Getting Better, Faster:

The Case for Optimizing access to Precision Medicines in the Wake of the Revolution in Cancer Care

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CONECTed

Collective Oncology Network for Exchange, Cancer Care Innovation, Treatment Access and Education

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Contents

Revolution: Upheaval, cataclysm, transformation, (drastic or radical or major) change, sea change, metamorphosis

Oxford Thesaurus (meaning 2)

"A new era of personalised cancer medicine will touch every aspect of cancer care—from patient counselling, to cancer diagnosis, tumour classification, treatment and outcome—that demands a new level of in-depth education and collaboration between researchers, cancer specialists, patients and other stakeholders."

Delivering Precision Medicine in Oncology Today and in Future—The Promise and Challenges of Personalised Cancer Medicine: a position paper by the European Society for Medical Oncology (ESMO)

Abbreviations

ACT	Adoptive Cell Transfer
ALK	Anaplastic Lymphoma Kinase
AML	Acute Myeloid Leukemia
ASCT	Autologous Stem Cell Transplant
ASIR	Age-Standardized Incidence Rates
BCG	Bacillus Calmette-Guerin
CADTH	Canadian Agency for Drugs and Technologies in Health
CAPCA	Canadian Association of Provincial Cancer Agencies
CAR	Chimeric Antigen Receptor
CDIAC	Cancer Drug Implementation Advisory Committee
CGP	Clinical Guidance Panel
CI	Confidence Interval
CML	Chronic Myeloid Leukaemia
CPAC	Canadian Partnership Against Cancer
CPTP	Canadian Partnership for Tomorrow Project
CRISPR	Clusters of regularly interspaced short palindromic repeats
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
dMMR	Mismatch Repair deficient
DNA	Deoxyribonucleic acid
DR	Distant recurrence risk
ESMO	European Society for Medical Oncology
FLT3 ITD	FLT3 Internal Tandem Duplication
GO–CART	Getting better Outcomes with Chimeric Antigen Receptor T-cell therapy
HL	Hodgkin's Lymphoma
HR	Hazard Ratio
HSCT	Hematopoietic Stem Cell Transplant
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IDH	Isocitrate dehydrogenase
INESSS	Institut National d'Excellence en Santé et en Services Sociaux
MEA	Managed Entry Agreements
MEK	Mitogen-activated protein kinase
MIPC	Median International Price Comparison
MSI-H	Microsatellite Instability-High
NICE	National Institute for Health and Care Excellence
NIHB	Non-Insured Health Benefits Program
NOC	Notice of Compliance
NOC/c	Notice of Compliance with Conditions
NTRK	Neurotrophic Receptor Kinase
OR	Odds Ratio
OS	Overall Survival
PAG	Provincial Advisory Group

pCODR	pan-Canadian Oncology Drug Review
pCPA	pan-Canadian Pharmaceutical Alliance
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
pERC	pCODR Expert Review Committee
PFS	Progression-Free Survival
PMPRB	Patented Medicine Prices Review Board
RWE	Real-World Evidence
TCGA	The Cancer Genome Atlas
WM	Waldenström's Macroglobulinemia
WT1	Wilms Tumor 1

Executive Summary

Cancer is the leading cause of death in Canada today and the number of people diagnosed each year continues to increase. Thankfully, a wave of new, more effective and better tolerated treatment options is starting to achieve significant advances in survival rates for many tumour types. Fuelled by the personalised medicine revolution, precision oncology uses companion diagnostics to characterise a patient's tumour profile so that targeted therapies may be used that are directed against the specific characteristics of that tumour. This revolution in precision oncology marks a major advance from the days of 'cut, burn and chemo'.

Cancer is a complex disease and the field of precision oncology is still in its infancy. Many tumour types still have no targeted treatment option, and seemingly inexplicable inconsistencies in response to targeted therapy between different tumour types typify the challenges ahead. What is clear from the successes to date in the field of precision oncology is that these hurdles represent opportunities. As our knowledge of oncogenesis and metastasis expands, new opportunities arise for the development of targeted therapies and the companion diagnostics needed to ensure they are used only in those patients they will benefit.

In some ways, Canada is well-placed to be at the vanguard of this revolution: Canada is home to some of the top cancer research institutes in the world. Unfortunately, our ability to capitalise on our academic prowess is hampered by an antiquated philosophy regarding the evaluation and regulatory approval of experimental treatments, a fragmented approach to healthcare delivery across the provinces and territories, and a resistance from payers to appreciate the intersection of innovation, futility, value and cost.

The COVID -19 pandemic exposed the gaps in our healthcare delivery systems and the desperate need we have for a pan-Canadian data management system. Steps are being taken to fill the data gaps, to align provincial data gathering and collection, and to develop ways to share data across systems. The federal Canadian Institute for Health Information (CIHI) has been mandated by the federal government to lead its efforts in this area. This will be very important to achieve these goals so we can access the cancer drugs that we need.

There is beginning to be a recognition of the need for a process to collect and share relevant real-world evidence. Government agencies including Health Canada, the Canadian Agency for Drugs and Technologies in Health have begun collaboration to tackle this important but complex area.

It is also heartening to see that provinces have updated their cancer strategies post-pandemic and those without formal strategies are now working toward putting them in place. Additionally, we see signs of regional collaborations such as the creation of the **Atlantic Clinical Trials Network**, which effectively increases the population of patient partners from One Million in Nova Scotia to approximately 2.5 million across Atlantic Canada. This will benefit cancer research greatly.

While these positive changes are occurring, there is still reliance on numerous regulations and processes designed for yesterday's health system that create barriers to accessing treatments that can transform the lives of Canadians living with cancer, and these patients do not have the luxury of time for governments and private health insurance companies to find a solution.

This document presents the opportunities created by the precision oncology revolution; outlines the current approval and reimbursement processes and the challenges therein, and presents a business case for a new approach to ensure people living in Canada have timely access to treatments that can transform their cancer experience, and can do so in a manner aligned with the five main principles in the *Canada Health Act*: public administration, comprehensiveness, universality, portability and accessibility.

Recommendations Summary

1. **Streamline clinical trial approvals** – Health Canada must streamline these processes so all redundant and/or unnecessary steps are removed.
2. **NOC/c** – This should be the standard approach to drug approval used by Health Canada for oncology drugs.
3. **Demand Phase IV trials** – Health Canada must make it a condition of approval for sale that manufacturers follow patients in trials after the Phase II or Phase III approvals throughout the life cycle of use.
4. **Compassionate access through manufacturers**- CADTH must make it a condition of approval of a drug trial in oncology that a certain number of compassionate access spots are allocated to patients who do not meet the eligibility criteria for the trial.
5. **Review of diagnostic tests companion** – These require integration with oncology treatments into the relevant drug/biologics health systems reviews rather than being treated as a separate approval managing through a separate silo.
6. **Pathologists**- Adequate and appropriately specialized pathology support must be resourced to ensure appropriate diagnosis and treatment in the era of precision medicine and personalized treatments.
7. **Phase II trial approvals**- CADTH and INESSS should accept applications with Phase II data and should provide conditional recommendation for approval where preliminary safety and efficacy data support this decision, subject to a satisfactory pricing agreement being concluded. The benefits, harms and uncertainty for life threatening and serious, chronic conditions are far different than for other patient populations. These must be developed with patient groups and used rather than the standard QALY measurements.
8. **CDIAC activities at CADTH**- CADTH must work with patient groups and all other relevant stakeholders to ensure transparency of this process as well as a full consultation on the algorithms to be used for the process. Meaningful patient engagement is required at all decision-making levels.
9. **A Rare Disease Strategy** – In 2019 Health Canada announced their commitment to developing a detailed national strategy and distinct pathway for funding and access to expensive drugs for rare diseases. The strategy was supposed to be implemented by 2022.
10. **pCPA negotiations**- pCPA, now a separate incorporated agency, must work with CADTH and other relevant stakeholders to further develop a negotiation process that involves risk sharing, pay for performance, managed entry agreements and other conditions that will ensure an appropriate recognition of the ethical issues of withholding effective drugs from patients as well as the need for cost sharing and re-negotiation following reasonable periods of time throughout the life cycle of the

drug/biologic. While negotiations are taking place, pCPA and the manufacturer must develop a process to ensure cost sharing so that patients obtain treatments during the period of negotiations.

11. **Reinvestment of savings back into the drug budget** – Savings from cost containment measures including the oncology biosimilars and generic drug reimbursement strategies should be reinvested into the oncology drug budget.
12. **Real world evidence (RWE)** – All stakeholders gathering real world evidence must be convened by federal/provincial governments with the partnership of patient groups to develop a common strategy for defining RWE, for determining a patient led process for determining what RWE to gather, for determining how to link RWE sites, and for determining resources required as well as any other tactics required.
13. **Private payer engagement** – Private payers should develop their own price negotiations strategy and methods based on their business model, independent of the public pCPA model.
14. **Value based health care** – The federal government must convene a Summit in partnership with patient groups including the provinces and all other relevant stakeholders to develop a Strategy for achieving patient outcomes determined value-based health care and the tactics to achieve this health systems transformation.
15. **National pharmacare** – The federal government must work with patient representatives and other relevant stakeholders to ensure that the design of national pharmacare programme does not result in anyone eligible for drug coverage in Canada receiving less coverage than they now have.
16. **Alignment of systems** – The federal and provincial governments in partnership with patient groups should convene a multi-stakeholder Working Group to develop a Strategy to assess health systems across jurisdictions to ensure alignment, lack of duplication and inefficiencies across these systems.
17. **Social determinants of health-** The federal and provincial governments in partnership with patient groups should convene a multi-stakeholder Working Group to develop a Strategy to assess health systems across jurisdictions to ensure alignment and ongoing cooperation with ministries responsible for social determinants of health.
18. **Precision oncology research:** Indigenous Nations need to exert, extend, and utilize their sovereignty under treaty rights to create policies allowing Indigenous populations to gain access to health systems that provide precision oncology options including emerging anti-cancer pharmaceutical options from prevention to survivorship. Indigenous Nations need to be at the forefront of cancer related clinical research at cancer institutes and research centers. By doing so, informed decisions can be made to be part of innovative clinical trials to determine if emerging science, medicines, process, and technologies are effective for their Nations and improvement of patient and community outcomes.
19. **Precision medicine in pediatric cancer requires policy change** – In almost all countries in the world, there are more mechanisms for pay, coverage, and support for items such as pediatric care than adult populations. This is likely true for pediatric oncology medicines and policy agreements and is likely a good first step is to examine payee mechanisms for precision oncology treatment as well as research.

20. **International research:** Working in an international context between international research outfits (out of country) or via organizations such as the United Nations or the World Health Organization with sovereign Indigenous Nations are also options. To parallel recommendations shared by non-governmental organizations such as the World Health Organization and other non-governmental organizations often perform scoping studies in low- and middle-income countries internationally. These organizations could work independently with sovereign First Nations, Inuit, or Métis governments to build research infrastructure in medicine to guide tailored solutions led by Indigenous governments, independently.
21. **Tribal and band consultation:** Structured and timed need assessments, policy review, and government-to-government consultations are important steps to emerging fields such as precision oncology. The division of jurisdiction between on reserve health coverage (federal to sovereign nation) and province (for off-reserve Indigenous populations) has created gaps in accessing health services and potentially the inclusion of clinical trials or precision oncology processes. A key to addressing these health and treatment disparities is to strive towards universal coverage and more importantly parity in process through ongoing and government to government tribal consultation with structured goals with accompanying deadlines.
22. **Gender programming:** Gender planning for precision oncology needs to be reviewed and included in next steps for clinical care and research. For example, cervical cancers seem to be an area of interest for prevention and treatment in Indigenous populations due to the higher incidence rates and higher mortality. Other areas of prevention include those related to cancers of the lung, liver and gastrointestinal tract. Thus, cancer prevention must be considered in the context of precision oncology, and prevention strategies must be made inclusive and must address gender-related barriers to access to care.
23. **Environment and historical contexts:** Research also needs to review how precision oncology is affected by other risk factors for cancer including exposures, behaviors or other individual characteristics that may lead to cancer. These include overall access to care, community infrastructure (geographic, reserve/non-reserve, urban, sub-urban, near environmental waste sites) and the lasting effects of colonialism (historical traumas). These are important features to consider in future research and how these have influence on the global context of precision oncology and the cancer care continuum.

1 Introduction

Cancer is the leading cause of mortality in Canada, responsible for 28% of all deaths.[1] Although age-standardized incidence rates are not increasing, the growing Canadian population, particularly the growing older Canadian population, means the number of people diagnosed with cancer is increasing inexorably (**Error! Reference source not found.**).[1] In 2021, it was estimated that in Canada, 44% of men and 43% of women would develop cancer in their lifetime, and about 26% of men and 22% of women are expected to die as a result.[1]

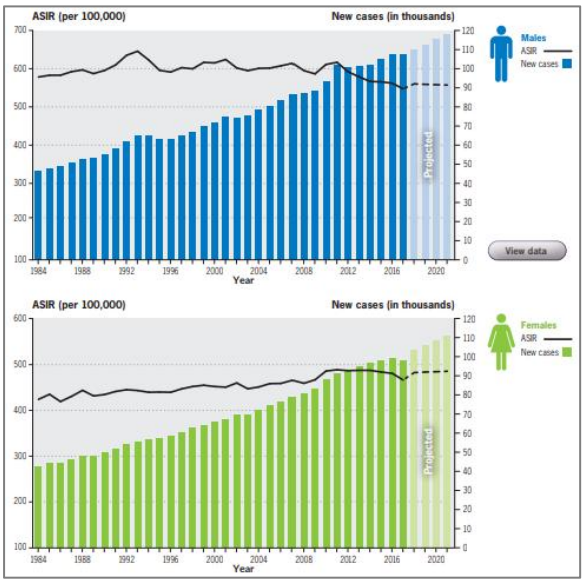


Figure 1. New cases and age-standardized incidence rates (ASIR) for all cancers, Canada (excluding Quebec), 1984-2021. Source: Canadian Cancer Statistics 2021.[1]

For example, the mean cumulative cancer risk at age 70 for women born with a deleterious ***BRCA1*** mutation is 57% for breast cancer and 40% for ovarian cancer.[3] For those with a deleterious mutation in ***BRCA2***, the cumulative risks for breast and ovarian cancer are 49% and 18%, respectively.[3] And it is still within living memory that the only treatment for those women who developed breast cancer was a **radical mastectomy**, often including both breasts and underlying muscles. This severely disfiguring surgery was considered necessary to prevent **recurrence**, but in reality had little effect on disease progression.[4]

More recently, treatment options have improved dramatically: In the 1970's the first effective **chemotherapy** for breast cancer was identified, followed by selective **estrogen receptor modulators** and then **aromatase inhibitors** in the 1990's. Then, towards the end of the last century, breast cancer treatment heralded a revolution in cancer treatment: the approval in 1998 by Health Canada of trastuzumab for the treatment of **malignancies** over-expressing the **HER2** protein.[5]

Companion diagnostics are an often-overlooked facet of the **precision medicine** revolution. They are used identify those patients who will benefit from a targeted therapy and, just as important, those who will not. The choice of test and its **sensitivity** and **specificity** is crucial for ensuring the right treatment for the right patient, and also that the treatment is tested in the right patient population.

Trastuzumab (Herceptin®, Roche) was the first example of what has since become known as the revolution of **personalised medicine**, also known as precision medicine or **targeted therapy**.[6,7] Trastuzumab is indicated for use in a well-defined population (patients whose tumors over-express the HER2 protein) that are identified using a specific test, or **companion diagnostic** (in this case the HercepTest® kit).[5,8]

Precision medicine is not a new concept: **Cross-matching** of blood is a classic example of using a validated test (**blood typing**) to tailor the treatment (**transfusion**) to the individual needs of the patient.

Since that signal event when trastuzumab was

approved there has been an explosion in precision medicine. It is a tragedy that, notwithstanding the advances in research and development that created trastuzumab, for many cancers, treatment has not moved forward significantly from the 'cut, burn and chemo' approach of the last century.

There are many reasons for this. As research expands its horizons, new targets are identified. The process of identifying new targets, and then developing targeted therapies, validated tests, and the standard process of developing products for clinical use, takes time and resources. There is a failure rate; not just the well-recognised attrition associated with pharmaceutical development, but also when testing products that have already revolutionised treatment for one cancer, in new areas (for example the challenge of **BRAF V600E mutation**-positive **metastatic** colorectal cancer, discussed later in this document). The commercial potential of new products is an important consideration for companies deciding where to target their efforts; small patient populations create an obvious restraint, but so does intense research focus: multiple competitors dilute the market opportunity, and continuing innovation may make a new treatment redundant before it has realised its full potential. The good news is that development continues apace, and cancers considered virtually untreatable are now the subject of intense scrutiny.

Fuelling this revolution, and the foundational technology for precision medicine, is genetics. Although much of cancer biology is based on the central tenet that it is a genetic disease caused by a clone of cells that expands in an unregulated fashion because of **somatically-acquired mutations**, this view contributed little to cancer treatment until the 21st century.[6] For example, even though one of the main diagnostic features of chronic **myeloid leukemia** – the **Philadelphia chromosome** – was identified and described in 1959, its utility as a therapeutic target was not exploited for another 40 years.[9,10] Since then the technological advances that enabled the sequencing of the human **genome**, in concert with the quantum leap in **bioinformatics**, has allowed the identification of more and more of the genetic **mutations** associated with cancer. Some of these may contribute directly to the **genesis** and evolution of a **tumour cell line** (for example, the BRAF V600E or V600K mutation in malignant melanoma),[11] or may confer a **susceptibility** to the development of certain cancers. As well, as mentioned previously, women with mutations in either the BRCA1 or BRCA2 genes have a dramatically increased risk of developing breast and/or ovarian cancer.[3]

Is cancer caused by genes or environment?

Ultimately, all cancer is genetic in origin: changes in the genome disrupt the normal control mechanisms for cell proliferation, differentiation, and/or survival.

However, some cancers run in families and so clearly have a genetic predisposition. The BRCA gene, for example, is a tumor suppressor gene and people with a mutation that makes it less effective have a high predisposition to develop cancer.

Environmental factors are also important: Exposure to ultraviolet light (eg, sunlight or tanning beds) increases the risk for skin cancer; smoking increases the risk for lung cancer; but this is because these environmental factors increase exposure to carcinogens which make the spontaneous mutations that give rise to cancers more likely.

2 Prevalence and incidence of cancer in Canada

The prevalence of cancer in Canada is very high; as of January 2018, approximately 1.5 million Canadians who had received a diagnosis of Cancer in the previous 25 years were still alive at that time.[12] As previously mentioned, the overarching age-standardized **incidence** rate for cancer is not increasing.[1] First Nations are, however, the exception: Although the incidence of cancer has historically been lower in aboriginal populations than in the general population, it is now increasing dramatically.[13]

There are also changes in incidence for specific cancer types in the general population that are not apparent in the overarching statistics. Notably, lung cancer rates are declining in men but increasing in women Figure 2. Age-standardized incidence rates (ASIR) for selected cancers in Canada (excluding Quebec), 1984–2019. Data for 2015–2019 are projected numbers. Source: Canadian Cancer Statistics 2015—2019 while melanoma's rates are increasing in both sexes (Figure 2).[14]

First Nations men and women in Ontario have a higher incidence of lung, colorectal and kidney cancers, while in British Columbia the same holds true for the age-standardised incidence of colorectal and cervical cancers.[15,16] Among the Metis living in Alberta, lung cancer is more common than in the rest of the population.[17] The highest incidence of lung cancer in the world may be found among "Circumpolar Inuit" from Alaska, Northwest Territories, Nunavut and Greenland.[18] The Inuit are also at extreme high risk for certain rare cancers such as nasopharyngeal cancer, but at low risk for prostate cancer.[18]

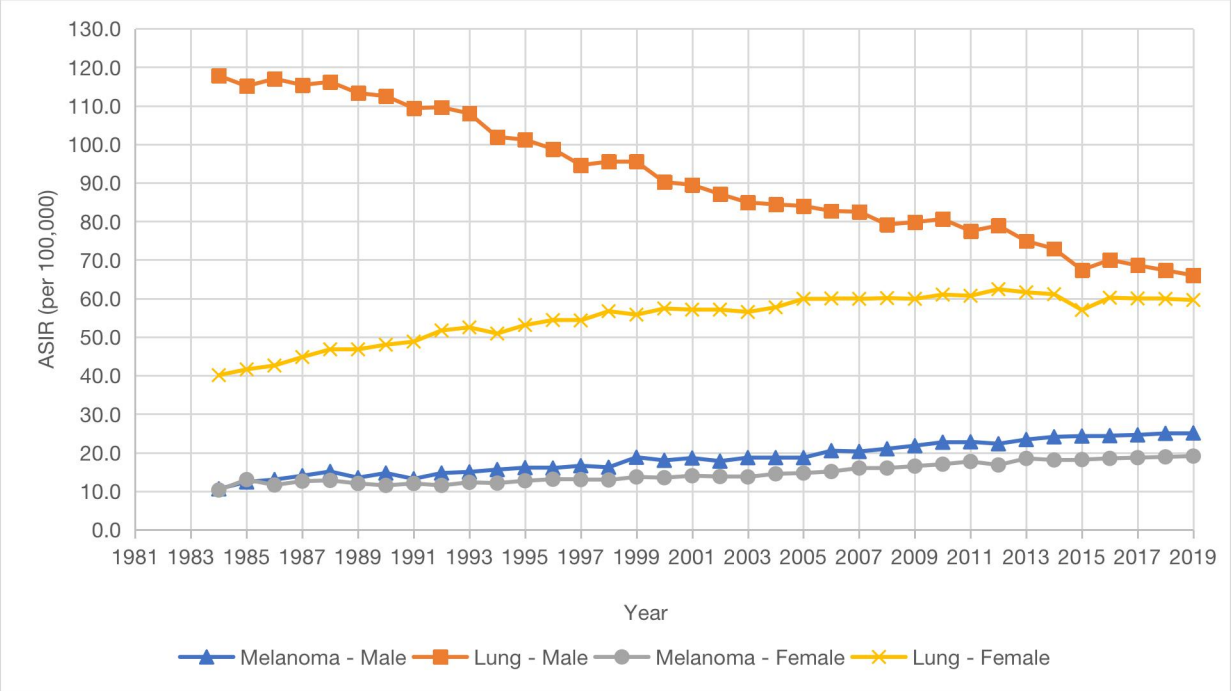


Figure 2. Age-standardized incidence rates (ASIR) for selected cancers in Canada (excluding Quebec), 1984–2019. Data for 2015–2019 are projected numbers. Source: Canadian Cancer Statistics 2019.[19]

Age-standardised incidence rates also cover an important societal factor: In general, cancer rates increase with age. However, when the aging population is factored in, the burden of

cancer on the older population becomes apparent (Figure 3). In 2021, nine out of ten cancer cases were projected to be diagnosed in Canadians over the age of 50.[1]

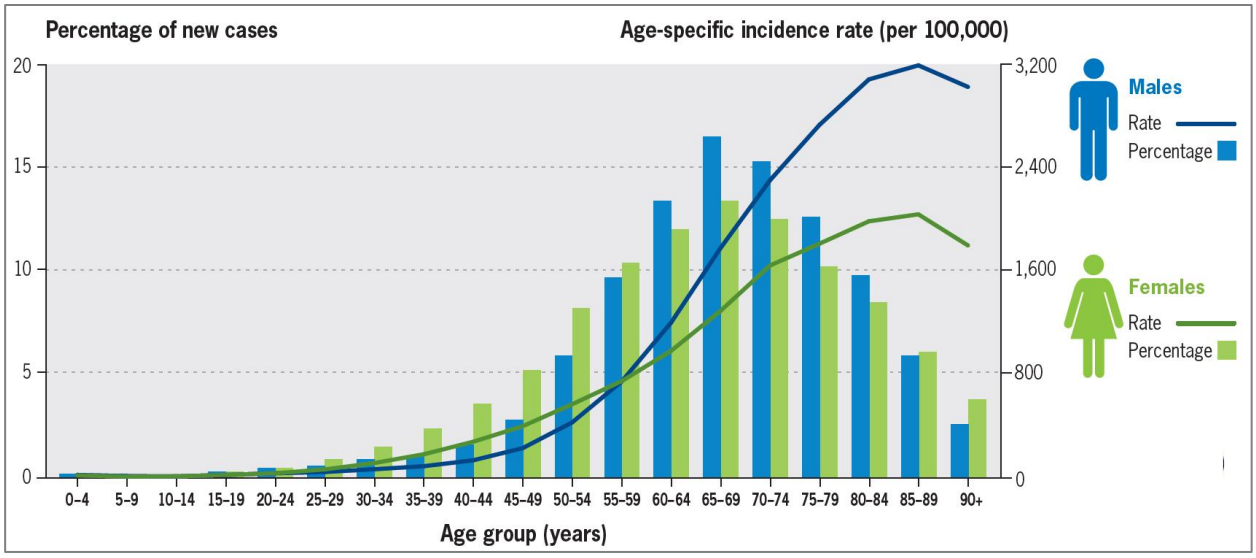


Figure 3. Percentage of new cases and age-specific incidence rates for all cancers, by age group and sex, Canada (excluding Quebec), 2015–2017. Source: Canadian Cancer Statistics 2021.[1]

For those Canadians who still adhere to the traditional 'retire at 65' philosophy, cancer is a condition primarily of retirees who rely on Federal and Provincial/Territorial-funded health services for their treatment. For the increasing number of Canadians 65 years or older who choose to continue working, this raises other concerns. In 2015, 19.8% of seniors worked at some point in the year; however, only 5.9% were in full-time employment.[20] As company health benefits are rarely extended to part-time employees, it is likely that most of those working seniors also rely on Federal and Provincial/Territorial-funded health services for their treatment.

As well as the imbalances between males and females, and younger and older populations, cancer incidence in different regions across Canada is decidedly uneven (Figure 4).[1] In general, the highest incidence rates for cancer are seen in the Eastern and Central Canada, and lowest in Western Canada and the Territories.[1] But there are also dramatic differences in incidence rates for individual cancers:

- Lung cancer incidence rates are estimated to be highest in New Brunswick for males and Nova Scotia for females, and lowest in British Columbia, presumably reflecting smoking habits.[1]
- Colorectal cancer incidence rates for both males and females are highest in Newfoundland and Labrador, which may be a consequence of dietary choices.[1]
- The higher incidence of lung, colorectal, kidney and cervical cancers, myeloma, and cancers of the stomach, liver, gallbladder and vulva in First Nations women in Ontario may be related to a higher prevalence of smoking and obesity observed in that population.[16]

- First Nations people in Ontario and British Columbia had lower cancer survival rates than non-First Nations peoples in those Provinces, although this was not seen amongst the Metis population in Alberta.[15-17]

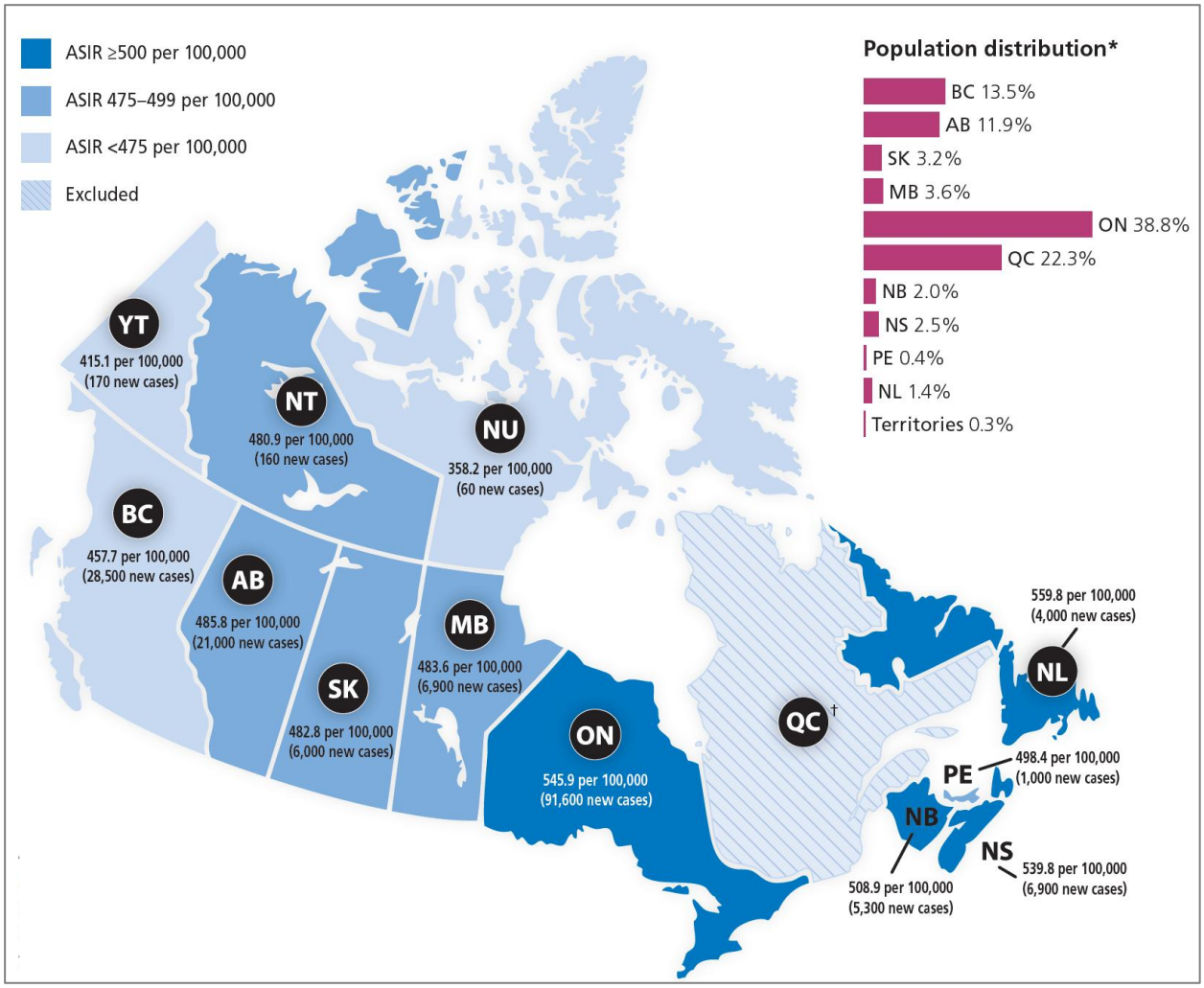


Figure 4. Geographic distribution of projected new cancer cases and age-standardized incidence rates (ASIR) by province and territory (†Quebec excluded), 2021. Source: Canadian cancer statistics 2021.[1]

Adult cancers command much of the focus on prevention and treatment. But it is important to remember that Canadians of all ages are affected; 2021 estimates showed that approximately 4,000 children, adolescents and young adults (between 0 and 29 years old) will be diagnosed with cancer in 2021.[1] The second most common cause of death for Canadian boys and girls aged 1-14 years (after accidental death), the incidence of childhood cancers are slowly increasing over time.[21,22]

Little is known about the causes of childhood cancers; however, it is well recognised that cancers in children are different from those in adults.[23,24] Childhood cancers tend to have shorter latency periods and be more aggressive and invasive than those affecting adults. In addition, the more common types of cancer occurring in children are different, with leukemia (35%), central nervous system (17%) and lymphomas (13%) being the most common.[1]

The good news is that the five-year survival rate for Canadian children with cancer has improved from 71% in the late 1980s to 82% in the early 2000s.[23] Unfortunately, since then survival rates for many pediatric cancers, including those for acute myeloid leukaemia, many brain tumours, bone tumours, neuroblastoma, and sarcomas such as rhabdomyosarcoma, have stalled and remain the lowest among pediatric cancers.[1,25] And many of those who survive childhood cancer have to contend with life-threatening health conditions that directly result from the harsh treatment with chemotherapy and radiation they received, as well as an increased lifetime risk of being diagnosed with a second primary malignancy.[12,26,27]

> Approximately 40% of childhood cancer survivors will experience late-effects from their treatment that are classified as life-threatening, disabling, and even fatal at 30 years post diagnosis.
>
> By age 45, 80% of survivors have a life-threatening health condition.

New treatment options for this vulnerable group of Canadians used to be rare: in Canada between 1984 and 2017 only two drugs had been developed and approved for the primary use in pediatric, adolescent and some young adult cancers:

- Teniposide (Vumon), approved in 1980 for acute lymphoblastic leukemia (ALL)
- Clofarabine (Clolar), approved in 2004 for ALL

However, from 2017 to 2020 (the latest year there are data for) there have been six additional approvals:

2017:

- Pegaspargase (Oncaspar) for ALL

2018:

- Dinutuximab (Unituxin) for neuroblastomas
- Tisagenlecleucel (Kymriah) for B-cell ALL

2019:

- Larotrectinib (Vitrakvi) for solid tumours that have a Neurotropic Tyrosine Receptor Kinase (NTRK) gene fusion

2020:

- Selpercatinib (Retevmo) for thyroid cancer
- Treosulfan (Trecondyv) for AML or myelodysplastic syndrome (MDS)

Recently, whole genome sequencing has shown promise in improving diagnoses and treatment options in children with cancer, including revealing treatment that otherwise might not have been considered. The study also highlighted the importance of expert interpretation of these data: some genetic variants may have been missed except for the careful analysis and interpretation provided by the study's expert panel.[28] Another study reported that mutations in the TP53 gene is associated with poor outcomes in children with aggressive B-cell lymphoma, identifying a sub-set of patients (those without the mutation) who would benefit from less intensive treatment with reduced toxic side effects while still maintaining a high chance of survival.[29]

2.1 What the COVID-19 pandemic taught us about the state of cancer care in Canada

The COVID-19 pandemic was a hugely disruptive event for all of society, but especially for healthcare systems around the world. It also provided a unique opportunity to pressure-test the resilience of our Federal, Provincial and Territorial cancer programs.

Unfortunately, the results were not good. According to a report from All.Can Canada, Alberta, British Columbia, and Quebec reported a 20-23% drop in cancer diagnoses from June – September 2020. It is predicted that cancer care disruptions during the pandemic could lead to 21,247 more cancer deaths in Canada over the next decade, representing 355,173 years of lost life due to pandemic-related diagnostic and treatment delays.[30]

The Canadian Cancer Society reported similar challenges: delayed cancer screenings, suspended clinical trials and heightened anxiety levels due to concerns about receiving appropriate care were documented time and time again through the pandemic.[31] As alluded to above, cancer screening and early detection services were put on hold during the first wave of the pandemic (Figure 5).

Cancer screening type	AB	BC	NB	NL	NS	ON	PE	QC
BREAST CANCER	↓68%	↓37%		↓39%	↓62%	↓53%	↓18%	↓37%
COLORECTAL CANCER	↓35%	↓13%	↓29%	↓25%	↓65%	↓56%	↓31%	↓30%
CERVICAL CANCER	↓26%	↓39%	↓28%	↓23%	↓35%	↓47%	↓76%	

Figure 5. Reduction in cancer screening in March–December 2020, compared with the same time window in 2019. Source: Canadian Cancer Society, 2023.[31]

Using mathematical and various simulation models, researchers assessed the impact of provincial screening program interruptions for breast and colorectal cancer in Canada. For breast cancer screening, a six-month interruption could lead to about 670 additional advanced breast cancers and 250 additional breast cancer deaths. For colorectal cancer, a six month delay in screening could increase colorectal cancer cases by about 2,200 with 960 more colorectal cancer deaths.[31]

All.Can Canada's report identified seven outcomes as critical to a quality diagnosis experience:[30]

1) Swiftness of the diagnosis process
2) Validation of concerns by primary care providers
3) Excellent patient-provider communication
4) Effective provider-provider communication
5) Better information
6) Integrated psychosocial support
7) Coordinated and managed care

3 Taxonomy of precision oncology

3.1 Personalized Medicine

Personalized medicine refers to the tailoring of medical treatment to the individual characteristics of each patient.[32] Precision medicine takes this further, and uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. In precision oncology, specific information about a person's tumour is used to help diagnose, plan treatment, find out how well treatment is working, or to make a prognosis.[33]

Nowhere in medicine has the impact of precision medicine been greater than in cancer treatment and **oncologists** often use the term interchangeably with 'precision medicine' and 'precision oncology'. In precision oncology, specific information about a person's tumour is used to help diagnose, plan treatment, find out how well treatment is working, or to make a prognosis.

3.2 Precision diagnostics

Precision diagnostics, often called companion diagnostic tests, are at the centre of precision oncology, enabling treatment to be targeted to a specific difference found in cancer cells (compared with normal cells in the body). Precision diagnostics are essential for the first step in this process: To identify those patients with a specific difference (a **biomarker**) in their cancer. Such tests can be used to identify **predictive** or **prognostic biomarkers**.[34] Tests for predictive biomarkers ensure targeted medications are prescribed only to patients most likely to benefit from them. Just as important, use of these tests protects those who are unlikely to benefit from adverse effects as well as ensuring valuable resources within the health system are used wisely. Prognostic biomarkers provide information on the likely trajectory or outcome of a cancer or treatment.[6] Some tests may be both predictive and prognostic, for example FLT3 mutations in acute myeloid leukemia (AML).[35]

Examples of prognostic biomarkers

- Loss of function mutations in the *BRCA1* and *BRCA2* genes predispose carriers to an increased risk for breast cancer
- Oncotype DX gene panel assesses the probability of relapse of breast cancer within 10 years

Examples of predictive biomarkers:

- Gain of function mutations in the *KRAS* gene in colorectal cancer predict response to EGFR inhibitors
- EGFR inhibitors are now mandated as first-line therapy instead of chemotherapy in patients with EGFR-positive advanced NSCLC
- V600E mutation in the *BRAF* gene in malignant melanoma predicts response to BRAF inhibitors

Examples of biomarkers that are both prognostic and predictive:

- **FLT3 ITD** mutation predicts earlier and increased risk for relapse in AML, and response to FLT3 inhibitors

Given the significance of biomarkers in guiding therapeutic decision-making, it is essential that the tests used are validated, specific (minimal false positive results), sensitive (minimal false

negative results) reproducible (including between different testing laboratories) and generate results within the appropriate timeframe to inform clinical decision-making.[34]

3.3 Therapeutic approaches in precision oncology

Most of the treatments used in precision oncology can be classified as small molecule drugs, **monoclonal antibodies**, and **immune modulators**.

3.3.1 Small molecule drugs

Small molecules represent the majority of pharmaceutical products, generally well-defined chemical structures and are manufactured through a reproducible chemical process. This allows for a consistent product regardless of the manufacturer, in turn making it relatively easy to produce generic versions once these molecules lose exclusivity. Small molecules can penetrate the cell membrane to interact with targets inside a cell and are usually designed to interfere with the enzymatic activity of the target protein.[36]

The first targeted small molecule approved for precision oncology was imatinib, which inhibits the BCR-ABL **tyrosine kinase** created by chromosome rearrangements in chronic myeloid leukemia and acute lymphoblastic leukemia, as well as PDG-derived tyrosine kinases that are overexpressed in gastrointestinal stromal tumors.[37,38] Other examples include alectinib, which blocks the activity of **anaplastic lymphoma kinase** (ALK) and is used to treat ALK-positive non-small-cell lung cancer,[39] and bortezomib, a proteasome inhibitor used to treat multiple myeloma.[40]

3.3.2 Biologics

Biologics differ from small molecule drugs not just in their size (they are typically orders of magnitude bigger than small molecule drugs), but also in their complexity and their manufacturing process. A biologic is manufactured in a living system such as a **microorganism** or cell. Many biologics are produced by **genetically engineering cells** using **recombinant DNA** technology. Unlike small molecule drugs, the complexity and manufacturing process of biologics makes it difficult, and sometimes impossible, to characterize a complex biologic by testing methods available in the laboratory.[36]

The cells used to produce biologics can be sensitive to minute changes in their environment, which may affect the quality of the final product and how it acts as a medication. To ensure the quality, consistency and purity of the finished product, biologics manufacturers tightly control the source and nature of starting materials, and consistently employ hundreds of process controls that assure predictable manufacturing outcomes.

Therefore, for biologics, "the product is the process" and the process controls for biologics are unique to each product and are not applicable to a manufacturing process/product created by another manufacturer. These process controls are often confidential, making it difficult or impossible for another manufacturer to make an identical biologic. For this reason, follow-on biologics (also known as subsequent entry biologics or **biosimilars**), unlike generic versions of small molecule drugs, are not considered interchangeable with the original product by Health Canada.[36]

3.3.3 Monoclonal antibodies

Monoclonal antibodies are a type of biologic that targets cancer cells by recognising and binding to specific molecules (called an antigen) that are either only found or over-expressed on the on the surface of malignant cells. Once bound, monoclonal antibodies exert their anticancer effect through a number of mechanisms, including marking the cell for attack by the body's immune system (*e.g.,* elotuzumab, blinatumomab); inhibiting proteins that are essential for tumour growth and proliferation *(e.g.,* cetuximab); stimulating **apoptosis** (cell suicide; *e.g.,* necitumumab), or through a number of these processes *(e.g*. trastuzumab suppresses cell growth and proliferation, and also marks cells5 for immune destruction).

Bacillus Calmette-Guerin (BCG) is more generally known as a vaccine against tuberculosis. It is also a successful treatment for patients with non-invasive bladder cancer. When put directly into the bladder via a catheter, BCG activates the immune system which also attacks the bladder cancer cells.

Another group of monoclonal antibodies, sometimes called antibody-drug conjugates, act simply as a targeting mechanism to deliver toxins directly to the cancer cell. These toxins may be in the form of a chemical (*e.g*., brentuximab vedotin or trastuzumab deruxtecan) or a radioactive isotope (*e.g.,* ibritumomab tiuxetan). This approach can improve the effectiveness of existing monoclonal antibodies; for example, treatment with trastuzumab deruxtecan can extend life for patients with HER2-positive metastatic breast cancer whose disease has progressed following treatment with a combination of HER2 antibodies and a taxane.[41] As a consequence, the UK National Institute for Health and Care Excellence (NICE) has now recommended trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after one or more anti-HER2 treatments, as well as for adjuvant treatment of HER2-positive early breast cancer.[42]

3.3.4 Precision medicine

One of the recent breakthroughs in cancer research has been the explosion in understanding of how to harness the immune system to recognize and attack tumour cells.

One approach is to mark the tumour cells using a monoclonal antibody for the immune system to attack (which is how elotuzumab and blinatumomab have their anticancer effect).

Another approach, which has been used successfully for years in bladder cancer, is to use a biological response modifier (in the case of bladder cancer, BCG) to trigger an inflammatory reaction in the area of the tumour. This activates the immune system around the tumour and the activated white blood cells then attack the tumour cells.[43]

Cancers can exploit the immune system's naturally occurring 'off switches,' so-called **immune checkpoints**. Two key immune checkpoints are Programmed Cell Death Protein 1 (PD-1), which promotes tolerance when bound to its ligand PD-L1, and Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) which down-regulates immune responses when bound to the proteins CD80 or CD86 on the surface of antigen-presenting cells in the immune pathway.[44] Since the discovery that many cancers express proteins which can activate PD-1 and CTLA-4, checkpoint inhibitors - treatments that block these interactions and allow the immune system to recognise and attack the cancer cells – have been developed. Some drugs block the PD-1

receptor (e.g., nivolumab and pembrolizumab) while others (e.g., atezolizumab) inactivate PD-L1. Ipilimumab inhibits activation of CTLA-4.[44] Since PD-1 and CTLA-4 work independently of each other to suppress the immune system, checkpoint inhibitors are often used in combination to block both pathways simultaneously.[45] Checkpoint inhibitors are typically effective when used against cancers that express the PD-L1 marker, but not all patients respond. Recently, a marker on immune cells called LAG-3 has been identified as a predictive marker for poor responses to checkpoint inhibitors in patients with melanoma and also in patients with bladder cancer, helping inform patients of their prognosis and helping them make decisions regarding their treatment options.[46]

A rapidly emerging immunotherapy approach is called adoptive cell transfer (ACT): collecting and using patients' own immune cells to treat their cancer. Chimeric Antigen Receptor (CAR) T-cell therapy is a form of ACT made from the patient's own T-lymphocytes. The cells are genetically modified in a laboratory to express synthetic receptors on their surface that recognise antigens unique to tumour cells, and then put back into the patient where they attack the cancer and multiply to create a long-lasting protection.[47] The CAR-T therapy tisagenlecleucel has a synthetic receptor that recognises the CD19 protein, which is present in approximately 80% of cases of acute lymphoblastic anemia (ALL), the most common cancer in children.[47] At the moment, it seems that CAR-T technology is more suited to attacking cancer cells in blood tumors than in solid tumors.[48]

Vaccination is also a way to prime the immune system to generate a long-lasting protection against disease, and one being actively explored in oncology. One example under development is galinpepimut-S which resembles the Wilm's Tumor 1 (WT1) protein – one of the most common cancer-associated proteins – and elicits a strong immune response against WT1-expressing cells.[49] As the immune system 'remembers' WT1, it will also protect the patient against any WT1-expressing cancer cells that may arise in the future.[49]

CRISPR is a way of editing genes in cells and is being researched in cancer therapy as a way to 'delete' the PD-1 gene from patients' T-lymphocytes, and also as a way to create chimeric antigen receptor (CAR) T cells.[50] It definitely shows incredible promise in many additional applications in oncology as well.

4 Where are we now and the promise of precision oncology

Precision oncology has already transformed treatment and outcomes of certain cancers, and this effect continues to grow. As our knowledge of the genetic and molecular variants underpinning the development and evolution of cancers expands, so new validated tests to detect them and treatments to address their effects will be developed.

The use of precision diagnostics also means these novel treatments will be used only in those who will benefit, increasing overall efficacy and reducing wasteful exposure of those who will not. Finally, the targeted nature of these treatments will ameliorate what has been a major disadvantage for traditional cancer therapies: off-target adverse effects because their cytotoxicity is not limited to neoplastic cells but also impacts other rapidly proliferating populations of normal cells.[44] Our expanding knowledge of biomarkers also has the potential to identify patients at increased risk for treatment-related injury, so alternatives may be identified proactively.[6]

The impact in terms of cost savings to both the public system and for private insurers cannot be minimized. This will be discussed in detail below in the section titled "Cost/Benefit of Personalized Medicine to Health Systems."

4.1 Where are we now?

For some cancers, the benefits of precision oncology are already manifest. Examples include chronic myelogenous leukemia, lung cancer and malignant melanoma, as described below.

One-year survival rates following HSCT for CML vary from 87% to 46%, depending on disease stage and donor type.

4.1.1 Chronic Myelogenous Leukemia

The signal event for the benefits of precision oncology was the approval in 2001 of imatinib mesylate for the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia (CML).[37,51] Prior to its approval, **antimetabolites** (e.g., cytarabine, hydroxyurea), alkylating agents, interferon alfa 2b, and steroids were used as treatments of CML in the chronic phase with bone marrow transplant (HSCT) being the only curative treatment.[52-54] Since the advent of imatinib, CML has become the first cancer in which a standard medical treatment may give the patient a normal life expectancy, and the number of HSCTs performed due to CML has decreased dramatically (Figure 7).[55,56]

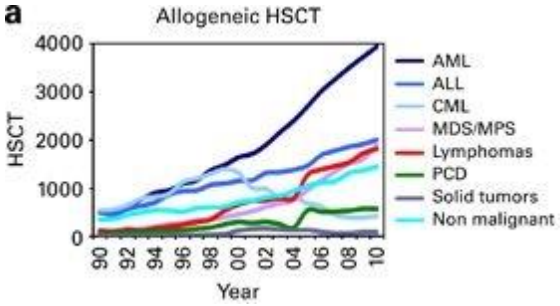


Figure 6. Main indications and absolute numbers of patients receiving allogenic HSCT from 1990-2010 reported in the 2010 EBMT survey. Source: Passweg et al, 2012.[56]

A critical factor for achieving and maintaining a molecular response in people with CML with imatinib is adherence to what is for most essentially a life-long therapy. Non-adherence is correlated with treatment failure and encompasses a complex range of influencers that include medication tolerability, patient education, ease of taking and patient support. A real-world analysis of patient adherence and persistence with imatinib and two alternative therapies (nilotinib, dasatinib) in clinical practice reported adherence rates of 83% for imatinib, with 90% of patients remaining on treatment for at least one year.[57] Stable remission is possible in some patients following withdrawal of imatinib treatment, however. One study reported that 47% of people treated with imatinib were still in **remission** 24 months after treatment was stopped, and those that relapsed responded to re-initiation of imatinib therapy.[58]

4.1.2 Lung cancer

Being the leading cause of cancer death in Canada warrants special attention. Although improvements in the treatment of non small-cell lung carcinoma and small-cell lung carcinoma (the two main classes of lung cancer) have been eked out with incremental advances rather

than revolutions like those seen with CML and malignant melanomas, they are real nonetheless and bring meaningful benefits to many Canadians.[59] Only ten years ago, treatment was limited to surgery, platinum-based chemotherapy and radiotherapy. Chemotherapy, while improving life expectancy and progression-free survival, brought with it a high cost in terms of quality of life due to side effects such as nausea and vomiting. Since then, targeted therapies and their associated diagnostic tests, have improved the quality, as well as the quantity, of life, especially for the ~50% of patients who are diagnosed at the advanced stage of the disease.

Targeted therapy in lung cancer started with the epidermal growth factor receptor (EGFR) inhibitors such as erlotinib and more recently omisertinib.[60-62] Since their original approval for lung cancer, EGFR inhibitors have been used earlier and earlier in treatment and are now the preferred first-line therapy for patients whose cancer is positive for EGFR gain of function mutations.[63] These medications have the benefits of being orally administered at home, as well as a much-reduced side effect profile compared with the standard chemotherapy regimens. Many other targeted therapies have since proven advantageous in patients whose lung cancer is susceptible, based on their predictive biomarker status. These include ALK (anaplastic lymphoma kinase) and ROS1 inhibitors (also now indicated for first line use in appropriate patients), VEGF (vascular endothelial growth factor), BRAF, KRAS (Kirsten Rat Sarcoma) G12C, MEK and TRK inhibitors.[39,64-69] Immunotherapy with the PD1/PD-L1 has also shown benefit for patients who are positive for these markers.[70,71]

4.1.3 Malignant melanoma

More recently, malignant melanoma has been revolutionized by application of two forms of precision oncology: small molecules that target BRAF and MEK inhibitors, and immune checkpoint inhibitors, that are biologics.

Over the last half century, the incidence of melanoma in most developed countries has risen more than any other form of cancer, with rates increasing by 360% in the UK since the late 1970s. Early diagnosis and resection will cure nine of ten cases of stage I melanoma. Historically, the prognosis for regional and distant metastatic melanoma (stages III and IV, respectively) is variable but generally poor, with 5-year survival rates for stage III of 13%–69% and as low as 6% in stage IV.[45]

About half of all melanomas have a mutation to the BRAF gene (the V600E or V600K mutation) promoting tumour growth.[11] BRAF inhibitors such as vemurafenib and dabrafenib block the activity of these variants. These drugs have shown response rates ranging from 48% to 59% in phase II and III trials – rates not previously seen in patients with metastatic melanoma.[72-74] Unfortunately, these responses are not that durable due to the development of acquired resistance and median **progression-free survival** (PFS) ranges from 5.1 to 6.8 months.[72,75]

One possible cause of acquired resistance is downstream mutations in the MEK gene, which acts on the same pathway as BRAF.[76] Treatment with the MEK inhibitor trametinib has also shown similar median PFS (4.8 months) and response rates (48%) as BRAF inhibitors when administered as **first-line therapy** in this patient population,[77] but when used in combination with dabrafenib median PFS was roughly double that for monotherapy (11.0-11.4 months).[78,79] Significantly, a **retrospective** real-world analysis of a Spanish expanded access program reported comparable outcomes: 89% of patients achieved a clinical response, with 42.5%

progression-free at 12 months.[80] Similar results have been reported in clinical trials with the BRAF inhibitor vemurafenib in combination with the MEK inhibitor cobimetinib.[76]

Treatment with immune checkpoint inhibitors has also dramatically improved the outcome for people with metastatic malignant melanoma: a **meta-analysis** of Phase II and III trials for three checkpoint inhibitors (ipilimumab, nivolumab and pembrolizumab) reported a near-doubling of median PFS and **overall survival** (OS; **HR**: 0.85; **95% CI**: 1.49-2.27) compared with the trial control arms.[45] Similarly, response rates were more than four times higher for the checkpoint inhibitor trial arms (**OR**: 4.48; 95% CI: 2.77-7.24). The combination of nivolumab + ipilimumab resulted in better outcomes, both in terms of survival and treatment response, than ipilimumab alone.[45] Interestingly, an Australian **real-world study** of patients with unresectable stage IIIc/IV metastatic melanoma who received ipilimumab in the first year following reimbursement through the Pharmaceutical Benefits Scheme reported a higher 2-year overall survival rate than that recorded in the key registration trial, highlighting the importance of early access with the promise of future evidence.[81]

4.1.4 Cautious optimism

The successes of precision oncology are indisputable. It is important, however, also to recognise and acknowledge that laboratory theory does not always translate into the anticipated benefit in clinical trials.

Some targeted therapies have generated impressive early response rates, however, the effects have not been durable (as already mentioned for malignant melanoma), while for others the expected outcome has proved elusive. For example, in a Phase II trial, the BRAF inhibitor vemurafenib did not show meaningful clinical benefit in patients with BRAF V600E-positive metastatic colorectal carcinoma, in marked contrast to its effect on BRAF V600E-positive melanoma.[82] Also, a trial of the combination of atezolizumab (a PDL-1 inhibitor) and cobimetinib (a MEK inhibitor) *versus* regorafenib (a multikinase inhibitor, including activity against BRAF V600E) in patients with heavily pretreated locally advanced or metastatic colorectal cancer did not show an improvement in survival.[83] The good news is that in a recent study almost half (48%) of patients who received triple therapy with binimetinib, encorafenib and cetuximab responded to therapy, with a median PFS of 8 months and a median OS of 15.3 months.[84]

Targeted therapies are also not without tolerability challenges: in patients with melanoma, moderate to severe side effects occurred in approximately 10% of those receiving pembrolizumab and 20% of those receiving ipilimumab. Almost 7% and 10% of patients receiving pembrolizumab and ipilimumab, respectively, had to stop treatment because of side effects.[79] One of the earlier clinical trials of the much-anticipated CAR-T therapy (the ROCKET trial) was placed on hold by the FDA following two patient deaths from severe neutotoxicity.[85]

These setbacks are to be expected, as with any novel technology, and reinforce the need for commitment and persistence to achieve the maximum benefit. Manufacturers consider this a cost of doing business and argue that the price of drugs must include this cost to them of

taking the risk of research and development. Payers are concerned that the early Phase II and even Phase III data may not show resilience over time and are reluctant to fund these expensive drugs early in their life cycle. Patients need these drugs and want early access, prepared to risk adverse events for the potential benefit of longer life and greater enhanced quality of life. These often-competing interests are important to consider in finding a solution to timely access needs.

4.2 What the future may hold

4.2.1 Broader reach

The revolution already seen in CML and malignant melanoma is anticipated in other conditions. For example, Acute Myeloid Leukemia (AML), if left untreated, usually results in death within days or weeks.[86] Current induction and consolidation chemotherapy regimens, among the most aggressive in oncology, result in disease remission in 65-70% although this figure is lower in those over 60 years of age. (The median age at diagnosis is 68 years[87]). About 25%–40% of people over the age of 60 are expected to survive 3 years or more.[86] Now the most common reason for **HSCT**,[55,56] if performed during first remission, the 5-year disease-free survival rate following HSCT is 30%–50%.[87]

One of the indicators of poor prognosis is a mutation to the FLT3 gene called FLT3 internal tandem duplication (ITD). People with this mutation tend to have higher rates of relapse with the relapse occurring sooner that in other people with AML.[88] Midostaurin has recently been approved for the treatment of patients with newly diagnosed FLT3 ITD-positive AML in combination with standard chemotherapy regimens, with a reported 23% improvement in OS (Median overall survival was 74.7 months (95% confidence interval [CI], 31.5 to not reached) in the midostaurin group and 25.6 months (95% CI, 18.6 to 42.9) in the placebo group (one-sided P=0.009 by stratified log-rank test). Disease-free survival was also longer in the midostaurin group, partly due to a lower risk for relapse.[89] Other FLT3 ITD inhibitors are undergoing clinical trial evaluation; in patients who had received intensive chemotherapy and were relapsed or refractory to salvage therapy, quizartinib achieved significantly higher remission rates than historical controls (40% vs 3%; $p<0.0001$), enabling a greater proportion to proceed to HSCT (40% vs 8%) and representing a novel treatment strategy – 'Bridge to transplant.'[90]

With other novel treatments showing promise in AML including isocitrate dehydrogenase (IDH) inhibitors, the B-cell leukaemia/lymphoma-2 inhibitor venetoclax (already approved in Canada for the treatment of chronic lymphocytic leukemia) and CD33-targeted therapy, a future with much improved outcomes for this aggressive blood cancer seems close to becoming a reality.[90]

For lung cancer, incidence rates among males have been declining for over 20 years, and since 2012 among females.[14] However, it remains the most commonly diagnosed cancer and the leading cause of cancer death in Canada, attributed in part to a late diagnosis (49% of lung cancer is diagnosed at Stage IV, an advanced, incurable stage).[14,59] Beyond the decreased incidence, the good news is that in 2019 the five-year survival rate for lung cancer increased by 2% to 19% from previous statistics.[59] While these rates remain among the lowest for all types of cancer, lung cancer's high prevalence means this modest improvement in outcomes translates into a positive impact for many Canadians.

Treatments, and outcomes, have been improving steadily for people living with breast cancer, through the development of hormone receptor antagonists, HER2 monoclonal antibodies, and their evolution into antibody-drug conjugates. Now those patients with the hardest to treat form of breast cancer, triple-negative breast cancer, whose tumors carry the PD-L1 marker, can benefit from the addition of pembrolizumab to their treatment regimen – a treatment approach now ratified by CADTH.[91,92] Advances in prognostic gene markers has also helped identify women with a very low risk for breast cancer recurrence who do not benefit from radiotherapy, allowing them to be spared with painful treatment.[93]

4.2.2 Greater knowledge

Fuelling the disruptive influence of precision oncology is an ever-increasing wealth of knowledge. The Cancer Genome Atlas (TCGA),[94] with analysis of approximately 10,000 specimens from 33 types of cancer, is providing invaluable information on the 'mutational landscape' of cancer sub-types as well as identifying new potential therapeutic targets.[95,96] Initiatives such as the International Cancer Gene Consortium (https://icgc.org/) and TRAcking Cancer Evolution through therapy (Rx) (http://tracerx.co.uk/)are adding to the understanding of how tumours evolve over time and with treatment, and strategies to optimize therapies already available.

Machine learning is contributing to the development of a forecasting tool which uses multiple patient-specific biological and clinical factors to predict which patients are likely to benefit from immune checkpoint inhibitors and which are not, thereby reducing unnecessary expense and exposure to potential side effects.[97]

Sometimes, advances in cancer care come from a new perspective on existing technologies, such as the Terry Fox Research Institute-funded development of a clinical risk calculator software that accurately classifies, nine out of ten times, which spots or lesions (nodules) are benign and malignant on an initial lung computed tomography (CT) scan among individuals at high risk for lung cancer.[98] In other cases, advances leverage the latest technologies, like evaluating the use of circulating microRNA as an early detection tool for lung cancer.[99] Improving the early detection rate for cancers with new approaches such as these can greatly improve the chances of survival for Canadians.

4.2.3 New paradigms

Mirroring this knowledge revolution in oncology has been an erosion in traditional, organ-specific stratification of treatments. In addition to its transformative effect in CML, imatinib has been proven effective in the treatment of a host of

Cancers for which imatinib is approved for use:

- Philadelphia chromosome-positive acute lymphoblastic leukemia
- Myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene re-arrangements
- Sub-types of systemic mastocytosis without the D816V c-Kit mutation
- Advanced hypereosinophilic syndrome and/or chronic eosinophilic leukemia with FIP1L1-PDGFRα rearrangement
- Unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans
- Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors

other hematologic conditions and gastrointestinal tumours.[37] BRAF inhibitor use has expanded beyond malignant melanoma to include non-small cell lung cancer[100,101] and is showing promise as part of triple therapy in colorectal cancer.[84]

The mechanisms by which checkpoint inhibitors have their effect make them attractive across a host of malignancies. Indeed, the first medication to receive a '**tissue/site-agnostic**' approval from the FDA was pembrolizumab (For treatment of patients with unresectable or metastatic, **microsatellite instability**-high (MSI-H) or **mismatch repair deficient** (dMMR) solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan).[102]

Consolidating the philosophy, larotrectinib, a highly selective inhibitor of neurotrophic receptor kinases (NTRKs), has been approved for use in patients with solid tumours that have an NTRK gene fusion without a known **acquired resistance mutation**, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.[103]

This approach may become the rule rather than the exception: In the evaluation of targeted therapies, basket trials have emerged as an approach to test the hypothesis that targeted therapies may be effective independent of tumor type, as long as the molecular target is present.[104] **Basket trials** can be used to evaluate a single drug in multiple tumour types each with the same target; in multiple tumour types, some of which may have different molecular targets, or to evaluate multiple targeted in the same tumour type.[104] A major advantage of the basket design is that the efficacy of a targeted agent can be determined with fewer patients and in a shorter amount of time compared with the traditional trial designs. Equally important, the basket trial design enables early termination of study arms not likely to show efficacy.[105] Fewer patients and a shorter amount of time also streamlines the evaluation process, ultimately allowing patients to access efficacious treatments sooner.

5 Canada in the fight against cancer

Canada has some of the best cancer treatment survival rates in the world, and doctors are pointing to the country's frequently maligned public health care system as the reason. In a report on worldwide cancer survival rates, Canada ranked near the top of the 31 countries studied with an estimated five year survival rate of 82.5 per cent.[106] Examples follow.

The Princess Margaret Research Institute, the research arm of the Princess Margaret Cancer Centre, is one of the top 5 cancer research centres in the world.[107] and University of Toronto is ranked #3 globally in oncology by The Center for World University Rankings.[108] Other globally recognized oncology centres include the Alberta Children's Hospital and the Ottawa Hospital.

The Canadian Partnership for Tomorrow Project (CPTP), Canada's largest group of volunteer research participants (population cohort) and among the largest population cohorts in the world, was built to address key questions about what causes cancer and chronic disease.[109] Following a decade of investment and leadership from The Canadian Partnership Against Cancer (CPAC), the CPTP has grown to be an internationally recognised resource for cancer research. [110]

As mentioned previously precision diagnostics are at the heart of personalized medicine and the growth of precision medicine highlights the need for accurate, reproducible assays that generate consistent results across the vastness of Canada. The Canadian Multicenter 22C3 immunohistochemistry (IHC) laboratory-developed test (LDT) Validation Project was initiated to harmonize the quality of PD-L1 22C3 IHC LDT protocols across Canadian pathology laboratories and recently reported successful implementation with 75% of laboratories achieving acceptable diagnostic sensitivity and specificity for PD-L1 testing of lung cancer samples.[111] This represents major step in ensuring timely access to life-saving treatments for patients with this difficult-to-treat cancer.

A world-leader in the translation, manufacture and adoption of cancer immunotherapies, BioCanRx is a network of Canadian scientists, clinicians, cancer stakeholders, academic institutions, NGOs and industry partners working together to accelerate the development of leading-edge immune oncology therapies for the benefit of patients. BioCanRx invests in translating Canadian technologies from the lab into early phase clinical trials, and addresses socio-economic considerations necessary for their adoption by health-care systems.[112]

The Getting better Outcomes with Chimeric Antigen Receptor T-cell therapy (GO–CART) program is a BioCanRx Research Excelerator to safely and effectively translate CAR-T cell therapy for hematological malignancies. Although only a small number of clinical trials have been undertaken with this ground-breaking technology, potential issues with safety, efficacy, and economic viability have already been identified. GO-CART's mandate is to create a clinical trial protocol better than any previously designed cellular therapy trial in the CAR-T arena using stakeholder engagement throughout the process, ultimately accelerating the translation of potentially transformative therapies.

Another BioCanRx project is using an innovative approach to establish a platform to support the decision-making process regarding reimbursement and implementation of CAR T-cell therapy in the future. Although shown to be effective in selected populations, the high cost of CAR T cell therapy, along with substantial usage of health care resources (highly personalized therapy and significant monitoring required) may potentially restrict patient access to this type of treatment in the future. Results of this research will provide an evidence-based evaluation of this therapy and its place in the health system, and serve as a foundation for clinical trial researchers and policy makers for improving oncology care.

The Terry Fox Research Institute (TFRI) launched a precision medicine project in pediatric oncology called PROFYLE (PResicion Oncology For Young people). PROFYLE is providing $16.4 million to molecularly profile pediatric tumours in patients across Canada. This is done through the creation of a platform for tissue bio-banking, disease modelling and genome sequencing that utilizes the expertise in hospitals and research facilities. This platform will allow a paediatric oncology patient to access a pan-Canadian network of expertise, diagnostic tools, and treatments. Put into action, this means that a child can have a biopsy done in one province, the molecular signature identified in another, then specialists only available in a third province can make recommendations on the best treatment plan.[113]

Overall, Canada is a global leader in the frontier of new precision treatment options for people with cancer. What is important is to ensure the Canadian population at large have the access needed to realise the benefits of this home-grown, and often publicly funded, research.

6 Access, affordability and appropriate access: The Canadian challenge

Cancer is deadly and traditional treatment modalities are crude, destructive to healthy as well as cancerous cells, and often of limited effectiveness when cancers have spread. This group of diseases imposes major burdens on both the patient and their formal and informal caregivers in numerous ways. Clinical experience has shown that the earlier a person is diagnosed and treated, the better their chances of survival and enhanced quality of life. People with cancer, therefore, do not have time to wait; for them, expeditious access to effective precision oncology treatments is paramount. As a result, efficient and effective regulatory approval for sale of treatments in Canada and approval for reimbursement from public or private reimbursement programmes are of paramount importance.

The pathway to access for new precision oncology therapies in Canada is unfortunately tortuous and often redundant, relying on an antiquated combination of federal and provincial processes (**Error! Reference source not found.**). While steps have been taken in recent years to improve efficiencies, much remains to be done. This pathway is not fit for purpose in the age of precision medicines.

6.1 Federal and provincial/territorial jurisdictions in health

Healthcare resides jointly within the federal and provincial/territorial jurisdictions. This is primarily a result of the *Canada Health Act* that, in effect, commits the federal government to funding basic hospital and physician services for eligible people across Canada.[114] This leaves an important, and growing, gap in health care coverage: coverage for drugs.

The provinces and territories have taken responsibility for providing a degree of public drug coverage. The federal government also provides transfer payments to

Challenges to equitable access for First Nations peoples

Accessing health services for First Nations living in rural, remote and isolated communities often means leaving their communities, even to receive basic health care.

The multi-jurisdictional nature of First Nations health services delivery also presents a distinct set of challenges for accessing and coordinating cancer screening and treatment, not to mention the inclusion of First Nations individuals in clinical trials or precision oncology practice assessments.

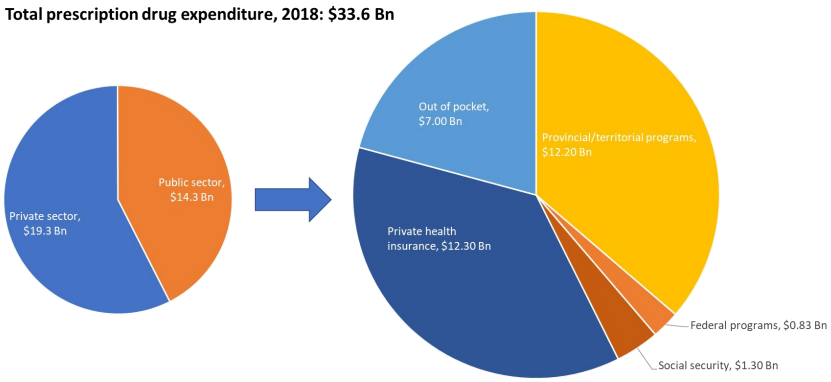
For First Nations, distinct historical and cultural factors contribute to unique views of cancer, which may explain lower rates of participation in prevention, early diagnosis, and treatment programs. Many health care professionals are unaware of this, creating barriers to effective cancer care as they generally do not understand and are unable to address First Nations' perceptions of cancer.

Precision medicine is a highly technical discipline requiring skilled acquisition and testing of diagnostic samples as well as experienced administration and monitoring of therapies. Limitations in operational requirements, as well as a lack of available required skills, can render the most effective of treatments unimplementable in rural, remote and isolated communities.

the provinces to fund some of this cost. Each province or territory has developed its own plan with eligibility criteria, funding rules and list of treatments covered. Provinces carry out some of these activities jointly using pan-Canadian processes (described below) but ultimately each province makes its own budget, listing and eligibility decisions.

Unsurprisingly, this has led to inequities in public drug coverage across the country – a provincial "postal code lottery." Private drug plans provide additional coverage for some, either through group insurance that employers (usually larger employers) and unions provide or through individual plans.

In addition to geography, access to funds often becomes crucial to treatment access. Unfortunately, as many cancers disproportionately affect older people who may well be relying on Federal and Provincial/Territorial-funded health services for their treatment, access to



medications not publicly covered means access denied.

Figure 7. Prescription drug spending by source of finance, Canada, 2018. Source: CIHI. Drug spending at a glance.[115]

6.1.1 Federal jurisdiction

Health Canada, a federal government body reporting to the federal Minister of Health, approves clinical trials undertaken in Canada; approves treatments for sale in Canada; monitors the ongoing safety profile and manufacturing quality of treatments after sale, and carries out a number of other regulatory functions.

Clinical trial approval

There are concerns that Canada takes too long to approve trials, puts too much "red tape" on trial design and monitoring and takes too long to approve treatments for sale. Of course, this is in the eye of the beholder. For people with life-threatening and serious debilitating illnesses that severely adversely impact quality of life and even survival, the faster they can access a treatment the better. They are also more likely to accept a higher tolerance for adverse events and side effects than other patient populations.

The Health Canada clinical trial approval process requires an extensive dossier of information about the treatment for the trial including its structure, biological function (both on- and off-target effects), effect in animals (called pre-clinical data; this includes how it is absorbed and

metabolised as well as data on side effects and efficacy), manufacturing and packaging processes, and of course its effect in humans (called clinical data). Clinical data requires an extensive range of experiments be undertaken to assess (among other things) its safety, efficacy, how long it stays in the body and how it is removed, interactions with other drugs, and how best to administer it. Studies in humans typically start with a very small number of people (Phase I or II trials) and expand to a larger population that is typical of those that have the condition (Phase II or III trials). As the trials progress to include patients with the condition, it is important that they receive the best treatment currently available so new medications are usually added to this regimen and compared with placebo (a dummy treatment).

Generating these data raise potential challenges including:

- In rare conditions, such as cancers with a specific mutation profile, identifying enough patients with that condition who are willing to participate in a clinical trial can be a challenge, especially when considering that the speed of change in the field of oncology means clinical trials must be completed quickly if they are to deliver meaningful results.
- In conditions where there is a standard of care (and in the vast majority of cancers, that means chemotherapy, radiation and/or surgery), novel therapies are either tested as an add-on; in patients with advanced disease, or in those who have relapsed after treatment with the standard of care. The upshot of this is the initial indication achieved for precision oncology treatments often covers only a small proportion of the total who may benefit, and potentially those whose disease has progressed to the extent that achievable benefits are limited (both of which have consequences when determining the societal value of a novel therapy).
- There are occasions where Phase II trials show such a clear and profound advantage for the treatment over the comparator that ethically the trial is stopped after Phase II and all trial participants put on the treatment arm. This may well impact the decision of payors about whether to include the drug for reimbursement.
- Trial design eligibility requirements often limit access to people with no known comorbidities or other medical factors that might adversely impact trial outcomes. This means that we do not answer the question in a trial of the outcomes in a real-world environment.
- Trials by design are for a limited time frame. This means that a trial cannot answer the question of whether of long-term safety and efficacy in trial participants. This is a strong argument for requiring Phase IV trials for treatments for life threatening and serious chronic illnesses.

Approval for sale

Health Canada's target review time for a standard submission is 300 days after which the product is issued a **Notice of Compliance** (NOC). Health Canada has taken steps to improve review timelines, introducing two approaches to expedited review:

- A **Notice of Compliance with Conditions** (NOC/c) may be granted for a drug product with promising clinical benefit, providing that it possesses an acceptable safety profile based on a benefit/risk assessment and is found to be of high quality. Submissions that

are granted NOC/c status are subject to shorter review targets (~200 days).[116] In 2016 seven products were granted NOC/c, six of which were oncology products. An NOC/c is an authorisation to market a drug contingent on completion of additional studies to confirm its health benefit as manufacturers often use data from Phase I and II trials only in such submissions.[117]

- Priority Review allows the "fast-tracking" of eligible New Drug Submissions and Supplemental New Drug Submissions intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions. The target priority review time is 180 days.[118] In 2016 Health Canada authorised ten products through priority review, three of which were oncology products.[116]

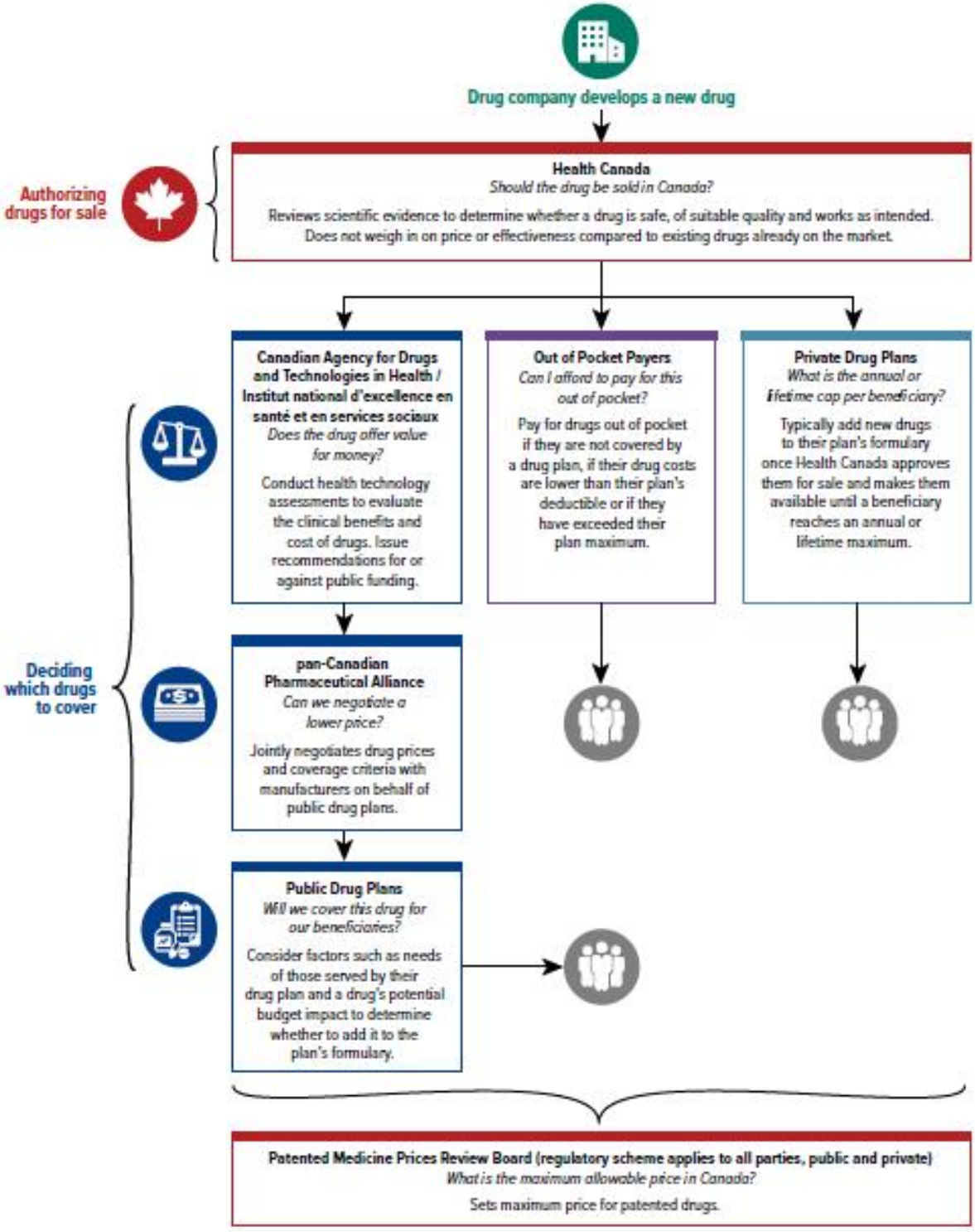


Figure 8. Decision makers and decision-making processes in Canada. Source: Advisory Council on the Implementation of National Pharmacare.[119]

There have been some improvements in the review of cancer drugs for sale with the decision by Health Canada to join Project Orbis. Initiated by the U.S. Federal Drug Agency Oncology Center Of Excellence in 2019, Project Orbis is an international partnership designed to give cancer patients faster access to promising cancer treatments by providing a framework for concurrent submission and review of oncology products among international partners. Successful applicants are those with cancer treatments of high impact and clinically significant. Canada joins Singapore, Australia, Brazil, Switzerland, the UK and Israel in this FDA initiative. Health Canada worked with the FDA and Australia's Therapeutic Goods Administration (TGA) on the first project Orbis submission. This led to Health Canada's timely approval of a treatment for women with advanced endometrial cancer in September 2019. Since then, Health Canada has participated in many Project Orbis submissions. In its first year (June 2019 to June 2020), a total of 60 oncology marketing applications were received, representing 16 unique projects, and resulting in 38 approvals.[120] As of 17 March 2023, 73 treatments have been approved with 52 granted marketing approval in Canada [121]

Regulatory review of a treatment is one factor for approval of a new treatment. Diagnostic tests are at the centre of the precision oncology revolution and essential to identifying those patients who may benefit from targeted treatments (as well as ensuring these valuable resources are not squandered on those who will not), and the process of developing, validating and gaining regulatory approval for a new test is not insubstantial.

Health Canada classifies diagnostic tests as medical devices, which are regulated by the Therapeutic Products Directorate's Medical Devices Bureau. Biologic products are regulated by the Biologics and Genetic Therapies Directorate. Devices intended to be used for **pharmacogenomic testing** are classified as Class III (moderate risk) medical devices and require a pre-market scientific assessment of the safety and effectiveness by the Medical Devices Bureau.[122] Health Canada encourages manufacturers to apply for a medical device licence for a companion diagnostic test as they progress through their drug development program; however, there is no provision for joint application and review processes for the drug and the companion test.[122] This may be a challenge for manufacturers in coordinating and aligning the review processes given that the regulatory review timelines for devices and medications are different.

6.1.2 Approving drug entry price into Canada

The Patented Medicine Prices Review Board (PMPRB) is an independent, quasi-judicial federal body with a dual regulatory and reporting mandate, to ensure the prices of patented medicines sold in Canada are not excessive, and to report on pharmaceutical trends and on the research and development spending by patentees.[123] For these purposes, it reports to the federal Minister of Health.

Currently a critical component of the price review process is the Median International Price Comparison (MIPC) Test which uses the median of the ex-factory prices of the same strength and dosage form of the drug product from seven comparator countries (France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States) to set the Maximum Average Potential Price for a new patented drug product.[124]

This process is widely recognised as out-of-date, not least because of the processes to negotiate drug prices collectively now implemented by those actually responsible for public

funding of medications, the provinces/territories and some federal plans outlined below under the jurisdiction of the pan-Canadian Pharmaceutical Alliance. The federal government has implemented changes to the *Patent Act* regulations and guidelines by amending the comparator countries to Australia, Belgium, UK, France, Germany, Italy, Japan, the Netherlands, Norway, Spain and Sweden (notably removing the US which has the highest comparator price).

6.1.3 Federal coverage for oncology drugs

While for the most part funding for oncology care is under the mandate of the provinces and territories, there are three pathways through which the federal government may fund cancer care:

- As mentioned above, the *Canada Health Act* commits the federal government funding basic hospital and physician services for eligible people across Canada. This includes medications administered in hospitals, but not those administered in out-patient settings.[114,125]
- The Non-Insured Health Benefits Program (NIHB) provides coverage to registered First Nations and recognized Inuit for a specified range of medically necessary items and services that are not covered by other plans and programs.[125] Of note, Metis drug costs are covered through a patchwork of provincial and territorial agreements.
- The federal Special Access Programme[126] administered by Health Canada allows drugs not approved for sale in Canada but approved in other jurisdictions to be provided on a case by case basis to patients in Canada with the approval of their doctor and the manufacturer. Payment by the patient is at the discretion of the company. Safety data are not collected. This is not intended to replace a requirement by the manufacturer to apply for approval for sale in Canada so it is not generally a permanent solution to access to such a product.

6.2 Pan-Canadian health jurisdiction

6.2.1 The Canadian Partnership Against Cancer

Founded in 2007, CPAC is an independent organization funded by the federal government to be the steward of the Canadian Strategy for Cancer Control, with a mandate to accelerate action on cancer control for all Canadians. The goal of CPAC is to translate learning into pervasive and impactful front-line policy and practice across Canada for the benefit of all cancer patients or those at risk of cancer.[127]

The Partnership's efforts span the continuum of cancer control – from prevention and screening through diagnosis and clinical care to palliative care and survivorship – and cuts across that continuum with initiatives to monitor and improve cancer system performance and mobilize evidence to drive policy and practice improvements.

Central to this effort is influencing health system administrative structures and policies to meaningfully create systemic clinician behaviour change that measurably supports patient and family needs, including a focus on the unique needs of underserved populations who have not yet benefited equitably from the Canadian Strategy for Cancer Control (health inequities are greatest for those living in rural, northern and remote Canadian communities).[128] It is important to note that while CPAC may work closely with the provinces and territories on policy development, its mandate is to influence; it has no capacity to direct.

A key priority for CPAC is working across all jurisdictions to assist them in implementing a culturally responsive action plan for cancer control with and for First Nations, Inuit and Métis communities, and CPAC has worked closely with those communities to understand the unique challenges they face.[129-131]

The Canadian Cancer Control is presently under review to be refreshed for the next ten years.

6.2.2 Determining value for public payors

Issuance of a NOC or NOC/c only allows a product to be sold in Canada; ensuring it is reimbursed by provincial and territorial drug programs requires an entirely different process.

Created in 1989 by Canada's federal, provincial/territorial governments, the Canadian Agency for Drugs and Technologies in Health (CADTH) was born from the idea that Canada needs a coordinated approach to assessing health technologies to determine their value for public reimbursement.[132] Tasked with providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care systems, it has recently moved from a health technology assessment role to a health technology management role following drugs along their life cycle. As part of that role, it has begun to develop policies and practices about the use of real world evidence in determining the value of a drug under review.

Until a few years ago CADTH used the pan-Canadian Oncology Drug Review (pCODR) process to conduct health technology assessments (HTAs) for oncology products.[1] A few years ago CADTH began to merge the policies and practices of pCODR and the Common Drug Review to review non-cancer drugs. Among the changes enacted, CDR now permits people to see the recommendations for a drug in draft format and comment on them. Unfortunately, the Quality Adjusted Life Years (QALYs) for cancer drugs has been lowered from $100,000 to the CDR threshold of $50,000. It also has begun developing algorithms to sequence the use of cancer therapies. These changes have generally not worked to the benefit of oncology reviews.

> Separate HTA assessment bodies in Canada (CADTH and INESSS for Quebec) only adds to the potential for access inequities, as these groups have shown themselves quite capable of reaching different conclusions from the same data.

In December 2018, CADTH also assumed the functions previously undertaken by the Cancer Drug Implementation Advisory Committee (CDIAC) of the Canadian Alliance of Provincial Cancer Agencies. This role is to consolidate clinical expert opinion from site-specific provincial tumour leaders and individual clinical experts to provide advice on how new drugs can be integrated into therapy with currently funded drugs with the goal of achieving greater consistency in drug funding decisions across Canada. CADTH will now review the development of algorithms for each new cancer drug or indication submitted to pCODR, to indicate how the new therapy could be placed and potential sequencing of other existing therapies. This should further enhance transparency of this process, to enhance patient and other stakeholder engagement, and to help stakeholders to better understand the cancer drug

[1] For non-oncology products CADTH uses the Common Drug Review process.

funding landscape in Canada, and not to affect any reimbursement recommendation by pERC.[133]

Also in 2018, the federal Government announced an initiative to allow aligned review processes for Health Canada and HTA organizations (CADTH and INESSS).[134,135] Prior to this, HTA organizations would accept submissions up to 180 days before an expected NOC issuance. The new initiative should reduce duplication between submissions, allow for real-time discussions between Health Canada and the HTA organizations, and help minimise potential delays between NOC and HTA recommendation. Importantly, when adopting this new initiative companies may now submit HTA submissions as early as four months after the start of Health Canada's review (for standard submissions. For a priority review the HTA submission should be made as soon as possible after the Health Canada submission while for the NOC/c pathway there should be at least a three-week gap). Health Canada has also introduced the concept of rolling reviews, which allows eligible sponsors to provide data for a trial as it becomes available for up to 155 days after Health Canada approves the drug for this process.[136]

While this is a welcome step, alignment is also needed across borders to expedite access. The Canadian regulatory review processes, post-marketing requirements and HTA evidence requirements align, but not perfectly, with those of other regions. Consider for example the recent rejection by pERC of brentuximab vedotin for the treatment of adult patients with Hodgkin Lymphoma (HL) after failure of at least two multi-agent chemotherapy regimens who are not candidates for autologous stem cell transplant (ASCT).[137] This represents up to 54 patients a year, a small proportion of the approximately 900 Canadians diagnosed with HL each year and the supporting evidence for the application was derived from a trial designed to fulfill a requirement of the conditional marketing authorisation of brentuximab vedotin in the European Union.[138] The trial enrolled a total of 60 patients from Europe and Asia who were considered ineligible for ASCT and had received a median of two prior therapies (range, 1-7); 82% of patients had received > 1 prior therapy. Results from the study were also used for health economic modelling purposes. Granted, these eligibility criteria do not align perfectly with the pCODR requested reimbursement criteria. However, given the challenges in conducting trials in such small patient populations it is unfortunate that this was the primary reason for rejecting the submission, particularly considering the results mentioned earlier for Australian patients who received ipilimumab in the first year of reimbursement.[81] Again, such narrow and rigid application of guidance runs the risk of discouraging pharmaceutical companies from submitting applications in Canada for small patient groups, if the prospective revenues are limited and the cost associated with a complete application are significant, and unique to Canada.

In February 2019 CADTH announced a new collaboration with the UK National Institute for Health and Care Excellence (NICE) to offer parallel scientific advice to pharmaceutical companies, and in September 2022 this was expanded to include the Australian Government Department of Health and Aged Care, Healthcare Improvement Scotland, Health Technology Wales, and the All Wales Therapeutics and Toxicology Centre.[139] This Parallel Scientific Advice service features joint summaries highlighting areas of alignment between the two health technology assessment agencies, as well as separate advice reports from CADTH and NICE.[140]

This new initiative may help eliminate disconnects similar to that described above for brentuximab vedotin.

6.2.3 Defining the value of precision oncology

> *"It is precision that promises improved patient outcomes and reduced health care costs. It is precision that offers a viable solution to the challenges facing our health care system, including the affordability and accessibility of new cancer interventions in our current economic environment."*
>
> Edward Abrahams, PhD President Personalized Medicine Coalition [NOVARTIS]

Defining value of therapeutic interventions to ensure access is increasingly important and a necessary strategy for ensuring healthcare affordability. The maximization of population health is viewed to be a fundamental objective of any health care system, albeit subject to a finite budget. Precision medicine allows valuable health resources, and the technologies they make available, to be focused on those patients who will benefit (maximising return) while also avoiding exposure for those who will not (minimising investment).[141] For example, the application of the Oncotype DX® genomic assay, which estimates 10-year distant recurrence risk (DR) for breast cancer, is providing insights into the value of traditional chemotherapy regimens in women with hormone-positive, HER2-negative breast cancer. Results from the TAILORx study demonstrated that women with low RS score (0-25) – approximately 80% of the study participants – derive no benefit from adding chemotherapy to endocrine therapy while those with RS scores greater than 25 achieves substantial benefit.[142] Notably, clinical pathology parameters such as tumour size, histological grade, and clinical risk category did not predict chemotherapy benefit. Without the RS, 73% of women in the study identified as high clinical risk would have been overtreated, and 43% of those identified as low clinical risk would have been undertreated for their breast cancer.[142]

Unfortunately, there are no specific federal, provincial or territorial reimbursement processes for companion diagnostics, and private insurance assists with costs related to prescription drugs but generally not diagnostic tests.[143] As funding decisions for genetic tests are made at the provincial level, decisions may vary across jurisdictions, inadvertently creating a barrier to access to a life-saving medication for patients relying on both public and private coverage. Not all provinces have dedicated processes in place to review, fund, and implement such tests which may put pressure on individual hospitals to evaluate and offer new genetic tests. When the local decision is made to offer the test, usually it is done without additional funding.[142]

Precision medicine also limits off-target toxicities – the Achilles heel of chemotherapy and a major reason why such precision oncology treatments may be administered in the patient's home rather than in the resource-intensive hospital setting. For example, in 2010, a 5-month study at an intensive care unit (ICU) of a comprehensive cancer centre found that 22.9% of all ICU admissions were due to adverse drug reactions. The average length of stay for each patient was 6.2 days and the mortality rate was 28%.[144]

A survey of a broad spectrum of payers (government, private, and large employer payers, regional and national health plans) and oncologists highlighted a troubling disparity between the groups in assessing the value of precision oncology treatments.[144] Both groups believe that precision oncology interventions can improve patient outcomes in a cost-effective manner;

that the cost of precision diagnostic testing is worth the potential long-term savings, and precision medicine in oncology offers a solution to the rising costs of health care, mainly by avoiding waste in the system. But when asked who should ultimately determine whether an intervention provides value, half of the payers believed that all stakeholders, including oncologists, payers, patients, and government, should define value while 60% of oncologists believed that this was their responsibility only.

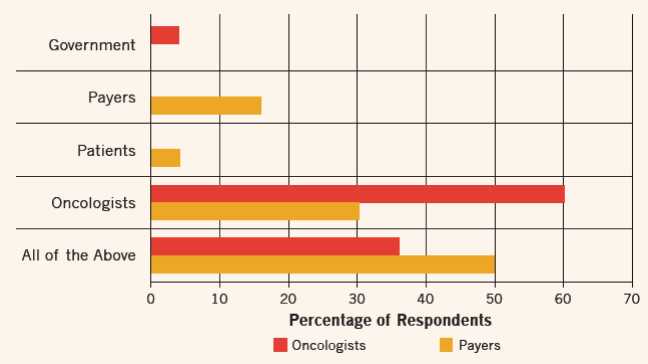


Figure 9. Who should ultimately determine if a new oncology intervention provides value? Source: Novartis Oncology, 2014.[144]

Adding to the disconnect, a 2008 Zitter Group survey found that while two-thirds of oncologists believe a treatment should extend life by 3 to 6 months to constitute a survival benefit, payers believe a treatment should extend survival by at least 10 months to constitute a survival benefit. Until there is consensus on what constitutes value across all stakeholders, it is likely that the debate around the adoption of such products in the public health system will continue. And patients will remain the unwitting and unwilling victims of this debate.

There also appears to be a growing disparity between the evidential standards for regulatory approval and those accepted by CADTH. While Health Canada is prepared to grant an NOC/c on the basis of positive Phase II data, CADTH appears more reticent, at times at odds with the recommendations of its own clinical guidance panel (CGP). While such a disconnect seems completely incongruous in the modern world of increasing harmonization at a global level in drug approval processes, it is an embarrassment to Canada that the standards accepted by Health Canada (who are ultimately responsible for determining safety and efficacy) are considered unacceptable for use in HTAs.

As reported in the Faces of Lung Cancer 2019 report,[59] many targeted therapies have been approved (often with NOC/c) by Health Canada based on results from Phase 2 trials. But all-too-often those same data are considered invalid by CADTH for establishing a net clinical benefit – an essential step for calculating the cost-benefit for any new product. Thus, treatments that are accepted by Health Canada to benefit patients are consigned to the purgatory of technically being available for use to save lives but in practice having to wait until Phase 3 trials have completed before the necessary funding applications may be submitted. It gets worse even when a submission is considered valid by CADTH: according to the its 2021–2022 annual report, 84% of reimbursement recommendations for oncology products were positive.[145] But that is a little disingenuous: CADTH received 33 reimbursement submissions in 2021. Of those, one was withdrawn, eight received recommendations of "Do not reimburse",

and the remaining 24 received recommendations of "Reimburse with clinical criteria and/or conditions". Every single one of those 24 recommendations had a condition for the drug price to be reduced.[146]

These delays in access are substantial and have a huge impact: by way of illustration, on 15th April 2016 pembrolizumab received NOC/c for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 and who have disease progression on or after platinum-containing chemotherapy.[147] It took another two years for this indication to be funded by most provincial health authorities.[148] For a disease estimated to result in the death of over 21,000 Canadians in 2020 administrative barriers that result in these kinds of delays are scandalous and an embarrassment for our nation. For reference, and to compound the travesty of the Canadian processes, approval in the US occurred on 4th September 2014.

Another example: pCODR issued a negative recommendation for ibrutinib in the setting of relapsed Waldenstrom's Macroglobulinemia (WM), a rare and incurable type of non-Hodgkin lymphoma, despite the observation of the CGP that the results observed in the non-comparative phase II trial represented excellent disease control in a heavily pre-treated population. Furthermore, they noted that "second-line treatment is frequently given intravenously, is of relatively limited effectiveness in terms of progression-free survival and may have significant toxicity, especially myelosuppression. New treatments with high response and progression free survival rates, especially oral therapies, are highly desirable."[149] While the pERC noted ibrutinib's ability to control symptoms, with fewer toxic side effects than available therapies, in an easy to take-at-home pill format that is extremely important to patients, it cited the lack of a phase III RCT where it believed such a trial was feasible, as a justification for the negative recommendation.[150]

And again: daratumumab, given in combination with dexamethasone, received a negative pCODR recommendation in the setting of 4th-line treatment of multiple myeloma.[151] Again the rationale was that a phase III randomized controlled trial would be feasible to determine the efficacy of daratumumab compared with available treatment options or best supportive care. This was despite feedback from clinician and patient stakeholders, and the CGP, that a trial comparing daratumumab to best supportive care was not feasible for pragmatic and ethical reasons. Furthermore, the CGP stated that it would be unethical to enrol patients in a trial comparing daratumumab with best supportive care when the toxicity and effectiveness of the suggested best supportive care had proven detrimental to these patients. Eventually, CADTH granted a recommendation of "Reimburse with clinical criteria and/or conditions" (yes, cost reduction was one of the conditions) on 5th March, 2020.[152]

While CADTH states clearly that it will accept almost any data as part of a submission, there are clearly exceptions to this rule.

The exceptions appear to be those where CADTH determines that the implementation of a Phase III trial will not be feasible. Where the results of the Phase II trial provide overwhelming evidence that those on drug survived and/or had profoundly enhanced quality of life, requiring a Phase III trial without at least making a conditional recommendation for reimbursement where appropriate preliminary evidence of safety and efficacy are shown is certainly unethical. The issue of how to negotiate price where such a degree of long-term uncertainty exists should be managed by pCPA (described below).

6.2.4 Achieving funding

Contingent on a positive recommendation from CADTH/INESSS with conditions including an appropriate price point, the drug file generally is sent to the pan-Canadian Pharmaceutical Alliance (pCPA). This organization is the creation of the Council of the Federation (the Premiers), and although not founded on a piece of legislation, it is funded by the provinces/territories and PMPRB claw back funds. Recently, pCPA has become an incorporated entity. It is too early to determine whether this recent incorporation will have a substantive impact on the manner in which pCPA does its work. At a minimum it will be able to sign contracts in its own name. The pCPA conducts joint provincial/territorial/federal negotiations for brand name, generic drugs, biologics and biosimilars in Canada with a mandate to enhance patient access to clinically relevant and cost-effective drug treatment options. The pCPA decides whether joint pan-Canadian negotiations will occur for the drug product and if that is the case, one jurisdiction will assume the lead. If an agreement is reached, a Letter of Intent will be signed by both the manufacturer and the lead jurisdiction. It is then up to each participating jurisdiction to make its final decision on funding the drug product through its own public drug plan and enter into a jurisdiction-specific product listing agreement with the manufacturer.[153,154] All of the negotiations are confidential.

Patient groups understand that generally pCPA negotiates first dollar price reductions. It does not have a mechanism to renegotiate after a certain period of time has passed. As oncology treatment have become increasingly tolerable to the patient and are more available orally, at least in part due to the precision oncology revolution, so the requirement for treatment within the hospital setting has lessened.

A tsunami of oncology treatments will be coming through pCPA over the next few years. This is problematic. We know that there is a need for more nuanced negotiating tactics by pCPA in an era of precision and personalized medicine. There is a need for real world evidence both from people who were in the trial after the trial ends and also from other people taking the drug who were not in the trial. This will allow pCPA to negotiate pay for performance agreements, and other creative contracts, that include renegotiation after a reasonable period of time to collect real-world evidence (RWE) following the use of the treatment under real-world conditions.

Although all government agencies claim to be collecting real world evidence, including Health Canada, CADTH, the Canadian Institute for Health Information (CIHI), pCPA and provincial cancer agencies, there is no evidence that they are all collecting relevant information; that they are sharing or consolidating information or that pCPA is using this information to develop contracts that recognize Phase II trial data or the implications of precision medicine based on genetics and companion diagnostics.

While managed formularies have existed since the 1990's in Canada, such adoption of CADTH recommendations to guide these decisions is an approach which may both delay and limit access to such therapies in future.[155,156]

Many other countries have developed and adopted alternative reimbursement agreements. Such agreements align reimbursement with pre-specified goals, including financial, performance-based, or a combination of the two.[157] Such agreements are popular with payers

as they reduce both financial risk and uncertainty about a treatment's outcomes, while for manufacturers they help secure market access, particularly for products and patient segments with little real-world evidence (RWE), demonstrate the value of a treatment, and shift a payer's focus from cost to value.[157]

For example, Managed Entry Agreements (MEAs) have become popular over time in the European Union, particularly Italy and the UK, Australia, and the US (where they are commonly referred to as value-based contracts).[158] Unfortunately, Canada has been reticent to adopt this approach, although the pCPA office has confirmed it is exploring MEAs in some negotiations.[158] One of the key challenges in Canada for adoption of MEAs is the need for comprehensive data sources to support RWE assessment. The lack of such data systems within many provinces – notably Ontario and Quebec – combined with the limited interoperability of those datasets that are in place has been identified as a major barrier in negotiating MEAs.[157] Ultimately, the outcome for people living in Canada with cancer is more delay in access to potentially life-giving therapies.

6.3 Provincial jurisdiction

6.3.1 Provincial and territorial stakeholders in oncology care

The overlap and redundancy that typifies the Canadian oncology care and reimbursement pathways continue at the level of the provinces and territories.

Cancer services fall under the remit of each province's health ministries and are often implemented through the provincial cancer care agencies (Table 1). The cancer care agencies work to reduce the burden of cancer by promoting the highest quality of care and services for all eligible people in Canada that are affected by cancer in their respective province, coordinating their activities through the Canadian Association of Provincial Cancer Agencies (CAPCA). CAPCA provides a forum for the leaders of Canada's cancer control systems to discuss, learn from and collaboratively address issues that affect the delivery of cancer care in Canada.

While each province and territory is autonomous and implements its own strategic plan and priorities, CAPCA has committed to work across provincial discipline-specific and organizational boundaries in pursuit of a sustainable, efficient and safe cancer delivery system. This has led to a number of initiatives, including:

- *The Cancer Drug Funding Sustainability Initiative.* CAPCA is working with CADTH, INESSS and the pCPA to ensure Canadian patients continue to have access to innovative and effective cancer treatments and that our cancer system is achieving maximum value for the money invested.
- *The Safe Use and Handling of Oral Anti-Cancer Drugs in Community Pharmacy: A Pan-Canadian Consensus Guideline* (2016). As oral cancer drug therapy becomes more common, enabling patients to self-administer their cancer treatments, it has highlighted the need for standardized processes and safeguards for the use, handling and disposal of these often-toxic chemicals, whether it be at the community pharmacy or by patients and their caregivers.
- *Expanding lung cancer screening:* CAPCA and CPAC have collaborated on the development of a standardized lung cancer screening business case to facilitate

planning and decision-making at the jurisdictional level for the implementation of provincial/territorial organized lung cancer screening programs. By 2023, CAPCA and CPAC will have established system readiness to implement organized lung cancer screening programs by leveraging pan-Canadian expertise in lung screening trials and leveraging implementation experience from the development of previous breast, colorectal, and cervical screening programs.

- Through the establishment of the *Systemic Therapy Safety Council* in 2007, CAPCA has made a marked impact in the improvement of patient safety through the creation of Guidelines for Developing Ambulatory Chemotherapy Preprinted Orders, and support for national incident reporting systems for both medication and radiation treatment incidents.

Table 1. Provincial and territorial government authorities and agencies responsible for providing cancer care.

Provincial/territorial health authority	**Provincial/territorial cancer care agencies and programs**
British Columbia Ministry of Health Services	British Columbia Cancer Agency
Yukon Health and Social Services	Whitehorse General Hospital coordinates care and treatment for people with cancer in Yukon
Alberta Health Services	Cancer Control Alberta – Alberta Health Services
Northwest Territories Health and Social Services	The majority of NWT patients are referred to the Cross Cancer Institute in Edmonton, Alberta
Saskatchewan Ministry of Health	Saskatchewan Cancer Agency
Manitoba Health	CancerCare Manitoba
Nunavut Department of Health	Nunavut residents access cancer care from neighbouring provinces.
Ministry of Health and Long-Term Care	Cancer Care Ontario
Ministère de la Santé et des Services Sociaux	Direction Québécoise de Cancérologie
New Brunswick Ministry of Health	New Brunswick Cancer Network
Nova Scotia Department of Health and Wellness	Cancer Care Nova Scotia
Prince Edward Island Department of Health and Wellness	Prince Edward Island Cancer Treatment Centre
Newfoundland and Labrador Department of Health and Community Services	Eastern Health Cancer Care, Newfoundland and Labrador

Table 2. Federal and Provincial Indigenous Health Insurance Authorities and their Eligibility Criteria

Federal and provincial Indigenous Health insurance authority	**Eligibility**
Non-Insured Health Benefits (NIHB) Program[125]	An eligible client must be a resident of Canada and any of the following: • A First Nations person who is registered under the Indian Act (commonly referred to as a status Indian) • An Inuk recognized by an Inuit land claim organization • A child less than 18 months old whose parent is a registered First Nations person or a recognized Inuk
First Nations Health Authority (FNHA)[159]	Eligibility extends to include all First Nations people who are residents of British Columbia (excluding persons who receive health benefits by way of a First Nations organization pursuant to self-government agreements with Canada).
Nunatsiavut Government's Non-Insured Health Benefits (NIHB) Program[160]	Available to beneficiaries of the Labrador Inuit Land Claim Agreement
Nunavik's Insured/Non-Insured Health Benefits (INIHB) Program[160]	Available to beneficiaries of the James Bay and Northern Quebec Agreement

6.3.2 Provincial/Territorial public coverage

CADTH provides recommendations to provinces and territories regarding reimbursement. The provinces and territories can then decide whether to join the pCPA negotiations. Even those that do are not required to list drugs for the negotiated price once negotiations are complete or in fact at any point. This has led to the patchwork quilt description of drug coverage across the country. As described above, provinces (except Ontario) have their own separate cancer agencies that provide advice on this issue as well. One of the most startling differences we see is the situation where Ontario and some Atlantic provinces do not list oral cancer drugs for coverage while all other provinces do. This is one of the anomalies some people trust that national pharmacare (discussed below) will resolve.

There is also the issue of quality assurance of companion diagnostic tests. Given the significance of their results, there is a need to ensure reliable high-quality testing in order to maximize the benefit that can be derived from the associated medication. Reliability and quality of testing can be assured through establishing an effective framework for clinical laboratory operations, medical testing, and diagnostic devices.

Hospitals and private laboratories offering genetic testing are subject to provincial regulations related to laboratory operations, accreditation, and quality control. However, the significant variation in the regulatory framework across the different provinces and territories is a growing concern, especially given the lack of national guidelines on harmonization and good practice.[161] Another related issue is the need for clarity regarding the legal implications to

Canadian health care institutions and their laboratories of using proprietary companion diagnostic tests, or equivalent laboratory-developed tests, including the on- and off-label uses of such tests.[161]

Related issues are the need for adequate and also specialized pathology support for the analysis of specimens in order to determine appropriate personalized and precision treatments for oncology patients.

6.3.3 Private insurance role in cancer treatment coverage

Medication reimbursement is also covered by private payors as well as public drug plans for those who have insurance. With the migration towards community-based oncology medications and the high price of these treatments, these expensive medications have started to account for an increasing share of expenditure. [123] Private drug plans have responded by establishing their own gatekeeping processes, for example, Manulife's DrugWatch program, guided by CADTH HTAs.[162,163] Ultimately, the establishment of these product listing agreements (PLAs) implies more barriers to Canadians living with cancer in accessing potentially life-giving therapies. There are also inherent inefficiencies related to private insurance coverage for drugs, which will be discussed further in the next section.

6.3.4 The national pharmacare debate

Canada's public health system has evolved immeasurably since Tommy Douglas introduced the first provincial hospital insurance program. In 1964, the Royal Commission on Health Services recommended that Canada implement a universal, public pharmacare program following the introduction of universal coverage of medical care (the latter being put in place by Lester B Pearson in 1966). In 1997, the National Forum on Health, chaired by then Prime Minister Jean Chrétien reaffirmed this recommendation, as did the 2002 Romanow commission.[164] Also in 2002, the Standing Senate Committee on Social Affairs, Science and Technology Report on the State of the Healthcare System in Canada recommended introducing catastrophic drug coverage, and also called for the federal government to work closely with the provinces and territories to establish a single national formulary. In 2018 the House of Commons Standing Committee on Health Pharmacare Now: Prescription Medicine Coverage for All Canadians (2018) commissioned a study by the Office of the Parliamentary Budget Officer to examine the potential for cost savings associated with national pharmacare, which found that, if implemented, it could reduce total annual prescription expenditures by $4.2 billion.

In 2019 the Advisory Council on the Implementation of National Pharmacare released its final report: A Prescription for Canada: Achieving Pharmacare for All.[119] The report made 60 recommendations addressing the principles of pharmacare, terms of coverage, Government collaboration, Indigenous engagement, creating a Canadian drug agency, developing a national formulary and implementing it (starting with essential medicines), a national strategy on appropriate prescribing and use of drugs, and also for expensive drugs used to treat rare diseases, financing national pharmacare, the legislative framework, support for transition to a national formulary, information technology and drug data, and supporting federal measures.

The report includes some stark insights into the fragmented, uneven, unequal and unfair state of drug coverage in Canada:

- Canadians spent $34 billion on prescription medicines in 2018, which is more than the amount spent on doctors.
- Drug funding relies on a confusing patchwork of more than 100 government-run drug insurance programs and more than 100,000 private drug insurance plans. Despite this, about 7.5 million Canadians either don't have prescription drug insurance or have inadequate insurance to cover their medication needs.
- About 60% of Canadians are enrolled in private drug plans (primarily employer-sponsored benefit plans), but these plans cover only 36% of total system-wide spending on prescription drugs, partly because working Canadians are younger and healthier.
- Only 27% of part-time employees have heath benefits. This is particularly relevant with the explosion of the gig economy: those most likely to work part-time or in contract roles (women, people with low incomes and young people) are less likely to have health benefits.
- One in five Canadians struggle to pay for their prescription medicines. This includes many people with insurance because of copayments, coinsurance and deductibles.
- Three million don't fill their prescriptions because they can't afford to. Of these, 38% had private insurance coverage and 21% had public coverage, but it did not cover enough of the drug costs to make them affordable.
- One million Canadians cut spending on food and heat to be able to afford their medicine. Many take out loans, even mortgage their homes.
- The existing system is inherently inefficient: Administration costs are generally three times higher in the private sector than the public sector, and that gap has widened over time. Between these higher administrative costs and the amount kept as profits, private insurance adds considerable costs to an already expensive sector.

We propose that the government enact national pharmacare through new legislation embodying the five fundamental principles in the Canada Health Act:[114] _ENREF_1

Universal: all residents of Canada should have equal access to a national pharmacare system;

Comprehensive: pharmacare should provide a broad range of safe, effective, evidence-based treatments;

Accessible: access to prescription drugs should be based on medical need, not ability to pay;

Portable: pharmacare benefits should be portable across provinces and territories when people travel or move; and

Public: a national pharmacare system should be both publicly funded and administered.

Overall, the result is a non-system where too many people fall through the cracks leading to ill health and greater costs to the health system due to extra visits to physicians and hospitals when people's health fails as a result of lack of access to medicines. A recent study looked at what would happen if out of pocket costs were removed from medications for just three diseases—diabetes, cardiovascular disease and chronic respiratory conditions. It concluded

there would be 220,000 fewer visits to emergency departments and 90,000 fewer hospitalizations annually—a potential saving of up to $1.2 billion a year.

In addition to a detailed roadmap and set of recommendations, the report also included a timeline, with major milestones due on 2022 (Figure 11). Pandemic notwithstanding, there has been little, if any, sign of action to date.

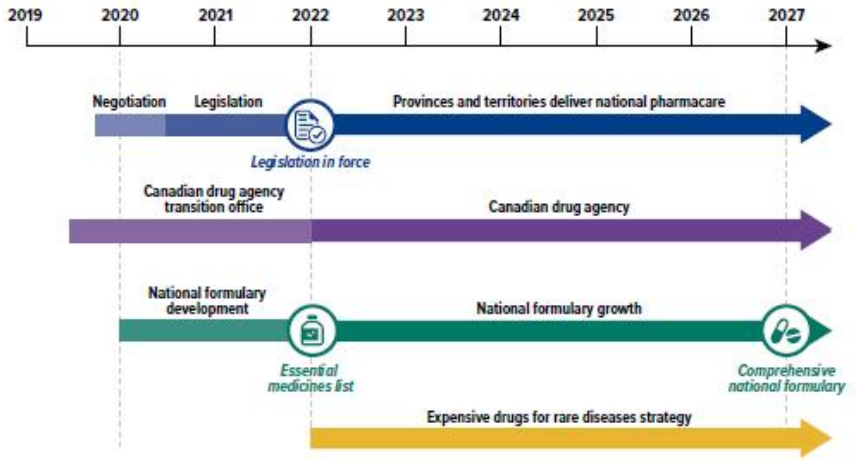


Figure 10. Timelines for pharmacare implementation, as presented in the A Prescription for Canada: Achieving Pharmacare for All Final Report.[119]

Every developed country with a universal health care system – except Canada – provides universal coverage of medically necessary prescriptions. Although $35m was allocated in 2019 to Health Canada to establish a Canadian Drug Agency Transition Office to work with provinces, territories, and other partners to develop a vision and mandate for the Canadian Drug Agency, it remains to be seen how much longer Canadians will have to wait for a national pharmacare program to be launched.[165]

7 The Economic incentives for reimbursement of Personalized Medicine

As mentioned in Section 6 above, there are several important reasons for both public and private payers to consider reimbursement of new and innovative drugs and companion diagnostics. Of course, this is not likely achievable under the present health budgeting by provinces. Presently, a percentage of each heath budget is allocated to different areas e.g. hospitals, doctors, administration, drugs. Rather we need a Value-Based Health Care (VBHC) system based on a population funding approach, bundling the services needed for each population rather than forcing people to fit themselves into the existing funding model. The International Consortium for Outcomes Measures (ICHOM) strongly supports this approach internationally with some success. In Canada, the Conference Board of Canada is championing this approach, as have oncology patient groups at the national "Patients Redefining Health Care Summit." Recently, the Conference Board of Canada collaborated with the Segal Cancer Centre at the Jewish General Hospital (JGH) of the Centre intégré universitaire de santé et de services sociaux (CIUSSS) du Centre-Ouest-de-l'Île-de-Montréal to

explore opportunities to improve the systematic collection and use of PROs to support patient care and clinical excellence, focussing on people with colorectal cancer. The report recognized that implementation of PROs, a primary pillar of value-based healthcare (VBHC), is a significant organizational undertaking involving care teams, patients or population representatives, integrated information technology, and support services. But when care teams use PROs, they facilitate patient-centred care and foster better engagement between patients and their healthcare team. On an organizational and system level, aggregation of PROs can support decision-making on services and patient trajectories or pathways.

8 Recommendations to meet the challenges of timely, equitable access, affordability and appropriate prescribing in Canada

Canada is beginning to adapt and capitalize on the opportunities realized by precision oncology, but all too often the pace of change lags other similar jurisdictions globally. It certainly is not changing the health systems in Canada to match the pace of innovation and patient needs.

For example, while the participation of all provinces and territories in the pCPA is welcomed, their ability to opt out of the decision-making process is not. As well, the clear overlap between the mandate for CADTH and proposed changes to PMPRB seems illogical at best and inefficient and wasteful at worst.

While the joint initiative between CADTH and NICE is a move forward, it still only highlights the

What is Value-Based Health Care?

The current focus has been on minimizing short-term costs and battling over who pays what. The problem is that many of the strategies, organizational structures and practices are badly aligned with value for the patient. The major problem the system is facing today is not technology but management.

Value-Based Health Care is a new vision of the healthcare system in which the focus of every stakeholder is on improving value for patients relative to the dollars expended.

Value should be measured for the patient, not the health plan, hospital, doctor, or employer. In measuring value for patients, patient outcomes are multidimensional and far more complex than just survival. Recovery time, return to work and quality of life factors including independence, pain, range of motion, and emotional wellbeing during the process of care all matter. When measuring value, outcomes and costs should be measured across the whole cycle of care, including rehabilitation, and not just for isolated interventions or procedures. This should be done at the level of medical conditions since that is the only way outcomes and costs can be compared directly to determine value.

Simply minimizing costs is the wrong goal and will lead to counterproductive results. Eliminating waste and unnecessary services is beneficial, but cost savings should come from true efficiencies not from cost shifting, restricting care (rationing) or reducing quality.

There are opportunities for major improvements in healthcare value through new medical technologies. Even more important will be new ways of organizing, measuring, and managing healthcare delivery over the full cycle of care.

Source: Porter et al. 2006.[2]

differences between HTAs, rather than addressing them.

As precision oncology moves towards the holy grail of transcending traditional approaches for specific patient populations, HTA requirements must reflect this revolution and reflect the value of the indirect as well as the direct costs associated with cancer treatment in its reimbursing formula and decision-making model. This is particularly pertinent to Canada, where travel to the nearest cancer centre places a significant burden on those living in remote communities.

A central tenet of implementing precision oncology is targeted therapy for those patients who will benefit. This must be balanced by consensus on both what constitutes acceptable benefit, and also the definition of futility. There are clear differences between two key stakeholders – payers and oncologists – in terms of what defines acceptable benefit and whose decision it is to make such a call, which must be resolved. Patient perspectives on reasonable benefit/harm/uncertainty ratios are paramount.

Precision oncology is a disruptive technology and its adoption will inevitably require the development of new service models with redefined professional competencies and responsibilities. Professional standards will need to evolve to keep pace if we are to build capacity for these new skills, not to mention respecting the already significant investment healthcare professionals have undertaken to achieve their current level of knowledge and experience. Ongoing professional education will be essential if all stakeholders are to stay current with the changing therapeutic landscape. Synonymous with this is a breakdown of established funding structures and redirection of funding to reflect changing treatment paradigms. The re-allocation of funds should also reflect the trend for oral cancer drugs that are administered in the patient's home; why a funding model deemed acceptable for the inception of universal healthcare over 50 years ago should be considered appropriate for the modern era is incredulous.

Then there's data. Just as validated diagnostic testing is the gatekeeper to precision medicine, so the robust collection of real-world evidence and its rigorous analysis is the foundation of determining value, and consequent to that supporting novel approaches to funding agreements. Haiti, Rwanda, Malawi, and Lesotho have effective electronic medical record system; Canada's most populous provinces do not.[166] Without real-world evidence to justify reimbursement, why would pharmaceutical companies bring their products here? Without real-world data, how will we address such challenges as treatment sequencing and combination therapy in an ever-more complex therapeutic environment? Without real-world data Canadians must rely on other sources such as Australia for the evidence of just how truly effective novel treatments can be.[81] The ethics of such wilful disregard of what is now standard in the developed world rigidly combined with the rigid insistence on comprehensive data to support access must be subjected to serious contemplation.

Specific recommendations are as follows:

1. **Streamline clinical trial approvals** – Health Canada must streamline these processes so all redundant and/or unnecessary steps are removed.
2. **NOC/c** – This should be the standard approach to drug approval used by Health Canada for oncology drugs.
3. **Demand Phase IV trials** – Health Canada must make it a condition of approval for sale that manufacturers follow patients in trials after the Phase II or Phase III approvals throughout the life cycle of use.
4. **Compassionate access through manufacturers**- CADTH must make it a condition of approval of a drug trial in oncology that a certain number of compassionate access spots are allocated to patients who do not meet the eligibility criteria for the trial.
5. **Review of diagnostic tests companion** – These require integration with oncology treatments into the relevant drug/biologics health systems reviews rather than being treated as a separate approval managing through a separate silo.
6. **Pathologists**- Adequate and appropriately specialized pathology support must be resourced to ensure appropriate diagnosis and treatment in the era of precision medicine and personalized treatments.
7. **Phase II trial approvals**- CADTH and INESSS should accept applications with Phase II data and should provide conditional recommendation for approval where preliminary safety and efficacy data support this decision, subject to a satisfactory pricing agreement being concluded. The benefits, harms and uncertainty for life threatening and serious, chronic conditions are far different than for other patient populations. These must be developed with patient groups and used rather than the standard QALY measurements.
8. **CDIAC activities at CADTH**- CADTH must work with patient groups and all other relevant stakeholders to ensure transparency of this process as well as a full consultation on the algorithms to be used for the process. Meaningful patient engagement is required at all decision-making levels.
9. **A Rare Disease Strategy** – In 2019 Health Canada announced their commitment to developing a detailed national strategy and distinct pathway for funding and access to expensive drugs for rare diseases. The strategy was supposed to be implemented by 2022.
10. **pCPA negotiations**- pCPA, now a separate incorporated agency, must work with CADTH and other relevant stakeholders to further develop a negotiation process that involves risk sharing, pay for performance, managed entry agreements and other conditions that will ensure an appropriate recognition of the ethical issues of withholding effective drugs from patients as well as the need for cost sharing and re-negotiation following reasonable periods of time throughout the life cycle of the drug/biologic. While negotiations are taking place, pCPA and the manufacturer must develop a process to ensure cost sharing so that patients obtain treatments during the period of negotiations.
11. **Reinvestment of savings back into the drug budget** – Savings from cost containment measures including the oncology biosimilars and generic drug reimbursement strategies should be reinvested into the oncology drug budget.

12. **Real world evidence (RWE)** – All stakeholders gathering real world evidence must be convened by federal/provincial governments with the partnership of patient groups to develop a common strategy for defining RWE, for determining a patient led process for determining what RWE to gather, for determining how to link RWE sites, and for determining resources required as well as any other tactics required.
13. **Private payer engagement** – Private payers should develop their own price negotiations strategy and methods based on their business model, independent of the public pCPA model.
14. **Value based health care** – The federal government must convene a Summit in partnership with patient groups including the provinces and all other relevant stakeholders to develop a Strategy for achieving patient outcomes determined value-based health care and the tactics to achieve this health systems transformation.
15. **National pharmacare** – The federal government must work with patient representatives and other relevant stakeholders to ensure that the design of national pharmacare programme does not result in anyone eligible for drug coverage in Canada is receiving less coverage than they now have.
16. **Alignment of systems** – The federal and provincial governments in partnership with patient groups should convene a multi-stakeholder Working Group to develop a Strategy to assess health systems across jurisdictions to ensure alignment, lack of duplication and inefficiencies across these systems.
17. **Social determinants of health-** The federal and provincial governments in partnership with patient groups should convene a multi-stakeholder Working Group to develop a Strategy to assess health systems across jurisdictions to ensure alignment and ongoing cooperation with ministries responsible for social determinants of health.
18. **Precision oncology research:** Indigenous Nations need to exert, extend, and utilize their sovereignty under treaty rights to create policies allowing Indigenous populations to gain access to health systems that provide precision oncology options including emerging anti-cancer pharmaceutical options from prevention to survivorship. Indigenous Nations need to be at the forefront of cancer related clinical research at cancer institutes and research centers. By doing so, informed decisions can be made to be part of innovative clinical trials to determine if emerging science, medicines, process, and technologies are effective for their Nations and improvement of patient and community outcomes. A second precision oncology related recommendation is a focus on policy change with pediatric cancer patients. In almost all countries in the world, there are more mechanisms for pay, coverage, and support for items such as pediatric care than adult populations. This is likely true for pediatric oncology medicines and policy agreements and is likely a good first step is to examine payee mechanisms for precision oncology treatment as well as research.
19. **International research:** Working in an international context between international research outfits (out of country) or via organizations such as the United Nations or the World Health Organization with sovereign Indigenous Nations are also options. To parallel recommendations shared by (Drake et al., 2018), non-governmental organizations such as the World Health Organization and other non-governmental organizations often perform scoping studies in low and middle income countries internationally. These organizations could work independently with sovereign First

Nations, Inuit, or Métis governments to build research infrastructure in medicine to guide tailored solutions led by Indigenous governments, independently.

20. **Tribal and band consultation:** Structured and timed need assessments, policy review, and government-to-government consultations are important steps to emerging fields such as precision oncology. The division of jurisdiction between on reserve health coverage (federal to sovereign nation) and province (for off-reserve Indigenous populations) has created gaps in accessing health services and potentially the inclusion of clinical trials or precision oncology processes. A key to addressing these health and treatment disparities is to strive towards universal coverage and more importantly parity in process through ongoing and government to government tribal consultation with structured goals with accompanying deadlines.
21. **Gender programming:** Gender planning for precision oncology needs to be reviewed and included in next steps for clinical care and research. Cervical cancers seem to be one of interest areas for prevention and treatment in First Nations populations due to the higher incidence rates and higher mortality cervical cancer patterns. Other areas of prevention include concerns related to cancer concerns in the noted areas of lung, colorectal, and liver. Thus, recommendations include the review and consideration for precision oncology as it relates to prevention oncology should to be inclusive all genders including viewpoints of “Two-Spirit” (LGBT) community members.
22. **Environment and historical contexts:** Research also needs to review how precision oncology is affected by other risk factors for cancer including exposures, behaviors or other individual characteristics that may lead to cancer. These include overall access to care, community infrastructure (geographic, reserve/non-reserve, urban, sub-urban, near environmental waste sites) and the lasting effects of colonialism (historical traumas). These are important features to consider in future research and how these have influence on the global context of precision oncology and the cancer care continuum.

9 Conclusion

Precision oncology, still only in its infancy, is already sending shockwaves through cancer treatment. At the moment the ‘early adopter’ therapies seem overly expensive; placing an undue burden on the health system. Such catastrophizing was also *de rigeur* when statins first became available; when heart disease was the leading cause of death in Canada, and when coronary artery bypass graft recipients filled wards in hospitals across the land. Now, it is cancer’s time. And this time it will be done with precision.

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11 Glossary

BRCA1	Breast cancer type 1 susceptibility protein. A tumour suppressor gene
95% confidence interval	An estimate of the amount of uncertainty in a result
Acquired resistance	The ability to resist the activity of a particular agent to which the cancer was previously susceptible
Antimetabolites	A substance that interferes with the normal metabolic processes within cells
Apoptosis	Programmed cell death
Aromatase inhibitors	A drug that inhibits the enzyme aromatase and by that means lowers the level of the estrogen estradiol
Basket trials	Trials (or studies) designed to test the effect of one drug on a single mutation in a variety of tumor types, at the same time
Bioinformatics	An interdisciplinary field that develops methods and software tools for understanding biological data
Biologics	A medicinal preparation made from living organisms and their products
Biomarker	A characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes or response to a therapeutic intervention
Biosimilars	Also known as follow-on biologic or subsequent entry biologic, a biologic medical product that is almost an identical copy of an original product that is manufactured by a different company
Blood typing	The classification of human blood according to immunological compatibility based on the presence or absence of specific antigens on red blood cells
BRAF V600E mutation	A specific mutation in the BRAF gene which makes a protein involved in cell signalling and growth
Chemotherapy	The treatment of disease by the use of chemical substances, especially the treatment of cancer by cytotoxic and other drugs
Companion diagnostics	An in vitro diagnostic device or an imaging tool that provides information essential for the safe and effective use of a corresponding therapeutic product
Cross-matching	A test of the compatibility of a donor's and a recipient's blood or tissue
Estrogen Receptor Modulators	Agents that bind to estrogen receptors but act either as agonists or antagonists in different tissues
First-line therapy	The preferred, standard, or first choice treatment option
FLT3 ITD	Internal tandem duplications of the FLT3 gene. A type of mutation associated with poor prognosis in acute myelogenous leukemia
Genesis	Creation
Genetically engineered	Alteration of the DNA of a cell for purposes of research, the manufacture of specific proteins, correcting genetic defects, or making improvements to plants and animals
Genome	The genetic material of an organism
Haematopoietic stem cell transfusion	Transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow

Hazard Ratio	A comparison between the probability of events in a treatment group, compared to the probability of events in a control group.
HER2	Human epidermal growth factor receptor 2. A protein that identifies a certain type of breast cancer
Immune checkpoints	Regulators of the immune system which prevent the immune system from attacking cells indiscriminately
Immune modulator	Interventions that activate, boost, or restore normal immune function
Incidence	The rate at which an event occurs
Leukemia	A cancer of the blood-forming tissues, including the bone marrow and lymphatic system
Malignancies	Cancers
Meta-analysis	Examination of data from a number of independent studies of the same subject, in order to determine overall trends
Metastatic	The spread of cancerous cells from an initial or primary site to a different or secondary site
Microorganism	A microscopic organism, especially a bacterium, virus, or fungus
Microsatellite instability	A type of DNA abnormality most commonly caused to defective mismatch repair
Mismatch repair	A system within the cell for correcting errors in DNA that works by detecting and replacing bases in the DNA that are wrongly paired
Molecular response	A negative polymerase chain reaction or other negative molecular test. Polymerase chain reaction tests are very sensitive tests to detect the presence of specific genetic material
Monoclonal antibody	An antibody produced by a single clone of cells or cell line and consisting of identical antibody molecules
Mutations	A change in the structure of a gene
Myeloid	Relating to bone marrow
Notice of Compliance	Health Canada approval to make a drug or biologic commercially available
Notice of Compliance with Conditions	Health Canada approval to make a drug or biologic commercially available, conditional on certain post-marketing requirements being met
Odds ratio	A statistical measure of the strength of an association between two events
Oncologists	A medical practitioner qualified to diagnose and treat tumors
Overall survival	The percentage of people in a group who are alive after a length of time—usually a number of years.
Personalised medicine	A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease
Pharmacogenomic	The study of how variations in the human genome affect the response to medications
Philadelphia chromosome	An abnormal chromosome characteristically found in the malignant cells of CML
Precision medicine	An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person

Predictive biomarker	A biomarker that provides information on the probability of response to a particular therapy
Prevalence	The total number of cases of a disease in a given population at a specific time
Prognostic biomarkers	A biomarker that provides information on the natural history of disease, independent of treatment
Progression-free survival	The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse.
Radical mastectomy	Surgical removal of the entire breast
Real-world study	Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data
Recombinant DNA	DNA molecules formed by laboratory methods of genetic recombination
Remission	Diminution or abatement of the symptoms of a disease
Retrospective analysis	An analysis of past events or situations
Sensitivity	Also called the true positive rate. A measure of the proportion of actual positives that are correctly identified as such
Somatically-acquired mutations	Mutations that occur in cells other than sperm and egg, and therefore are not passed on to children
Specificity	Also called the true negative rate. A measure of the proportion of actual negatives that are correctly identified as such
Subcutaneous	Under the skin
Susceptibility	Sensitivity to a particular treatment
Targeted therapy	A type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cell
Taxonomy	Classification
Tissue/site-agnostic	A type of therapy that uses drugs or other substances to treat cancer based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body.
Transfusion	The act of transferring donated blood, blood products, or other fluid into the circulatory system of a person or animal
Tumour cell line	A population of cells that has the capability to proliferate indefinitely, resulting in cancer
Tyrosine kinase	A protein that functions as an "on" or "off" switch in many cellular functions