PIP Digest

Canadian Cancer Research Alliance
Alliance canadienne pour la recherche sur le cancer

Patient Involvement in Cancer Research Program
Programme de Participation des Patients à la recherche sur le cancer

CLINICAL TRIALS: Precision Medicine and Clinical Trials

This PIP Digest will help you understand what "precision medicine" is and how it is changing clinical trials.

Key concepts

- Definition of precision medicine
- How clinical trial design is affected by precision medicine
- Canadian initiatives in precision medicine

Related PIP Digests

- Cancer Research: What is a Clinical Trial?
- Cancer Research: Big Data and Precision Medicine

What is Precision Medicine?

"We are living in perhaps one of the most profound periods of advancement in biology and medicine, leading to a medical revolution that will contribute to precision medicine and transform health and medicine…It can be envisaged that the main focus in healthcare will progressively shift—in a safe, efficient and cost-effective manner—from treating disease to managing health."[1]

"Learn from every individual, apply to every individual, earlier and earlier, in real-time."[2]

Precision medicine, also known as personalized, predictive, preventive, and participatory (P4) medicine,[3] is a patient-centred, system-wide approach to preventative and treatment-focused health care. It draws on an individual's unique molecular data, genome, lifestyle, and environment to provide the right treatment to the right person at the right time. It departs from symptom-based approaches, and in the case of cancer, from site-specific medical management.

Precision medicine emerged from converging technological and social developments. Technological advances have enabled medical professionals to capture "omics" data more quickly (see table on the following page) and at increasingly lower costs. Innovations in information sciences like new methodologies, deep learning algorithms, and cloud computing — make it faster to collect, analyze, and act on "omics" data. Technology has also enabled comprehensive electronic health records, which can document all interactions with the health system over a lifetime.

[1]Beckman JS & Lew D. (2016). Reconciling evidence-based medicine and precision medicine in the era of big data: challenges and opportunities. *Genome Medicine*, 8(134). DOI 10.1186/s13073-016-0388-7
[2]Butte, AJ. (2016). It takes a genome to understand a village: Population scale precision medicine. PNAS, 113(44):12344-6.
[3]Hood L & Friend SH. (2011). Predictive, personalized, preventive, participatory (p4) cancer medicine. *Nature Reviews Clinical Oncology*, 8:184-7.

Progress in artificial intelligence has reduced cost barriers and increased analytic capacity, making it possible to deliver customized interventions to a broader swath of the population.

On the social front, connected technologies, social media, and electronic devices have empowered patients and non-patients alike. People not only interact with and support others afflicted with similar diseases across the geographic borders, but they also expect to play a more active role in managing their own health and contributing to the health research process.

Precision medicine already empowers earlier detection, more precise diagnosis, effective, targeted treatments, and greater patient empowerment. Longer-term, it offers hope that individuals at high risk will have effective options to thwart cancer before it develops.

MULTI-OMICS
In terms of human health, multi-omics (also known as integrative omics) is a field of study that integrates different types of molecular information such as:

Genomics: Study of the structure, function, and expression of our genes. Genomics focuses on identifying genetic variations associated with disease, response to treatment, and patient prognosis.

Epigenomics: Study of epigenetic changes - processes that regulate how and when certain genes are turned on and turned off.

Transcriptomics: Study of all the RNA molecules within our cells, known as the transcriptome. These studies focus on messenger (m)RNA molecules, genes that are being actively expressed as protein products at a given time or situation as well as non-coding RNAs, the RNAs in a cell that are not translated into a protein.

Proteomics: Study of proteins within our cells, including their structure and function.

Metabolomics: Study of metabolites, those small molecules made when the body breaks down food, drugs, chemicals, or its own tissue.
Microbiomics: Study of the genetic material of the microbes - bacteria, fungi, protozoa, and viruses - that live on and inside us. The human microbiome is enormously complex.
Phenomics: Study of an individual's physical and biochemical traits (phenotypes) produced over the course of development and in response to genetic mutations and environmental influences.

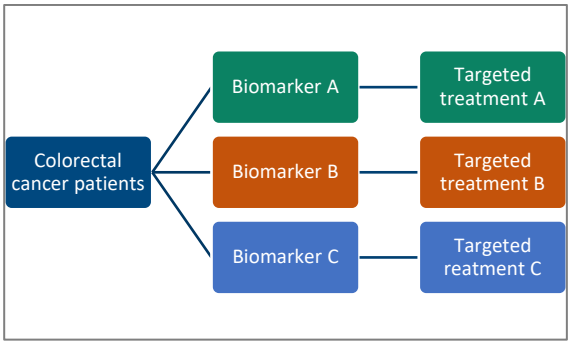
Precision Medicine and Clinical Trial Design

Precision medicine requires new approaches to designing clinical trials and, new ways to analyze trial results. In a traditional clinical trial, people with cancers that meet specific eligibility criteria receive randomly assigned new treatments or standards of care. Precision medicine trials, though, evolve to match the cancer patient's molecular profile.

A **master protocol** is a broad term for a trial that evaluates simultaneous sub-studies with multiple hypotheses. Each sub-study has its own protocols. Patient eligibility is often related to specific tumor types, histologic types, and/or molecular markers. Master protocols include platform (adaptive) trials, umbrella trials, and basket trials.

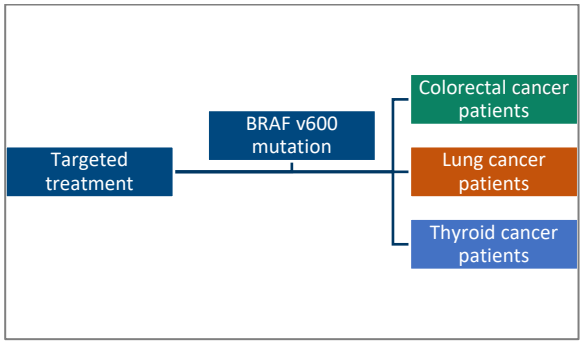
A **platform or adaptive trial** design uses data accumulated during one stage of the trial to modify the approach for subsequent stages. Adaptations proceed according to predetermined schedule and process to ensure the trial retains scientific validity. It gives researchers flexibility as the trial progresses to identify the best clinical intervention to provide the best treatment to new trial recruits. Adaptations may include increasing or reducing drug dosages, changing sample sizes, modifying patient selection criteria, stopping a toxic intervention, or adjusting the mix of interventions.

Umbrella trials test how well new drugs or other interventions work in patients who have the same type of cancer but different gene mutations or biomarkers. Patients receive treatments based on the specific mutation or biomarker found in their cancer. Umbrella trials can allow new drugs to be tested and approved more quickly than traditional clinical trials.



Example of an umbrella trial design

Basket trials (also called bucket trials) test how well a new drug or other intervention works in patients who have different types of cancer but the same mutation or biomarker. The treatment targets the specific mutation or biomarker found in their cancer. Like umbrella trials, basket trials may accelerate testing and approval phases for new drugs and may be useful for studying cancers with rare genetic changes.



Example of a basket trial design

Why is the collection of biospecimens important?

Biospecimen collection is increasingly important in the era of personalized medicine. The analysis of cancerous tissue helps researchers better understand the effects of the treatment as well as the molecular processes involved in drug

response or drug resistance. For adaptive trials, collecting and analyzing biospecimens is critical as it may inform trial modifications required to optimize clinical intervention. Analysis of biospecimens also helps generate hypotheses for subsequent research.

Because the collection of cancerous tissue can be impractical, invasive, risky, or painful for patients, a big focus of biomarker research activity is on liquid biopsies. A **liquid biopsy** involves the analysis of biological fluids for biomarkers of disease, such as circulating tumour cells, circulating tumour DNA, RNA, and exosomes. New technologies that can detect smaller and smaller amounts of substances and cells make it increasingly effective to test blood, urine, saliva, sputum, stool, pleural fluid, or cerebrospinal fluid. Liquid biopsies have the potential to revolutionize cancer research and cancer care, although their use in clinical settings is still years away.

Implementing Precision Cancer Care in Canada

Terry Fox Research Institute's Marathon of Hope Cancer Centres Network

The vision of the Terry Fox Research Institute's Marathon of Hope Cancer Centres Network is "to create a pan-Canadian platform for personalized and precision cancer medicine by linking high performing 'Comprehensive Cancer Centres' together across Canada to move innovations in cancer research to the front-lines of cancer control by piloting innovations while embedded in the health system to benefit patients in the real world and by leveraging existing research and innovation capabilities to be more effective and efficient, and building on Big Data breakthroughs."[4]

Linking cancer centres into a Network that shares molecular, imaging, clinical and outcome information on cancer cases will help position Canada as a leader in precision medicine and will accelerate improvements in health outcomes for cancer patients. A key Network deliverable is the creation of a sharable dataset of 15,000 cancer cases, which includes genomic, imaging, clinical and outcome data, by 2023.

In the spring of 2019, TFRI was awarded $150M by the Federal government for the Network. An additional $49M was awarded to TFRI and Imagia, a Montréal-based company, for the creation of a Digital Health and Discovery Platform that will enable the Network to share the data it creates and leverage new disruptive technologies like artificial intelligence. For more information, see https://www.marathonofhopecancercentres.ca/.

[4]Dr. Victor Ling, presentation to the CCRA Board of Directors, October 21, 2016.

Exactis

EXACTIS

Exactis is a pan-Canadian network funded by the federal government and various partners to provide accelerated access to clinical trials for precision cancer therapies to patients who have their cancer molecularly profiled with its unique digital cancer registry called Personalize My Treatment (PMT). With PMT, Exactis facilitates recruitment and matching of patients to precision oncology clinical trials and provides expertise in the development and management of biomarker-driven trials. See https://www.exactis.ca/.

Precision Medicine Policy Network

Precision Medicine Policy Network
Shaping the application of genomics to health care

Initiated in 2016, the Precision Medicine Policy Network is composed of research leaders from the 17 Genomics and Personalized Health Large Scale Applied Research Projects funded by Genome Canada and its provincial partners. It focuses on accelerating the translation of genomics research and technologies into practical healthcare applications for patients by providing best-practice guides, training programs, policy briefing documents, and implementation templates/tools in four high priority areas: research ethics review; health economics and health technology assessment; knowledge transfer and implementation in health systems; and intellectual property and commercialization. For more information, see http://precisionmedicinepolicynetwork.org/.

View these videos to expand your knowledge of precision medicine:

- UC San Francisco (UCSF). *Precision Medicine* (YouTube) December 2, 2015 [1:49 minutes] https://www.youtube.com/watch?v=HQKFgfMO5Sw
- The Economist. *Personalised medicine could lead to a breakthrough in cancer in 2017* (YouTube) December 7, 2017 [2:41 minutes] https://www.youtube.com/watch?v=JGk2k1mWMk8
- BC Cancer has been a leader in precision medicine. This *Nature of Things* program is about the BC Cancer's Personalized Onco-Genomics (POG) program, a clinical research initiative that has genomic sequencing embedded into the diagnostic and treatment planning for patients with incurable cancers. *Cracking Cancer* - The Nature of Things with David Suzuki, June 19, 2017 [44:08 minutes] https://www.youtube.com/watch?v=7apqs6_dlhA
- If you are interested in more information on "omics," a very good eight-part series is provided by NASA. You can access all parts at: https://www.youtube.com/watch?v=m7X6mugpijQ&list=PLiuUQ9asub3TReMNgv6kDFwNsRuCWAVcw *Omics: Exploring Space Through You.* Each part is about 4 minutes in length and the videos were published from April to August in 2016.

Reviewer: Craig Earle, MD
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