



The Terry Fox Research Institute's Ontario Dialogue: how will personalized medicine change health care?

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ABSTRACT

This is the final instalment in a series of three articles by the Terry Fox Research Institute about its pan-Canadian dialogue series, *Cancer: Let's Get Personal*, a public research and outreach project undertaken in 2010. The dialogues served to launch a national and continuing conversation on personalized medicine with the medical and scientific communities and the public, including cancer survivors, patients, and caregivers. Participants at the Ontario dialogue, held in Toronto, October 18, 2010, discussed the challenges that Canadians and the health care system face as they move forward on a pathway created by advanced science and technology that will phenomenally transform cancer care and treatment. The one-size-fits-all approach to treating cancer patients is being rapidly eclipsed by an approach that treats patients and their tumours as individually as possible. As a result, a paradigm shift is occurring both in the laboratory and in the clinic, creating new approaches to conducting research and delivering treatment and care that place each and every patient—and tumour—at the centre of treatment. New approaches and practices in health care are necessary to ensure successful uptake and implementation of these advances for the benefit of all Canadians.

Participating partners and supporters of the Ontario dialogue were the Ontario Institute for Cancer Research and the University Health Network.

KEY WORDS

Patient-centred care, personalized medicine, cancer, genomics, DNA sequencing, health system, clinical

trials, treatment, privacy, information, access, consent, cost effectiveness

1. INTRODUCTION

This meeting report is the third and final instalment in a series by the Terry Fox Research Institute (TFRI) about its pan-Canadian dialogue series, *Cancer: Let's Get Personal*, a public research and outreach project. The two previous dialogues were held on each of Canada's coasts. The inaugural discussion took place in Atlantic Canada (St. John's, Newfoundland and Labrador) in April 2010, and the second was held on the west coast, in Vancouver, British Columbia, May 12, 2010. The series was launched to encourage a conversation across the country about personalized medicine and how society and the health care system must prepare for it.

The final dialogue focused on four specific areas:

- What does personalized medicine mean?
- What is the patient perspective?
- What changes to health care will occur?
- What are the challenges to personalized medicine?

"We are told that the science and technology are here today to enable personalized medicine, but what does that actually mean, and are we ready for it?" asked Dr. Victor Ling, TFRI's president and scientific director, setting the stage for the evening's discussion.

Moderated by *CBC News: Morning* anchor Heather Hiscox (Figure 1), the Ontario discussion focused on the state and effectiveness of current approaches to treating cancer, the changes needed at the societal and health care system levels to move personalized medicine forward, the importance of evidence-based research to determine the most cost-effective and efficient ways to apply personalized medicine in a beneficial way for all, the need for balance in sharing and applying new information, and the importance of placing patients at the centre of their own care in a world in which technology and science are advancing with lightening speed. Considerable discussion



The Terry Fox Research Institute
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FIGURE 1 Left to right: Dr. Amit Oza, Mrs. Debra Gordon, Dr. Elizabeth Eisenhauer, Dr. Craig Earle, and moderator Heather Hiscox (at podium).

centred on inefficiencies and gaps in drug development to date and on the current trend in clinical trial design to tailor therapeutic treatment to individuals and their tumours.

2. DISCUSSION

2.1 Taking Aim with Smarter, Sharp-Shooting Drugs

Dialogue co-chair Dr. Robert Rottapel, who heads the Ontario Institute for Cancer Research—TFRI Selective Therapies Program, a \$23-million research program funded in Ontario to identify and develop new drug targets for cancer, explained the advances to date in cancer research and in the work of his team. “Essentially, we are searching for the Achilles heel of cancer. In order to find the susceptibilities that are idiosyncratic to cancer, we require new tools, new engineering, new mathematics, new computers, and new chemistry that are integrated in a common effort. Not long ago, it would typically take weeks to complete a single experiment. Now, we can literally do hundreds of thousands of experiments within just a couple of weeks.”

Today, cancer is viewed as a diverse set of diseases, and this diversity is starting to be understood with high resolution at a genetic level. These insights will enable researchers and clinicians to match unique cancer variants with specific therapeutics or with combinations of therapies in a much more effective manner. The hope is that an answer will soon be found for the question “Which cancer patient, with which type of tumour, should be treated with which therapy?”

How has today’s situation—shifting the strategy of cancer investigation and treatment from a one-size-fits-all approach to that of identifying and treating cancer in a manner that is as individual as the patient—come to be? The traditional application of a standard of care and treatment for tumours (be it chemotherapy, radiation, or surgery—or a combination thereof) and for the people having those tumours will be no more in this brave new world.

The approach is now about providing specific drugs to individual patients—in fact, the best drug to the best patient, as determined by the molecular make-up of the patient’s individual tumour.

Clinical trialist and staff physician at the Princess Margaret Hospital Dr. Lillian Siu, who specializes in new anticancer drug development, described the evolution of drugs to target specific cancers, explaining that a greater understanding of cancer cells and the molecules within them has, during the last 10 years, set us on a path for the development and creation of molecularly targeted drugs: “Today we have all kinds of new gadgets and tricks to try [to] fool the cancer.”

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Personalized medicine means different things to different people. To scientists, it means genes and proteins. For oncologists, it is about how to give the best drug to the patient so [that] they can benefit from it. To the patient, it is about the drug with the least toxicity, but which gives the best benefit. Funders can use it to save money[, directing] treatments cost-effectively.

— Dr. Lillian Siu

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In an era of personalized medicine, we want to be even smarter in how those cancer tools are deployed, said Siu. “How do we use these molecularly targeted drugs intelligently and in a more personalized approach and, hopefully, ... we’ll see even more progress to try to eradicate this deadly illness.”

Personalized medicine means different things to different stakeholders, she advised, but the bottom line is that it is the next step that must be taken. “Drugs are expensive. It’s really about how to match our patients to the best drug. It is a balance, a therapeutic balance, [meant to obtain] the biggest bang for the least buck in terms of money, efficacy, and toxicity,” she said in explanation of the shifting paradigm driving cancer research and care today.

Every drug should be personalized and should be given only to those who benefit, said Siu. “That should be our charge. We are trying to get the best out of our drugs. So people who won’t benefit won’t be given the toxic drugs [that] they don’t need, and those who will benefit will get these drugs. And, hopefully, it will be cost-effective, because you are channelling the right things to the right people.”

Progress has been made, she explained, but much more work remains to be done to develop drugs that effectively treat cancer. Cancer has many drivers—the “patriarch” of the family who makes decisions and calls the shots—and many bystanders. Blocking the drivers may produce a response; on the other hand, blocking the bystanders (changes in the cancer that probably don’t play a critical role) will not produce much benefit. “The goal then, is to identify the drivers

versus the bystanders.” Siu pointed to successes in finding drivers in some cancers, such as chronic myelogenous leukemia, in which the drug Gleevec (Novartis Pharmaceuticals, St. Louis, MO, U.S.A.) blocks the driver called Abl. Also, many interesting drugs are now in development for solid cancers such as melanoma and kidney cancer; they are examples of how, as cancer becomes better understood, the process of drug development also improves. But there is still a long way to go in developing effective therapies for individuals and their specific tumours. “Of the last 20 molecular drugs approved by the [U.S. Food and Drug Administration] in the last decade, fewer than one half are what we call personalized; we should strive to do better than this in the next decade to come.”

2.2 Patients as Individuals First

A nurse and a patient, Mrs. Debra Gordon has been on both sides of the health care system. Diagnosed with ovarian cancer 2 years ago, she provided an informed and insightful look at life for cancer patients undergoing treatment and at the need for more effective and tailored treatments that are specific to an individual's cancer. She underwent surgery and the “gold standard” chemotherapy for her disease, which initially resulted in shrinkage of the tumour. But the cancer recurred, and to avoid repeating the standard treatment (which had brought hair loss, nausea, fatigue, and suffering) for a second time, she enrolled in two clinical trials. The first was successful for about 6 months; the second was stopped after an evaluative cycle. “I want you to know [that it's] very stressful ... and very worrisome to me and for my family [to learn] that the disease was progressing, and [that] the therapy was not working as expected.” In her view, personalized medicine would strive beyond the “one size fits all” adage. It would avoid unnecessary side effects in sick people who are suffering and would avoid losing precious time in their fight against their disease.

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As a patient, personalized medicine means that personalized therapy options can be chosen based on medicine and not instinct. It means personalized medicine would help treat chronic disease, guide physicians with predictive and preventive forms of personalized medicine, help the physician make the most effective decisions for each patient on an individual level. It would help with dosing for patients, [and] avoid oversights based on familial, historic, and environmental influences and genetic variations.

— Mrs. Debra Gordon

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Knowledge enables patients to make informed decisions, and while some who learn of an illness find it unsettling and may want to avoid the reality of the

disease, others find it helpful to have information to support a proactive approach to treatment. In addition to the value that comes from having knowledge at one's fingertips, Gordon said that “it is exciting to fathom the possibility that high-risk individuals could be identified and their treatment targeted and geared toward specific disease vulnerabilities—for example, chemotherapy based on tumour gene-expression profiles. Evidence-based results are needed. Research funding and ideas are integral to continue this movement, because personalized medicine could help control disease and reduce excessive costs by changing how we diagnose and treat common, acute, and chronic disease.”

2.3 Shifting Focus in Research and Drug Design and Treatment

What will health care look like when the promise of personalized medicine is realized?

Dr. Craig Earle is a medical oncologist with the Odette Cancer Centre at Sunnybrook Health Sciences Centre in Toronto, Ontario, and director of health services research for both Cancer Care Ontario and the Ontario Institute for Cancer Research. He used the example of a patient diagnosed with pancreatic cancer to present the blunt and stark reality about how modest treatments are today, despite all the clinical trials and investment. The patient was shocked to learn there are only about three drugs for pancreatic cancer, and at best, they extend life only for a few months. “So why do we have so little to offer?” asked Earle.

“Part of it is the approach we've taken up until now in research and drug development. We have a one-size-fits-all approach to doing research. We have traditionally done studies to find those drugs that will have an effect on the largest proportion of patients. So, typically, if a drug doesn't cause cancer shrinkage in 15% or more of the patients, we throw it away. Now, 15% seems low, but even in a blockbuster drug it would work in only half the patients, leaving the other half with it not working.”

Additionally, treatment approaches have been largely trial and error, commencing with the drug that works in the most patients. If that drug doesn't work, research moves on to the next one, and so on, until, hopefully, something is found that will help the particular patient. “Until now, if we had a drug ‘X,’ and it caused shrinkage in only about 5% of patients, we would have discarded it as not working in enough patients to be worth pursuing. But the switch that's coming is we are starting to look at this and say, ‘What is it about that 5% that made that drug work?’” The new approach, he said, tries to gain an understanding about each patient and each patient's tumour.

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As everyone is different, so too are their tumours different.... If we had 1000 drugs, and they worked

in a few percent of people, and we really understood and could predict it, we would probably have something that could work for everybody. Unfortunately, not only do we not only not really understand the tumours, but for a lot of the drugs, we don't really understand how they work.

— Dr. Craig Earle

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Dr. Elizabeth Eisenhauer, who chairs the research advisory group for the Canadian Partnership Against Cancer and co-chairs the Canadian Cancer Research Alliance, provided constructs of two areas of challenge today for personalized medicine. The first concerns adaptation within the clinical research paradigm to identify new therapies in an intelligent fashion in parallel with the development of diagnostic tests for biomarkers. The second relates to how the system of health care delivery will need to position itself to respond to the era—the one that we are actually in now, she said. As director of the Investigational New Drug Program of the National Cancer Institute of Canada Clinical Trials Group, Eisenhauer explained that the challenge of current drug development programs is really in answering one question: Does this drug work?

“What we need to actually shift to is a process that is simultaneously asking the question: Does this drug work, *and* who does it work best in? So this means we need a different approach to our clinical trial design. It means that every patient on a trial of novel therapies needs to have tumour samples made available to study—and that is a huge challenge. We need to collaborate with willing scientists who have set up robust and validated assays to actually test these tumour samples, and that is also a very big challenge.” Further, she said that more thinking must be done about where the results of the research will eventually go. “There is no point in designing trials of what we know will be expensive therapies associated with expensive testing and completely ignoring data gathering that will provide the health economic cost–benefit arguments and details that we will need to make the case for having these treatments available through the public system.”

Eisenhauer warned that clinical research in the future will likely be more complex and more expensive and will raise new kinds of ethical issues.

2.4 System and Societal Challenges of a Paradigm Shift

Eisenhauer predicted that, within the health system, there will be an even greater series of challenges, and among the questions to be faced are these:

- How will society handle all the possible information that could be available about patients and the genetic makeup of tumours?

- How do we actually connect the dots to the information that matters in decision-making?
- How does society make decisions about the level of gain that is needed (in terms of survival) in cancer outcomes?
- What degree of gain is worth what cost to the health system?
- What about the quality of molecular testing and diagnostics?

“This is a conversation that we shouldn’t be having only in this room[, or] in this province. This is a Canada-wide, systems-wide series of conversations,” she said. Importantly, Dr. Eisenhauer discussed some of the obvious answers to some of the questions posed. For example, “a test that costs a thousand dollars to tell you which patients require a drug that costs tens of thousands of dollars and has only a trivial [effect] on their outcome and survival, is not the direction in which we need to be going. Also, it is not useful at all to have tons of relevant information stored in digitized systems that practitioners either don’t know is there or don’t know how [to use].”

She offered five potential solutions to help address the challenges:

- Development of an intelligent electronic record system to “make decisions easily available to the right practitioners at the right time so that the right patient gets the right treatment.”
- Creation of a system of national reference laboratories to conduct highly technical diagnostic and biomarker assays to ensure efficiency and quality.
- Development of “participatory science” to prepare for, and respond to, the coming change. “We can’t continue to be reactive on a case-by-case basis. We need to have transparent and principled decision-making about how we’re going to make the choices involving scientists, medical experts, health economists, patients, public policymakers, ethicists, to agree on these principles and to engage the public in an understanding of what gains and costs we are prepared to balance against each other,” she said.
- Exploration of innovative approaches to practitioner adoption of knowledge—a big gap that she believes is looming and that she cautions should not be left to the charge of the pharmaceutical industry.
- Acknowledgment by the health care system that it has a role in innovation and education. “It isn’t just about *adoption* of new technologies; it’s about *evaluating* whether in the real world they have the effect we think they should. Because if they don’t, why do we keep [using] them?”

Moderator Heather Hiscox opened the floor to audience questions and conversation, remarking that the speakers’ comments helped to open eyes to the

scope of the change offered today by technology and knowledge. “This is going to bring about a fundamental shift in health care and how medicine is practiced, and improve, ideally, cancer care for individuals.”

“How will clinical trials work in the future?” and “What is the incentive for a drug company to come up with new drugs in the era of personalized medicine?” she asked.

Today, there are two routes along the path to personalized medicine and drug development and treatment: The first is the more traditional approach, in which the agent is studied in the entire population, and the data gathered is used to understand which population subsets experience benefit. The second is to develop a drug that particularly affects a mutated or altered molecular target, and then to enrol only patients with that particular alteration in a trial. Both approaches involve risks. The risk in the first approach is the possibility of missing activity because the sensitive subgroup is too small; the risk in the second route is the possibility of misidentifying the population that will benefit and excluding them from the study.

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The idea of the blockbuster cancer drug ... is starting to fade away, and more of the big pharma and biotech companies are embracing an approach to drug discovery and development that is actually looking ... more personalized.

— Dr. Elizabeth Eisenhauer

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Still, patients may have to explore options on their own and to look beyond the borders of their country to find a personalized approach that works for them, said Debra Gordon and other cancer survivors in the room.

One of the most complex challenges to be faced in the future is the explosion in the amount of information that will be available and the regulations surrounding use of and access to that information by a variety of stakeholders—from the patients and doctors themselves (making informed decisions about their care), to the pathologists and the basic scientists who require access to tumour and tissue samples to move laboratory and clinical trials forward effectively. Compelling ethical and legal issues are involved, as are the questions surrounding access by patients to a new range of information (knowing what their genetic markers look like, for example). The health care system is not equipped to manage this explosion of knowledge at many fundamental levels. Health teams will need to integrate this information at the level of routine health checks, diagnosis, and follow-up supervision, remarked Dr. Christopher Paige, dialogue co-chair and Vice-President, Research, for the University Health Network.

The information currently available is mostly unregulated, good and bad information being equally

circulated, remarked Mrs. Gordon’s oncologist, Dr. Amit Oza, senior staff physician and professor of medicine at Princess Margaret Hospital, University of Toronto. “The difficulty is in trying to actually look at the information [that] patients are able to access, and look at it meaningfully. Does this [information] accurately represent new treatment options and opportunities? Or is information potentially misleading and could [it], in fact, be detrimental? When studies are done without clinical-trial rigor, it becomes very difficult to analyze and validate that information and [to] advise the patient.”

Asked Mrs. Abigail Carter–Langford, corporate privacy officer for the University Health Network, where does a patient portal and a patient’s access to their full chart to engage more fully in the conversation come in?

She advised that one school of thought regarding patient access to information is that such access should come after the fact as a record of the care that was provided. The other is that access should be provided with the goal of enabling the patient to be an informed decision-maker at the time of care and with the support necessary to understand and contextualize the information. “What I tend to hear more about in my practice is the fear and distress from [patients] that comes from not having that information. I don’t hear concerns from patients about being too informed and having the opportunity to dialogue with the clinician,” Carter–Langford said. Currently, the health care system is not set up to give patients and clinicians the time required for these discussions.

2.5 What Are Patients Consenting To?

Another key issue involves how patient information and tissue or tumour samples are accessed and used—at the individual and the system level. What do people actually consent to concerning personal information?

For example, what if an individual’s entire genome were to be sequenced, and the result were to reveal a number of things about that person unrelated to the cancer but potentially influential in their life or that of their children? Medical and radiation oncologist, and TFRI senior advisor, Dr. Simon Sutcliffe posed further questions: Did you consent to having that information uncovered? Who can access that information? Who can share that information? Do you consent for that information to be meaningfully used by the health care system?

As personal medicine is embraced, these and other crucial questions must not only be asked, but addressed and resolved.

2.6 Who Will Have Access to Personalized Medicine?

Access to personalized medicine is a double-edged sword, said Earle. “There are a lot of great things

that we're able to do, but if they're not managed appropriately, it could potentially be the recipe for bankrupting the health care system."

The solution lies in finding a transparent way to decide the value for each of these technologies, whether they be tests or treatments, and how to incorporate them into the health care system, whether universally (publicly) or privately funded, and so on, said Earle and Eisenhauer.

3. THE WAY OF THE FUTURE

The consensus in the audience attending the Ontario dialogue (as well as the other two dialogues) is that personalized medicine is a path that society wants and needs to explore. But, in moving forward, preparations have to be ramped up. The challenges are complex, and they must be addressed. Solutions must involve the participation of civil society, and the public must be neither complacent nor ignorant of the options. Many audience members underlined that, to help make informed decisions, Canadians need to look to their values and to what they value in the health care system and in society.

Dialogue co-chair Christopher Paige summarized the ideas this way: "From everything we heard here tonight, it is feasible, it's here, and in some cases,

it works.... The big issue is how extensive and how quickly we can grow it, and amongst all the rubble of information that's going to be collected, how can we find the gems that will really make the difference?"

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To view the complete remarks of the participants in the Ontario dialogue, please visit www.tfri.ca/dialogues.

4. CONFLICT OF INTEREST DISCLOSURES

SS chairs a strategic advisory panel for the Centre of Excellence in Personalized Medicine, a federal- and industry-partnered initiative, for which he receives honoraria. KC and CJP have no financial conflicts of interest.

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