patients together in one place at one time. Thanks to generous support from the Rogers family and from the Peter and Melanie Munk Charitable Foundation, doctors at the Peter Munk Cardiac Centre have developed a Digital Cardiovascular Health Platform. This platform – a digital storage repository that holds a vast amount of data until needed – draws together more than 40 databases with information from thousands of patients across Ontario, in real time.

Some of those databases include the Ontario Laboratories Information System, which tracks patients' blood test results, the Canadian Institute for Health Information Database, which tracks patient outcomes, and data from the Peter Munk Cardiac Centre's own Cardiovascular Biobank, a physical repository containing more than 50,000 blood and tissue samples. After they provide consent, each new patient admitted to the centre will automatically have their data added to the data lake.

To ensure patient privacy, the digital platform was developed in consultation with the Privacy Office at University Health Network and the Information and Privacy Commissioner of Ontario.

"We think we're as secure as we can possibly be because we've integrated privacy considerations into the actual construction of the platform," Dr. Rubin says.

A TRIP INTO *THE MATRIX*

Dr. Heather Ross, cardiologist and Director of the Ted Rogers and Family Centre of Excellence in Heart Function and the Cardiac Transplant Program at the Peter Munk Cardiac Centre, led the development of the digital platform alongside her colleague Dr. Cedric Manlhiot, Director of the Cardiovascular Data Management Centre at the Ted Rogers Centre. Dr. Ross, who holds the Loretta A. Rogers Chair in Heart Function, says the first time data streamed into the lake was a real "wow" moment.

"It was like *The Matrix*," she recalls, referring to the futuristic 1999 sci-fi film. "All this information was coming in, but you had to know how to read it. That's when I knew [precision cardiac medicine] was possible."

Dr. Ross is involved in many of the Peter Munk Cardiac Centre's research projects, which aim to harness the power of artificial intelligence to "find patterns in the chaos," as she puts it. The centre has already partnered with one of Canada's AI leaders, the Vector Institute for Artificial Intelligence, a Toronto-based, independent, not-for-profit corporation dedicated to excellence in this area. The Peter Munk Cardiac Centre is planning to hire a team of AI specialists in-house, in collaboration with the Vector Institute.

The hope is that any physician or surgeon at the Peter Munk Cardiac Centre will be able to access the expertise of the AI group to investigate factors they think could make a difference in the efficacy of patient treatment.

PREDICTING THE BEST TREATMENT FOR EACH PATIENT

Genetics have played a prominent role in oncology in the quest for subpopulations, but Dr. Patrick Lawler, a cardiologist who leads the Molecular Epidemiology and Precision Medicine Group at the Peter Munk Cardiac Centre, says biomarkers may be better indicators in cardiology.

Biomarkers are measurable substances or characteristics in the body that may indicate disease, such as proteins or enzymes. For example, blood cholesterol is a well-known biomarker of risk for heart disease.

"I think everyone is interested in the concept of genetics, but there's a lot that happens between the genome and what we see it manifesting as [in the body]," Dr. Lawler says.

Using powerful computers, scientists can comb through thousands of biomarkers to see which ones may be associated with a disease.

"There might not be a single perfect marker, but a compilation of markers," says Dr. Slava Epelman, a clinician-scientist with the Peter Munk Cardiac Centre and the Loretta Rogers Chair in Immunobioengineering at the Ted Rogers Centre for Heart Research.

Once subpopulations of patients with these biomarkers have been identified, researchers could then conduct clinical trials to determine if particular treatments are more effective for particular groups, a technique known as predictive enrichment.

Machine learning could also be used to predict the success of that treatment for a particular patient. Machine learning is an application of AI that allows computers to learn and improve without being explicitly programmed.

The machine learning program would be fed patient, treatment and outcome data from previous cases, then it would build a predictive model to be used in new cases. Knowing the chances of success for specific sub-

sets of patients could help doctors decide which treatment option is best.

Alternatively, computer models could predict which patients are likely to be readmitted to hospital after their procedure, allowing physicians to step in early and prevent cardiac complications.

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> **Dr. Patrick Lawler,** cardiologist, Peter Munk Cardiac Centre

'A BIG PARADIGM CHANGE'

Perhaps the most fascinating aspect of the precision medicine approach is that it has the power to redefine diseases altogether. That is because instead of diseases being classified according to their symptoms, as they currently are, they could be classified according to the molecular pathways underlying them.

Dr. Lawler explains this is the cardiac equivalent of cancers being classified and treated not based on where in the body they occur (like bowels, skin or lungs), but by the genetic pathway driving them.

"The whole precision medicine initiative offers us an opportunity to look fresh at the way we've traditionally defined diseases," says Dr. Lawler. "It's a big paradigm change. It's rethinking a lot of things that are quite ingrained in how we do things."

Ultimately, the hope is that precision medicine will pave the way for the Peter Munk Cardiac Centre to create a learning health system – one that bridges the gap between research and practice. This learning system would automatically evolve as new data is fed into it, thereby providing doctors with the most up-to-date, effective treatments for their patients.

In this way, "patients truly become partners in their care, because they're helping us generate data that lets us improve their care," Dr. Rubin says.

But it is a stepwise process. Currently, there is enough data to begin to identify, or stratify, broad subpopulations, but not all patients pooled into the data lake have their genomic or blood work information available – at least not yet – limiting how precise the stratification can be.

Dr. Vivek Rao, head of the division of cardiovascular surgery at the Peter Munk Cardiac Centre and the Peter Munk Cardiac Centre Chair in Advanced Cardiac Therapeutics, says the way forward is to emphasize how astonishingly powerful the precision medicine approach is and ask patients to contribute their biological samples to help build the databases further.

"The more patients that we treat, the more data that we'll have, the more we can fine-tune the algorithms to appropriately treat the patients," he says.

Precision cardiac medicine is a goal that the Peter Munk Cardiac Centre's best and brightest believe in. After all, the field of oncology has seen marked changes in how cancer is understood and treated, and cardiology is catching up fast.

"The time it will take until that becomes a reality is rapidly shortening, thanks to the global collective work of many, including quite a few here," Dr. Lawler says. ■

THE BENEFITS OF PRECISION MEDICINE

Understanding the mechanisms of disease

Although cardiologists have a good understanding of how cardiac diseases or disorders manifest themselves and how to treat them, the genetic or molecular mechanisms underlying those diseases aren't as clearly understood. Having the ability to analyze large amounts of data using artificial intelligence is a step toward a better understanding.

DR. PHYLLIS BILLIA, cardiologist, Peter Munk Cardiac Centre Research Lead and Co-Director of the Peter Munk Cardiac Centre Cardiovascular Biobank, explains: "Disease modelling will [enable us] to develop a better understanding of pathogenesis, or what underlies the disease process. Until we have a better understanding of the heart disease process, we are unable to target the genetic problem."

Finding or developing the right treatments

Once cardiologists know the underlying cause of a disease, they are better able to target treatments to subpopulations based on their disease profile or lifestyle attributes.

DR. VIVEK RAO, head of the division of cardiovascular surgery at the Peter Munk Cardiac Centre and the Peter Munk Cardiac Centre Chair in Advanced Cardiac Therapeutics, hopes to use precision medicine to tailor blood-thinning medication doses for his patients after surgery. Those medications are given at a low dosage after surgery, and that dosage is gradually increased over time until the medication has the desired effect. But some people are sensitive to the medication and can have a bad reaction, while others are more resistant and it takes a long time to get to a dosage that works. Dr. Rao hopes to find the genes associated with sensitivity and resistance, so that his patients can get the right dose right away.

DR. THOMAS FORBES, division head of vascular surgery and the R. Fraser Elliott Chair in Vascular Surgery at UHN, wants to get to the point of predicting a patient's individual outcome following endovascular aneurysm repair. According to Dr. Forbes, the standard, quoted risk of complication following surgery is approximately 1.6 per cent, but this number fluctuates greatly between patients. "Just like not all patients [respond to Aspirin] because of their genome, not all patients respond to endovascular aneurysm repair," he says. Dr. Forbes also notes that some patients may be able to avoid surgery altogether if pharmacological treatments could be tailored to individuals based on their biology.

Predicting future cardiac events

Cardiac researchers from the Peter Munk Cardiac Centre have several studies underway investigating how they can use clinical data, proteomics (the characterization of proteins), biomarkers, the cardiopulmonary exercise test (CPET) or cardio-linguistics to predict which patients may be at risk of heart failure. The aim is to anticipate cardiac events before they happen, rather than just responding to them when they do.

In a paper due to be published later this year, Dr. Heather Ross and her team show how the use of artificial intelligence, more specifically called neural networks, allows them to more accurately predict heart failure risk. A neural network is a computer program that works like a human brain, enabling a computer to learn from observational data. For example, neural networks allow Peter Munk Cardiac Centre researchers to analyze all variables of CPET data with every breath the patient takes, giving them a more accurate picture of heart failure risk.

DR. DOUGLAS LEE, the Ted Rogers Chair in Heart Function Outcomes at the Peter Munk Cardiac Centre, is working to predict the chances of readmission to hospital following treatment by analyzing patients' perspectives in addition traditional medical and biological data. His team will utilize patient-reported outcomes and the language patients use during conversational exchange with their healthcare professional (called cardio-linguistics). Combined with other measures, such as new biomarkers and machine learning, this could be a better predictor than what's currently available. "Ultimately it's patients who decide they're going to come back to hospital," he explains. "If a patient is not feeling well at home, and we're able to identify that earlier using data collected and entered by the patient, then we're probably better able to anticipate that this person might end up in the hospital. That's a missing link that hasn't been there before."

Better risk assessment

DR. DINESH THAVENDIRANATHAN, cardiologist and Director of the Cardiotoxicity Prevention Program at the Ted Rogers Centre for Heart Research, says risk assessment is particularly important in his field, cardio-oncology, because they are in the unique situation of dealing with two competing problems – heart issues and cancer. Dr. Thavendiranathan believes precision medicine could play a major role in helping balance the two. "[We need] to make sure we're not undertreating our patients from a cancer perspective, and to make sure that we're not missing [an] opportunity to prevent cardiovascular disease in these patients."

DR. CAROLINA ALBA, cardiologist at the Peter Munk Cardiac Centre and scientist at Toronto General Hospital Research Institute, hopes to use the data platform to assess which patients are good candidates for advanced heart therapies, such as heart transplants or a mechanical heart. She also hopes to give family doctors the tools to identify high-risk patients, so they can refer them in a timely manner to a cardiologist. "Some patients are referred to us too late, or maybe not referred at all," she says. ■

MANY CLUES ON THE ROAD TO BETTER CARE

The Peter Munk Cardiac Centre's Digital Cardiovascular Health Platform will contain vast amounts of data from thousands of patients. Here are some of the types of data that will contribute to the precision medicine paradigm:

CARDIO-LINGUISTICS

How a patient talks about their health to their doctor could provide clues about whether they will be readmitted to hospital.

CLINICAL MEASURES

Measures like blood pressure, X-rays or heart ultrasounds are collected from the patient in the clinic. They can help doctors diagnose disorders and keep a record of how that disorder affects that individual.

PATIENT OUTCOMES

Patients who have experienced cardiac issues in the past are often asked to record their recovery after treatment. This allows cardiologists to determine how effective their treatment was.

GENOME SEQUENCING

Some diseases are caused by changes in how the body's building blocks, or DNA, are ordered. By working out the precise order of DNA in both healthy and sick patients, scientists can figure out if there is a particular gene causing a disease and diagnose patients by sequencing their genes.

BLOOD SAMPLES AND BIOMARKERS

Biomarkers are proteins or other molecules that are made by different biochemical processes in the body. Having abnormal levels of those molecules could indicate the presence of a disease, predict how a patient will respond to therapy or provide doctors information about prognosis.

CARDIOPULMONARY EXERCISE TEST (CPET)

CPET allows cardiologists to see how fit a patient is following heart failure and determine how they are recovering. Information, such as how much oxygen a person is taking in, is recorded with every breath while a patient runs on a treadmill or pedals a bike.