The Conference Board of Canada

Tomorrow Can’t Wait:

The Value of Breakthrough Cancer Treatments for Canadians

Unpublished Technical Report

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Key Findings

- Cancer is a leading cause of death in Canada. But advancements have led to a greater understanding of the disease and to new breakthrough treatments that target cancer at the cellular or genetic level.
- Potential cumulative benefits of breakthrough cancer treatments in our study totalled 226,445 life years gained and $5.9 billion in potential economic value across five tumour types over the last decade.
- Several breakthrough treatments have received timely regulatory approval since 2011. Health Technology Assessment and reimbursement processes in Canada take longer than other countries. Which means Canadian patients have a significant delay in access to breakthrough treatments.
- Once treatments are approved and reimbursement decisions by provinces are made, there is still a gap in patients' access. For some cancers, this gap means significant lost economic value and, for Canadians facing cancer, lost tomorrows.
- Canada lacks comprehensive data on how many people have accessed, are accessing, or cannot access breakthrough cancer treatments.
- Canada can, however, accelerate and provide equitable access to breakthrough cancer treatments. Four system-level reforms could improve access:
    - improve current Health Technology Assessment, regulatory, and price negotiation processes to accelerate access to breakthrough treatments;
    - change the way these therapies are funded to facilitate value-based care and risk-sharing agreements;
    - enable and fund access to diagnostic services when breakthrough therapies are approved;
    - expand and integrate systems that collect and share data.

- Like many countries, Canada is facing a need to rebuild its health systems. But its capacity to support and integrate new value-based models of cancer care and governance is being strained and made ever more urgent by the COVID-19 pandemic. Nevertheless, doing so can ensure that eligible patients waiting for breakthrough treatments can receive them and experience more tomorrows.

Introduction

Cancer is the leading cause of death in Canada.[1] In 2020 cancer was responsible for 83,300 deaths. And there were 225,800 Canadians newly diagnosed with cancer.[2] In the absence of treatment, cancer is commonly a progressive and debilitating disease where malignant cells spread throughout the body in an uncontrolled manner, causing harm.[3] Breakthrough cancer medicines are continuously being developed to eradicate cancer while maintaining good quality of life for patients; and for some cancers, growing the population of survivors in remission or who have conquered the disease.

Canada does well on approving breakthrough treatments but is among the three slowest to reimburse them compared to most comparator countries from the Organisation for Economic Co-operation and Development (OECD).[4] With significant disparities between provinces in reimbursement. This includes access to drugs for rare diseases, oncology drugs, and drugs that have been granted accelerated or priority review status by regulatory authorities due to highly promising clinical trial results.[5] In 2020 Canada's mortality due the most prevalent cancers ranked high: eighth out of 17 comparator countries,[6] despite Canada's five-year net survival for all cancers combined increasing 8.6 percentage points between the 1992-to-1994 period to the 2015-to-2017 period.[7].

Canadian patients also have less access to clinical trials, which are commonly coordinated across a global network of participating trial sites or health care facilities.[8,9,10] Access to oncology innovation, such as breakthrough cancer treatments, can support survivorship and quality of life among Canadians vulnerable to or living with a cancer diagnosis.

1 in 2 Canadians are expected to develop cancer during their lifetime. And about 1 in 4 will die from cancer.[11] The everyday public health impact of cancer on Canadians, their families, health professionals, elected officials; and the priorities of health system administrators, researchers in the field and policy makers cannot be underestimated. There is an evolving debate concerning the value of access to breakthrough cancer treatments juxtaposed to concerns about the rising costs of cancer drugs and increasing budgetary pressures[12].

This report aims to capture the clinical and economic value of improving broader and more equitable and timely access to breakthrough cancer treatments for Canadian patients; and to explore strategic system-level levers to enhance/accelerate access to future breakthrough

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[1] Statistics Canada, Table: 13-10-0394-01.
[2] Canadian Cancer Society, "Cancer Statistics at a Glance."
[3] National Cancer Institute, "What Is Cancer?"
[4] Hoskyn, "Explaining Public Reimbursement Delays for New Medicines for Canadian Patients."
[5] Salek and others, "Factors Influencing Delays in Patient Access to New Medicines in Canada."
[6] Peer countries to Canada included: Australia, Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Japan, Netherlands, Norway, Sweden, Switzerland, United Kingdom, United States of America.
[7] Ellison, "The Cancer Survival Index: Measuring Progress in Cancer Survival."
[8] Hoskyn and Field, "Early Signs of Negative Impacts for Patients of Health Canada Pharmaceutical Pricing Reforms."
[9] McDougall Scientific, *Clinical Trials in Canada: A Country Overview*.
[10] Canadian Partnership Against Cancer, *Cancer System Performance: 2018 Report*.
[11] Canadian Cancer Society, "Cancer Statistics at a Glance."
[12] Godman and others, "Barriers for Access to New Medicines."

cancer treatments. Our quantitative approach assesses the clinical value of breakthrough cancer treatments indicated across five different tumour types on the health (life-years saved) of the Canadian population diagnosed with cancer and the associated value of life-years saved to the Canadian economy since 2011.

To respond to the evolving pressure that current Health Technology Assessment (HTA) approaches go beyond the standard multi-disciplinary process and methods of cost-effectiveness analysis, this report brings forward an approach to equitably evaluate new breakthrough treatments inclusive of value as defined by patients, society and economic productivity resulting from patient survivorship. We provide insight into the cost-value discourse of funding innovative therapies from the patient perspective of value, in terms of life years gained, contribution to society, and value to the Canadian economy. We subsequently examine the system evolution needed to enable continued and accelerated patient access to the most effective and safest therapeutic options available to advance quality of life and survivorship for Canadians facing cancer.

Breakthrough cancer treatments are defined in this report as targeted therapies and/or immunotherapies, which have ushered in the era of personalized or precision medicine. These therapies are advanced medicinal treatments based on genes, tissues, or cells.

The process of Health Technology Assessment (HTA) evaluates new treatment innovations to ensure that those paying for healthcare realize the most value (usually in terms of patient benefits or positive clinical outcomes) from their investment as possible. Created in the 1970's, Canada's models of health care procurement and delivery have sought to deliver systematic change and transformation to keep up with the scientific assessment of evidence and required regulatory processes to integrate new technologies into cancer care. However, many barriers remain to both adopting and fully realizing the value of breakthrough cancer therapies on the lives of Canadian patients living with or facing a cancer diagnosis, the broader population, and Canada's economy.

Value can be defined in many ways, depending on the stakeholder. Patients may define value in terms of physical health benefit and maintenance of a functional and rewarding quality of life. A reimbursement/payor-decision-maker may define value from a broader healthcare system and general population health perspective or from a budgetary perspective. Other stakeholders such as Finance or Economic Ministers and their Administrations may view value from a competitiveness and macro-economic perspective. However, the missing elements from all these points of view and criteria in decision- and policy-making are the explicit value to society and to the economy in the form of productivity and community gains. As a result, this analysis examines value in terms of potential economic productivity resulting from patient survivorship.

Rapid advancements in cancer care have significantly improved patient outcomes[13] but also raise concerns with providing and sustaining equitable access to new breakthrough innovations. The pace of scientific and medical innovation necessitates that the healthcare system adapts and that the policy and regulatory context evolves. There are a substantial number of potential life-years lost by Canadians living with a cancer diagnosis during regulatory, funding and price negotiation processes for advanced cancer medicines.[14] While other countries are facing similar

[13] Islami and others, "Annual Report to the Nation on the Status of Cancer."
[14] Gotfrit and others, "Potential Life-Years Lost: The Impact of the Cancer Drug Regulatory and Funding Process in Canada."

concerns, Canada's challenges are unique since healthcare is administered at the provincial/territorial level and there are well documented disparities in access to cancer care and health outcomes.[15]

Funding of health expenditures is a major source of tension. Federal health transfers to provinces have not kept up with population growth or health care cost inflation, and do not take into account the different population needs (e.g., larger demographic segments of aging populations in some provinces than in others) or fiscal realities (i.e., smaller proportional working populations and lower median incomes in some provinces compared to others).[16] This contributes to significant inequities in terms of the adequacy of funding especially for smaller provinces with a greater proportion of aging population cohorts.

Canada is facing an undeniable need to rebuild its health systems. And like many countries, Canada's capacity to support and integrate systemic models of value-based care is further strained by sustaining the response to - and emergent recovery from the COVID-19 pandemic. Nevertheless, the opportunity to reform cancer care systems and regulatory processes in the current context is critical. Doing so can ensure the volume of patients awaiting and eligible for new breakthrough treatments can receive them; and the system is aligned to efficiency address the introduction of the vast array of emerging breakthrough treatments expected to become available to patients in the coming years.[17]

Accessing Breakthrough Cancer Treatments in Canada

Canada is unique in the way that it funds and delivers health care services. Like many countries in the OECD, health care is mostly funded by the public sector (70% public, 30% private)[18]. However, unlike most other OECD countries, health care is administered and delivered by Canada's 13 provinces and territories by virtue of the Canada Health Act and the Constitution. As a result, patient access to care and the quality of care received can vary significantly across Canadian regions. Moreover, the breadth of publicly funded services is limited, but the extent of coverage for those services is incomplete. For example, "essential" services (as defined under the Act) such as hospital and physician care are free at the point of care for patients, but other "non-essential" services such as pharmaceuticals, dental, vision care, and occupational therapy are largely privately funded through a mix of private health insurance (mostly workplace group benefits) and household spending.[19] This is unlike other OECD countries with medicare whose public funds cover a wider variety of health services with a moderately equal proportion of cost sharing with patients at the point of care, through deductibles, co-payment models, and/or through premiums.[20]

Provinces have developed a vast array of publicly-funded programs to fill gaps for health services deemed "non-essential" as per the Canada Health Act (which was created in 1984[21]),

[15] Ahmed and Shahid, "Disparity in Cancer Care: A Canadian Perspective."
[16] Mackenzie, "The Canada Health Transfer Disconnect."
[17] Falzone, Salomone, and Libra, "Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium."
[18] Canadian Institute for Health Information, "National Health Expenditure Trends."
[19] Salek and others, "Factors Influencing Delays in Patient Access to New Medicines in Canada."
[20] Speer and Lee, "Toward a More Fair Medicare."
[21] Government of Canada, "Canada's Health Care System."

the largest of which enables access to pharmaceuticals. Coverage, eligibility, and reimbursement rules for prescription drugs differ widely between provinces.

Specifically, pharmaceutical coverage between provinces and within provinces varies according to a number of different factors: age, working status, income, type of disease, rarity of disease, type of drug, drug history, where the drug is administered, how new the drug is in terms of established clinical effectiveness, and so on.[22,23,24] As a result, gaining access to a drug for patients in their care, can be tremendously confusing and challenging for Canadian clinicians.

Canada's western provinces (British Columbia, Alberta, Saskatchewan and Manitoba) provide the full spectrum of cancer treatment through a network of cancer centres. These centres are governed by a centralized cancer agency which funds and delivers all aspects of cancer care including access to oncologists, diagnostic testing (radiology, radiation, lab) genetic companion diagnostic testing, surgeries, and drug therapy. These services, including drug therapies, are usually free to all patients at the point of care. The same way it would be for a patient in any province receiving care at a hospital. Coordination of cancer care in Ontario, Quebec, and the Atlantic provinces, follows a segmented approach. In these provinces, outside of standard pathways to oncologists, radiology and standard laboratory testing along the diagnostic process, patient access to advanced diagnostic testing is not guaranteed and largely dependent on whether advanced testing is available at the cancer centre where a patient is accessing services. Furthermore, access to advanced diagnostic testing in these provinces varies and may either not be publicly funded or only partially funded through private plans or at an out-of-pocket cost to the patient.[25,26] Likewise, cancer drugs are managed the same as access to drugs for other conditions. In provinces following a segmented approach, funding for drug therapies depends on whether the drug is a hospital-administered drug or a 'take-home' drug (i.e., dispensed at a pharmacy to the patient who takes the drug at home). Thus, coverage depends on the insurance status of the patient (workplace private plan, public program, or uninsured). These provinces may have a cancer organization that oversees some elements of the care offered at cancer centres; however, there is no province-wide budgetary oversight for 'take-home' cancer drugs or companion diagnostic testing.[27,28] Regardless of 'centralized' or 'segmented' provincial models, access to care and treatment in each province is also influenced by a variety of other contextual factors:

- Whether the patient's clinician/care team is highly informed about the required advanced diagnostic testing specific to new breakthrough treatments;
- patient's health insurance coverage capacity to support clinically indicated treatment options;
- whether the patient meets the provincially approved public plan's highly-defined (and restrictive) reimbursement criteria;

[22] Salek and others, "Factors Influencing Delays in Patient Access to New Medicines in Canada."
[23] Canadian Institute for Health Information, "Prescribed Drug Spending in Canada."
[24] Innovative Medicines Canada, Canada's Public Drug Coverage Database (used with permissions)
[25] Bonter and Manion, *Companion Diagnostics (CDx) Policy Discussion Paper: Issues, Gaps and Opportunities for Change in Canada*.
[26] Mohideen and others, "Identification of Gaps and Opportunities for Provincial Reimbursement of Oncology Companion Diagnostics in Canada".
[27] Government of Canada, "Appendix A: Funding of Oncology Medicines in Canada, by Province".
[28] Canadian Partnership Against Cancer, *Cancer System Performance: 2018 Report*.

- availability and ease of access to a manufacturer's compassionate access program or whether a clinical trial is available to the patient in the Canadian context[29].

Many breakthrough treatments have received timely approval by Canada's regulatory agency and health technology agencies over the past decade. But these therapies are not equally accessible to Canadians compared to citizens from peer countries.

This study constitutes the first synthesis of clinical life years and economic value gained from the world's most advanced breakthrough treatments for breast, prostate, lung, skin (melanoma) and blood (myeloma) cancers currently available to Canadians. Our approach brings forward an applied approach to respond to the evolving pressure that HTA approaches go beyond the current multi-disciplinary process and methods of cost-effectiveness analysis to support approval and funding decisions for new therapies. We provide insight into a segment of the cost-value discourse of funding breakthrough treatments from the patient perspective of value, in terms of life years gained, contribution to society and value to the Canadian economy. Other value-segments, such as health system efficiencies, utilization and social and economic implications for patients and caregivers were not within the scope of this report.

Approach and Methods

Quantitative Model – Estimating Clinical and Economic Value

This report quantifies the potential clinical and economic value of a select group of breakthrough cancer treatments over the 2011-2021 period. The time horizon of 2011-2021 was chosen as all breakthrough treatments under consideration were recommended for funding by CADTH for at least one cancer indication in our study during this time.

Estimated target population cohorts were calculated from the sum of annual cancer incidence data provided by Statistics Canada and estimated progression to the relevant stage of disease (based on rates identified through the published scientific literature).

In a quantitative sense, the clinical benefit of a breakthrough treatment is defined as the years of progression-free or metastasis-free survival (PFS/MFS) added to patients' lives by the treatment (beyond the standard of care). Based on expert guidance, median progression-free survival (PFS) was chosen as a suitable metric for the ability to maintain work (for working age adults) or the ability to contribute to society (for retirement age adults) while maintaining a reasonably functional quality of life. The use of PFS as a surrogate efficacy marker for survival because of treatment has had conflicting preference in the scientific literature. However, in recent years, the use of overall survival (OS) has become increasingly difficult as a primary efficacy outcome measure of a given treatment. This is in part due to the length of trials required (with improving duration of responses, treatment in earlier stages of disease, and increasing number of subsequent treatments), and because of data contamination from cross-over effects (for ethical reasons, patients in the control treatment arm who progress or do poorly, cross-over to the intervention arm). In most breakthrough cancer treatments PFS has been shown to improve, but

[29] The global share of oncology clinical trials initiated in Canada has steadily declined from 8.2% in 2014 to 4.9% in 2020, while the absolute number of trials in this period has remained relatively stable. Most oncology clinical trials initiated in Canada were multinational trials. Source: Innovative Medicines Canada, Research Note, Accessed November 22, 2021, http://innovativemedicines.ca/wp-content/uploads/2021/11/20211115_Research_Note_Oncology_CTs_CA_Int_EN_Final.pdf

this does not always translate to better OS for the reasons noted above. For these reasons, along with guidance from Canadian experts, we have relied on PFS as a measure of better quality of life and ability to work or otherwise contribute to society for four of the five cancers included in this study. Given the well-established evidence for melanoma, OS was used instead of PFS to support the quantification of economic value. Use of OS for this quantification was unique to melanoma only. (See Appendix: Detailed Quantitative Model Methodology for more details.)

Each innovation's PFS metric (except melanoma) was identified using the most relevant literature that has been used to inform that breakthrough treatment's CADTH recommendation. These metrics were then validated through expert working groups. Where multiple innovations were considered for a given cancer type, reported PFS metrics were weighted according to utilization rates reported from IQVIA. Where breakthrough treatments were used in multiple lines of therapy, PFS data in our model changed in accordance with the timeline of CADTH recommendations.

To estimate the clinical benefit, annual patient cohorts (separated by age) were tracked for the duration of their PFS under two scenarios – breakthrough treatment and standard of care. For each tumour type, patients first entered the model when the breakthrough treatment was first recommended for an indication by CADTH. The difference in PFS/MFS between treatment scenarios is used to represent the benefit of breakthrough treatment. Overall, the PFS/MFS years gained (due to the treatment) is the sum of PFS years gained across all annual patient cohorts.

For the purposes of this study, the economic value of a breakthrough treatment represents the value of lost production that has been avoided as a result of clinically realized treatment outcomes from the use of breakthrough therapies in our study. This is quantified by estimating the income that treated individuals would have been able to earn during the extended period of PFS years. This approach follows a modified human capital method (HCM) – one of two methods identified in Public Health Agency of Canada (PHAC) publications, such as the *Economic Burden of Illness in Canada* reports.[30] The HCM was chosen as opposed to the friction cost method given data limitations on patient labour market outcomes for the latter. However, use of the HCM requires some strong assumptions including zero involuntary unemployment. Estimates should therefore be considered as the *upper bound* of the value of lost production.[31]

To estimate productivity/the economic value of lost production that has been avoided, annual patient cohorts (separated by age) were tracked for the duration of their PFS under both breakthrough treatment and standard of care. PFS-years, per annual patient cohort – for breakthrough treatment and for standard of care – were multiplied by appropriate annual employment rates, retirement rates, and median income data (varying by age group) reported by Statistics Canada. Patients were assumed to remain on treatment and to continue working until progression.

[30] The Public Health Agency of Canada, *Economic Burden of Illness in Canada, 2010*.
[31] Ibid.

The difference in lost production avoided/income between the treatment scenarios were used to represent the benefit of the breakthrough cancer treatment. The overall gain in production was the sum of income gained across all annual patient cohorts.

The median income data used in each model was chosen to reflect the biological sex most commonly diagnosed with that cancer type. For example, the breast cancer models used median incomes data for Canadian females; and prostate used median income data for Canadian males.

Selection of Breakthrough Treatments in Cancer Care

The first criterion for the selection of breakthrough treatments in cancer care to be included in our modelling approach was: an immunotherapy and/or targeted therapy currently approved in Canada. The second criterion required that the therapeutic class of the breakthrough therapy was used to treat at least one of the cancer tumours in our study: prostate, breast, lung, melanoma; and the leading blood cancer tumour type, myeloma. From these two criteria, a list of 24 innovative therapies approved for use in Canada were identified from a literature review. Breakthrough treatments across cancer tumour types were short-listed through consultation with clinical oncologists, patient representatives, Health Technology Assessment (HTA) professionals and pharmaceutical manufacturers all with expert knowledge of cancer care treatments approved in Canada and corresponding patient treatment pathways. These experts (11 in total) ranked each breakthrough treatment according to its level of innovation (defined as: breakthrough, transformational, or incremental); and its impact with respect to advancing/sustaining patient quality of life, survival, and/or health care system efficiencies (i.e., reduced hospitalization rates, average length-of-stay and Emergency Department visits, to name a few).

The classes of breakthrough treatment innovations and their respective tumour types that were identified as high-impact and transformational, or high-impact and breakthrough, or high-impact and incremental were included in the modelling approach. Data availability to support specific modelling criteria were also assessed to determine the feasibility of quantification of value for each respective breakthrough treatment included in the model. Breakthrough treatments were further filtered for inclusion in the model based on having received a positive or conditional recommendation by the Canadian Agency for Drugs and Technologies in Health (CADTH) by 2020. Treatments included in the model also needed to have successfully completed a negotiation with the pan-Canadian Pharmaceutical Alliance (pCPA) by 2020; and have registered sales in the Canadian market in 2020. Breakthrough treatment innovations that did not meet the inclusion criteria were reviewed qualitatively by our experts to the extent that they demonstrate ongoing innovation and benefit for patients in our respective tumour classes. (A full list of innovations and rationale for modelling inclusion and exclusion is listed in the Appendix – Detailed quantitative model methodology).

The typical patient journey was then mapped out using randomized clinical trials, other studies in the literature, clinical practice guidelines, and clinician input for each tumour type. The patient journey was mapped with consideration to several factors, including disease prognosis at diagnosis, survival rates, quality of life, availability of treatments and how these factors changed over time - before and after the introduction of the breakthrough treatment for a given tumour type.

Approach for Modeling Value

Benefits of breakthrough cancer treatment are relatively straightforward to determine for individual patients. However, the magnitude of the benefit at a population level depends on the number of patients that were able to access breakthrough treatment innovations and for whom estimated health outcomes may be feasibly and robustly tracked during a given study period.

Access to robust and timely data is a significant issue across Canada's 13 different health systems, as they manage and track cancer treatment delivery and outcomes differently (96 different databases).[32] Access to pan-Canadian data is further exacerbated by privacy requirements and the associated cost and time of acquiring high-quality, reliable, interoperable, and comparable data to support analyses. Moreover, utilization of breakthrough therapies for cancer treatment appears to differ by tumour type, patient eligibility for these therapies, and the dates upon which breakthrough treatments came to market in Canada. While treatment rates utilizing approved breakthrough innovations in Canada have been increasing over the past decade, for at least one tumour included in this study, namely lung cancer, overall treatment rates have been surprisingly low.[33,34] This can be the result of late-stage of diagnosis and the patient's health status at the time of diagnosis.[35] In cases with significant disease spread and rapid decline in quality of life, patients may opt for palliative care instead of treatment or may (given factors outlined above) not be eligible for – or able to financially afford available breakthrough treatment. Factors contributing to treatment rates in cancer are discussed in the 'Enabling Faster Access to Cancer Drugs in Canada' section of this report.

An effort was made to quantify the value of breakthrough cancer treatments based on estimates of the actual number of patients that benefitted from these therapies. Due to the inherent data limitations surrounding estimates of actual utilization of breakthrough treatments by Canadian patients over the last decade the present analysis represents a broad approach to assessing economic value. Our approach estimates economic value based on universal utilization of breakthrough therapies across the five most prevalent cancer tumours included in this study.

Estimates of the potential universal eligible population were generated by relying on incidence data (newly-diagnosed cases) and cancer progression or recurrence rates. Two types of benefits were calculated: health benefit and economic benefit. Health benefit represented the improvement in survival outcomes for the breakthrough therapy versus the standard of care, expressed as number of life years gained. Economic benefit represented the increased economic value due to lost production avoided, expressed as the avoidance of lost annual income associated with the number of life years gained.[36]

Based on a review of the literature and input from our expert advisory board and manufacturer committee, life years gained were calculated using progression free survival (PFS) outcomes for several reasons, including: a) the ability to more accurately attribute the benefit directly to the

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[32] CanREValue Collaboration Data Working Group, *Mapping Canadian Provincial Data Assets to Conduct Real-World Studies on Cancer Drugs*.
[33] Seung and others, "Real-World Treatment Patterns and Survival in Stage IV Non-Small-Cell Lung Cancer in Canada."; Consultations with subject matter experts.
[34] Stock-Martineau and others, "Evolution of Systemic Treatment Uptake and Survival in Advanced Non-Small Cell Lung Cancer."
[35] Lung Cancer Canada, "Myths and Facts."
[36] In the case of retired individuals (defined as individuals over 65), retirement income was used instead of employment income.

use of the breakthrough treatment versus the use of subsequent treatments; b) the ability to capture the period of better health (i.e., progression-free disease) and, therefore, higher likelihood of returning to work or resuming active social engagement (for retired individuals) and associated productive and economic activity; and, c) the fact that, while both PFS and OS are usually the primary efficacy outcomes measured in clinical trials and upon which regulatory and reimbursement decisions are made (PFS more often than OS), due to data maturity on OS, PFS has become widely accepted as an appropriate surrogate measure of survival.

A notable exception to the use of PFS was made in two cases. In the indication for non-metastatic castration-resistant prostate cancer the primary outcome was metastasis-free survival (MFS). The FDA, Health Canada, and other regulators, as well as CADTH and other international reimbursement decision-making agencies base their recommendations on primary outcome measures, in this case, accepting metastatic-free survival is an appropriate measure of survival benefit. The second exception was in the case of metastatic or unresectable melanoma, where OS was identified in the literature as a more appropriate measure of survival benefit for immunotherapies specifically.

Qualitative Approach - Enabling Faster Access to Cancer Drugs in Canada

Our guiding question to explore the critical levers and facilitators needed to advance patient access to safe and effective cancer treatments was: *What will it take to optimize both patient access to - and the impact of - forthcoming breakthrough cancer treatment innovations on the population health of Canadians into the next decade?*

To answer this question, we interviewed eighteen key informants representing different stakeholder groups: clinicians (n=3), patient advocates (n=3), former payors (n=3), health technology assessment representatives (n=4), health policy researchers (n=2), and former government officials (n=1). These individuals were chosen (convenience sample) from the Advisory Committee established for the project, the Innovative Medicines Canada (IMC)/BIOTECanada Joint Oncology Project Team (JOPT), and additional experts recommended by our advisors. Our key informants represented ten members of the Advisory Committee, two members of the JOPT committee, and 6 invited experts. The interview questions were created based on the results of a brief survey of the our Advisory Committee and the JOPT committee, which asked them to indicate their level of interest in featuring specific policy issues relevant to breakthrough innovations in cancer, based on a selection of topics informed by the literature review. Interviews were recorded and their content was subject to a qualitative analysis (Appendices: Detailed Qualitative Methodology). Six main themes emerged from our analysis and are described in the section: Enabling Faster Access to Cancer Drugs in Canada of this report. Each theme's synthesis was supplemented by a selective and non-systematic literature review pertaining to the issues raised by the key informants.

Limitations

There are several important limitations in our quantitative analysis to keep in mind when interpreting the modeling results.

Our model does not represent all cancers, or all possible breakthrough treatments within each tumour type selected. Moreover, the more recent breakthrough treatments are modeled for a shorter window than the earlier treatments approved during our study period, and as a result, the full measure of benefit of recent breakthrough treatments are underestimated.

As previously mentioned, actual provincial or pan-Canadian utilization rates of the breakthrough treatment innovations we included in our study were not available. The literature contains studies reporting on treatment rates in individual provinces (public-administrative data only, not private data) or in individual cancer centres, but these papers tend to profile utilization rates for an entire class of medicines, which include an array of therapies beyond just the breakthrough treatments in our study, or conversely can be limited to just one breakthrough therapy, or too few therapies indicated for the tumour types included in our study. As a result, it is impossible to ascertain the extent of patients that actually benefited from any or all of the breakthrough treatments defined within the scope of our modelling. Thus, our model presents a hypothetical scenario assuming that all eligible patients received treatment for either the standard of care, or the breakthrough treatment.

The estimated number of patients that could potentially have benefitted from new breakthrough treatments may be underrepresented due to the lack of comprehensive longitudinal administrative data across Canada. Data for the province Quebec for instance was notably lacking for the majority of the study period. Our estimate of eligible patients in Quebec was therefore based on historical proportion of national incidence rates. Likewise, inconsistent reporting by different agencies of the stage of cancer at diagnosis led to some assumptions being made of advanced and metastatic disease. Further, incidence rates by stage at time -of-diagnosis was not available for all of the five tumour types. Much of the epidemiological data on progression and metastasis rates were informed from US or European data, which were assumed to apply to Canada; and US mortality and survival rates were referenced in some cases where more recent data were available rather than citing available (dated) Canadian cancer statistics.

We were unable to acquire data or credible estimates linking utilization of individual or class of breakthrough treatments to utilization of other health care services for a given indication at the patient level, and as a result, the impact on the healthcare system or on workplace health plans by the utilization of breakthrough treatments was not modelled.

Canadian data on working rates and durations for cancer-diagnosed patients during or following treatment were not available, let alone by tumour type or by therapy group. As a result, the productivity gains are entirely hypothetical, assuming the same age-standardized employment rate and median incomes in the cancer-diagnosed population as in the general population, and between the control and breakthrough treatment cohorts. Our model essentially assumes that all diagnosed cancer patients continue to work equally for the duration of their therapy's median PFS, and that the patient stops working at the median PFS point. Essentially, the difference between the two therapy groups assumes that the breakthrough treatment group worked and received their salary for a longer duration represented by the extra PFS months (or life years gained). The drop in working rate at diagnosis, and the ability to start working again earlier or stay at work longer in the breakthrough treatment group compared to the standard of care group is not reflected. The impact on disability payments by employers is likewise not reflected in the quantitative model.

Quality of life is an important patient-reported outcome of treatment and is increasingly being reported in clinical trials. It is also utilized in health technology assessments to calculate quality-adjusted life years (QALYs), i.e., adjusted survival benefit to reflect the impact on quality of life conferred by the treatment intervention being reviewed. Given the lack of consistency in the quality-of-life data reported across clinical trials over the study period for the various breakthrough treatments and their associated standard of care, assessment of benefit based on

quality of life was not quantified in our model. We have provided reports on quality of life improvement from supporting studies for illustrative purposes only.

Our model does not capture other benefits such as societal benefit, caregiver benefit, mental health benefit, or broader health system value or downstream costs. Furthermore, our model does not acknowledge the value of advancing biotechnology innovation in Canada through the adoption of new breakthrough innovations to advance Canadian-context research and new discoveries.

Results

Prostate Cancer

Incidence, Prognosis, and Treatment Pathway

Prostate cancer is the fourth most common cancer globally[37], and in Canada[38], with approximately 23,000 new cases diagnosed every year (118 per 100,000). Globally, prostate cancer is the leading cancer among males, at 20% of all cancers diagnosed, followed by lung cancer and colorectal cancer[39]. Prostate cancer age- standardized incidence rates (ASIR) have seen the largest annual decreases between 1984 and 2015, at 9.1%, largely due to guideline changes discouraging the use of Prostate-Specific Antigen (PSA) testing in some populations in the United States (US) and shortly after in Canada.[40] Rates are highest in Alberta (AB), Ontario (ON), and Saskatchewan (SK), and lowest in the Atlantic provinces: Nova Scotia (NS), Prince Edward Island (PEI), and New Brunswick (NB). [41]

In Canada, prostate cancer has the third highest mortality rate among men, accounting for 9.5% of all male cancer deaths in 2019 followed by lung/bronchus and colorectal cancers; prostate cancer is also the second highest probable cause of cancer death over a lifetime in men.[42] In 2019, an estimated 4,100 men died from prostate cancer, at a rate of 22.2 per 100,000.[43] The age-standardized mortality rate (ASMR) for prostate cancer has decreased annually by 2.8% per year from 1994-2015, which reflects advances in radiation therapy and the introduction of innovative hormonal therapies. [44] The Canadian evidence for the role of PSA testing in reducing the mortality rate is conflicting.[45] Despite varied access to and utilization of provincial testing programs, mortality rates are relatively similar across the country, ranging from 20 and 21 per 100,000 in Quebec (QC) and ON to 28 and 29 per 100,000 in Newfoundland and Labrador (NL), Manitoba (MB) and SK. [46]

The 5-year and 10-year net survival rates for prostate cancer in Canada are the third highest for men, as well as for men and women combined, at 93% and 90%, respectively for patients diagnosed between 2012-2014. However, the 5-year survival rate drops from 97% for men 45-74 years of age, to 87% for men between 75-84 years of age, and to 57% for men 85-99 years of age. [47] Although these data are not available in Canada, in the US, the 5-year survival rate differs widely depending on the clinically defined stage of cancer at diagnosis: 100% for localized and regional stages (stages 1-3), compared to 30.5% for metastatic disease (stage

[37] World Health Organization, “Cancer.”
[38] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2019*.
[39] Ibid.
[40] Ibid.
[41] Ibid. Note, no data available for Quebec.
[42] Ibid.
[43] Ibid.
[44] Ibid.
[45] Ibid.
[46] Ibid.
[47] Ibid.

4).[48] In Canada, survival rates are estimated to have increased by 7.2 percentage points in the interval from 1992-1994 to 2012-2014. [49]

Most cases of prostate cancer in Canada are diagnosed among men between the ages of 60-69[50], at stages I and II.[51] Most deaths (just over half) occur in men over 80 years of age.[52] Prostate cancer screening is accepted to have contributed to an over-diagnosis and as a result incidence rates in earlier stages of the disease have declined over time, while they have remained steady and slightly increased for later stages of the disease. [53,54] PSA screening is now recommended in only particular situations depending on a patient's risk profile, and the ongoing frequency of testing is dependent on the initial PSA results.[55]

The clinical course of the disease is dependent upon the PSA count and the risk profile of individual patients. If non-metastatic at diagnosis, patients with a low-risk profile or a low PSA count are often observed until metastasis or higher PSA volume is indicated through routine monitoring. At that time, they may proceed to radiation treatment. For higher risk/PSA-volume patients, the standard of care is androgen-deprivation therapy (ADT) using luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, with or without treatment intensification, if the patient's status indicates it. However, progression is inevitable in the majority of patients to a state termed castration-resistance prostate cancer (CRPC).[56,57] Newer, targeted androgen-blocking therapies have become available since the early 2010s. These agents are androgen receptor-axis-targeted therapies (ARAT) used to treat metastatic disease. ARAT therapies have been shown to be effective for non-metastatic patients no longer responding to ADT or systemic therapies. [58,59,60,61]

[48] Terris, "Metastatic and Advanced Prostate Cancer."
[49] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2019*.
[50] Ibid.
[51] LeBlanc, Demers, and Shaw, "Recent Trends in Prostate Cancer in Canada." This data is based on Alberta and Manitoba ASIR between 2005-2015.
[52] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2019*.
[53] LeBlanc, Demers, and Shaw, "Recent Trends in Prostate Cancer in Canada."
[54] Rendon and others, "Canadian Urological Association Recommendations on Prostate Cancer Screening and Early Diagnosis."
[55] Ibid.
[56] pan-Canadian Oncology Drug Review, *Abiraterone Acetate (Zytiga) for Metastatic Castration-Resistant Prostate Cancer.*
[57] Kirby, Hirst, and Crawford, "Characterising the Castration-Resistant Prostate Cancer Population: A Systematic Review."
[58] Rendon and others, "Canadian Urological Association Recommendations on Prostate Cancer Screening and Early Diagnosis".
[59] So and others, "Canadian Urological Association-Canadian Urologic Oncology Group Guideline on Metastatic Castration-Naive and Castration-Sensitive Prostate Cancer". In these guidelines, Chemotherapy = docetaxel; ARAT = androgen-receptor-axis targeted therapy: abiraterone acetate (Zytiga), enzalutamide (Xtandi), apalutamide (Erleada).
[60] pan-Canadian Oncology Drug Review, *Abiraterone Acetate (Zytiga) for Metastatic Castration-Resistant Prostate Cancer.*
[61] Saad and others, "2021 Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) Guideline: Management of Castration-Resistant Prostate Cancer". ARAT therapy includes abiraterone acetate (Zytiga), apalutamide (Erleada), enzalutamide (Xtandi), or darolutamide (Nubeqa).

Breakthrough Treatment Innovations in Pharmacotherapies - ARAT Therapies

Until 2010, ARAT therapies were not available for the treatment of prostate cancer, and until 2018 were not available for non-metastatic castration-resistant cancer. One can view the growth of options for patients since 2010 by referencing the Canadian Urological Association's 2010 guidelines for castration-resistant prostate cancer.[62] At the time, there were no options beyond ADT therapy, which eventually becomes ineffective resulting in the progression of the cancer to metastatic disease within 1-2 years for non-metastatic patients; nor were there options beyond ADT and systemic chemotherapy for metastatic patients.

Over the course of 2011-2021, a new generation of androgen-blocking therapies were introduced and made progressively available for a broader range of indications: approved for the metastatic indication initially, and subsequently for non-metastatic disease. In 2020[63], ARAT was demonstrated to be effective in the treatment of metastatic castration-naïve or sensitive stages (before ADT). At the time of this analysis the latter approval was not yet recommended for funding in Canada and not eligible for inclusion in the proposed model.

Androgens, namely testosterone and dihydrotestosterone (DHT), play a role in the growth of cancer cells in the prostate. Treatment decreases or blocks androgen production in the testicles and other parts of the body (adrenal glands) and blocks the action of androgens throughout the body to prevent prostate cancer cells from being able to use it.[64] Initial hormone therapy, i.e., ADT, blocks production of androgens in the testicles.[65] Newer ARAT therapies either inhibit an enzyme (CYP17) responsible for synthesizing testosterone from cholesterol (abiraterone acetate) or block the binding action of androgen cells to the androgen receptor on prostate cancer cells (enzalutamide, apalutamide, and darolutamide).[66]

ARAT therapies were the first transformative innovations in prostate cancer since about 1950. Systemic chemotherapy became widely available in early 2000 for advanced prostate cancer; however, no options were available for non-metastatic prostate cancer other than ADT until ARAT therapies were approved and adopted for non-metastatic cancer in the late 2010s.[67]

ARAT therapies have significantly improved the prognosis of metastatic cancer but have drastically transformed it for non-metastatic cancer. Evidence indicates that in metastatic castration-resistant prostate cancer (mCRPC), abiraterone acetate and enzalutamide significantly increased median Progression Free Survival (PFS) to 5.6 and 8.3 months from 3.6 and 2.9 months, respectively. Median Overall Survival (mOS) improved to 15.8 and 18.4 months, respectively, when used post-chemotherapy, with few side effects (Table 1). When used pre-chemotherapy, PFS was doubled to 16.5 months for abiraterone acetate, and more than doubled (not reached at 12 months) for enzalutamide (65% were still alive at 1-year, compared to 14% for the control group). The risk of death was reduced by 19% and 29%, respectively, and quality of life measures were significantly improved (Table 2).

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[62] Saad and Hotte, "Guidelines for the Management of Castrate-Resistant Prostate Cancer."
[63] CADTH, *Final Recommendation for Apalutamide (Erleada) for Metastatic Castration-Sensitive Prostate Cancer.*
[64] National Cancer Institute, "Hormone Therapy for Prostate Cancer."
[65] Canadian Cancer Society, "Hormone Therapy for Prostate Cancer."
[66] National Cancer Institute "Hormone Therapy for Prostate Cancer."
[67] Shah and Vaishampayan, "Therapy of Advanced Prostate Cancer: Targeting the Androgen Receptor Axis in Earlier Lines of Treatment."

In non-metastatic CRPC (nmCRPC), ARAT therapies more than doubled median PFS and/or metastasis-free survival (MFS) to reach 40, 37 and 40 months, for apalutamide, enzalutamide, and darolutamide, respectively, and risk of death was reduced by 22%, 27%, and 31%, respectively, reaching 74 months and 67 months in median OS for apalutamide and enzalutamide. For darolutamide OS was not reached for either group. (Table 3).

Table1 – mCRPC Post-Chemo Indication

ARAT therapy	Median PFS	Median OS	QoL
Abiraterone acetate (Zytiga)[68]	5.6 months	15.8 months	13.8 months to FACT-P deterioration
Standard (prednisone monotherapy)	3.6 months	11.2 months	8.3 months to FACT-P deterioration
Improvement	2 months (HR=0.673, CI: 0.585, 0.776)	4.6 months (HR=0.74, CI: 0.638, 0.859)	5.5 month delay in FACT-P deterioration[69]
Enzalutamide (Xtandi)[70]	8.3 months	18.4 months	9 months to FACT-P deterioration 28% pain progression BPI-SF
Standard (prednisone monotherapy)	2.9 months	13.6 months	3.7 months to FACT-P deterioration 38% pain progression BPI-SF
Improvement	5.4 months (HR=0.40, 95% CI 0.35 to 0.47)	4.8 months (HR=0.63, 95%CI: 0.53-0.75)	5.3 month delay in FACT-p deterioration[71] 10% less pain progression

PFS = progression-free survival; OS = overall survival; QoL = Quality of Life; HR = hazard ratio; CI = confidence interval; FACT-P = The Functional Assessment of Cancer Therapy-Prostate

[68] Fizazi and others, “Abiraterone Acetate for Treatment of Metastatic Castration-Resistant Prostate Cancer: Final Overall Survival Analysis of the COU-AA-301 Randomised, Double-Blind, Placebo-Controlled Phase 3 Study.”
[69] Luo and Graff, “Impact of Enzalutamide on Patient-Related Outcomes in Metastatic Castration-Resistant Prostate Cancer: Current Perspectives.”
[70] Scher and others, “Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy.”
[71] Luo and Graff, “Impact of Enzalutamide on Patient-Related Outcomes in Metastatic Castration-Resistant Prostate Cancer: Current Perspectives.”

Table 2 – mCRPC Pre-Chemo Indication

ARAT therapy	Median PFS	Median OS	QoL
Abiraterone acetate (Zytiga)[72,73]	16.5 months	34.7 months	12.7 mths delay to FACT-P deterioration 25.2 mths delay to chemo 7% withdrawal due to AEs
Standard (prednisone monotherapy)	8.2 months	30.3 months	8.3 mths delay to FACT-P deterioration 16.8 mths delay to chemo 4% withdrawal due to AEs
Improvement	8.3 months (HR=0.53, CI 0.45 to 0.62)	4.4 months (HR=0·81, CI 0·70–0·93)	4.3 mths delay to FACT-P deterioration; 8.4 mths delay to chemo elevated withdrawal due to AEs
Enzalutamide (Xtandi)[74,75,76]	20 months	36 months	11.3 mths delay to FACT-P deterioration 28 months delay to chemo 6% withdrawal due to AEs
Standard (prednisone monotherapy)	5.4 months	31 months	5.6 mths delay to FACT-P deterioration 10.8 months delay to chemo 6% withdrawal due to AEs
Improvement	14.6 months (HR= 0.32, CI 0.28–0.37)	5.0 months (HR=0.83; 0.75-0.93)	5.7 mths delay to FACT-P deterioration; 17.2 mths delay to chemo (HR=0.35; 0.3-0.4) Same withdrawal due to AEs

PFS = progression-free survival; OS = overall survival; QoL = Quality of Life; HR = hazard ratio; CI = confidence interval; FACT-P = The Functional Assessment of Cancer Therapy-Prostate

[72] Ryan and others, “Abiraterone Acetate plus Prednisone versus Placebo plus Prednisone in Chemotherapy-Naive Men with Metastatic Castration-Resistant Prostate Cancer (COU-AA-302).
[73] Rathkopf and others, “Updated Interim Efficacy Analysis and Long-Term Safety of Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer Patients without Prior Chemotherapy (COU-AA-302)”.
[74] Beer and others, “Enzalutamide in Metastatic Prostate Cancer before Chemotherapy.”
[75] Beer and others, “Enzalutamide in Men with Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study”.
[76] Armstrong and others, “Five-Year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer from the PREVAIL Trial”.

Table 3 – nmCRPC Indication

ARAT therapy	Median MFS*	Median OS	QoL
Apalutamide (Erleada)[77,78]	40.5 months	73.9 months	FACT-P score of 8.38.[79]
Standard (ADT)	16.2 months	59.9 months	FACT-P score of 6.60
Improvement	24.3 months (HR=0.28, CI 0.23-0.35)	14 months (HR=0.78, CI: 0.64 - 0.94)	No statistical difference in FACT-P between tx and placebo. Comparable treatment-emergent adverse events (TEAEs)
Enzalutamide (Xtandi)[80,81]	36.6 months	67 months	Clinically meaningful symptom worsening delayed from tx as assessed by EORTC QLQ-PR25 urinary (median 36·86 months vs 25·86) and bowel symptoms (33·15 vs 25·89)[82] Time to pain progression, tx vs. standard (HR=0.75, 95% CI 0.57-0.97)
Standard (ADT)	14.7 months	56.3 months	(see cell above)
Improvement	21.9 months (HR=0.29; CI: 0.24-0.35)	10.7 months (HR = 0.73, CI: 0.61, 0.89)	Treatment showed a clinical benefit by delaying pain progression and symptom worsening.
Darolutamide (Nubeqa)[83,84] * *Did not meet inclusion criteria for modelling at time of writing]*	40.4 months	NR	FACT-P (total) = 112.9[85]
Standard (ADT)	18.4 months	NR	FACT-P (total) = 111.6
Improvement	22 months (HR=0.41, CI 0.34-0.50)	NR. HR=0.69, CI: 0.53–0.88	Patient-reported outcomes were similar between tx and placebo groups. MFS improved.

MFS = metastasis-free survival*; NR = median overall survival *not reached* at the time of analysis, i.e. >50% of patients were still alive; FACT-P = The Functional Assessment of Cancer Therapy-Prostate

[77] Small and others, “Final Survival Results from SPARTAN, a Phase III Study of Apalutamide (APA) versus Placebo (PBO) in Patients (Pts) with Nonmetastatic Castration-Resistant Prostate Cancer”.
[78] Smith and others, “Apalutamide Treatment and Metastasis-Free Survival in Prostate Cancer”.
[79] pan-Canadian Oncology Drug Review, *Final Clinical Guidance Report Apalutamide (Erleada) for Castration-Resistant Prostate Cancer*.
[80] Hussain and others, “Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer”.
[81] Sternberg and others, “Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer”.
[82] Tombal and others, “Patient-Reported Outcomes Following Enzalutamide or Placebo in Men with Non-Metastatic, Castration-Resistant Prostate Cancer (PROSPER).
[83] Fizazi and others, “Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide.”
[84] Fizazi and others, “Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer.”
[85] Fizazi and others, “Supplement to: Fizazi and others Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer.”

Recent (2019) clinical practice guidelines in Canada have incorporated this body of evidence to recommend ARAT therapies as standard of care for both metastatic and non-metastatic CRPC as well as metastatic CSPC (castration-sensitive, i.e., concurrent with ADT initiation). Early intervention for early-stage prostate cancer generally includes either active surveillance, external beam radiation or surgery for low-risk/low-PSA volume patients or ADT for high-PSA volume or high-risk patients.[86,87] Upon progression of the tumour, clinical practice guidelines recommend different treatment options, including ARAT therapy in both the castration resistant and metastatic settings.[88]

Once the cancer metastasizes, guidelines recommend clinical trial participation. If none are available, ARAT therapies are recommended either before or after chemotherapy (in addition to ADT), followed by – or in addition to – bone-targeted therapy. Bone metastases have a 90% frequency in men with castration-resistance prostate cancer (CRPC). As a result, pain, fractures, spinal cord compression and bone marrow failure are among the causes for a decline in quality of life requiring concomitant treatments to be considered.[89] For newly diagnosed metastatic prostate cancer, guidelines now recommend radiation along with ADT, along with chemotherapy or ARAT therapies, or chemo followed by ARAT.[90]

The implications of these improvements are immensely promising for patients in terms of life years gained and quality of life improvements, reduced burden for their caregivers, and economic value to patients, the health system, Canada's biotechnology sector and broader local and national economies.

The next section presents the results from our quantitative model estimating the actual and potential annual economic- and clinical-value (life years gained) of ARAT therapies.

"ARAT prostate cancer therapies have been instrumental to providing longer survival for our patients, but also improved quality of life, and a convenient medical therapy given that it is taken orally and does not require coming to hospital for infusional chemotherapy."
- Dr. Tony Finelli, M.D., MSc., FRCSC, Chief of Urology, GU Site Lead at the Princess Margaret Cancer Centre

[86] American Cancer Society, "Hormone Therapy for Prostate Cancer."
[87] So and others, "Canadian Urological Association-Canadian Urologic Oncology Group Guideline on Metastatic Castration-Naive and Castration-Sensitive Prostate Cancer." In these guidelines, Chemotherapy = docetaxel; ARAT = androgen-receptor-axis targeted therapy: abiraterone acetate (Zytiga), enzalutamide (Xtandi), apalutamide (Erleada). Both of these anti-androgens are used with low-dose prednisone.
[88] Saad and others, "2021 Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) Guideline: Management of Castration-Resistant Prostate Cancer."
[89] Ibid.
[90] So and others, "Canadian Urological Association-Canadian Urologic Oncology Group Guideline on Metastatic Castration-Naive and Castration-Sensitive Prostate Cancer."

Value of ARAT Therapies in Prostate Cancer

Estimated Potential Benefit

In Canada, 72% of newly-diagnosed prostate cancers are localized, 17% are regional, and 8% are metastatic (3% are unknown).[91,92] About 10-20% of prostate cancers become castration-resistant, or CRPC, within 5 years, and virtually all patients treated with ADT will eventually progress. Around 85% of castration-resistant cancers are metastatic.[93] About 50% of all new cases of prostate cancers eventually become metastatic.[94]

The available data on utilization of oncology therapies did not allow for the identification of patients who received chemotherapy, and consequently, the use of ARAT therapies before or after chemotherapy was impossible to determine. Thus, the metastatic CRPC eligible patient population was not differentiated between post or prior to chemotherapy. Instead, we utilized the total metastatic CRPC population starting in 2013 when the first ARAT therapy was approved for use prior to chemotherapy (in addition to post-chemo).

Based on incidence rates and eligible sub-populations using epidemiologic research, there were a total of 139,620 patients in Canada who could have benefited from ARAT therapies between 2011-2021. Increased median progression/metastasis free survival benefits (compared to standard of care) can be observed as early as 3 months following ARAT treatment initiation for metastatic CRPC, to 15 months after treatment initiation for non-metastatic CRPC. Clinical benefits in non-metastatic CRPC have been demonstrated beyond 3 years, which was recommended for reimbursement in 2018. Consequently, our model estimates progression-free life years gained up to 2024 for treatments initiated in the eligible patient population up to 2021.

Total life years gained from using ARAT therapies compared to standard of care totaled 112,641 for those potentially eligible patients (starting in 2013 after the indication was granted for metastatic castration-resistant prostate cancer prior to chemotherapy). This can be further divided up by metastatic and non-metastatic indications. Cumulative potential progression-free life years gained for metastatic patients totaled 82,810 (starting in 2013), and 29,830 for non-metastatic patients (starting in 2018) (Table 4). For better comparability, this is equivalent to a total of 743 life years gained for 100 annual potential metastatic patients (900 patients total, between 2013 and 2021) and a total of 792 life years gained for 100 annual potential non-metastatic castration-resistant patients (400 patients total, between 2018 and 2021).

[91] LeBlanc, Demers, and Shaw, “Recent Trends in Prostate Cancer in Canada.”
[92] So and others, “Canadian Urological Association-Canadian Urologic Oncology Group Guideline on Metastatic Castration-Naive and Castration-Sensitive Prostate Cancer.”
[93] Kirby, Hirst, and Crawford, “Characterising the Castration-Resistant Prostate Cancer Population: A Systematic Review.”
[94] Terris, “Metastatic and Advanced Prostate Cancer.”

Table 4 – Estimated Potential Cumulative and Average Life Years* Gained per Patient, by Metastatic and Non-metastatic Indications, ARAT Therapies, 2011-2021

Indication	Total Eligible Patients	Total Life years* gained	Average Life Years* gained per patient
Metastatic CRPC (2013-2021)	*100,778*	82,810	0.83
Non-metastatic CRPC (2018-2021)	*15,071*	29,830	1.98
All Prostate	*115,849*	112,641	0.98 (patient weighted average)

* Progression-free or metastasis-free life years. Benefit continues beyond 2021 due to length of average life-years gained beyond one year.

Total estimated economic benefits from using ARAT therapies compared to standard of care totaled $3.2 billion for those potentially eligible patients between 2011-2021 (Table 5). Average economic benefit per metastatic and non-metastatic CRPC patient ($23,238 and $56,148, respectively) was derived by differencing economic benefit by year and cohort between innovation and comparator groups, then averaging over the period. In total, this can be broken down to $2.3 billion for metastatic CRPC and $0.9 billion for non-metastatic CRPC. For better comparability, this is equivalent to a total of $21.0 million in economic benefit gained for 100 annual potential metastatic patients (900 patients total, between 2013 and 2021) and $22.5 million gained for 100 annual potential non-metastatic castration-resistant patients (400 patients total, between 2018 and 2021).

Table 5 – Estimated Potential Cumulative and Average Economic Benefit per Patient, by Metastatic and Non-metastatic Indications, ARAT Therapies, 2011-2021

Indication	Total Economic Benefit*	Average economic benefit* per patient
Metastatic CRPC (2013-2021)	$2.3 billion	$23,238
Non-metastatic CRPC (2018-2021)	$0.9 billion	$56,148
All prostate	$3.2 billion	$27,519 (patient weighted average)

* Benefit continues beyond 2021 due to length of average life-years gained beyond one year.

Treatment Rates – ARAT Therapies for Prostate Cancer

The lack of comprehensive and accurate utilization data for advanced cancer therapies in Canada makes it challenging to estimate population treatment rates. However, one can look to the rate of growth of claims for ARAT therapies to understand the pace of adoption of ARAT therapies by clinicians and funding agencies.

In 2011, the first ARAT therapy received Health Canada approval and was reviewed by the interim Joint Oncology Drug Review (iJODR); and 2011 also saw the first claims in the Ontario

public drug claims database. The number of claims for ARAT therapies in Canada, where data are available[95] grew by 94% [Cumulative Annual Growth Rate – (CAGR)] and costs by 85% (CAGR) between 2011-2020, and monthly patients in Ontario increased by 80% (CAGR) in the same period. The greatest single year increase in monthly patients in Ontario occurred in 2012 following the Health Canada approval and iJODR recommendation[96] of abiraterone (Zytiga) for metastatic castrate-resistant prostate cancer in 2011 (initially approved for second line use after chemotherapy).[97]

We also explored the degree to which access and utilization may influence variation in treatment rates by care setting, region of residence or other factors. Input from a urologic oncologist in an Ontario hospital / cancer clinic centre[98] indicated that in their practice, 80-90% of all patients diagnosed with metastatic castration-resistant prostate cancer currently receive a first-line therapy, usually in the form of an ARAT therapy. However, an examination of real-world data in Ontario between 2013-2017 found significantly lower access/utilization rates. Utilization of life-prolonging therapy increased among castration-resistant prostate cancer patients within 2 years of death, from around 23% in 2013 to 58% in 2017, abiraterone having the highest use at 66%, followed by docetaxel (50%), enzalutamide (17%) and others. This study found that access and utilization of these therapies differed according to type of treating physician, as well as by patient age and health status, but did not change according to patient income, region of residence: rural vs urban, or metastatic status at diagnosis.[99]

Although the utilization of ARATs in prostate cancer has increased significantly over our study period and treatment rates appear to have reached near the totality of prostate cancer patients in at least some cancer centres, as recommended in the most recent clinical practice guidelines, there remains significant discrepancy between oncology specialists practicing in academic care settings compared to oncologists practicing in the community. According to a survey conducted among Canadian urologists, 89% of academic specialists treated patients with agents approved for nmCRPC compared to only 50% of community physicians. In the event of disease progression, 78% vs 24% opted to continue therapy, respectively; and 74% vs 36% favored genetic testing for newly diagnosed mitochondrial pyruvate carrier (mPC).[100,101] The literature also highlights inequitable access to these therapies across Canadian provinces.[102] Equity of access is also of paramount concern for patients and clinicians alike.

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[95] Note that public IQVIA retail oncology data for Alberta, British Columbia, Saskatchewan and PEI are not available, and as such not included in this analysis.
[96] Note abiraterone received a Health Canada Notice of Compliance July 27, 2011, and was reviewed through the interim Joint Oncology Drug Review process - the precursor to the CADTH pCODR review process. Source: CADTH, *Drugs Reviewed under the Joint Oncology Drug Review Process* https://www.cadth.ca/sites/default/files/pcodr/pcodr-ijodr-drugs-provfund.pdf.
[97] Source: IQVIA Pharmastat. Used with permission.
[98] Dr. Tony Finelli, M.D., MSc., FRCSC, Chief of Urology, GU Site Lead at the Princess Margaret Cancer Centre.

[99] Leigh and others, “Barriers to Access of Contemporary Treatment for Lethal Prostate Cancer: An Ontario Population-Based Study."
[100] Hotte and others, “Real-World Management of Advanced Prostate Cancer: A Canadian Comparison of Academic Specialists and Community-Based Prostate Cancer Physicians.”
[101] Leigh and others, “Barriers to Access of Contemporary Treatment for Lethal Prostate Cancer: An Ontario Population-Based Study.”
[102] Woon and others, “Disparity in Public Funding of Therapies for Metastatic Castrate-Resistant Prostate Cancer across Canadian Provinces.”

It is also unclear how the adoption of ARAT therapies by Canadian clinicians and provincial funding programs compares with other developed nations. Although most new treatments ultimately receive funding at least in part, this process takes longer in Canada than in other countries[103], and clinicians and patients must overcome significant hurdles and barriers in order to access these therapies in a timely fashion to stop disease progression and maximize prognosis for patients.

Impact on Patients' Ability to Work

This analysis assumes the same employment rates between the standard of care for prostate cancer and innovation therapies (See Appendix – Detailed Quantitative Model Methodology). In a recent scoping review of prostate cancer survivors, rates on patient's returning to work were over 70% within the first year of treatment.[104] It is also worth noting that a recent study of German patients diagnosed with prostate, colorectal and breast cancer before the age of 60 (N=1,558) reported that 90% of patients returned to work within two years of diagnosis[105]. After an average of 8.3 years since diagnosis, 63% of patients continued to work at their original job. Returning to work also did not differ with respect to the type of advanced therapy, tumour site, gender, or marital status. To inform our model qualitative information was also sought through consultation with specialists about treatment rates in their clinical practice; and with prostate cancer patients themselves inquiring about the impact of treatment on their ability and intent to maintain an active work life. For prostate cancer, it would appear that ARAT therapies potentially improve patients' ability to work.

Key Take-aways for Innovations in Prostate Cancer

The last decade has seen tremendous progress in the treatment of prostate cancer in Canada and around the world, largely due to the development and adoption of ARAT therapies in the advanced stages of prostate cancer. Metastatic cancer patients who previously had very few options and a very poor survival prognosis, now have options that have doubled their life expectancy. Non-metastatic cancer patients who previously had no options until they progressed to metastatic disease, now have options to significantly delay metastatic disease and improve their chance of surviving beyond 5 years. By delaying metastatic disease, patients have a longer period of time in an earlier disease state that has less negative impact on their day to day lives.

Our model estimates the potential value of universal access to and utilization of ARAT therapies for prostate cancer patients in Canada over the past ten years. Grounded in clinical outcomes evidence for these indicated therapies, if all eligible Canadian patients received access to these treatments, our model estimates a gain of 112,641 progression-free life years and $3.2 billion in additional potential economic value compared to the current standard of care. While the current utilization of these therapies by Canadian patients over the study period was not feasible to benchmark due to lack of pan-Canadian data availability, nevertheless, even if 50% of eligible patients received ARAT therapies in the same period, this would represent a potential of 56,300

[103] Salek and others, "Factors Influencing Delays in Patient Access to New Medicines in Canada."
[104] Ko, Oliffe, and Bottorff, "Prostate Cancer Treatment and Work: A Scoping Review".
[105] Arndt and others, "Return to Work after Cancer. A Multi-Regional Population-Based Study from Germany".

life years gained, and $1.6 billion of economic value to Canadian patients and Canada's economy since 2010.

Improved screening rates appear to have improved access to care and treatment in the last few decades; and the treatments that we focused on in this study are anticipated to yield significant improvements in the long-term prognosis of prostate cancer patients, particularly in the more advanced stages of the disease, where prognosis has been modest for decades.[106,107]

Opportunities exist for Canada to increase and accelerate adoption of these innovative therapies to fully realize the value and benefits to Canadians.

Summary

Evidence indicates that ARAT therapies can result in 1-year (average) of progression free survival. That is to say on average, each Canadian prostate cancer patient could delay their disease worsening by one year and maintain their current state of prostate health.

If all eligible patients in Canada received ARAT therapies since 2010 an estimated 112,641 progression-free life years may have been realized: and $3.2 billion in potential economic value to Canadian patients and Canada's economy.

If just 50% of eligible Canadian patients received these therapies, a potential ~56,300 life years may have been realized; and $1.6 billion in potential economic value to Canadian patients and Canada's economy since 2010.

[106] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2019*.
[107] Canadian Cancer Society, *Survival Statistics for Prostate Cancer*.

Lung Cancer

Incidence, Prognosis, and Treatment for Non-small Cell Lung Cancer (NSCLC)

Lung cancer is the most commonly diagnosed cancer globally[108] and remains the leading cause of cancer deaths in most developed nations, including Canada.[109] Nearly 90% of all lung cancers are classified as non-small cell lung cancer (NSCLC).

It is estimated that 86% of lung cancer cases are attributable to modifiable risk factors such as tobacco use (72%), radon gas and asbestos, air pollution, and lifestyle factors of physical inactivity and diet (low fruit and vegetable consumption). [110]

Males have traditionally had a higher incidence and mortality rates (20% and 30%, respectively) than women. Age-standardized lung cancer incidence and mortality rates have declined significantly in men over the last 30 years (by 41% and 45%, respectively) but in contrast, incidence and mortality have increased moderately among women until 2012, with a slight decline in recent years. As a result, the gap in incidence and mortality rates have converged between males and females. The decline in lung cancer incidence rates is largely attributed to declining tobacco smoking rates among both men and women. [111]

Lung cancer has one of the worst 5-year survival rates of all cancers at only 19%. Nearly half of all lung cancers are diagnosed at stage 4, well beyond early treatment and curative intervention opportunities, which explains the extremely low survival rate. Females have a higher 5-year survival rate than men (22% vs 15%). Survival rates have improved modestly by 5.4 percentage points from 1992-1994 to 2012-2014. Three-year survival declines with more advanced stage of lung cancer at diagnosis (71% for stage 1, to 5% for stage 4). [112]

There are no systematic screening programs for lung cancer in Canada, although efforts have begun to implement organized programs following studies demonstrating significant reductions in mortality rates among current or former heavy smokers screened using low-dose computer tomography (LDCT). Recommendations from the Canadian Task Force on Preventive Health Care include screening in adults aged 55 and above who currently smoke or quit within 15 years, using LDCT, in conjunction with smoking cessation programs.[113]

Innovations in Pharmacotherapies for NSCLC – Targeted Therapy

Until the mid-2000s there were no targeted therapy options for NSCLC patients. The only options were surgery, radiation therapy, chemotherapy, or palliative care. Surgery is often the only treatment used in the treatment of early-stage lung cancer. In the early-to-middle stages of lung cancer, adjuvant chemotherapy or radiation may be recommended after surgery. However,

[108] World Cancer Research Fund, “Worldwide Cancer Data.”
[109] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics: A 2020 Special Report on Lung Cancer*.
[110] Ibid.
[111] Ibid.
[112] Ibid.
[113] Ibid.

patients need to meet clinical health status requirements (functional and performance) in order to be eligible for surgical or chemotherapy pathways.[114,115]

Since patients are typically diagnosed with advanced stages of lung cancer, with more than half of those diagnosed over 75 years of age,[116] surgery is rarely a clinically viable treatment option for most patients.[117] Furthermore, patients also tend to be ineligible to receive chemotherapy due to their poor health (functional and performance) status[118]. As a result, the treatment pathway for lung cancer patients primarily includes radiation and palliative care.

In 2004, the first breakthrough targeted therapy, epidermal growth factor receptor (EGFR) inhibitor, was approved in Canada.[119] The discovery of the *EGFR* mutations in patients who benefited from EGFR inhibitors in clinical trials in the 1990s ushered in a new era of molecular target discoveries. The anaplastic lymphoma kinase (*ALK*) mutations were then discovered as an effective target and the first ALK+ inhibitor[120] was approved in Canada in 2013.[121] Other genetic targets followed, including *RET*, *ROS*, and *BRAF*, as well as *KRAS*. Additionally, a new generation of therapies targeting the immune system, called immune checkpoint inhibitors, or immunotherapy, have recently been approved for patients who exhibit PD-1 and PD-L1 antibodies.[122] These advanced PD-1 and PD-L1 immunotherapies provide substantial improvements in overall survival and improved quality of life for the lung cancer patient population not eligible for targeted therapies. Most lung cancer patients do not habour the genetic mutations that make them a candidate for targeted therapies: about 15% of Canadians are eligible for EGFR inhibitors while 5% are eligible for ALK inhibitors. As a result, immunotherapies fill a gap the majority of lung cancer patients in Canada.

EGFR and ALK inhibitors were first approved as second or third-line therapy for advanced NSCLC; newly diagnosed NSCLC patients had to wait until 2010 and 2015 for evidence to show that these treatments were also effective as first-line therapy.[123]

Epidermal Growth Factor Receptor - Tyrosine Kinase Inhibitor (EGFR TKI) Therapies

There were four EGFR therapies approved and funded during our study period for advanced NSCLC with activated *EGFR* mutations, introduced in second-line, followed by first-line.

[114] American Cancer Society, “Treatment Choices for Non-Small Cell Lung Cancer, by Stage.”
[115] Wakelee, Kelly, and Edelman, “50 Years of Progress in the Systemic Therapy of Non–Small Cell Lung Cancer.”
[116] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics: A 2020 Special Report on Lung Cancer*.
[117] Adam Lackey and Jessica S Donington, “Surgical Management of Lung Cancer.”
[118] Wakelee, Kelly, and Edelman, “50 Years of Progress in the Systemic Therapy of Non–Small Cell Lung Cancer.”
[119] Government of Canada, “Notice of Compliance (NOC) Database.”
[120] Wakelee, Kelly, and Edelman, “50 Years of Progress in the Systemic Therapy of Non–Small Cell Lung Cancer.”
[121] Government of Canada, “Notice of Compliance (NOC) Database.”
[122] Wakelee, Kelly, and Edelman, “50 Years of Progress in the Systemic Therapy of Non–Small Cell Lung Cancer.”
[123] Government of Canada, “Notice of Compliance (NOC) Database.”

EGFR is a growth-signaling protein receptor on the surface of cells that is activated after ligand binding.[124] It is a receptor in the family of ErbB receptors that include HER2, and HER4.[125] It was first noticed among non-smokers, usually women of Asian descent.[126] The most common mutations are in the *EGFR* gene in exons 18-21, which is the region that encodes the tyrosine kinase domain (TK).[127] EGFR TK inhibitors (EGFR TKIs) work by blocking the EGFR pathway from within the cell and by preventing growth proteins from binding to the cell, thereby hindering excessive growth of the cancer cell. Some EGFR TKIs also block associated pathways in the ErbB family of receptors. However, most patients treated with first or second-generation EGFR TKIs will develop resistance to treatment, often through a mutation in the *EGFR T790M* gene. The third-generation EGFR TKI, only one of which is available in Canada (osimertinib), overcame this resistance by targeting the *T790M* mutation as well as displaying activity at the original exons. New EGFR TKIs are currently in development to overcome resistance among T790M mutation-positive patients, as well as other resistance gene targets.[128]

EGFR TKIs have significantly improved the prognosis of advanced NSCLC patients with more and more *EGFR* mutations. In patients with EGFR+ mutations, first and second-generation inhibitors gefitinib, erlotinib, and afatinib improved median PFS by 150% to 180% to 9.5, 9.4 months, and 11.1 months, respectively, when used as first-line therapy (Table 6). The newer generation EGFR TKI, osimertinib prolonged median PFS in patients who developed resistance and progressed on an earlier generation EGFR TKI by double, to 10.1 months, from 4.4 months on standard of care (chemotherapy). Further, osimertinib, when used in first-line, nearly doubled median PFS compared to gefitinib and erlotinib to 18.9 months compared to 10.2 months. Side effects were comparable to or improved over other EGFR TKIs (Table 6). Another EGFR TKI, dacomitinib, demonstrated a median PFS of 14.7 months versus 9.2 months with gefitinib and also reflected a median OS to 34.1 months versus 27.0 months, respectively.[129]

Table 6 – EGFR Inhibitors in *EGFR*+ Patients, in First-line

EGFR-inhibitor	Median PFS	Median OS	QoL
gefitinib (Iressa)[130]	9.5 months	ND (22 months)	Patients receiving gefitinib experienced statistically significant ($p<0.0001$) improvement in QoL and lung cancer symptoms.[131] FACT-L (total)= 70.2%
Standard (chemotherapy)	6.3 months	ND (22 months)	FACT-L (total)= 44.5%

[124] Chang, Choi, and Lee, "Mechanisms of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Resistance and Strategies to Overcome Resistance in Lung Adenocarcinoma."
[125] Weaver, "In Depth Overview of Tyrosine Kinase Inhibitor Treatment of EGFR + Lung Cancer."
[126] Wakelee, Kelly, and Edelman, "50 Years of Progress in the Systemic Therapy of Non–Small Cell Lung Cancer."
[127] Melosky and others, "Canadian Consensus: A New Systemic Treatment Algorithm for Advanced EGFR-Mutated Non-Small-Cell Lung Cancer."
[128] Weaver, "In Depth Overview of Tyrosine Kinase Inhibitor Treatment of EGFR + Lung Cancer."
[129] Mok and others, "Updated Overall Survival in a Randomized Study Comparing Dacomitinib with Gefitinib as First-Line Treatment in Patients with Advanced Non-Small-Cell Lung Cancer."
[130] AstraZeneca Canada Inc, *IRESSA (Gefitinib), Product Monograph*.
[131] Ibid.

Improvement	3.2 months (HR=0.74; 0.36-0.64)	ND	Improvement in survival, QoL scores and lung cancer symptoms from tx
erlotinib (Tarceva)[132]	9.4 months	22.9 months	Low compliance in lung cancer symptom scale. As such, analysis of quality of life regarded as inconclusive.[133]
Standard (chemotherapy)	5.2 months	18.8 months	See above
Improvement	4.2 months (HR=0.42; 0.27-0.64)	4.1 months (HR=0.80;0.47-1.37)	See above
afatinib (Giotrif)[134,135]	11.1 months	ND (28.2 months)	More people on afatinib over chemotherapy showed improved global health status and physical and cognitive functioning[136]
Standard (chemotherapy)	6.9 months	ND (28.2 months)	See above
Improvement	4.2 month (HR=0.58; 0.43-0.78)	ND	Global health status/QoL improved with afatinib compared to chemotherapy
osimertinib (Tagrisso)[137,138,139] – 2nd line after EGFR TKIs	10.1 months	26.8 months	The proportion of patients with improvement in global health status was higher with osimertinib (37%) than with chemotherapy (22%) [OR, 2.11; 95% CI, 1.24 to 3.67; *P* = .007][140]
Standard (chemotherapy)	4.4 months	22.5 months	See above
Improvement	5.7 months (HR=0.30; 0.23-0.41)	4.3 months (HR = 0.87; 0.67-1.0)	Improvement in HRQoL and survival with tx
osimertinib (Tagrisso)[141]	18.9 months	38.6 months	Patient reported outcomes were similar between treatments[142]

[132] Hoffmann-La Roche Limited, *TARCEVA (Erlotinib), Product Monograph*.
[133] Rosell and others, "Erlotinib versus Standard Chemotherapy as First-Line Treatment for European Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer (EURTAC)."
[134] Boehringer Ingelheim Canada, *GIOTRIF (Afatinib), Product Monograph*.
[135] Yang and others, "Afatinib versus Cisplatin-Based Chemotherapy for EGFR Mutation-Positive Lung Adenocarcinoma (LUX-Lung 3 and LUX-Lung 6)."
[136] Yang and others, "Symptom Control and Quality of Life in LUX-Lung 3: A Phase III Study of Afatinib or Cisplatin/Pemetrexed in Patients with Advanced Lung Adenocarcinoma with EGFR Mutations."
[137] AstraZeneca Canada Inc, *TAGRISSO (Osimertinib), Product Monograph.*
[138] Papadimitrakopoulou and others, "Osimertinib versus Platinum–Pemetrexed for Patients with EGFR T790M Advanced NSCLC and Progression on a Prior EGFR-Tyrosine Kinase Inhibitor: AURA3 Overall Survival Analysis."
[139] Mok and others, "Osimertinib or Platinum–Pemetrexed in EGFR T790M–Positive Lung Cancer."
[140] Lee and others, "Patient-Reported Symptoms and Impact of Treatment with Osimertinib versus Chemotherapy in Advanced Non-Small-Cell Lung Cancer: The AURA3 Trial."
[141] AstraZeneca Canada Inc., *TAGRISSO, Osimertinib, Product Monograph*.
[142] Leighl and others, "Patient-Reported Outcomes from FLAURA: Osimertinib versus Erlotinib or Gefitinib in Patients with EGFR-Mutated Advanced Non-Small-Cell Lung Cancer."

Standard (EGFR inhibitor gefitinib or erlotinib)	10.2 months	31.8 months	See above
Improvement	8.7 months (HR=0.46; 0.37-0.57)	6.8 months (HR=0.8; 0.64-1.00)	HRQoL maintained with no clinically relevant symptom improvements in favor of either treatment arm

PFS = progression-free survival; OS = overall survival; QoL = Quality of Life; HR = hazard ratio; CI = confidence interval; ND = no significant difference (Post-trial treatments can have an effect of attenuating the measurable difference in OS [143]).

Consistent with these findings, recent Canadian clinical practice guidelines acknowledge the effectiveness and value of early and later generation EGFR TKIs and recommend standard *EGFR* mutation testing for all patients diagnosed with non-squamous NSCLC at the time of diagnosis, and again at progression for any new activated mutations. Osimertinib has become the preferred first-line therapy for patients with common *EGFR* mutations and for patients with brain metastasis, and as a first or second-line option in patients who have *de novo* resistance or have developed resistance through a *T790M* mutation.[144] First or second-generation EGFR TKIs should be used in first-line when osimertinib is not appropriate (gefitinib or erlotinib) or when the patient has uncommon *EGFR* mutations (afatinib). Other emerging strategies include combining gefitinib with select chemotherapy agents. [145]

Anaplastic Lymphoma Kinase *ALK*+ Therapies

There are four anaplastic lymphoma kinase (ALK) inhibitor therapies that have received a funding recommendation from CADTH during our study period for patients with activated *ALK* mutations in advanced NSCLC, but only three that have received public funding following successful pCPA negotiation. One received a negative recommendation for funding.

ALK is a gene that provides instructions for a protein called ALK receptor tyrosine kinase. This protein transmits signals from the cell surface to the inside of the cell to activate another protein inside the cell, which turns on a signaling pathway to activate a series of proteins responsible for cell growth and proliferation. This process by the ALK receptor tyrosine kinase is thought to be responsible for early development in nerve cells.[146] In a few patients with NSCLC, an event that leads to fusion of the *ALK* protein gene with another protein gene (EML4) results in tumour cells becoming dependent on that protein expression. This rearrangement of the *ALK* gene was identified among younger individuals, non-smokers, and mostly adenocarcinoma histology of NSCLC. Like EGFR TKIs, drugs that target the *ALK* gene work by binding to the abnormal ALK

[143] Villaruz and Socinski, "The Clinical Viewpoint: Definitions, Limitations of RECIST, Practical Considerations of Measurement."
[144] Melosky and others, "Canadian Consensus: A New Systemic Treatment Algorithm for Advanced EGFR-Mutated Non-Small-Cell Lung Cancer."
[145] Ibid.
[146] Medline Plus, "ALK Gene."

protein, blocking the downstream signaling pathway and inhibiting its growth. New generation ALK inhibitors have demonstrated greater effectiveness in patients with brain metastases.[147,148]

ALK inhibitors have a major impact on survival outcomes for patients with activated *ALK* mutations. The first generation of ALK inhibitors, crizotinib, used in first-line, extended median PFS by around 155% from 7.0 to 10.9 months, with further extension by the second-line use of another ALK inhibitor, ceritinib, effectively tripling median PFS from 1.6 months to 5.4 months. The first among the new generation of ALK inhibitors, alectinib, proved even more effective, extending median PFS after crizotinib use by 8.2 months to 9.6 months, from 1.4 months for chemotherapy standard of care (nearly a 10-fold increase), and tripled median PFS to 34.8 months when used in first-line, compared to the first-line ALK inhibitor crizotinib.

A real-world study of Canadian patients treated in Alberta between 2014-2019 shows that the use of crizotinib and alectinib (split 78/22 over the period) resulted in 17.0 months of median PFS; and reached 48.5 months in median overall survival (OS). (Table 7)

Another recent ALK inhibitor, brigatinib, has demonstrated a PFS of 24.0 months compared to 11.0 months PFS from crizotinib in first-line treatment.[149]

In light of the progressively improving survival outcomes of initial and newer generations of ALK inhibitors, the most recent Canadian consensus on *ALK*-positive tumours in advanced NSCLC was published in 2018. All patients with advanced non-squamous NSCLC are recommended to be tested for *ALK* rearrangement, and that alectinib or ceritinib are the preferred agents in first-line therapy, as well as for patients who have been treated and progressed with crizotinib. Newer ALK inhibitors should be considered as further treatments, and pemetrexed (chemotherapy) after all ALK inhibitors have been exhausted.[150]

The implications of these improvements are immensely promising for advanced NSCLC patients in terms of life years gained and quality of life improvements, reduced burden for their caregivers, and economic value to patients, the health system, Canada's biotechnology sector and broader local and national economies. In the next section, we present the results of the modeling to quantify the economic and clinical value (life years gained) of EGFR TKI and ALK inhibitor therapies.

[147] Weaver, "Understand ALK Inhibitor Treatment of ALK Positive Lung Cancer."
[148] Awad and Shaw, "ALK Inhibitors in Non–Small Cell Lung Cancer: Crizotinib and Beyond."
[149] Camidge and others, "Brigatinib versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial."
[150] Melosky and others, "Canadian Perspectives: Update on Inhibition of ALK-Positive Tumours in Advanced Non-Small-Cell Lung Cancer."

Table 7 – ALK Inhibitors in *ALK*+ Patients, in First-line (or Second-line if no First-line Indication*)

ALK inhibitor therapy	**Median PFS**	**Median OS**	**QoL**
crizotinib (Xalkori)[151] – 1st line	10.9 months	NR	Overall mean EQ-5D health utility index scores significantly greater (p< 0.05) for crizotinib than chemotherapy.[152]
Standard (chemotherapy)	7.0 months	47.5 months	See above
Improvement	3.9 months (HR=0.45, CI 0.35-0.60)	NR	General health status, physical functioning, global QoL, fatigue, and pain significant improved by tx
ceritinib (Zykadia)[153,154] – 2nd line AFTER crizotinib*	5.4 months	NR	Significant improvement in overall health status (EQ-5D index, p<0.001) with tx compared to chemo[155]
Standard (chemotherapy)	1.6 months	NR	See above
Improvement	3.8 months (HR=0.49, CI 0.36-0.67)	NR	Significant improvement in lung cancer symptoms and overall health status with tx.
alectinib (Alecensaro)[156] 2nd line AFTER crizotinib*	9.6 months	NR	Alectinib patients reported more improvement in baseline symptoms compared to chemotherapy[157] Median time to deterioration = 8.1 months
Standard (chemotherapy)	1.4 months	NR	Median time to deterioration = 1.9 months
Improvement	8.2 months (HR=0.15, CI 0.08- 0.29)	NR	Alectinib improved HRQoL and symptom burden compared to chemotherapy

[151] Solomon and others, “Final Overall Survival Analysis from a Study Comparing First-Line Crizotinib versus Chemotherapy in ALK-Mutation-Positive Non-Small-Cell Lung Cancer.”
[152] Blackhall and others, “Patient-Reported Outcomes and Quality of Life in PROFILE 1007: A Randomized Trial of Crizotinib Compared with Chemotherapy in Previously Treated Patients with ALK-Positive Advanced Non–Small-Cell Lung Cancer.”
[153] pan-Canadian Oncology Drug Review, *Final Recommendation for Ceritinib (Zykadia) Resubmission for Metastatic Non-Small Cell Lung Cancer*.
[154] ClinicalTrials.gov, “LDK378 Versus Chemotherapy in ALK Rearranged (ALK Positive) Patients Previously Treated With Chemotherapy (Platinum Doublet) and Crizotinib.”
[155] Mok and others, “Patient-Reported Outcomes (PROs) in ASCEND-5.”
[156] pan-Canadian Oncology Drug Review, *Final Recommendation for Alectinib (Alecensaro) for Metastatic Non-Small Cell Lung Cancer.*
[157] Mazieres and others, “Patient-Reported Outcomes and Safety from the Phase III ALUR Study of Alectinib vs Chemotherapy in Pre-Treated ALK+ NSCLC.”

alectinib (Alecensaro)[158] 1st line	34.8 months	NR	Clinically meaningful improvements in lung cancer symptoms on tx[159] Duration of clinically meaningful improvement = Week 88
Standard (ALK inhibitor crizotinib)	10.9 months	57.4 months	Duration of clinically meaningful improvement = Week 68
Improvement	23.9 months (HR= 0.43, CI: 0.32-0.58)	NR (HR= 0.67, CI: 0.46 - 0.98)	Patient reported outcome data reflect better HRQoL
crizotinib or alectinib[160]** **(real-world study)**	17.0 months	48.5 months	Patient-reported outcomes not reported

PFS = progression-free survival; OS = overall survival; QoL = Quality of Life; HR = hazard ratio; CI = confidence interval; NR = not reached; EQ-5D = EuroQol 5-dimensional
* Second-line after crizotinib (first ALK inhibitor use)
** Real-World Evidence Canadian cohort study for Crizotinib and Alectinib, 78% of patients on crizotinib, 22% used alectinib (only available during 2018-2019 of entire study period 2014-2019)

Value of Targeted Therapies in NSCLC

Estimated Potential Benefit

In Canada, more than half of newly diagnosed lung cancers are advanced or metastatic. About 80-85% of lung cancers are categorized as non-small cell lung cancer (NSCLC). Only 26% of NSCLC cases are diagnosed in stages 1 or 2, 19% in stage 3, and 53% in stage 4 (metastatic) (2% are unknown).[161] Recurrence rates are high, varying from 30% in early stages, to 70% for stage 4, and 83% of recurrences are metastatic.[162,163] Studies indicate that 15% of patients with

[158] Mok and others, "Updated Overall Survival and Final Progression-Free Survival Data for Patients with Treatment-Naive Advanced ALK-Positive Non-Small-Cell Lung Cancer in the ALEX Study."
[159] Pérol and others "Patient-Reported Outcomes from the Randomized Phase III ALEX Study of Alectinib versus Crizotinib in Patients with ALK-Positive Non-Small-Cell Lung Cancer."
[160] Gibson and others, "Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors."
[161] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics: A 2020 Special Report on Lung Cancer*.
[162] Eldridge, "What Is Lung Cancer Recurrence?"
[163] Uramoto and Tanaka, "Recurrence after Surgery in Patients with NSCLC."

NSCLC show EGFR TK domain mutations (*EGFR*+), and 5% have a rearrangement in a gene called *ALK* (*ALK*+).[164,165,166,167,168]

Based on incidence rates and eligible sub-populations there were a total of 45,086 patients in Canada who could have benefited from *EGFR*+ and *ALK*+ therapies between 2011-2021. Increases in median progression free survival (compared to standard of care, usually chemotherapy in older clinical trials) can be observed as early as 6 months after first-line treatment. Clinical improvements in median PFS (compared to standard of care) have also been demonstrated beyond 10 or 18 months when *EGFR*+ therapies are used as second- or first-line therapy, respectively. Consequently, progression-free life years gained are estimated beyond 2021 for treatments initiated up to 2021.

For *ALK*+ therapies, increased median progression free survival (compared to the comparator) can be observed as early as 1.5 months when used in second-line therapy, or 7 months when used in first line therapy, and median increases in PFS are demonstrated up to 10 months following start of second-line therapy, or up to 35 months following start of first-line therapy.

Since *EGFR*+ therapies were approved in first-line use as early as 2010, benefits are modeled only in first-line for these patients. An exception was made for osimertinib, which was first approved during our study period for use in second-line (2017), followed by first-line in 2019, in which case, we first used second-line PFS data and then switched to first-line data only when the indication was obtained. PFS benefits are weighed between therapies according to proportional monthly patient counts in Ontario's public and private claims data, starting the year of CADTH recommendation. *ALK*+ therapies were also approved in second-line followed by first-line during our study period, so second-line PFS data is used to estimate value until the first-line indication was obtained, and then first-line PFS data is used for the remainder of the period, with the exception of alectinib, which had both first line and second line approved for funding in the same year, so first line PFS data was used for the entire period of study.

Total life years gained from using targeted *EGFR*+ and *ALK*+ therapies compared to standard of care totaled 22,764 for potentially eligible patients. This can be further divided up by *EGFR*+ and *ALK*+ therapies. Cumulative potential progression-free life years gained for patients with *EGFR*+ mutations totaled 13,328 (starting in 2011), and 9,436 for patients with *ALK*+ mutations (starting in 2013) (Table 8). For better comparability, this is equivalent to 409 life years gained for 100 annual potential patients with *EGFR*+ mutations (1100 patients total, between 2011 and 2021), and to a total of 847 life years gained for 100 annual potential patients with *ALK*+ mutations (900 patients total, between 2013 and 2021).

[164] Melosky and others, "Canadian Consensus: A New Systemic Treatment Algorithm for Advanced EGFR-Mutated Non-Small-Cell Lung Cancer."
[165] Canadian Agency for Drugs and Technologies in Health, *Initial Recommendation for Osimertinib (Tagrisso) for Advanced or Metastatic Non-Small Cell Lung Cancer.*
[166] American Cancer Society, "Treatment Choices for Non-Small Cell Lung Cancer, by Stage."
[167] Canadian Agency for Drugs and Technologies in Health, *Anaplastic Lymphoma Kinase Inhibitors for Advanced Non-Small Cell Lung Carcinoma.*
[168] Melosky and others, "Canadian Perspectives: Update on Inhibition of ALK-Positive Tumours in Advanced Non-Small-Cell Lung Cancer."

Table 8 – Estimated Potential Cumulative and Average Life Years* Gained per Patient, *EGFR*+ and *ALK*+ Therapies, 2011-2021

Indication	Total Eligible Patients	Total Life years* gained	Average Life Years* gained per patient
***EGFR*+ (2011-2021)**	*35,307*	13,328	0.37
***ALK*+ (2013-2021)**	*9,778*	9,436	0.94
Total	*45,086*	22,764	0.50 (patient-weighted average)

* Progression-free life years. Benefit continues beyond 2021.

Total estimated economic benefits from using *EGFR*+ and *ALK*+ therapies compared to standard of care totaled $486 million for those potentially eligible patients between 2011-2021 (Table 9). Average economic benefit per patient's utilizing *EGFR*+ and *ALK*+ therapies ($8,556 and $20,231, respectively) was derived by differencing economic benefit by year and cohort between innovation and comparator groups, then averaging over the period. In total, this can be broken down to $284 million for *EGFR*+ and $202 million for *ALK*+. For better comparability, this is equivalent to $8.7 million in economic benefit gained for 100 annual potential patients with *EGFR*+ mutations (1100 patients total, between 2011 and 2021) and $18.2 million gained for 100 annual potential patients with *ALK*+ mutations (900 patients total, between 2013 and 2021).

Table 9 – Estimated Potential Cumulative and Average Economic Benefit per Patient, *EGFR*+ and *ALK*+ Therapies, 2011-2021

Indication	Total Economic Benefit*	Average economic benefit* per patient
***EGFR*+ (2011-2021)**	$284 million	$8,556
***ALK*+ (2013-2021)**	$202 million	$20,231
Total	$486 million	$11,088 (patient weighted average)

* Benefit continues beyond 2021 due to length of average life-years gained beyond one year.

Since my diagnosis, there have been great advances in lung cancer research and survivorship. Lung cancer patients are living longer and getting stronger because of innovative therapies and research.

- Kim MacIntosh, a stage 4 lung cancer survivor
(Source: Lung Cancer Canada, Patient Stories webpage, used with permissions. https://www.lungcancercanada.ca/Resources/Patient-Stories/Kim-MacIntosh.aspx)

Treatment Rates - Targeted Therapies in NSCLC

The lack of comprehensive and accurate treatment utilization data in Canada makes actual determinations of benefit challenging. However, one can look to the drug reimbursement claims and their rate of growth for *EGFR*+ and *ALK*+ therapies to understand the pace of adoption of these breakthrough targeted therapies for NSCLC by clinicians and funding agencies.

In 2010 the first *EGFR*+ therapy for first-line use received Health Canada approval and was reviewed by the interim Joint Oncology Drug Review (iJODR). A subsequent increase in *EGFR*+ drug claims in the IQVIA public and private drug claims database was observed in 2011. The number of claims for *EGFR*+ therapies in Canada grew by 12% (CAGR) and costs grew by 27% (CAGR) between 2011-2020, and monthly patients associated with these claims in Ontario increased by 15% (CAGR) in the same period. The greatest single year increase occurred in 2012, following Health Canada's approval and iJODR's recommendation of Gefitinib (Iressa) in NSCLC for first-line use.[169]

The first *ALK*+ therapy was recommended for funding by CADTH for second-line use (after chemo) in 2013, and in first-line in 2015. The two subsequent therapies were introduced in a similar sequence, although they were indicated as second-line following an *ALK*+ therapy used in first-line (not chemo). By 2018, two out of the three *ALK*+ therapies were recommended as first-line and second-line. The number of claims for *ALK*+ therapies grew by 69% (CAGR) and costs grew by 59% (CAGR) between 2013-2020, and monthly patients in Ontario increased by 58% (CAGR) in the same period. The scale of growth is largely attributable to the significant uptake of breakthrough therapy use by clinicians and patients in this time frame. The greatest single year increase occurred in 2016 following the positive CADTH funding recommendation[170] of Crizotinib (Xalkori) in the first line for advanced *ALK*+ or *ROS1*+ Non-Small Cell Lung Cancer.[171]

We also explored the degree to which access and utilization may vary treatment rates by care setting, region of residence or other factors. Input from a practicing lung cancer clinician[172] indicated that utilization of pharmaceuticals in lung cancer patients has traditionally been very low, particularly for chemotherapy. However, the introduction and increased adoption of breakthrough targeted therapies has contributed to increased treatment rates overall. Nevertheless, depending on practice context and other clinical factors, utilization of targeted therapies remains dependent on testing for genetic mutations in the patient population.[173,174]

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[169] Source: IQVIA Pharmastat. Used with permission.
[170] Gefitinib (Iressa) received a Health Canada Notice of Compliance 2009 for first line use (https://health-products.canada.ca/noc-ac/info.do?lang=en&no=10885), and was reviewed through the interim Joint Oncology Drug Review process - the precursor to the CADTH pCODR review process https://www.cadth.ca/sites/default/files/pcodr/pcodr-ijodr-drugs-provfund.pdf
[171] Source: IQVIA Pharmastat. Used with permission.
[172] Dr. Paul Wheatley-Price, M.D., MBChB, FRCP (UK), Associate Professor and Medical Oncologist at University of Ottawa.
[173] Stock-Martineau and others, "Evolution of Systemic Treatment Uptake and Survival in Advanced Non-Small Cell Lung Cancer."
[174] Seung and others, "Real-World Treatment Patterns and Survival in Stage IV Non-Small-Cell Lung Cancer in Canada."

According to a lung oncologist interviewed for this analysis, only 65-85% of their patients receive testing for gene mutations. [175]

The rate of treatment using breakthrough targeted therapies in lung cancer has increased significantly over our study period and appears to have reached near totality of eligible lung cancer patients in at least some cancer centres across Canada, as recommended in the most recent clinical practice guidelines.[176,177] Nevertheless, access is clearly inequitable for Canadian patients living beyond the catchment area of regional cancer treatment centres.[178]

It is also unclear how the rate of growth in the adoption of lung cancer targeted therapies by Canadian clinicians and provincial funding programs compare with other developed nations. Although most new treatments ultimately receive funding, at least in part, this process takes longer in Canada compared to other countries, due to the pCPA process and other additional review processes by drug plans.[179] Furthermore, clinicians and patients must overcome significant hurdles and barriers as outlined above (e.g., access to diagnostics) in order to access these breakthrough therapies in a timely fashion to clinically impact disease progression and maximize prognosis for patients. Indeed, there were three additional therapies considered for this analysis currently available to Canadian clinicians, but only through private market access. These were excluded from our model due to negative, incomplete, or failed funding recommendations or negotiations.

Impact on Patients' Ability to Work

This analysis assumes the same employment rates between the standard of care for lung cancer and innovation therapies (See Appendix – Detailed Quantitative Model Methodology). As such, this analysis excludes estimates of productivity benefits due to reduced incidence and durations of absenteeism (short- and long-term disability) because of increased ability of patients and their caregivers to continue to work during - and as a result of – treatment,

> *"For patients of working age, who were working prior to diagnosis, I don't know what proportion keep working - I would guess that it would be 20-40% overall, but maybe 50-70% of those on targeted therapy. This is an estimate, I'm not aware of any data on this"*
>
> *– Dr. Paul Wheatley-Price, M.D., MBChB, FRCP (UK)*
> *Associate Professor and Medical Oncologist at University of Ottawa, Past President of Lung Cancer Canada*

[175] Dr. Paul Wheatley-Price, M.D., MBChB, FRCP (UK), Associate Professor and Medical Oncologist at University of Ottawa.
[176] Melosky and others, "Canadian Perspectives: Update on Inhibition of ALK-Positive Tumours in Advanced Non-Small-Cell Lung Cancer."
[177] Melosky and others, "Canadian Consensus: A New Systemic Treatment Algorithm for Advanced EGFR-Mutated Non-Small-Cell Lung Cancer."
[178] Ho and others, "Lung Cancer in Canada."
[179] Salek and others, "Factors Influencing Delays in Patient Access to New Medicines in Canada."

compared to the standard of care. To inform the model, qualitative information was sought through consultation with specialists about treatment rates in their clinical practice; and with lung cancer patients inquiring about the impact of treatment on their ability and intent to maintain an active work life.

For lung cancer, targeted breakthrough therapies have markedly improved patients' ability to work. This is significant given the trend toward advanced disease at the time of diagnosis and treatment, and the high incidence rates of this disease. The overall impact on employers/payors and on the government from reduced disability payments could be significant.

Key Take-aways for Innovations in Lung Cancer

The last decade has seen tremendous progress in the treatment of lung cancer in Canada and around the world, largely credited to the development and adoption of targeted breakthrough therapies in the advanced stages of NSCLC. With increasing availability of genetic testing, cancer patients who previously had very few options and a very poor survival prognosis, now have options that offer a manageable treatment side-effect profile and can double or triple their disease-free life expectancy.

Our model estimates the potential value of universal access to *EGFR*+ and three *ALK*+ therapies for NSCLC patients in Canada over the past ten years. Grounded in clinical outcomes evidence, if all eligible Canadian patients had received access to these indicated therapies, our model estimates that 22,764 progression-free life years would be gained and $486 million in economic value would be generated compared to the current standard of care. While it was not possible to benchmark the current utilization of these therapies by Canadian patients over the study period due to the pan-Canadian lack of (or delayed) adoption of breakthrough treatments and poor data availability across Canadian contexts of care, nevertheless, even if half of lung patients in Canada actually received targeted therapies in the same period, this would represent a potential of 11,382 life years, and $243 million of economic value to Canadian patients and Canada's economy since 2010.

Improved diagnostic testing rates appear to have improved prognosis in the last few decades (An expert clinician estimated that around 65-85% of eligible patients receive molecular genetic testing). It is expected that these new treatments will demonstrate significant improvements in the long-term prognosis of lung cancer patients, particularly in more advanced stages of the disease, where prognosis has been poor for decades. Opportunities exist for Canada to

> *"Ten years ago, the only treatment option we had for advanced lung cancer was chemotherapy…we're now starting to see the longer-term impacts of [targeted therapies], and so now the average life expectancy for people with advanced EGFR+ lung cancer is measured in many years, when previously it would have been many months"*
>
> *- Dr. Paul Wheatley-Price, M.D., MBChB, FRCP (UK)*
> *Associate Professor and Medical Oncologist at University of Ottawa, Past President of Lung Cancer Canada*

increase and accelerate adoption of these innovative therapies to fully realize the value and benefits to Canadians.

Summary

Evidence indicates that *EGFR*+ and *ALK*+ therapies can result in 6-months (average) improvement in progression free survival.

If all eligible patients in Canada received *EGFR*+ and *ALK*+ therapies since 2010 an estimated 22,764 progression-free life years may have been realized: and $486 million in potential economic value to Canadian patients and Canada's economy.

If just 50% of eligible Canadian patients received these therapies, a potential ~11,300 life years may have been realized; and $243 million in economic value to Canadian patients and Canada's economy since 2010.

Breast Cancer

Incidence, Prognosis, and Treatment Pathway

Breast cancer is the second most diagnosed cancer in Canada, with an estimated 27,200 new patients diagnosed in 2019.[180] Breast cancer is the most commonly diagnosed cancer among females, representing 25% of all new cancer cases nationwide.[181] Nearly 40% of breast cancer cases are diagnosed in females aged 30 to 59. The most important known risk factors are a family history of the disease, patient's age, and dense breast tissue.[182] Less than 1% of breast cancer patients in Canada are male.[183]

In 2019, there were an estimated 5,100 deaths from breast cancer in Canada. The age-standardized mortality rate for breast cancer patients in Canada fell from 42.7 deaths per 100,000 in 1986 to 22.4 per 100,000 in 2019. The decline in mortality is likely due to increased mammography screening since 1986 combined with the use of breakthrough therapies following surgical interventions[184]

Breast cancer survivorship in Canada five-years from diagnosis is 88% as most cases are diagnosed early, with over 80% diagnosed at an early stage (stage I or II).[185] This likely reflects the success of well-established breast cancer screening programs across Canada. As is typical of most cancers early detection is more likely to have a better prognosis than cancers detected at late stages. For example, 5-year net survival for stage IV female breast cancer is 22%, while for stage I survival is almost 100%.[186]

Regular screening with mammography, self-examination, and clinical examination can reduce mortality.[187] The Canadian Task Force on Preventive Health Care recommends that females aged 50–74 years with an 'average' risk profile be screened with mammography every two to three years.[188]

Innovations in Pharmacotherapies for Breast Cancer – Targeted Therapy

Breast cancer is categorized into three broad types depending on the role of the hormones estrogen or progesterone and of the Human Epidermal Growth Factor Receptor 2 (HER2) gene in the proliferation of cancer cells. In hormone receptor positive breast cancer, the hormones estrogen, progesterone, or both, play a role in the growth of tumour cells. HER2 is a protein receptor in the same family as EGFR (see lung cancer section), called ErbB receptors, that also include HER4, and contribute to growth of the cells based on signaling pathways from the

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[180] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2019*.
[181] Ibid.
[182] Shields and Wilkins, *An Update on Mammography Use in Canada*.
[183] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2018: A 2018 Special Report on Cancer Incidence by Stage.*
[184] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2019*.
[185] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2018: A 2018 Special Report on Cancer Incidence by Stage.*
[186] Ibid.
[187] Canadian Task Force on Preventive Health Care, "Recommendations on Screening for Breast Cancer in Average-Risk Women Aged 40–74 Years."
[188]Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2018: A 2018 Special Report on Cancer Incidence by Stage.*

surface of the cell to the inside of the cell. HER2 positive cancer means that the HER2 gene protein product is over-expressed, and this leads to more aggressive cancer and a worse prognosis. A HER2 negative cancer does not over-express the HER2 protein product. Hormone-positive cancer can either be HER2 positive or negative (HR+/HER-, or HR+/HER+). Triple negative breast cancer is a cancer in which hormone receptors play no part (hormone-negative), and HER2 gene is not over-expressed (HR-/HER2-).[189,190]

Since the 1930s the mainstay of breast cancer treatment was surgery – radical mastectomy, later modified, and in the 1980s breast-conserving surgery combined with radiation. In the late 1970s the first anti-estrogen drug was approved by the FDA to treat breast cancer, and in the late 1990s the first treatment for estrogen-positive breast cancer was approved. Chemotherapy was discovered to be effective in some breast cancer patients but not in all HER2 negative, hormone-positive patients.[191,192] Although hormone therapy remains the mainstay of hormone-positive breast cancer, resistance develops in nearly 50% of patients as the breast cancer becomes more advanced.[193]

The first targeted breakthrough therapy in breast cancer came in 2000 with the introduction of Herceptin (trastuzumab), which targeted the HER2 receptors on the surface of the breast cancer cell in HER2 positive cancers, and which affected 20-25% of breast cancers. Until the late 2010s, there was no targeted treatment for HER2 triple negative cancers (HR+/HER- and HR-/HER2-); and targeted treatments are still lacking.

CDK4/6 Therapies

There were two Cyclin-Dependent Kinases – CDK4/6 – breakthrough therapies approved and funded during our study period for advanced ER+/HER2- breast cancer for first-line use following endocrine therapy. A third breakthrough treatment received a positive CADTH funding recommendation but, at the time of our analysis, had not yet reached a funding agreement with the pCPA in time for inclusion. All three CDK4/6 inhibitors are recommended in the most recent international clinical practice guidelines.

Cyclin-dependent kinases, or CDKs, are one of many enzymes responsible for cell cycle progression (cell reproduction). They are activated when a cyclin, which is a family of proteins, binds to the CDK. There are different CDKs for different stages of the cell cycle. CDK 4 and CDK 6 enzymes activate the early phase of the cell cycle (from G1 to the S phase). In HR+ breast cancer, over-expression of the cyclin activating the CDK4/6 enzymes is common and is one of the mechanisms involved in resistance to hormone therapy. CDK4/6 inhibitors work by arresting the cell cycle through blocking at the G1 checkpoint phase. [194,195,196,197]

[189] Connor, “What Are CDK4/6 Inhibitors?”
[190] National Cancer Institute, “Milestones in Cancer Research and Discovery.”
[191] National Cancer Institute, “Advances in Breast Cancer Research.”
[192] National Cancer Institute, “Milestones in Cancer Research and Discovery.”
[193] Lam, Liu, and Lee, “A Review of CDK4/6 Inhibitors.”
[194] Ibid.
[195] Scitable by Nature Education, “CDK.”
[196] Shah, Nunes, and Stearns, “CDK4/6 Inhibitors: Game Changers in the Management of Hormone Receptor–Positive Advanced Breast Cancer?”
[197] Ammazzalorso and others, “Development of CDK4/6 Inhibitors: A Five Years Update.”

The first CDK4/6 inhibitor was approved and recommended for funding in Canada in 2016 shortly followed by a second inhibitor in 2018. These two breakthrough therapies have dramatically improved survival outcomes for patients with HR+/HER2- breast cancer.

Palbociclib and ribociclib improved median PFS to 27.6 and 25.3 months, respectively and are used in first-line treatment in combination with endocrine therapy, with no relevant difference in quality of life measures (ribociclib) (Table 10). Median OS data was not mature for palbociclib in the pivotal clinical trial but in a real-world study in a similar population in the US, 2-yr OS rate was 78.3% in the palbociclib group and 68% in the letrozole control group (risk reduction of 34%), and median OS was not reached for palbociclib but reached 43.1 months with letrozole alone (Table 10). Median OS was also not reached for ribociclib in its pivotal clinical trial, compared to 33 months for letrozole alone (Table 10) However, ribociclib + fulvestrant in the MONALEESA-3 trial showed a median OS improvement of 12.2 months (intent to treat population) and a median PFS improvement of 14.4 months (first line). Abemaciclib used in first-line improved median OS to by 9.4 months and median progression free survival to 16.4 months in the MONARCH 2 clinical trial.[198] The newest breakthrough therapy, abemaciclib, showed superior OS benefit when used in first-line in addition to fulvestrant, extending median OS by 9.4 months to 46.7 months, and median PFS by 7.1 months to 16.4 months. Sub-group analyses indicated better OS benefit in patient groups with poorer prognosis at baseline (primary endocrine resistance or visceral disease)

Table 10 – CDK4/6 Inhibitors in HR+/HER2- Advanced Breast Cancer Patients, in First-line (unless indicated otherwise)

CDK4/6 inhibitor	Median PFS	Median OS	QoL
palbociclib + letrozole[199]	27.6 months	NR	Change in FACT-B (total) = -0.11 (95% CI -1.42 to 1.21)
Standard (letrozole)	14.5 months	NR	Change in FACT-B (total) = 0.22 (95% CI -1.68 to 2.12)
Improvement	13.1 months (HR= 0.56; CI (0.46, 0.69)	NE	No significant difference between change in FACT-B (total) [p=0.782] between the palbociclib and the placebo arm despite increase in PFS.[200] HRQoL maintained.
palbociclib + letrozole[201]	20.0 months	NR (2-yr = 78.3%)	See above
Standard (letrozole)	11.9 months	43.1 months (2-yr = 68%)	See above

[198] Sledge and others, “The Effect of Abemaciclib plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy.”
[199] Rugo and others, “Palbociclib plus Letrozole as First-Line Therapy in Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer.”
[200] Rugo and others, “Impact of Palbociclib plus Letrozole on Patient-Reported Health-Related Quality of Life: Results from the PALOMA-2 Trial.”
[201] DeMichele and others, “Comparative Effectiveness of First-Line Palbociclib plus Letrozole versus Letrozole Alone for HR+/HER2− Metastatic Breast Cancer in US Real-World Clinical Practice.”

Improvement	9.1 months (HR= 0.58; 95% CI, 0.49–0.69)	NR (HR= 0.66; 95% CI, 0.53–0.82)	See above
palbociclib + fulvestrant[202,203] 2nd line AFTER endocrine tx	11.2 months	34.9 months	EORTC QLQ-C30 global QoL = 66.1
Standard (fulvestrant)	4.6 months	28.0 months	EORTC QLQ-C30 global QoL = 63.0
Improvement	6.6 months (HR=0.42; CI 0.27-0.64)	6.9 months (HR= 0.814; 95% CI 0.644, 1.029)	EORTC QLQ-C30 scores significantly favoured the tx arm (p=0.0313). Palbociclib plus fulvestrant maintained QoL.[204]
ribociclib + letrozole[205]	25.3 months	NR	EORTC QLQ-C30 scores maintained from baseline[206] Median time to 10% deterioration (TTD) in (HRQoL) not significantly different.
Standard (letrozole)	16.0 months	NR	EORTC QLQ-C30 scores maintained from baseline
Improvement	9.3 months (HR=0.57; CI 0.46 to 0.70)	NE	HRQoL maintained.
ribociclib + fulvestrant[207,208] – 1st line / 2nd line	33.6 months / 14.6 months	53.7 months	EORTC QLQ-C30 GHS scores maintained or improved during every cycle of treatment.[209]
Standard (fulvestrant)	19.2 months / 9.1 months	41.5 months	EORTC QLQ-C30 GHS scores maintained.
Improvement	14.4 months (HR=0.55; CI 0.42, 0.72) / 5.5 months (HR=0.57; CI 0.44, 0.74)	12.2 months	HRQoL maintained while significantly prolonging PFS

[202] Li and others, “Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors with Survival in Patients with Hormone Receptor–Positive Metastatic Breast Cancer.”
[203] Turner and others, “Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer.”
[204] Harbeck and others, “Quality of Life with Palbociclib plus Fulvestrant in Previously Treated Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer.”
[205] Hortobagyi and others, “Updated Results from MONALEESA-2.”
[206] Beck and others, “Patient-Reported Outcomes with Ribociclib-Based Therapy in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer.”
[207] Novartis Pharmaceuticals Canada Inc., *KISQALI, (Ribociclib), Product Monograph.*
[208] Slamon and others, “Ribociclib plus Fulvestrant for Postmenopausal Women with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer in the Phase III Randomized MONALEESA-3 Trial."
[209] Fasching and others, “Patient-Reported Outcomes (PROs) in Advanced Breast Cancer (ABC) Treated with Ribociclib+ Fulvestrant: Results from MONALEESA-3.”

abemaciclib + fulvestrant[210] *[Did not meet inclusion criteria for modelling at time of writing]	16.4 months	46.7 months	HRQoL maintained or improved[211]
Standard (fulvestrant)	9.3 months	37.3 months	HRQoL maintained or improved
Improvement	7.1 months (HR= 0.55; CI, 0.45-0.68)	9.4 months (HR=0.76; CI, 0.61-0.95)	HRQoL maintained from baseline and similar between tx arms, while abemaciclib significantly prolonging PFS

PFS = progression-free survival; OS = overall survival; QoL = Quality of Life; HR = hazard ratio; CI = confidence interval; NR = not reached; NE = not evaluable; NSAI = non-steroidal aromatase inhibitor; FACT-B = The Functional Assessment of Cancer Therapy-Breast; QoL = Quality of Life; EORTC = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; GHS = Global Health Score.

Consistent with this finding, recent international clinical practice guidelines now recommend CDK4/6 inhibitors (any of the three) in combination with endocrine therapy in advanced or metastatic breast cancer as first-line therapy, or as follow-on therapy in patients who have not had prior CDK4/6 exposure. Limited options exist for patients who develop resistance following CDK4/6.[212,213]

The implications of these improvements are immensely promising for advanced HR+/HER2- breast cancer patients in terms of life years gained and quality of life improvements, reduced burden for their caregivers, and economic value to patients, the health system, Canada's biotechnology sector and broader local and national economies. In the next section we present the results of the modeling attempting to quantify the economic and clinical value (life years gained) of two of the three CDK4/6 inhibitor therapies.

Value of Targeted Breakthrough Therapies in Breast Cancer

Estimated Potential Benefit

In Canada (similar to the US), around 16% of newly-diagnosed breast cancers are advanced or metastatic (stage 3 or 4). The vast majority are diagnosed in stages 1 or 2 (7% are unknown).[214,215] About 70% of breast cancers are hormone positive and HER2 negative.

[210] Sledge and others, "The Effect of Abemaciclib plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy."
[211] Kaufman and others, "Health-related Quality of Life in MONARCH 2: Abemaciclib plus Fulvestrant in Hormone Receptor-positive, HER2-negative Advanced Breast Cancer after Endocrine Therapy."
[212] National Comprehensive Cancer Network, "NCCN Clinical Practice Guidelines in Onoclogy: Breast Cancer."
[213] Cardoso and others, "5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer."
[214] Statistics Canada, Table 13-10-0761-01.
[215] National Cancer Institute, "Recent Trends in Seer Age-Adjusted Incidence Rates, 2004-2018, Breast."

Recurrence rates are around 30% of early stages, and 75% of patients presenting with metastatic disease have recurred from stages 1-3 to stage 4.[216,217]

Based on incidence rates and eligible sub-populations using epidemiologic research, there were a total of 46,707 patients in Canada who could have benefited from CDK4/6 inhibitors between 2011-2021 (starting in 2016). Improvements or extensions of median progression free survival (compared to standard of care) can be observed as early as 14 months following CDK4/6 inhibitor treatment initiation for first-line treatment, to beyond 2 years. Consequently, progression-free life years gained are estimated beyond 2021 for patients who initiated treatment up to 2021.

Since CDK4/6 inhibitor therapies were first approved for first-line use, benefits are modeled only in first-line for these patients. PFS benefits are weighed between therapies according to proportional monthly patient counts in Ontario's public and private claims data, irrespective of indication (first-line or second-line).

Total life years gained from using targeted CDK4/6 inhibitors compared to standard of care totaled 50,241 for those potentially eligible patients. (Table 11). For better comparability, this is equivalent to a total of 646 life years gained for 100 annual potential patients with HR+/HER2- advanced breast cancer (600 patients total, between 2016 and 2021).

Table 11 – Estimated Potential Cumulative and Average Life Years* Gained per Patient, CDK4/6 Therapies, 2011-2021

Indication	Total Eligible Patients	Total Life years* gained	Average Life Years* gained per patient
CDK4/6 inhibitors (2016-2021)	46,707	50,241	1.08

* Progression-free life years. Benefit continues beyond 2021.

Total estimated economic benefits from using CDK4/6 inhibitors compared to standard of care totaled $1,206 million for those potentially eligible patients between 2011-2021. For better comparability, this is equivalent to a total of $15.5 million in economic benefit gained for 100 annual potential patients with HR+/HER2- advanced breast cancer (600 patients total, between 2016 and 2021). (Table 12)

Table 12 – Estimated Potential Cumulative and Average Economic Benefit per Patient, CDK4/6 Therapies, 2011-2021

Indication	Total Economic Benefit*	Average economic benefit* per patient
CDK4/6 inhibitors (2016-2021)	$1.2 Billion	$25,818

* Benefit continues beyond 2021.

[216] O'Shaughnessy, "Extending Survival with Chemotherapy in Metastatic Breast Cancer."
[217] Caswell-Jin and others, "Change in Survival in Metastatic Breast Cancer with Treatment Advances: Meta-Analysis and Systematic Review."

Treatment Rates - CDK46 Inhibitors for HR+/HER- Advanced Breast Cancer

The lack of comprehensive and accurate specific treatment-related patient utilization data in Canada makes actual determinations of benefit challenging. However, one can look to the rate of growth of CDK4/6 inhibitors drug reimbursement claims to understand the pace of clinician and funding agency adoption of targeted therapies for breast cancer.

In 2016, the first CDK4/6 inhibitor was recommended for funding by CADTH in first-line, and the second one in 2018, also in first-line. The number of claims for the two publicly-funded CDK4/6 inhibitors grew by 299% (CAGR) and cost subsequently grew by 268% (CAGR) between 2016-2020. Monthly patients in Ontario increased by 239% (CAGR) in the same period. The greatest single year increase occurred in 2016-2017 following the positive CADTH funding recommendation of palbociclib (Ibrance) in ER+/HER2- advanced breast cancer (first line after endocrine therapy).[218]

The third CDK4/6 inhibitor noted above has not yet received a public funding recommendation but has been utilized and reimbursed in Canada through private insurance since 2019.

We also explored the degree to which access and utilization may influence variation in treatment rates by care setting, region of residence or other factors. Input from a breast cancer clinician indicates that treatment rates among advanced breast cancer patients are very high, around 95%, and that most patients (90%) with HR+/HER2- disease receive targeted therapy such as CDK4/6 inhibitors.[219] This is significantly higher than treatment rates found in a study conducted on a patient cohort in Ontario treated with breast cancer between 2012-2016. Among metastatic breast cancer patients, 66% received endocrine therapy, but this was before the first CDK4/6 was available, so one can presume this was the pre-breakthrough treatment standard of care (aromatase inhibitors).[220] This indicates that treatment rates may have increased as a result of CDK4/6 inhibitors.

However, it is unclear whether high treatment rates with CDK4/6 inhibitors apply equally among all HR+/HER2- advanced breast cancer patients equitably across Canada or are instead reflective of access to treatment due to close proximity to centralized cancer treatment centres or coordinated models of care. As noted above, inequitable access to oncology therapies across Canadian provinces is well established.[221]

It is also unclear how the rate of growth in the adoption of breast cancer targeted breakthrough therapies by Canadian clinicians and provincial funding programs compares with peer nations. Although most new treatments ultimately receive funding at least in part, this process takes longer in Canada than in other countries[222], and clinicians and patients must overcome

[218] Source: IQVIA Pharmastat. Used with permission.
[219] Input from Dr. Sandeep Sehdev, MD, FRCPC, Medical Oncologist at The Ottawa Hospital Cancer Centre, dated May 13, 2021.
[220] Brezden-Masley and others, “A Population-Based Comparison of Treatment Patterns, Resource Utilization, and Costs by Cancer Stage for Ontario Patients with Hormone Receptor-Positive/HER2-Negative Breast Cancer.”
[221] Patented Medicine Prices Review Board, *Alignment Among Public Formularies in Canada.*
[222] Salek and others, “Factors Influencing Delays in Patient Access to New Medicines in Canada.”

significant hurdles and barriers to access these therapies in a timely fashion to clinically impact disease progression and maximize prognosis for patients.

Impact on Patients' Ability to Work

This analysis assumes the same employment rates between the standard of care for breast cancer and breakthrough therapies (See Appendix – Detailed Quantitative Model Methodology). As such, this analysis excludes estimates of productivity benefits due to reduced incidence and durations of absenteeism (short- and long-term disability) because of increased ability of patients and their caregivers to continue to work during - and as a result of - treatment compared to the standard of care. To inform the model, qualitative information was sought through consultation with specialists about treatment rates in their clinical practice; and with breast cancer patients inquiring about the impact of treatment on their ability and intent to maintain an active work life.

"Of those who were working prior, if we look at all breast cancer types about 30% continue to work initially on diagnosis of late stage metastatic disease. If looking specifically at the most common type of breast cancer (ER+ He2 neg, the subject of this survey and candidates for CDK 4/6 targeted therapies) it would be more like 60%. … This fraction has not changed much over 10 years, however with CDK 4/6 targeted they are often able to continue to work much longer commensurate with the longer delay of cancer progression demonstrated in trials." – Dr Sehdev

"Of the incurable population, specifically the ER/PR+ Her2neg type of breast cancers that are candidates for CDK 4/6 targeted therapies, their need for support is dynamically changing over their life journeys. Initially on average they need little or no support outside of emotional support, transportation etc. (unless elderly or in pain). I would estimate 10%. Later on, most will need support for >50% of their time. The burden has been shifted 1-2 yrs later into their timelines by CDK 4/6 targeted therapies (my estimation) so that fractionally less of their lives [is] dependent on others."

For breast cancer, targeted breakthrough therapies potentially improve patients' and caregivers' ability to work by 1-2 years longer. This is significant given that this is the most common form of breast cancer. The overall impact to employers and to the government from reduced disability payments could be significant.

Key Take-aways for Innovations in Breast Cancer

The last decade has seen tremendous progress in the treatment of breast cancer in Canada and around the world, largely attributable to the development and adoption of targeted breakthrough therapies in advanced stages of breast cancer. With more access to molecular testing of cancer tumours, cancer patients who previously had very few options and poor survival prognosis now have options that have nearly doubled their disease-free life expectancy with a manageable side effect profile and improving survivorship beyond 5 years.

Our model estimates the potential value of universal access to two CDK4/6 therapies for breast cancer patients in the past ten years. Grounded in clinical outcomes evidence for these

indicated therapies, if all eligible Canadian patients received access to these breakthrough therapies, our model estimates that approximately 50,000 progression-free life years would be gained and $1,206 million in potential economic value would have been generated compared to the current standard of care.

Improved screening rates appear to have improved access to care and treatment in the last few decades.[223] The breakthrough treatments that we focused on in this study are demonstrating significant improvements in the long-term prognosis of breast cancer patients, particularly in more advanced stages of the disease, where prognosis has been modest in Stage 4 for decades[224].

> "CDK4/6 inhibitors have provided an important treatment option for metastatic breast cancer patients with HR+ breast cancer; this has both improved the quality of life for these patients, extended progression free survival which is often associated with a better quality of life and has increased overall survival."
> - Cathy Ammendolea, Chair of the Board for the Canadian Breast Cancer Network

Summary

Evidence indicates that CDK4/6 therapies can result in 10-months (average) of progression free survival.

If all eligible patients in Canada received CDK4/6 therapies since 2010 an estimated 50,241 progression-free life years may have been realized and $1.2 billion in potential economic value to Canadian patients and Canada's economy.

If just 50% of eligible Canadian patients received these therapies, a potential ~25,000 life years may have been realized; and $600 million in economic value to Canadian patients and Canada's economy since 2010.

[223] ReThink Breast Cancer, "Breast Cancer Statistics in Canada."
[224] Canadian Cancer Society, "Survival Statistics for Breast Cancer."

Melanoma

Incidence, Prognosis, and Treatment Pathway

In 2020, 8,000 Canadians were estimated to have received a diagnosis of melanoma. An estimated 1,300 Canadians died from melanoma in 2020.[225] The incidence rate is increasing for males and females at about 2% per year. Based on the most recent Canadian data (2013-2019) melanoma has one of the highest increasing incidence rates and the lowest and progressively declining mortality rates.[226] The staging breakdown of late-stage melanoma was found to be 10.4% stage III and 3.9% stage IV (2011-2015 data).[227] It also has one of the highest increasing incidence rates, but among the lowest (and declining) mortality rates (based on US data - 2013-2017).[228]

Of the tumour types included in this study, melanoma has the youngest diagnosed population. Melanoma is the fourth most commonly diagnosed cancer for Canadians in the age groups of 15-29 and 30-49, representing 7% of new cancer cases nationwide. The incidence of melanoma is lower in older age groups, being 4% for Canadians aged 50-69 years and 3% for Canadians over 70 years.[229]

Deaths from melanoma occur in younger age groups compared to the other tumour types in this analysis. For Canadians aged 15-29 and 30-49, 4% of cancer deaths are from melanoma. Deaths from melanoma are not as common in older cohorts. In Canada, five-year age-standardized net survival increased by 4.7% between 1992-1994 and 2012-2014.[230] Melanoma often presents early and with early detection and treatment survival is high; with a five-year net survival of 88%.

Innovations in Breakthrough Pharmacotherapies for Melanoma – Immunotherapy

Surgical intervention has been the primary standard of care for treatment of malignant melanoma and is curative in many cases. Even the 5-year survival rate for patients with stage 4 melanoma, can range from 10%-20%. Until 2011, chemotherapy was the only option since the approval of dacarbazine in 1975, but it and other chemotherapy combination protocols have yielded little benefit, with low response rates, substantial treatment-related toxicity and poor survival outcomes. [231,232]

Within a span of five years, six new drug therapies were introduced to treat advanced melanoma that have significantly impacted survival outcomes: immunotherapy ipilimumab (Yervoy) in 2011, targeted therapies vemurafenib (Zelboraf) in 2012, and dabrafenib (Tafinlar) and trametinib (Mekinist) (used in combination) in 2013 for BRAF gene mutations; and finally,

[225] Brenner and others, “Projected Estimates of Cancer in Canada in 2020.”
[226] Canadian Cancer Statistics Advisory Committee, *Cancer Statistics 2021*.
[227] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2018: A 2018 Special Report on Cancer Incidence by Stage.*
[228] Hurlbert, “2020 Melanoma Mortality Rates Decreasing.”
[229] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2019*.
[230] Ibid.
[231] Bhatia, Tykodi, and Thompson, “Treatment of Metastatic Melanoma.”
[232] American Cancer Society, “Treatment of Melanoma Skin Cancer, by Stage.”

the PD-1 immune checkpoint inhibitors, pembrolizumab (Keytruda) and nivolumab (Opdivo) in 2015 and 2016, respectively.[233]

Breakthrough immunotherapies have radically changed the treatment not only of melanoma but nearly all solid tumours. In fact, the discovery of immune checkpoints in cancer treatment was so revolutionary and impactful in medicine that the Nobel Prize for Physiology and Medicine was awarded in 2018 to the two researchers responsible for its discovery.[234]

Ipilimumab was the first immune checkpoint inhibitor, targeting the CTLA-4 pathway (more below), initially indicated in melanoma alone. However, the arrival of PD-1/PD-L1 immune checkpoint inhibitor therapies (PD-1 inhibitors) transformed it further and became among the first truly "tumour-agnostic" therapies. The first officially-termed tumour-agnostic treatment, larotrectinib, was recently approved in 2019 by Health Canada.[235] PD-1 inhibitors have now received approval and funding for treatment of many solid tumours, including melanoma, Hodgkin lymphoma, renal cell carcinoma, hepatocellular carcinoma, non-small cell lung cancer (squamous and non-squamous), urothelial carcinoma, head and neck squamous cell carcinoma, esophageal carcinoma, pleural mesothelioma, and colorectal cancer.[236] It has been approved further by Health Canada in several additional cancers (which have yet to receive funding in Canadian provincial public plans): endometrial carcinoma, B-cell lymphoma, bladder cancer, and select cancers that exhibit microsatellite instability (high) or mismatch repair deficient tumours.[237,238]

PD-1 Immune Checkpoint Inhibitors

Programmed cell death protein 1 (PD-1) is a protein on the surface of the body's T- and B-cells and other immune cells. T-cells are a type of lymphocyte (a form of white blood cell) whose function is to kill cancer cells (natural killer T-cells, NKT) and to help organize an immune response to help kill tumours (helper T-cells). Natural killer cells, another kind of lymphocyte (not the same as NKT), also play an important role in attacking cancer cells.[239,240]

When a T-cell's PD-1 is expressed, the T-cell becomes activated to attack tumour cells. However, tumour cells have adapted an immune mechanism to resist attack from T-cells through their own "counter-protein", the programmed cell death ligand 1 (PD-L1), which binds to the T-cell's PD-1 (ligand means binding site) and turns off the immune response, i.e., de-activates the T-cell, and thus avoids its own death. Studies have found that certain types of tumour cells express more PD-L1 than others through various signaling pathway mechanisms.[241,242] However, efficacy studies have shown that PD-L1 over-expression alone is a poor

[233] Patented Medicine Prices Review Board, "New Patented Medicines Reported to PMPRB."
[234] Han, Liu, and Li, "PD-1/PD-L1 Pathway: Current Researches in Cancer."
[235] Bayer Inc., "Health Canada Approves VITRAKVI® (Larotrectinib), the First Tumour Agnostic Cancer Treatment for Advanced Solid Tumours Harbouring an NTRK Gene Fusion."
[236] Canadian Agency for Drugs and Technologies in Health, *Reimbursement Review Reports*.
[237] Merck Canada Inc., *KEYTRUDA, (Pembrolizumab), Product Monograph*.
[238] Bristol-Myers Squibb Canada Co., *OPDIVO, (Nivolumab), Product Monograph*.
[239] Mallick, "The Role of T-Cells in Cancer."
[240] Han, Liu, and Li, "PD-1/PD-L1 Pathway: Current Researches in Cancer."
[241] Mallick, "The Role of T-Cells in Cancer."
[242] Han, Liu, and Li, "PD-1/PD-L1 Pathway: Current Researches in Cancer."

predictor of outcomes.[243] PD-1 inhibitors, pembrolizumab and nivolumab, are monoclonal antibodies (MABs) that work by binding to PD-1 on the T-cell and thus prevent it binding with the PD-L1 on the tumour cell. As a result, the T-cell is able to complete its immune function and attack the tumour cells.

Pembrolizumab and nivolumab obtained funding recommendations in 2015 and 2016 in unresectable (cannot be removed by surgery) or metastatic melanoma, respectively. Both molecules have been tested in combination with ipilimumab, which is another immune checkpoint MAB inhibitor that acts on a different and complementary immune pathway, the CTLA-4. Nivolumab in combination with ipilimumab showed superior results to ipilimumab treatment alone in the treatment of melanoma.[244] Pembrolizumab combined with ipilimumab is currently undergoing trials in advanced melanoma with some promising results.[245]

The use of progression free survival (PFS) as a surrogate efficacy marker for survival outcomes has long been controversial (as noted above in the Approach and Methodology section). As we discuss, in most breakthrough anticancer targeted therapies, improvement in PFS can be beneficial to patients in terms of symptom relief and quality of life, however, do not always translate to better overall survival (OS).[246] However, this does not seem to apply to immunotherapies and particularly to the PD-1 inhibitors pembrolizumab and nivolumab, as demonstrated in a meta-analysis. PFS and OS results were found to bear no correlation and the OS benefit was deemed far superior to PFS benefit. Moreover, a phenomenon called “pseudo-progression” seems to occur with immunotherapies whereby the tumours appear to continue their progression before responding to treatment and shrinking. Using traditional measures of progressive disease using RECIST criteria, a patient who has abnormal response patterns would be marked as having had progressive disease even though they responded to the treatment later. A working group has proposed new guidelines specific to immune therapies called iRECIST. These take into account delayed or abnormal response patterns demonstrated by tumour shrinkage and treatment response after appearing to have progressive disease.[247]

This can be observed in the efficacy results for the first trials of PD-1 inhibitors. Median PFS more than doubled but remain significantly shorter than median OS (Table 13). Median PFS increased to 6.9 and 11.6 months from 2.9 and 3.7 months using nivolumab and pembrolizumab compared with ipilimumab alone, and the combination of ipilimumab with nivolumab increased median PFS to 11.5 months. Median OS however increased to 38.7 and 36.9 months, respectively, for pembrolizumab and nivolumab, compared to 17.1 and 19.9 months for ipilimumab alone. The combination of nivolumab with ipilimumab prolonged OS further to over 72.1 months (median OS not reached), compared to 19.9 months for ipilimumab alone. (Table 13)

The change in disease progression criteria can be observed in later trials in the adjuvant setting (resectable melanoma), where “recurrence-free survival rates” were used rather than median progression free survival durations. This has implications for estimations of benefit such as pharmacoeconomic studies for HTA processes or as used in this study where we rely strictly on

[243] Larkin and others, “Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma.”
[244] Rausch and Hastings, “Immune Checkpoint Inhibitors in the Treatment of Melanoma.”
[245] Southall, “Ipilimumab-Pembrolizumab Combination Appears Promising for Advanced Melanoma”.
[246] Gyawali, Hey, and Kesselheim, “A Comparison of Response Patterns for Progression-Free Survival and Overall Survival Following Treatment for Cancer With PD-1 Inhibitors.”
[247] Ibid.

extended durations of benefit. However, this was not possible for the new revised criteria in the adjuvant setting. As a result, this population and indication are excluded in this study.[248,249]

Table 13 – PD-L1 Inhibitors in Metastatic or Unresectable Melanoma Patients

PD-L1 inhibitor	Median PFS	Median OS	QoL
pembrolizumab (Keytruda)[250]	11.6 months	38.7 months	EORTC QLQ-C30 GHS/HRQoL score decrease -1.9[251]
Standard (ipilimumab)	3.7 months	17.1 months	EORTC QLQ-C30 GHS/HRQoL score decrease -10.0
Improvement[252]	7.9 months (HR= 0.54, CI: 0.44-0.67)	21.6 months (HR=0.73, CI: 0.57-0.92)	GHS/HRQoL scores was better maintained compared to standard of care
Nivolumab (Opdivo)[253]	6.9 months	36.9 months	No clinically meaningful deterioration in any tx arm
Standard (ipilimumab)	2.9 months	19.9 months	No clinically meaningful deterioration in any tx arm
Improvement	4 months (HR=0.53; CI, 0.44 to 0.64	17 months (HR=0.83, CI: 0.67 - 1.03)	Patient reported GHS/QoL (EORTC QLQ-C30) was maintained during prolonged treatment[254]
Nivolumab + ipilimumab (Opdivo)[255,256]	11.5 months	72.1 months	No clinically meaningful deterioration in any tx arm
Standard (ipilimumab)	2.9 months	19.9 months	No clinically meaningful deterioration in any tx arm
Improvement	8.6 months (HR = 0.42, CI: 0.35 - 0.51)	52.2 months	Patient reported GHS/QoL (EORTC QLQ-C30) was maintained during prolonged treatment[257]

PFS = progression-free survival; OS = overall survival; QoL = Quality of Life; HR = hazard ratio; CI = confidence interval; EORTC QLQ-C30= The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; GHS= global health status; HRQoL =Health-Related Quality of Life; VAS = visual analog scale

[248] Ascierto and others, “Adjuvant Nivolumab versus Ipilimumab in Resected Stage IIIB–C and Stage IV Melanoma (CheckMate 238).”
[249] Eggermont and others, “Longer Follow-up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma."
[250] Robert and others, “Pembrolizumab versus Ipilimumab in Advanced Melanoma (KEYNOTE-006): Post-Hoc 5-Year Results from an Open-Label, Multicentre, Randomised, Controlled, Phase 3 Study.”
[251] Petrella and others, “Patient-Reported Outcomes in KEYNOTE-006.”
[252] Note results are for subset in KEYNOTE-006 analysis for those that were naïve to systemic treatment (reflects first line treatment results).
[253] Larkin and others, “Five-year survival with combined nivolumab and ipilimumab in advanced melanoma.”
[254] Schadendorf and others, “Patient-Reported Quality of Life (QoL) of Advanced Melanoma Patients in a Phase 3 Study of Nivolumab".
[255] Wolchok and others, “CheckMate 067: 6.5-Year Outcomes in Patients (Pts) with Advanced Melanoma”.
[256] Larkin and others, “Five-year survival with combined nivolumab and ipilimumab in advanced melanoma.”
[257] Schadendorf and others, “Patient-Reported Quality of Life (QoL) of Advanced Melanoma Patients in a Phase 3 Study of Nivolumab".

The consistent finding of superior benefit with breakthrough immunotherapies in advanced melanoma is identified in the recent American Society of Clinical Oncology (ASCO) guidelines. The guidelines also recognize the increasing incidence and cost associated with longer term survival outcomes and longer durations of treatment. The guidelines recommend the use of either pembrolizumab or nivolumab for one year in patients with resectable advanced melanoma (stage 3+) as adjuvant therapy for one year, regardless of BRAF gene status. In patients with unresectable or metastatic melanoma, either nivolumab alone or in combination with ipilimumab, or pembrolizumab, are recommended regardless of BRAF gene status. In both settings, BRAF gene targeted therapies can be offered in patients with BRAF mutations instead of or following anti-PD-1 therapies.[258]

The implications of these breakthrough treatments are immensely promising for advanced melanoma patients in terms of life years gained and quality of life improvements, reduced care burden for their caregivers, and economic value to patients, the health system, Canada's biotechnology sector and broader local and national economies. In the next section we present the results of the quantitative model to estimate the economic value and clinical value (life years gained) of PD-1 inhibitors. Note that for the reasons listed above, benefits for melanoma have been modeled based on OS improvement, not PFS.

Value of Targeted Therapies in Melanoma

Estimated Potential Benefit

The vast majority (~70%) of melanoma patients are diagnosed in stages 1 or 2. The remaining of those newly diagnosed are categorized as either stage 3 or metastatic (stage 4) respectively.[259,260] A small proportion of stage 3 are unresectable (assumed 15% for purposes of this analysis). Five-year recurrence rates are around 10% and 30% for stages 1 and 2 of disease, 63% for stage 3 of disease, and 51% of recurrences are metastatic.[261]

Based on incidence rates and eligible sub-populations using epidemiologic research, there were a total of 7,414 patients who could have benefited from PD-1 inhibitors between 2011-2021 (starting in 2015). Improvements in median overall survival (compared to standard of care) can be observed as early as 17 months following PD-1 inhibitor treatment initiation, to beyond 3-6 years later. Consequently, overall-survival life years gained are estimated beyond 2021 for patients who initiated treatment up to 2021.

Even though PD-1 inhibitors received positive CADTH funding recommendations in 2019 and reached a pCPA funding agreement in 2020 for adjuvant stage 3 (resectable), benefits are only modeled in the first funded indication, metastatic or unresectable melanoma for the reason listed above. Since these are intravenous therapies that are administered in hospitals whose utilization data cannot be measured accurately (like take-home cancer therapies that can be measured through drug reimbursement patient-level data), OS benefits are weighed between the two therapies (pembrolizumab and nivolumab+ipilimumab combination) assuming a 50/50 split. Moreover, based on clinician input that nivolumab + ipilimumab better illustrates the

[258] Seth and others, "Systemic Therapy for Melanoma: ASCO Guideline."
[259] National Cancer Institute, "Recent Trends in SEER Age-Adjusted Incidence Rates, 2004-2018: Melanoma of the Skin."
[260] Romano and others, "Site and Timing of First Relapse in Stage III Melanoma Patients."
[261] Hematology Oncology Associates of Fredericksburg, "Stage III Melanoma."

potential number of patients who have benefitted from nivolumab, we have utilized the combination's OS duration for the purpose of modelling the nivolumab benefit.

Our model estimates the potential value of universal access to PD-1 inhibitors for melanoma cancer patients in Canada since 2015. Grounded in clinical outcomes evidence for these indicated therapies, if all eligible Canadian patients had received access to these indicated therapies, our model estimates that 21,600 total life years would have been gained from using PD-1 inhibitors compared to standard of care, which was ipilimumab. (Table 14). For better comparability, this is equivalent to 2,025 life years gained for 100 annual potential patients with unresectable or metastatic melanoma (700 patients total, between 2015 and 2021).

Table 14 – Estimated Potential Cumulative and Average Life Years* Gained per Patient, PD-1 Inhibitors, 2011-2021

Indication	Total Eligible Patients	Total Life years* gained	Average Life Years* gained per patient
PD-1 inhibitors (2015-2021)	*7,414*	21,600	2.89

* Overall survival life years. Benefit continues beyond 2021.

Total estimated economic benefits from using PD-1 inhibitors compared to standard of care totaled $572 million for those potentially eligible patients between 2011-2021. For better comparability, this is equivalent to $54 million in economic benefit gained for 100 annual potential patients with unresectable or metastatic melanoma (700 patients total, between 2015 and 2021). (Table 15)

Table 15 – Estimated Potential Cumulative and Average Economic Benefit per Patient, PD-1 Inhibitors, 2011-2021

Indication	Total Economic Benefit*	Average economic benefit* per patient
PD-1 inhibitors (2015-2021)	$572 million	$76,624

* Benefit continues beyond 2021.

Treatment Rates – PD-1 Inhibitors for Advanced Melanoma

The lack of comprehensive and accurate drug utilization data in Canada makes actual determinations of benefit challenging. However, one can look to the rate of growth of PD-1 inhibitors market sales to understand the pace of adoption of breakthrough immune checkpoint inhibitors by clinicians and funding agencies. Note that given the multiple uses for PD-1 inhibitors, market sales cannot be isolated for melanoma alone.

In 2015 the first PD-1 inhibitor was recommended for funding and the second one in 2016 for use in melanoma. Sales grew by 91.8% (CAGR) between 2017-2020. The greatest single year increase occurred in 2018.[262] Given that these medicines are approved for multiple tumour types, it is unclear which indication the increase in sales aligns with; however it is probable that the funding approval in 2017 for a PD-1 inhibitor for metastatic Non-Small Cell Lung Cancer[263] could have resulted in a larger increase in sales due to the relatively larger population size compared to metastatic melanoma, which is the focus of this section of our analysis.

We also explored the degree to which access and utilization may influence variation in treatment rates by care setting, region of residence or other factors. Input from two melanoma clinicians and from a patient advocate indicate that treatment rates among advanced melanoma patients are very high, at around 90%, and that most patients (70-90%) receive a PD-1 inhibitor.[264] A real-world study of effectiveness of ipilimumab conducted in Ontario for second-line use in metastatic melanoma patients in 2012-2015 compared to 2008-2012 indicated that ipilimumab was used in around 57% of patients as second-line (with no prior use of ipilimumab).[265] PD-1 inhibitors were not available until 2015 in this setting. This indicates that treatment rates may have increased as a result of PD-1 inhibitors.

However, it is unclear whether high treatment rates of PD-1 inhibitors apply equally among all unresectable and metastatic melanoma patients across the country or living outside of the catchment area of major cancer treatment centres. The literature indicates that health system disparities exist in the timely diagnosis of melanoma in Ontario, contributing to delayed

[262] Source: IQVIA Canadian Drug Stores and Hospitals. Used with permission.
[263] pan-Canadian Pharmaceutical Alliance, “Keytruda (Pembrolizumab): Non-Small Cell Lung Cancer.”
[264] Input from Dr. Scott Ernst, Medical Oncologist, London Regional Cancer Program, dated May 10, 2021; Dr. Wilson H. Miller, Jr., MD, PhD, Professor, Departments of Oncology and Medicine, McGill University; and Kathleen Barnard, President, Save Your Skin Foundation, both dated May 18, 2021.
[265] Dai and others, “Real-World Comparative Effectiveness of Second-Line Ipilimumab for Metastatic Melanoma.”

diagnosis and diagnosis of more advanced stages of melanoma, and worse survival outcomes in certain populations.[266] Moreover, there is unequal access to oncology therapies across Canadian provinces.[267]

It is also unclear how the rate of growth in the adoption of PD-1 inhibitor therapies by Canadian clinicians and provincial funding programs compares with other developed nations. Although most new treatments ultimately receive funding at least in part, this process takes longer in Canada than in other countries[268], and clinicians and patients must overcome significant hurdles and barriers in order to access these therapies in a timely fashion to clinically impact disease progression and maximize prognosis for patients. Indeed, there was an additional melanoma patient population (adjuvant stage 3) that obtained a positive funding recommendation but that treatment was still undergoing funding negotiations by provincial drug plans at the time of this analysis (over 2 years later). Moreover, there were additional indications approved by the FDA (US) for both pembrolizumab and nivolumab that are not yet approved in Canada or are approved by Health Canada but not yet funded. These treatment options may currently be utilized by clinicians for patients either in a clinical trial setting, or off-label, or for those who have private drug coverage. Irrespective of these determinants of lack of equitable access to these treatments, the lost opportunity for Canadian patients both in terms of time-to-treatment, which can ultimately prolong their lives, and capacity to remain actively employed (lost economic value).

"Some are calling these innovative medicines for some patients curative, and how one day melanoma may be a chronic disease."
- Kathleen Barnard, Founder, Save Your Skin Foundation

Impact on Patients' Ability to Work

This analysis assumes the same employment rates between the standard of care for advanced melanoma and innovation therapies (See Appendix – Detailed Quantitative Model Methodology). As such, this analysis excludes estimates of averted lost production due to reduced incidence and durations of absenteeism (short- and long-term disability) because of increased ability of patients and their caregivers to continue to work during - and as a result of - treatment compared to the standard of care. To inform the model, qualitative information was sought through consultation with specialists about treatment rates in their clinical practice; and with patients diagnosed with melanoma inquiring about the impact of treatment on their ability and intent to maintain an active work life.

> *"50% still work on treatment (depends upon age and employment demands). 10 years ago, only 10% would have tried to work) ... Most (75%) caregivers try to keep working if possible. This has increased since the introduction of Immuno-oncology over the past 10 years." – Dr Scott Ernst* [269]

[266] Mavor and others, "Disparities in Diagnosis of Advanced Melanoma".
[267] Patented Medicines Prices Review Board, *Alignment Among Public Formularies in Canada.*
[268] Salek and others, "Factors Influencing Delays in Patient Access to New Medicines in Canada."
[269] Dr. Scott Ernst, Medical Oncologist, Professor, Department of Oncology, Schulich School of Medicine and Dentistry, Western University.

"Today, 80% of patients keep working. It's a huge shift from 10 years ago. Even patients with side effects from immunotherapies are back to work. From our patient surveys we found it didn't differ by status… 70% of caregivers are working age and most of the time they spend caregiving is navigating their loved one through the process" – Kathleen Barnard, patient advocate [270]

"Those patients who are working when they come to get therapy typically stay working. The number of patients who stop working due to side effects for more than a few days is relatively small, under 10%. Obviously, not everybody with a diagnosis of advanced melanoma wants to keep working, and they may decide they have other priorities." – Dr Wilson Miller [271]

For melanoma, it would appear that breakthrough immunotherapies improved patients' and caregivers' ability to work by five to eight-fold. This is significant given that this cancer generally impacts a younger population with a higher long-term employment rate compared to the other tumours we focused on in this study. The overall impact to employers and to the government from reduced disability payments could be significant.

Key Take-aways for Innovations in Melanoma

The last decade has seen tremendous progress in the treatment of melanoma in Canada and around the world, largely thanks to the development and adoption of breakthrough immunotherapies and targeted therapies in advanced melanoma. With more access to molecular testing of cancer tumours, cancer patients who previously had very few options and poor survival prognosis now have options that have doubled or in some cases quadrupled their life expectancy with a manageable side effect profile, improving survival beyond 5 years.

The introduction of two PD-1 inhibitor therapies over the last decade had the potential to progressively result in around 21,600 overall-survival life years gained and $572 million in economic benefit compared to the standard of care. While the current utilization of these therapies by Canadian patients over the study period was not feasible to benchmark due to pan-Canadian lack of (or delayed) adoption and poor data availability across Canadian contexts of care, nevertheless, even if 50% of eligible patients received PD-1 inhibitors in the same period, this would represent a potential10,800 life years gained, and $286 million of economic value to Canadian patients and Canada's economy since 2015.

Despite increasing incidence rates, improved awareness of signs and symptoms combined with more effective breakthrough therapies appears to have improved prognosis in the last decade,[272] particularly in the more advanced stages of the disease, where prognosis has been modest for decades (15-20% chance of survival at 5 years for stage 4 melanoma)[273].

[270] Kathleen Barnard, President, Save Your Skin Foundation.
[271] Dr. Wilson H. Miller Jr., M.D., Ph.D., Professor, Departments of Oncology and Medicine, McGill University.
[272] Hurlbert, "2020 Melanoma Mortality Rates Decreasing."
[273] Canadian Cancer Society, "Survival Statistics for Melanoma Skin Cancer."

Opportunities exist for Canada to increase and accelerate adoption of these breakthrough therapies to fully realize the value and benefits to Canadians.

> *"PD-1 therapies have been a dramatic improvement in therapy, first in melanoma and then many other cancers…Now the majority of advanced cancer is treated at one point or another with immunotherapy, almost all of which includes a PD-1 inhibitor or PD-L1 inhibitor."*
> *– Dr. Wilson H. Miller, Jr., M.D., Ph.D,*
> *Professor, Departments of Oncology and Medicine, McGill University.*

Summary

Evidence indicates that PD-1 inhibitor therapies can result in 2-years and 10-months (average) of progression free survival.

If all eligible patients in Canada received PD-1 inhibitor therapies since 2015 an estimated 21,600 progression-free life years may have been realized: and $.5 billion ($572 million) in potential economic value to Canadian patients and Canada's economy.

If just 50% of eligible Canadian patients received these therapies, a potential ~10,800 life years may have been realized; and $286 million in economic value to Canadian patients and Canada's economy since 2015.

Multiple Myeloma

Incidence, Prognosis, and Treatment Pathway

In 2020, 3,400 Canadians were estimated to be diagnosed with multiple myeloma and it was estimated that 1,600 Canadians died as a result of complications of the disease.[274] Since 2007 the incidence rate for multiple myeloma has increased by 2.6% per year for males and 0.6% per year for females.[275] This increase may be the result of improved detection or an increased prevalence of known risk factors.

In Canada, most myeloma patients are diagnosed between 70-80 years of age. The most frequently reported age of diagnosis is 70 years.[276] A significant increase in survival has been seen for blood-related cancers like multiple myeloma. Between 1992-1994 and 2012-2014, there was a 16.8% increase in five-year age-standardized net survival – the fourth highest increase of a range of select cancers reported by Canadian Cancer Statistics.[277] As of 2020, in Canada, the five-year age-standardized net survival for myeloma had increased 23 percentage points to 50%, reflecting significant improvements in survival outcomes.[278]

Innovations in Pharmacotherapies for Myeloma

Myeloma, or commonly called multiple myeloma, is a cancer affecting the immune system's plasma cells, which are mostly found in the bone marrow. Plasma cells are created by B-cells, a type of lymphocyte (described in melanoma section above). When the body responds to infection, plasma cells make the antibodies (called immunoglobulins) to fight the infection. Normal plasma cells lack the capacity to replicate but tumourous plasma cells produced by dysfunctional B-cells have the capability to replicate and produce an abnormal protein called a monoclonal-protein (M-protein). This crowds out other healthy blood cells in the bone marrow, leading to a weakened immune system, anemia, poor blood clotting, and bone loss. When a single plasma tumour is found in a bone it is called a solitary plasmacytoma, but when multiple tumours are found in a single or multiple bones, it is called multiple myeloma. Plasma tumours or plasmacytoma can also form outside of the bones (extramedullary plasmacytomas).[279,280]

Discovered in the 1980s, the main treatment for myeloma is a stem cell transplant. Hematopoietic stem cells are the precursor to blood cells (platelets, red blood cells and white blood cells) and are manufactured in the bone marrow. A stem cell transplant is where a patient's own healthy stem cells are drawn from the body (historically directly from the bone marrow but now simply from the blood) before the patient is treated with systemic therapy and radiation to attack the plasma cells (or when the patient is in remission). The healthy stem cells are reinserted into the patient after treatment to regenerate healthy cell development and growth. A transplant can occur right away after treatment or be deferred until after relapse

[274] Brenner and others, "Projected Estimates of Cancer in Canada in 2020."
[275] Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2019*.
[276] Myeloma Canada, "Multiple Myeloma: Incidence and Prevalence in Canada."
[277]Canadian Cancer Statistics Advisory Committee, *Canadian Cancer Statistics 2019*.
[278] Statistics Canada, "Cancer Survival Statistics, 2020 Update."
[279] American Cancer Society, "What Is Multiple Myeloma?"
[280] Huff and Matsui, "Multiple Myeloma Cancer Stem Cells."

(disease progression). It can also be done more than once depending on the patient's health status. However, relapse is clinically inevitable in all myeloma patients. [281,282]

Before stem cell transplant was discovered, multiple myeloma patients had very few treatment options. The usual treatment was with an alkylating agent (a type of chemotherapy drug), the first of which was discovered in the 1950s, with prednisone added later. This improved median survival from 6 months to 3-4 years. Following transplant, existing and new agents were discovered to be effective in the treatment of myeloma, including thalidomide, an anti-angiogenic agent, which was a drug previously marketed in the mid 20th century for nausea and vomiting in pregnant women, but caused birth defects, and was subsequently taken off the market in 1961. However, clinical studies demonstrated benefit in a subset of myeloma patients, and this spurred additional discoveries of anti-angiogenic agents (lenalidomide and pomalidomide), and new classes of medicines including proteasome inhibitors (bortezomib, carfilzomib, ixazomib) between the mid-2000s and mid-2010s. More recently, targeted MAB therapies (daratumumab and isatuximab targeting the CD38 protein, or elotuzumab targeting the SLAMF7 protein) have been shown to be effective. Currently, patients with active myeloma are usually given a combination of 2-3 drugs from one or two classes of medicines with corticosteroids (usually dexamethasone).[283]

CD38 Antibodies

CD38 antibodies were developed after the discovery that the CD38 protein is highly expressed on myeloma cells. CD38 proteins play several functions including receptor binding to immune T-cells, and enzymatic activity contributing to immune response modulation. The binding of the CD38 antibody not only induces myeloma cell death but also promotes T-cell expansion to build up the immune response to myeloma tumour cells.[284]

To date, at time of writing, only daratumumab (Darzalex) has been approved for funding in Canada, in second-line use for relapsed refractory multiple myeloma (RRMM) after failure of one of the first two-line combinations (lenalidomide OR bortezomib + dexamethasone), and is currently undergoing funding negotiations for newly-diagnosed multiple myeloma (it received a positive CADTH recommendation in 2019 and 2020).[285] An additional CD38 antibody, isatuximab (Sarclisa), received a positive CADTH recommendation in April 2021 for third-line use and is currently awaiting the start of funding negotiations by provincial drug plans; and, at the time of writing, a CADTH review is currently ongoing for its use in second-line.[286,287]

Although novel breakthrough agents introduced in the mid-2000s progressively improved response rates and survival, it was the combination of CD38 antibodies with them that has generated the best disease-free and survival durations.

[281] American Cancer Society, "Stem Cell Transplant for Multiple Myeloma."
[282] Canadian Cancer Society, "Stem Cell Transplant."
[283] American Cancer Society, "Drug Therapy for Multiple Myeloma."
[284] Nooka and others, "Daratumumab in Multiple Myeloma."
[285] pan-Canadian Pharmaceutical Alliance, "Sarclisa (Isatuximab)."
[286] Canadian Agency for Drugs and Technologies in Health, "Isatuximab (Sarclisa) for Multiple Myeloma."
[287] Canadian Agency for Drugs and Technologies in Health, "Isatuximab."

In the second-line setting, daratumumab more than doubled median PFS to 45 months from 17.5 months when added to lenalidomide and dexamethasone (Ld), and to 16.7 months from 7.1 months when added to bortezomib and dexamethasone (Bd). OS data were not mature in any of the groups in both studies, but PFS2, i.e., PFS of a subsequent line of therapy, was also measured as a surrogate, exploratory endpoint. This can be more meaningful when OS data is not available. PFS2 was not reached at 42 months (3.5 years of follow-up) in the daratumumab + Ld arm compared to 31.7 months without daratumumab, representing a risk reduction of disease progression upon subsequent therapy of 37%. Likewise, PFS2 reached 34.2 months by adding daratumumab to Bd compared to 20.3 months without daratumumab, representing a risk reduction of disease progression upon subsequent therapy of 52% (Table 16).

In the first-line setting for patients ineligible for stem cell transplant (usually elderly or less healthy patients), median PFS was not reached after 56 months (4.5 yrs) when daratumumab was combined with Ld and represented a risk reduction of 46%. Median PFS2 was also not reached for the daratumumab arm compared to 51 months in the Ld arm. Likewise median OS was not reached but at 56 months (nearly 5 years), survival rates were 66% compared to 53%, representing a risk reduction of death of 32%. Adding daratumumab to bortezomib, melphalan and prednisone (Vmp) similarly improved median PFS to 36.4 months from 19.3 months. Median PFS2 was not reached in the daratumumab arm but reached 42 months in the Vmp arm representing a risk reduction of disease progression of 45% upon subsequent therapy. While median OS was not reached, overall survival was 75% at 42 months for daratumumab + Vmp compared to 62% without daratumumab, representing a risk reduction of death of 40% (Table 16).

Newer treatment isatuximab, although not approved for funding at the time of writing, has also demonstrated benefit in third-line setting added to another immunomodulator (pomalidomide, a derivative of lenalidomide) and dexamethasone, and nearly doubled median PFS to 11.5 months, extended median PFS2 to 17.5 months, and median OS to 24.6 months (risk reduction of 40%, 24%, and 24%, respectively). Daratumumab was also originally studied in third-line (or greater) setting as monotherapy (as a single-arm study with no control) and it demonstrated a similar median OS duration (20 months) but lower median PFS duration (4 months).[288] It resulted in a negative funding recommendation by CADTH and is not currently used in this setting as monotherapy.

[288] Usmani and others, “Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma.

Table 16 – CD38 Antibodies in Multiple Myeloma Patients

CD38 antibody	Median PFS	Median PFS2*	Median OS	QoL
Third-line				
Isatuximab (Sarclisa) + pomalidomide + dexamethasone[289,290] *[Did not meet inclusion criteria for modelling at time of writing]	11.5 months	17.5 months	24.6 months	No significant change in GHS/QoL was identified for Isa-Pd vs significant worsening for Pd;[291] For pain and fatigue, no change was observed for Isa-Pd, while symptoms increased for Pd PF scores significantly worsened for Pd but not for Isa-Pd, and the decline was significantly greater for the Pd arm
Standard (pomalidomide + dexamethasone)	6.5 months	12.9 months	17.7 months	
Improvement	5 months (HR= 0·60, CI: 0·44–0·81)	4.6 months (HR 0.76; 95% CI 0.58–0.99)	6.9 months (HR 0.76; 95% CI 0.58–1.01)	
Second-line				
daratumumab (Darzalex) + lenalidomide + dexamethasone[292]	44.5 months	NR (>3.5 years of follow-up)	NR	EORTC QLQ-C30 GHS, physical functioning, pain: Significantly greater Mean changes from baseline, but low magnitude of changes[293]
Standard **(lenalidomide +dexamethasone**)	17.5 months	31.7 months	NR	

[289] Attal and others, "Isatuximab plus Pomalidomide and Low-Dose Dexamethasone versus Pomalidomide and Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma (ICARIA-MM)."
[290] Richardson and others, "Updates from ICARIA-MM, a Phase 3 Study of Isatuximab (Isa) plus Pomalidomide and Low-Dose Dexamethasone (Pd) versus Pd in Relapsed and Refractory Multiple Myeloma (RRMM)."
[291] Houghton and others, "Health-Related Quality of Life in Patients with Relapsed/Refractory Multiple Myeloma Treated with Isatuximab plus Pomalidomide and Dexamethasone: ICARIA-MM Study."
[292] Bahlis and others, "Daratumumab plus Lenalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Extended Follow-up of POLLUX, a Randomized, Open-Label, Phase 3 Study."
[293] Plesner and others, "Health-related Quality of Life in Patients with Relapsed or Refractory Multiple Myeloma."

Improvement	27.0 months (HR = 0.44, CI: 0.35-0.55)	HR= 0.53; CI, 0.42-0.68	NR	
daratumumab (Darzalex) + bortezomib + dexamethasone[294]	16.7 months	34.2 months	NR	<10 EORTC QLQ-C30 global health status (GHS) to 8 cycles;[295] >8 mths, Improvements GHS & pain
Standard (**bortezomib +dexamethasone**)	7.1 months	20.3 months	NR	<10 EORTC QLQ-C30 global health status (GHS)
Improvement	9.6 months (HR = 0.31, CI: 0.24-0.39)	13.9 months (HR= 0.48; CI: 0.38-0.61)	NR	
First-line, ineligible for stem-cell transplantation				
daratumumab (Darzalex) + lenalidomide + dexamethasone[296,297]	NR (follow-up at 47.9 months) 56-mth = 52.5%	NR	NR 56-mth = 66.3%	EORTC QLQ-C30 GHS score improvement = 4.5[298] Pain score improvement = -17.9
Standard **(lenalidomide +dexamethasone)**	34 months 56-mth= 28.7%	51 months	NR 56-mth = 53.1%	EORTC QLQ-C30 GHS score improvement 1.5 Pain score improvement = -11.0
Improvement	HR= 0.54, CI: 0.43-0.67	HR= 0.65; (CI: 0.52-0.83)	HR = 0.68 (p=0.0013)	GHS: p=0.0454[299] Pain: p=.0007
daratumumab (Darzalex) + bortezomib +	36.4 months 42-mth = 48%	42-mth = 68%	36-mth rate = 78% 42-mth = 75%	Between-group differences were significant for EORTC QLQ-C30 GHS

[294] Mateos and others, “Daratumumab, Bortezomib, and Dexamethasone versus Bortezomib and Dexamethasone in Patients with Previously Treated Multiple Myeloma."
[295] Hungria and others, “Health-related Quality of Life Maintained over Time in Patients with Relapsed or Refractory Multiple Myeloma Treated with Daratumumab in Combination with Bortezomib and Dexamethasone.”
[296] Kumar and others, “Updated Analysis of Daratumumab plus Lenalidomide and Dexamethasone (D-Rd) versus Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM).”
[297] Helwick, “Overall Survival Benefit With Upfront Daratumumab Plus Lenalidomide/Dexamethasone for Newly Diagnosed Transplant-Ineligible Patients With Multiple Myeloma.”
[298] Perrot and others, “Health-Related Quality of Life in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma: Findings from the Phase III MAIA Trial.”
[299] Knop and others, “Health-Related Quality of Life in Patients with Newly Diagnosed Multiple Myeloma Ineligible for Stem Cell Transplantation."

melphalan + prednisone[300,301]				(p = 0.0240) and EQ-5D-5L VAS (p = 0.0160)
Standard **(bortezomib + melphalan + prednisone)**	19.3 months 42-mth = 14%	42-mth = 50%	36-mth rate = 68% 42-mth rate = 62%	
Improvement	17.1 months (HR= 0.42, CI: 0.34-0.51)	HR = 0.55 (p<0.0001)	HR=0.60 (CI 0.46-0.80)	Clinically meaningful improvements in pain in both groups

PFS = progression-free survival; PFS2* = PFS on subsequent line of therapy (defined as time from randomization to progression after the next line of subsequent therapy or death); OS = overall survival; HR = hazard ratio; CI = confidence interval; NR = not reached; IV = intravenous; SC = subcutaneous; QoL = Quality of Life; EORTC = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; EQ-5D-5L = EuroQol 5-dimensional descriptive system; GHS = Global Health Score; VAS = visual analog scale; PF = physical functioning

Consistent with the finding of superior PFS, PFS2 and OS benefit with the addition daratumumab to standard combinations in both RRMM settings and newly-diagnosed transplant ineligible myeloma patients. Recent European Society for Medical Oncology (ESMO) practice guidelines and guidelines convened by ASCO and Cancer Care Ontario have recommended that first-line treatment for patients eligible for ASCT be initiated with a three-drug combination including an immunomodulatory drug, proteasome inhibitor and steroids, followed by melphalan for conditioning for ASCT, and lenalidomide as maintenance therapy following transplant, (or bortezomib if intolerant to lenalidomide, or both (BL) if high-risk). The ESMO guidelines also allow for daratumumab + Bmd as induction before ASCT.

For newly diagnosed patients not eligible for ASCT, the Canadian guidelines recommend daratumumab + Vmp or VLd, and the ESMO guidelines additionally recommend daratumumab + Ld.

Upon disease progression following transplant, daratumumab can be used in any patient group regardless of previous therapy that did not contain daratumumab in combination with either a PI or an immunomodulator (or the latter two combined). Other targeted therapies such as MABs or newer immunomodulating or PI therapies can be used in combination following progression of daratumumab-containing therapies.[302,303] The implications of these improvements are immensely promising for multiple myeloma patients in terms of life years gained and quality of life improvements, reduced burden for their caregivers, and economic value to patients, the

[300] Mateos and others, “Overall Survival with Daratumumab, Bortezomib, Melphalan, and Prednisone in Newly Diagnosed Multiple Myeloma (ALCYONE).”
[301] Mateos, “Daratumumab Leads to PFS Improvement in Patients With Transplant-Ineligible Myeloma.”
[302] Mikhael and others, “Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline.”
[303] Dimopoulos and others, “Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up.”

health system, Canada's biotechnology sector and broader local and national economies. In the next section we present the results of quantitative model to estimate the clinical life years gained and economic value of daratumumab in RRMM.

Value of Breakthrough Targeted Therapies in Myeloma

Estimated Potential Benefit

In the US, which is presumed to be similar to Canada in terms of incidence and disease progression, nearly 90% of newly diagnosed myeloma is already at the multiple myeloma stage ("distant"), 22% obtain ASCT first, 78% obtain first-line systemic therapy. Virtually all patients ultimately relapse (assumed 85% for purposes of this analysis).[304,305,306]

Based on incidence rates and eligible sub-populations using epidemiologic research, there were a total of 12,596 patients with RRMM who could have benefited from daratumumab and other CD38 antibodies between 2011-2021 (starting in 2017). When used as second line therapy, median progression-free survival benefits (compared to standard of care) can be observed as early as 7 months (bortezomib + dexamethasone combo) to 17 months (lenalidomide +dexamethasone combo) following daratumumab treatment initiation, to beyond 2-4 years later (depending on the combination therapy). Consequently, progression-free life years gained are estimated beyond 2021 for patients who initiated treatment up to 2021.

Daratumumab received funding recommendation by CADTH in 2017 for both combinations in RRMM. An effort was made to determine whether the lenalidomide or bortezomib combination is used more frequently. However, given a lack of data on utilization, benefits are modeled assuming a 50/50 split of each combination, despite the combination with lenalidomide demonstrating longer term clinical benefit than the bortezomib combination.

Total life years gained from using CD38 antibody daratumumab compared to standard of care totaled 19,209 for those potentially eligible RRMM patients. (Table 17). For better comparability, this is equivalent to 763 life years gained for 100 annual potential patients with RRMM (500 patients total, between 2017 and 2021).

Table 17 – Estimated Potential Cumulative and Average Life Years* Gained per Patient, CD38 Antibody Daratumumab, 2017-2021

Indication	Total Eligible Patients	Total Life years* gained	Average Life Years* gained per patient
CD38 antibody daratumumab (2017-2021)	*12,596*	19,209	1.53

* Progression-free life years. Benefit continues beyond 2021.

[304] National Cancer Institute, *Recent Trends in SEER Age-Adjusted Incidence Rates, 2004-2018, Myeloma*.
[305] Gatopoulou and others, "Treatment Patterns of Relapsed and Refractory Multiple Myeloma in Europe."
[306] Majithia and others, "Early Relapse Following Initial Therapy for Multiple Myeloma Predicts Poor Outcomes in the Era of Novel Agents."

Total estimated economic benefits from using CD38 antibodies compared to standard of care totaled $437 million for those potentially eligible patients between 2011-2021 (Table 18). For better comparability, this is equivalent to $17.0 million in economic benefit gained for 100 annual potential patients with multiple myeloma (500 patients total, between 2017 and 2021).

Table 18 – Estimated Potential Cumulative and Average Economic Benefit per Patient, CD38 Antibody Daratumumab, 2017-2021

Indication	Total Economic Benefit*	Average economic benefit* per patient
CD38 antibody daratumumab (2017-2021)	$437 million	$34,699

* Benefit continues beyond 2021.

Treatment Rates – CD38 MABs in Multiple Myeloma

The lack of comprehensive and accurate patient utilization data of breakthrough therapies in Canada makes actual determinations of benefit challenging. However, one can look to the rate of growth of daratumumab market sales to understand its pace of adoption by clinicians and funding agencies.

Sales of daratumumab began in 2017 and grew by 201% (CAGR) between 2017-2020. The greatest single year increase occurred in 2019 following its positive CADTH funding recommendation and successful provincial funding negotiations (2018[307]) for both second-line daratumumab combinations in RRMM.[308]

We also explored the degree to which access and utilization may influence variation in treatment rates by care setting, region of residence or other factors. Input from a clinician and patient advocate indicates that treatment rates among RRMM patients are reasonably high. At least 60-70% of patients receive a mAB targeting CD-38 at some point on their treatment trajectory, most as a second line therapy.[309] Real-world studies of utilization patterns reveal that treatment rates increased among newly-diagnosed myeloma patients over time as a result of the introduction of novel breakthrough agents, especially lenalidomide and bortezomib.[310,311] However, a study examining treatment rates following lenalidomide treatment as first-line therapy in patients between 2007-2019 found that only 13.5% of patients received a

[307] pan-Canadian Pharmaceutical Alliance, “Darzalex (Daratumumab).”
[308] Source: IQVIA Canadian Drug Stores and Hospitals. Used with permission.
[309] Elie Kassouf, hematologist and medical oncologist at CISSS de Lanaudière, Quebec, Canada, interview: August 5th, 2021; Patient advocate: Martine Elias, MSc., Executive Director, Myeloma Canada, date, July 22nd, 2021.

[310] Mian and others, “Disparities in Treatment Patterns and Outcomes among Younger and Older Adults with Newly Diagnosed Multiple Myeloma.”
[311] Cowan and others, “Comparison of Outcomes and Utilization of Therapy in Multiple Myeloma Patients.”

daratumumab-based regimen – the authors noting that for most of the study duration daratumumab was not publicly-funded, and only available for 2-3 years at the tail-end of the time period. [312]

However, it is unclear whether high treatment rates of mAB targeting CD-38 apply equally among all RRMM patients across the country or to those living outside of the catchment area of major cancer treatment centres. The literature indicates that disparities exist in treatment outcomes between younger and older patients with multiple myeloma.[313] Moreover, there is well demonstrated access inequity to oncology therapies across Canadian provinces. [314]

It is also unclear how the rate of growth in the adoption of daratumumab and other CD38 therapies by Canadian clinicians and provincial funding programs compares with other developed nations. Although most new treatments ultimately receive funding at least in part, this process takes longer in Canada than in other countries[315], and clinicians and patients must overcome significant hurdles and barriers to access these therapies in a timely fashion. One study compared treatment patterns between Alberta, Canada, and the US, finding that lenalidomide and bortezomib were used more frequently and earlier in the US compared to Alberta, and lenalidomide, which has better survival outcomes, was preferred over bortezomib in the US whereas bortezomib was preferred in Canada.[316]

As previously mentioned, another 7,718 patients who met the criteria for the second CADTH "approved" indication (newly-diagnosed but ineligible for ASCT) could have received CD-38 antibodies such as isatuximab or daratumumab had these agents been approved for funding. Funding delays are currently pervasive in this context with newly-diagnosed multiple myeloma patients having waited on a funding decision for daratumumab for over two years. Another CD38 MAB antibody has also received the required approvals by Health Canada, as well as by CADTH, but funding negotiations in the MMRR setting have yet to commence. These innovative therapies are, however, available for patients through participation in a Canadian clinical trial or for those with eligible private drug coverage. Irrespective of these reasons for lack of equitable access to these treatments, the lost opportunity for Canadian patients both in terms of time-to-treatment, which can ultimately prolong their lives, and economic value is a notable concern.

Impact on Patients' Ability to Work

This analysis assumes the same employment rates between the standard of care for multiple myeloma and innovation therapies (See Appendix – Detailed Quantitative Model Methodology). As such, this analysis excludes estimates of productivity benefits due to reduced frequency and duration of absenteeism (short- and long-term disability) because of increased ability of patients and their caregivers to continue to work during - and as a result of - treatment compared to the standard of care. To inform the model, qualitative information was sought through consultation with specialists about treatment rates in their clinical practice; and with myeloma patients and/or

[312] Ibid.
[313] Mian and others, "Disparities in treatment patterns and outcomes among younger and older adults with newly diagnosed multiple myeloma."
[314] Patented Medicine Prices Review Board, *Alignment Among Public Formularies in Canada*.
[315] Salek and others, "Factors Influencing Delays in Patient Access to New Medicines in Canada."
[316] Cowan and others, "Comparison of Outcomes and Utilization of Therapy in Multiple Myeloma Patients."

patient advocates inquiring about the impact of treatment on their ability and intent to maintain an active work life.

For myeloma, it would appear that targeted therapies and daratumumab potentially do not substantially improve patients' and caregivers' capacity to maintain an active work life and/or continue to actively and meaningfully contribute to society. As outlined in the Approach and Methods section above, the economic value of an innovation is its positive effect on productivity, where "productivity" was defined as the value of avoided lost production as a result of clinically realized treatment outcomes from the use of innovations in our study. This is quantified by estimating the income that treated individuals would have been able to earn during the extended period of PFS years, irrespective of whether treatment improved patient and/or caregiver capacity to maintain an active work life. Given the age of diagnosis for myeloma is quite high, between 70-80, this finding is aligned with life span productivity expectations. This holds true for spousal caregivers as well but may result in a greater impact for patients cared for by a child. The complicated treatment protocols (3 to 4 different therapies at varied frequencies) require a higher frequency of hospital visits, which have both pre- and post-visit care and support requirements, specifically impacting productivity capacity for caregivers in their prime earning years.

Key Take-aways for Innovations in Myeloma

The last two decades has seen tremendous progress in the treatment of myeloma in Canada and around the world, largely due to the development and adoption of breakthrough immunomodulators, proteasome inhibitors, and monoclonal antibodies in multiple myeloma. With more access to molecular testing of cancer tumours, cancer patients who previously had very few options and a poor survival prognosis now have options that have more than doubled their disease-free and total life expectancy with a manageable side effect profile and have improved their chances of surviving beyond 5 years.

Our model estimates the potential value of universal access to CD38 antibody daratumumab therapies for myeloma patients in Canada since their funding approval. Grounded in clinical outcomes evidence for these indicated therapies, if all eligible Canadian patients have received access to these indicated therapies, our model estimates that approximately 19,209 progression-free life years would be gained and $437 million in economic value would be generated compared to standard of care. While the current utilization of these therapies by Canadian patients over the study period was not feasible to benchmark due to pan-Canadian lack of (or delayed) adoption and poor data availability, nevertheless, even if 50% of eligible patients received daratumumab in the same period, this would represent a potential 9,604 life years, and $218 million of economic value to Canadian patients and Canada's economy in our time period.

More effective breakthrough therapies appear to have improved prognosis in the last decade,[317] and newer therapies such as CD38 antibodies will only continue to improve survival over time as clinical evidence emerges. Opportunities exist for Canada to increase and accelerate adoption of these innovative therapies to fully realize the value and benefits to Canadians.

[317] Hurlbert, "2020 Melanoma Mortality Rates Decreasing."

Summary

Evidence indicates that CD38 antibodies can result in 1.5 years (average) of progression free survival.

If all eligible patients in Canada received CD38 antibodies since 2017 an estimated 19,209 progression-free life years may have been realized: and $437 million in potential economic value to Canadian patients and Canada's economy.

If just 50% of eligible Canadian patients received these therapies, a potential ~10,000 life years may have been realized; and $218 million in economic value to Canadian patients and Canada's economy since 2017.

Quantitative Modelling Summary

The last decade has seen tremendous improvement in disease-free (remission) and patient survivorship as a result of breakthrough treatments in cancer therapy. And the ecosystem of innovation in cancer care is well mobilized with new pathways and discoveries on the horizon. This study has uncovered and modeled a small fraction of the total clinical value to patients and the economy, focusing on a few classes of medicines used within five tumour types, and estimating the minimum benefit to potentially treatable individuals.

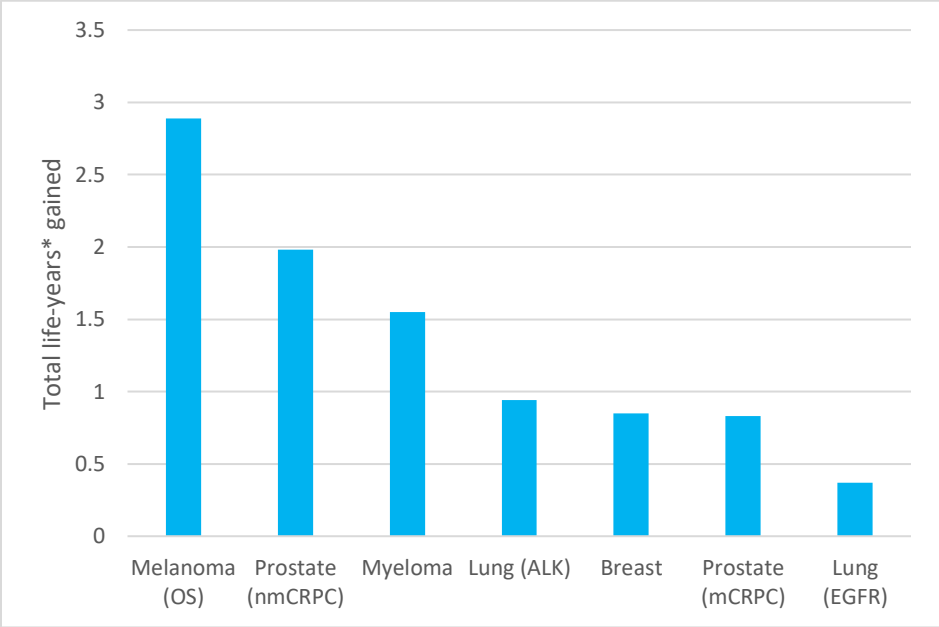
Total potential cumulative benefits of the selected breakthrough treatments in our study totaled 226,445 life years gained, and $5.9 billion in potential economic value across the five tumour types over the last decade (Table 19). In accordance with eligible population cohorts, advanced treatments for prostate, breast and lung cancer demonstrated the greatest portion of potential clinical impact (life- years gained) over the past decade for the most Canadian patients, followed by treatments for blood (multiple myeloma) and skin (melanoma) cancer. Simply in terms of total clinical and economic value, treatments for skin cancer (melanoma) demonstrated the greatest impact over the past decade, followed by treatments for non-metastatic castration-resistant prostate cancer, multiple myeloma, lung cancers (ALK+ targeted therapies for NSCLC) breast and metastatic castration-resistant prostate cancer. Figures 1 and 2.

Table 19: Summary of Model Results: Clinical value (Life Years Gained) and Economic gains (Lost production averted or production gained) Across Five Tumour Types from Select Targeted Therapies and Immunotherapies, 2011-2021

Tumour Type	Total Eligible Patients	Clinical Value *(Total life-years gained)*	Total Economic Value *(Lost production averted)*	Years medicine class active in study	Life -Years Gained per sample of 100 patients/year	Lost production averted per sample of 100 patients/year
Prostate (ARAT)	115,849	112,641	$3,176,743,145			
Metastatic castration-resistant	100,778	82,810	$2,330,948,452	2013-2021	743	$20,913,922
Non-metastatic castration-resistant	15,071	29,830	$845,794,693	2018-2021	792	$22,459,254
Lung	45,086	22,765	$486,266,236			
(*EGFR*+)	35,307	13,328	$283,740,394	2011-2021	409	$8,692,539
(*ALK*+)	9,778	9,436	$202,525,842	2013-2021	849	$18,207,856
Breast (CDK4/6)	46,707	50,241	$1,205,570,516	2016-2021	646	$15,490,644
Melanoma (PD-1)	7,414	21,600	$571,902,499	2015-2021	2,025	$53,636,542
Myeloma (CD38 MAB)	12,596	19,209	$436,936,509	2017-2021	763	$17,349,390
All 5 tumours	**227,652**	**226,455**	**$5,877,418,905**			

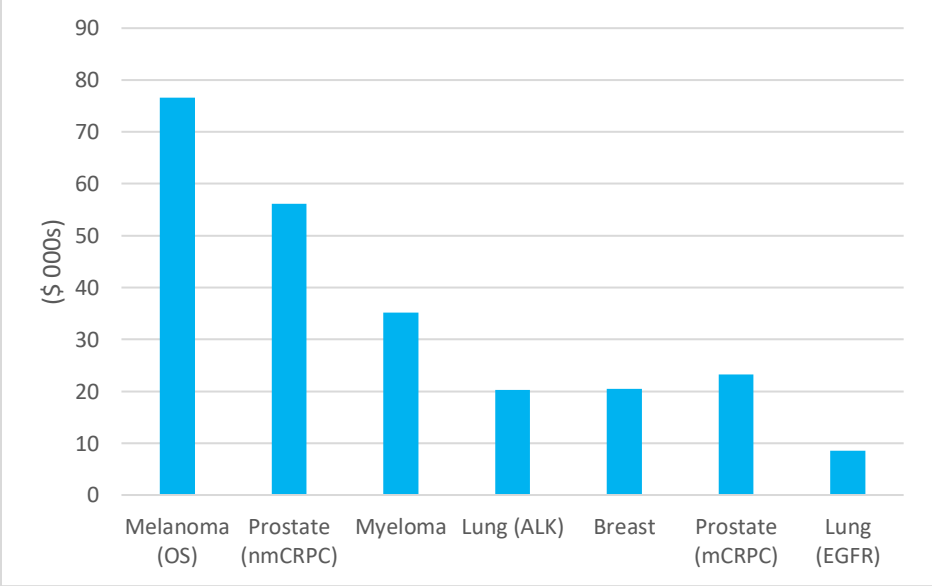
Note: for details on which line of therapy medicines in the class are utilized during the study period, see the complete quantitative analysis results (Appendix A.1) for the corresponding tumour type.

Figure 1. Average Clinical Value (per patient) by Tumour Type



*Life-years gained defined by PFS/MFS as a proxy of OS, or OS in years.

Figure 2. Average Economic Value – Lost production averted (per patient) by Tumour Type ($ 000s)



A Note for Health Technology Assessment Stakeholders

The above model was not designed as a cost-effectiveness assessment of breakthrough cancer treatment innovations used by patients in our five tumour groups for purposes of informing reimbursement decision-making by payers. Data required to conduct such an analysis were not available, such as potential health system and patient/caregiver costs impacts, nor was this approach defined within the scope of our analysis. Thus, it is not appropriate nor accurate to compare the estimated value of breakthrough cancer treatments calculated in this report for an individual patient or at a population level, to the cost of treatments for an individual patient or total cost of treatments in these five tumour groups over the last decade. Furthermore, methodological and ethical issues are inherent in taking such an approach to the analysis presented herein.

The current HTA process is dependent on defined outcomes included in the clinical studies relevant to our analysis. This is a key factor in agency deliberations resulting in funding recommendations at the provincial/territorial level. The evidence may not be fully mature leading to a degree of uncertainty in the conclusive direction of the clinical outcomes reported, which subsequently factors into the standard HTA economic analyses. Therefore, the current framework is based on understanding the outcomes and the impact on patients compared to other treatment options. Whereas cost-effectiveness evaluations tend to look at benefits from an individual patient perspective, our objective was to bring a population view of value, by exploring how much value society has gained as a result of a group of breakthrough cancer treatments over a prolonged period of time. This report provides insight into a segment of the cost-value discourse of funding breakthrough and other innovative therapies from the patient perspective of value at a population level, in terms of life years gained and associated contribution to society and value to the Canadian economy. It is one thing to acknowledge the benefit to an individual patient of prolonged life and improved quality of life due to a therapeutic innovation. It is quite another to appreciate the breadth of benefit due to the large number of patients who have been able to benefit (or could have benefitted, as illustrated in our findings), from a group of therapies. This view enables us to see how far we have come as a society, and to better appreciate, and welcome scientific discovery and therapeutic innovation. Other value-segments, such as health system efficiencies and social and economic implications for patients and caregivers were not within the scope of this report.

Although measures of productivity may be considered in HTA evaluations conducted by CADTH for public payers in Canada, this is only considered as a non-reference, or secondary perspective. Productivity assessments are outside the normal scope and measurements of incremental cost-effectiveness ratios (ICERs). However, studies have shown that including productivity, such as the same method used in this analysis (human capital method), has a favorable impact on cost-effectiveness and ICERs and can be critical to meeting cost-effectiveness thresholds and changing the outcome of reimbursement decisions[318].

[318] Yuasa and others, “Use of Productivity Loss/Gain in Cost-Effectiveness Analyses for Drugs.”

Although beyond the scope of this report to consider how the incremental value to society as a result of productivity gains impacts incremental cost-effectiveness ratios (ICERs) utilized in health technology assessments and other measurements of "value" in Canada, the value estimate in our period can be considered a net addition to existing estimates of value captured in cost-effectiveness analyses used by HTA agencies and payers. Adding this level of productivity value to existing HTA methods may provide a quantitative proxy for patient values which are often considered secondary or qualitative in decision making and valuation processes; and may support reconciliation between manufacturer-submitted and pan-Canadian Oncology Drug Review (pCODR) calculated ICERs and resulting "affordable" price points and negotiated terms of reimbursement. Regulatory agencies around the world are increasingly being encouraged to use non-health-related measures as factors in drug value assessments[319] and reimbursement agencies such as Scottish Medicines Consortium (SMC) in Scotland and National Institute for Health and Care Excellence (NICE) in the UK are also actively considering these, particularly for cancer drugs, and has resulted in an increase in the rate of positive reimbursement decisions.[320]

This report brings forward an evidence-based approach to HTA cost-effectiveness evaluations that takes a broader societal view by accounting for productivity gains. This can be considered an applied approach to the evolving discourse that HTA approaches in Canada and elsewhere must go beyond the current multi-disciplinary process and limited methods of cost-effectiveness analysis to support approval and funding decisions for new therapies[321,322] In taking this approach, payer budget allocations would require alignment with the same definition of value that includes economic and societal value outside of direct costs and value to health system.

[319] Angelis, Lange, and Kanavos, "Using Health Technology Assessment to Assess the Value of New Medicines.
[320] Morrell and others, "Cancer Drug Funding Decisions in Scotland".
[321] Chan and others, "The Past, Present, and Future of Economic Evaluations of Precision Medicine at the Committee for Economic Analyses of the Canadian Cancer Trials Group".
[322] The Economist Intelligence Unit, *How Health Technology Assessment Can Adapt to Improve the Evaluation of Novel Cancer Therapies in Europe*.

Enabling Faster Access to Cancer Drugs in Canada

Key Messages

What is the problem?

Several pressing challenges have been identified as key factors affecting Canadians' access to breakthrough cancer treatments:

- Delays due to fragmentation of regulatory and reimbursement processes
- Costs of breakthrough treatment innovations and limited funding
- Proliferation of breakthrough treatment innovations and uncertainty in the assessment of early scientific evidence
- Lack of a pan-Canadian approach/strategy to diagnostic testing

What changes are needed to address the problem?

Four system-level reforms could improve access:

- Make the current Health Technology Assessment, regulatory, and price negotiation processes work for breakthrough treatments.
- Change the way these therapies are funded to facilitate value-based care and risk-sharing agreements.
- Enable and fund access to diagnostic services when breakthrough therapies are approved.
- Expand and integrate systems that collect and share data.

How to Move Forward?

The key factor for making the necessary changes was identified as a multi-stakeholder concerted effort grounded in:

- Partnerships and collaboration, to develop an aligned vision for innovating current approval, evaluation, and reimbursement pathways to optimize patient access to new and promising health technologies.

All relevant stakeholders are called upon to engage in solution-oriented discussions to further explore opportunities within the proposed reforms, and define actionable steps necessary to move forward.

Background

Rapid advancements in cancer care, including earlier diagnosis and breakthrough treatments, have significantly improved patient outcomes[323] but continue to raise concerns around providing and sustaining equitable access to these costly treatments. The pace of innovation in cancer care necessitates that the healthcare system adapts and that the policy and regulatory context evolves. While other countries are facing similar concerns, Canada's challenges are unique and include: i) a vast geography and dispersed population with documented disparities in access to care and health outcomes[324] and ii) a complex publicly funded healthcare and cancer control system that it is primarily funded and administered at the provincial/territorial level.[325]

The pace of scientific discovery challenges health and cancer care systems to assess and evolve existing processes and policies governing safe and effective access to breakthrough cancer therapies that are available currently and those that will become available in the future. Our guiding question to explore the critical levers and facilitators needed to advance equitable patient access to safe and effective cancer treatments in Canada was: *What will it take to optimize access to (and the impact of) forthcoming breakthrough cancer treatments on the Canadian population's health into the next decade?*

Approach

We interviewed eighteen key informants representing the following stakeholder groups: clinicians (n=3), patient advocates (n=3), former payors/decision makers (n=4), health technology assessors (n=4), health policy researchers (n=2), and pharmaceutical industry representatives (n=2). Interview transcriptions were subject to a content analysis using qualitative research methods (please see Appendix A.2 for more detailed description of the qualitative methodology).

Results

Six primary themes were identified through qualitative analysis (see Figure 3).

The sections that follow are organized into 3 parts, where each theme is described along with its key sub-themes. Our synthesis of each theme is supported by representative quotes from the key informant interviews (refer to Appendix A2.2) and supplemented by relevant contextual information gathered through our supporting literature review.

[323] Islami and others, "Annual Report to the Nation on the Status of Cancer."
[324] Ahmed and Shahid, "Disparity in Cancer Care: A Canadian Perspective."
[325] Tikkanen and others, *International Health Care System Profiles: Canada*.

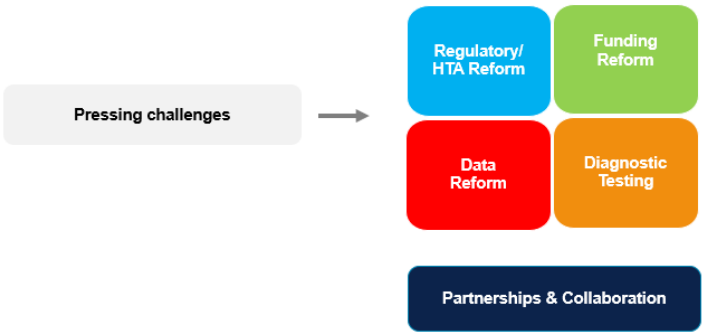


Figure 3 The six themes emerging from the analysis of the key informant interviews.

1) ***What is the problem?*** This theme captures stakeholders' perceptions of the *pressing challenges* (*theme 1*) facing Canada when it comes to access to breakthrough cancer treatments. These challenges represent the impetus for action to improve and innovate existing practices and policies.

2) ***What changes are needed?*** Four interrelated themes have been identified as key factors in the policy and regulatory context in Canada that require reform in order to foster an enabling environment for forthcoming breakthrough cancer treatments; and breakthrough treatments for other disease areas. These include: i) *regulatory/HTA reform*, ii) *funding reform*, iii) *diagnostics reform*, and iv) *data reform (themes 2-5)*.

3) ***How to move forward?*** The theme of *partnerships and collaboration (theme 6)* identifies a collective effort of multiple healthcare stakeholders (including federal and provincial/territorial governments, decision makers, regulatory and health technology assessment bodies, clinicians, patients, industry, and researchers) as a key enabler to realizing demonstrable system-level changes required to optimize access to breakthrough treatment innovations for Canadian patients.

Part 1: What is the problem?

The following four *pressing challenges* were identified when it comes to patient access to breakthrough cancer treatments in Canada:

- Delays due to fragmentation of regulatory and reimbursement processes
- Costs of breakthrough treatment innovations and limited funding
- Proliferation of breakthrough treatment innovations and uncertainty in the assessment of early scientific evidence
- Lack of a pan-Canadian approach/strategy to diagnostic testing enabling precision medicine

Delays Due to Fragmentation of Regulatory and Reimbursement Processes

Overall, delays in access to new and emerging breakthrough therapies was identified as the biggest pressing challenge. Timely access to new breakthrough treatments was described by one of our key informants as *"the ability to move efficiently through the process from regulatory review to reimbursement." (former payor).* The whole process was recognized to take more time in Canada than in comparable jurisdictions, particularly the US and Europe, despite various improvements that have occurred in the past decade.[326,327,328,329] However, according to our informants, the delays in Canada are specifically related to reaching reimbursement decisions pan-Canadian Pharmaceutical Alliance (pCPA) processes rather than regulatory or HTA processes.

Canada's regulatory approval and reimbursement process for cancer treatment, which our key informants described as "fragmented" and "lengthy" (see Appendix A2.2) commences with a regulatory review by Health Canada. The process proceeds with the structured Health Technology Assessment process by the Canadian Agency for Drugs and Technologies in Health's (CADTH) pan-Canadian Oncology Drug Review (pCODR) or the Institut national d'excellence en santé et services sociaux (INESSS) in Quebec. If the HTA by pCODR results in recommendations for public reimbursement of the drug, interested provinces engage in price negotiations with the drug sponsor via pan-Canadian Pharmaceutical Alliance (pCPA). This step is then followed by individual provincial/territorial processes to arrive at a funding decision.

Recent collaboration has made the process timelier. Health Canada is now a partner in Project Orbis, an initiative of the US Food and Drug Administration (FDA) Oncology Center of Excellence.[330] This international program's goal is to give patients faster access to promising cancer treatments. To accomplish this, Project Orbis partners (Singapore, Brazil, Australia, Switzerland, Canada, and United Kingdom [UK]) work together on the review of submissions for new cancer drugs. CADTH has a process for "Advance Notification of a Submission or Resubmission" to facilitate the pCODR review process.[331] In order to take advantage of this, sponsors of drugs must provide the required pre-submission documents at least 120 calendar days before the anticipated date of filing. The allows CADTH to complete its review in parallel with Health Canada to reduce the time between a regulatory and HTA decision.

[326] Younis and Skedgel, "Timeliness of the Oncology Drug Review Process for Public Funding in Canada."
[327] Salek and others, "Factors Influencing Delays in Patient Access to New Medicines in Canada."
[328] Salek and others, "Pan-Canadian Pharmaceutical Alliance (PCPA): Timelines Analysis and Policy Implications."
[329] Lexchin, "Health Canada's Use of Expedited Review Pathways and Therapeutic Innovation, 1995–2016."
[330] Government of Canada, "Project Orbis."
[331] Canadian Agency for Drugs and Technologies in Health, *Pan-Canadian Oncology Drug Review Pre-Submission, Submission and Resubmission Guidelines.*

A unique aspect in Canada is the presence of two health technology assessment bodies: CADTH's pan-Canadian (excluding Quebec) Oncology Drug Review (pCODR) for oncology[332]; and Quebec's Institut national d'excellence en santé et en services sociaux (INESSS). Our key informants expressed high regard for the pCODR review process, which reportedly takes up to eight months.[333] Nonetheless, having two agencies in one country has been described by one of our informants as "*disjointed access*". The pCPA, which acts on behalf of the provinces to negotiate funding agreements with individual manufacturers, must include two (potentially different) decisions and criteria from the CADTH pCODR versus INESSS.

The pCPA negotiation process itself is also a unique aspect of Canada's drug approval process, namely, pCPA acts independently from the HTA recommendations. One of the advantages of pCPA is the development of common listing approaches, which helps to reduce inequity in listings. The pCPA process may take anywhere from 6 months to over 2 years and begins only after the HTA recommendation has been made. One of our key informants pointed to the lack of predictability with this process, with little transparency on when a drug is picked up by pCPA or how fast a review takes. Standards and metrics similar to what CADTH does for their review timelines could potentially improve timelines, expectation, and trust in the process. Even though the pCPA represents all provinces, a successful funding agreement does not guarantee funding by any individual provincial/territorial public plan.[334] Furthermore, provincial/territorial plans also differ in eligibility criteria for funding and the timing of availability, the latter being dependent on jurisdictional priorities, budget constraints and political pressures.[335]

While the rigour of the Canadian drug approval process has been viewed as an advantage for patient safety, the multiple steps and delays associated with each step (and between the steps) clearly illustrate a fragmented process where the ultimate result is inequitable and delayed access to treatments (breakthrough or otherwise). Lack of administrative resources in the public sector required to manage and herald the regulatory process and required supporting data more efficiently and expeditiously has been identified by our key informants as a major factor contributing to delays.

Costs of Breakthrough Treatment Innovations and Limited Funding

The cost of breakthrough cancer treatments was identified as a significant pressing challenge impeding patient access. The combination of the growing prevalence of cancer, the opportunity for targeted, personalized breakthrough treatments to prolong patient life, and the high prices of

[332] It is worth noting that CADTH has three expert committees that provide recommendations on the appropriate use of drugs, medical devices, and clinical interventions: 1) pan-Canadian Oncology Drug Review Expert Review Committee (pERC) for oncology drugs; 2) Canadian Drug Expert Committee (CDEC) for non-oncology drugs; and 3) Health Technology Expert Review Panel (HTERP): medical devices and clinical interventions. For more information see: CADTH, How CADTH Expert Committees Deliberate. Available at: https://www.cadth.ca/events/how-cadth-expert-committees-deliberate
[333] Canadian Agency for Drugs and Technologies in Health, *Procedures for the CADTH Pan-Canadian Oncology Drug Review.*
[334] Salek and others, "Factors Influencing Delays in Patient Access to New Medicines in Canada."
[335] Srikanthan and others, "Understanding the Reasons for Provincial Discordance in Cancer Drug Funding."

these treatments, particularly with combination treatments, adds increasing pressure on limited and inflexible healthcare budgets. The costs of treatments include not only the costs of the technology itself, but also the indirect costs of administration, obtaining and utilizing the technology, and the infrastructure and resources (e.g., including specialized clinical skills) that may be necessary for delivering it to patients. Some informants viewed the cost per patient for many therapies as unsustainable for the fiscal capacity of both public and private payor groups. For payors, affordability was a big issue, along with having to make decisions without sufficient evidence of value. Evidence highlights that decision makers must deal with uncertainty in grounding funding decisions for cancer drugs in the available scientific evidence, most of which stem from methodological limitations in clinical trials".[336] Furthermore, provincial/territorial funding decisions are also affected by individual budgets and priorities and lead to variation in cancer-drug coverage between provinces/territories.[337] These are key challenges affecting funding decisions and therefore impacting patient access to new breakthrough treatments in cancer care.

The differences in coverage across Canada and the unequal financial impact of cancer care to Canadian patients depending on their province/territory of residence, were highlighted by respondents. For example, significant differences between the provinces/territories exist with respect to time-to-reimbursement decisions and funding availability for cancer treatments through provincial/territorial level formularies and/or cancer programs. The western provinces (BC, AB, SK, MB) cover the costs of all funded cancer medications, including those administered intravenously in the hospital and take-home oral treatments. Other provinces/territories fully cover only those treatments administered in a hospital or a cancer clinic setting. Take-home oral medications are covered only for those who are eligible under the publicly administered drug program.[338] Therefore, the costs of take-home medications in some regions may be associated with significant out-of-pocket costs to patients due to co-payments and deductibles in both public and private plans.[339] Furthermore, provincial/territorial formularies and those of private insurers differ in the rules guiding the eligibility of the selection of medicines and the level of user-pay.

Funding was identified as a key factor that actually *"puts [breakthrough treatments] in the hands of patients".* Due to province-specific budget limitations, we learned that some advanced treatments may not be funded by some provinces, even today – despite having received approval by Health Canada and recommendation for funding from CADTH'S pCODR. As such, these drugs may only be accessible only to some Canadian patients who either have the means to afford them, who have private insurance that will pay for them or are supported by proactive clinicians aware of access pathways available through patient support programs. In a study

[336] Jenei and others, "Describing Sources of Uncertainty in Cancer Drug Formulary Priority Setting across Canada."
[337] Srikanthan and others, "Understanding the Reasons for Provincial Discordance in Cancer Drug Funding."
[338] Sorin, Franco, and Quesnel-Vallée, "Inter-and Intraprovincial Inequities in Public Coverage of Cancer Drug Programs across Canada."
[339] Roman, Dobrescu, and Hoskyn, "How Would a Single-Payer Publicly Funded National Pharmacare Program Affect the Quality of Access to Medicines for Canadian Patients?"

which evaluated provincial discordance in drug funding decisions, over 90% of surveyed policymakers stated that the most common reason to not fund a drug recommended by pCODR was budget constraints.[340] Discrepancies between regulatory approval and provincial/territorial reimbursement is one example of how the lack of adequate funding exacerbates inequities in access to breakthrough cancer treatments. In the absence of a national strategy for funding innovation in cancer care, our informants expressed that this lack of national coordination in terms of a pan-Canadian approach to cancer drug funding decisions will always lead to inequities in access.

Proliferation of Breakthrough Cancer Treatment and Uncertainty in the Evidence

Several informants used the word "tsunami" to describe the number of new cancer treatments and diagnostic molecular tests that have become available, with many more on the horizon. This incredible change in the landscape of cancer treatments poses specific challenges to clinicians and their patients as well as to payor decision makers.

The key issue for physicians (that impacts their patients) is keeping up with the changes. Oncologists practicing in a specialized cancer area, who may only treat a couple of tumour sites, may be less aware of the progress and leading-edge developments in other tumour sites, which may later become relevant to their specialization. Another issue is the level of documentation that is required on the clinician's part, especially if there are specific drug-related start/stop/and monitoring criterion that must be reported. Some of the treatment algorithms for breakthrough therapies are highly complex, which can make it more difficult for both patients and clinicians to understand the options that are available. Furthermore, there are regional differences in the treatments that are approved on provincial/territorial formularies and how they are sequenced. Hence, physicians must be highly familiar with defined treatment protocols and patient eligibility criteria for funding within their jurisdictions, so that they can dutifully inform and support the best available treatment decision in collaboration with their patients.

The large volume of drugs also creates challenges for decision makers. Funding decisions are made even more challenging because they are often based on data with a high degree of uncertainty about the survival benefit, long term safety/toxicity, or impact on patient quality of life.[341] Although other countries have made strides in adapting decision making to early scientific evidence and developed conditional funding processes and decision-making algorithms, Canada still lacks a coordinated capacity to develop and maintain outcomes-and risk-based agreements.[342,343] Decisions are entirely dependent on the budget impact and cost-effectiveness for a certain class of drugs that have very advanced clinically validated scientific evidence. At the same time, breakthrough treatment innovations are presenting for regulatory review earlier in the development lifecycle, with promising clinical trial results for smaller patient

[340] Srikanthan and others, "Understanding the Reasons for Provincial Discordance in Cancer Drug Funding."
[341] Cheema and others, "International Variability in the Reimbursement of Cancer Drugs by Publically Funded Drug Programs."
[342] 20Sense, *Outcomes-Based Agreements in Canada, The 20Sense Report*.
[343] OECD, *Addressing Challenges in Access to Oncology Medicines*.

populations, or with new types of clinical evidence (e.g., surrogate outcomes), which may be unfamiliar to decision-makers. Coupled with this are the driving forces of patients also having more information on breakthrough treatment innovations in care and an urgent desire to receive timely access to these innovations.[344]

Health Canada is in the process of adapting to different types of scientific evidence being generated and has developed its own Real World Evidence (RWE) framework to conduct long-term effectiveness and safety regulatory studies.[345] Given the technical and methodological challenges in RWE generation and use by different stakeholders, the Canadian Real-world Evidence for Value of Cancer Drugs (CanREValue) collaboration was recently established through funding from the Canadian Institutes of Health Research and its partners.[346] CanREValue consists of researchers, decision makers, payers, patients and caregivers, and is working towards establishing a framework for all Canadian provinces with regards to the generation and use of RWE specifically for cancer drug funding decision making.[347] However, at this point in time, according to our key informants, there are no processes in Canada to conduct RWE studies efficiently and to use that information to support decision making at the reimbursement level. Furthermore, it was highlighted that Canadian HTA and provincial decision makers have limited data and resources (i.e. staff, expertise, and budget) at their disposal to conduct RWE studies and revisit funding decisions made with early evidence.

Lack of a Consistency of Implementation and Reimbursement Processes for Diagnostic Testing

"…a lot of the modern innovative products come with a companion diagnostic, and we do a terrible job in this country of approving them, funding them, and evaluating them." (clinician)

A significant blind-spot in the system was noted when it comes to accessing diagnostic techniques such as comprehensive genomic testing and companion diagnostics, which are necessary to advance the application of precision medicine in cancer care. Precision medicine is "a medical approach wherein patient diagnosis and treatment is individualized based on the patient's unique biological, environmental, and lifestyle factors".[348] Diagnostic genomic testing allows for detection of specific mutations in particular genes found in tumours, which can then be targeted by specific therapeutic agents. It can also identify patient characteristics that will affect response to a given treatment. A comprehensive tumour profiling allows clinicians to detect all classes of genomic mutations, even though targeted breakthrough therapies may not yet exist for most of them. Having a comprehensive profile of the tumour is important and can help determine patients' eligibility for clinical trials that use this information to match patients with experimental therapies.

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[344] Lye, Binder, and Elias, *Improving Access to Innovative Cancer Therapies in Canada*.
[345] Government of Canada, *Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making.*
[346] Chan and others, "Developing a Framework to Incorporate Real-World Evidence in Cancer Drug Funding Decisions."
[347] Ibid.
[348] National Institutes of Health, "About the All of Us Research Program: Precision Medicine Initiative."

The key issues that our informants identified included inconsistencies and overall lack of transparency in the approval and reimbursement processes for companion diagnostics, which ultimately create inequities in access to breakthrough treatments.

Drugs and their companion diagnostics enabling precision medicine enter the health system through distinct pathways. Some diagnostics are considered medical devices, and go through appropriate regulatory approvals by Health Canada, while others are laboratory developed and are not subject to such regulations, though there are requirements around test validation and lab certification. The implication, however, is that funding decisions for diagnostic tests are not connected to funding decisions made by the provinces regarding the breakthrough therapies that require these tests.

There is lack of clarity around who is responsible for funding diagnostic testing, whether it is the laboratories, the drug programs, or the health centres where these tests are being administered or requested. This, in turn, leads to undesirable impacts on patients by: i) causing delays in access to treatment, ii) limiting patients' treatment choices, and iii) contributing to inequities in access related to inconsistent reimbursement processes across the country. It was noted that frequently the pharmaceutical manufacturer takes charge of investing in developing the infrastructure and expertise for, and covering the cost of, their drug's companion diagnostic test for individual patients to prevent access delays. However, it was noted that it is becoming impractical since the current context is no longer a "one drug one test" environment.

Diagnostic testing was described as fragmented and significant inequities were also noted stemming from geography (access impacted by the fact that specialized infrastructure is needed) and lack of coordination or standards of care across different diagnostic labs (quality control issue).

Key informants highlighted the fact that precision medicine is here to stay, and diagnostic testing is a critical factor in determining the right treatment pathway for patients, based on their unique genetic make-up. As such, any reform to the system to enable forthcoming breakthrough innovations in cancer care and other therapeutic areas must also tackle diagnostic testing.

Part 2: What Changes are Needed?

Based on the *pressing challenges*, four intricately related factors require attention and warrant reform to improve timely access to breakthrough cancer treatments for Canadians (See Table 20):

- **Adapting the existing Health Technology Assessment (HTA) and price negotiation pathways for rapid uptake of breakthrough therapies** so they are available to patients while price negotiations are under way. Current pathways for regulatory approvals and reimbursements need to work in an aligned and timely manner.
- **Changing the way breakthrough therapies are funded to facilitate value-based care and risk-sharing agreements**. Other countries have risk-sharing models such as managed entry and outcome-based agreements to deal with the uncertainty associated with the long-term value of breakthrough therapies in achieving patient outcomes.

- **Creating a national strategy and standards that enable and fund access to diagnostic services when breakthrough therapies are approved.** National standards and inter-provincial collaboration for diagnostics testing would establish consistent processes for technology appraisal and reimbursement that provinces and territories can adapt and adopt.
- **Expanding and integrating health data systems and infrastructure** so patient outcomes, real-world evidence, and new funding models can be monitored. Better and more timely data are needed to support long-term health system planning, evaluation, and implementation of risk-sharing models for new breakthrough treatments.

Table 20. Summary of Pressing Challenges and Elements of Reforms Proposed to Address Them.

Pressing Challenges	Regulatory, HTA and Price Negotiation reform	Funding reform	Data Infrastructure reform	Diagnostic testing reform
Delays due to fragmentation of regulatory and reimbursement processes	• Pan-Canadian policy framework prioritizing value based on outcomes • Early approval and reassessment mechanisms			
Costs of innovations and limited funding		• Risk sharing • Alternative funding sources and policies		
Proliferation of innovations and uncertainty in the evidence			• Broader value capture through Real World Evidence (RWE) • Data sharing and integration	
Lack of consistency in implementation and reimbursement processes for diagnostic testing				• Create national standards for provinces to adapt and adopt •Specialization and inter-provincial collaboration

Regulatory, HTA and Price Negotiation Reform

The following elements were identified as necessary:

- Pan-Canadian policy framework prioritizing value that is based on outcomes
- Early approval and reassessment mechanisms

Pan-Canadian Policy Framework Prioritizing Value Based on Outcomes

The importance of value assessment that is based on outcomes in decision making was emphasized by respondents. The current discourse must shift from *"tabulating costs and not outcomes".* The ability to assess value underscores defining what 'value' means in the first place and agreeing on the key metrics within 'value domains'. Our informants agreed that value was not just about efficacy, effectiveness or getting access to cheaper or more affordable drugs. "Cheaper" was not equated with "valuable." Health outcomes and the need to measure and tie outcomes to decision making and reimbursement were emphasized.

Given the significant uncertainty regarding the value of new breakthrough treatments to patients and their costs to the healthcare system, our key informants consistently expressed the need to have a systematic way of assessing the value of new innovations, then prioritizing them, and deciding what should be offered and what is reimbursable.

It was suggested that a nimble framework is needed and should be more permissive in letting promising breakthrough treatment innovations into the cancer care system sooner. The framework would require monitoring and surveillance mechanisms to move therapies out of the system should evidence emerge that does not support their proposed or purported value based on clearly defined evidence-informed outcomes to patients and the health and/or cancer care systems.

In the context of prioritizing promising treatments, the need for agreeing on the definition of 'promising innovation' was also highlighted. Some informants viewed the distinction between truly transformative innovations and those that add incremental value as important for making difficult choices when prioritizing which therapies should be funded. For example, chimeric antigen receptor T-cell (CAR-T) therapies (CAR-T), was viewed as transformational by some informants.

However, others viewed breakthrough treatment innovation more as a spectrum, rather than a binary value assessment of truly transformative innovative versus everything else. Incremental innovations were acknowledged as important in the "long term story of innovation". One of our informants described it in terms of the concept of "option value", which refers to the fact that even though the therapy might not cure someone, it may still give them an extra survival time, and thereby enable them to transition to and benefit from the next type of treatment. Consequently, recognizing incremental innovation should not be ignored in the prioritizing framework of promising breakthrough treatment innovations.

> *"The [doctor] always said that I was the example of where medicine was going to go because they'll never know which one of my four treatments was my lifesaver, or whether it was the combination of them all." (patient advocate)*

In summary, pan-Canadian policy framework:

- Enables value-assessment based on outcomes (not cost or efficacy only)
- Prioritizes the most promising innovations
- Agrees on definition of “promising” innovations

Early Approval and Reassessment Mechanisms

It was generally agreed that “prioritizing” innovation meant accelerating funding for some breakthrough treatment innovations, as well as potentially limiting funding for others. In cancer care, early access can impact the prognosis for a patient. A gap at the policy level in Canada was identified. Specifically, there are no nation-wide and cross-agency objectives providing early access to the most promising new therapies. Hence, there is a need to set up streamlined pathways and criteria to expedite access, especially for cases where the drug is the patient’s only option but has not yet been approved and/or funded. This includes access through clinical trials, or pre-approval mechanisms, as well as post-approval but with pre-reimbursement mechanisms (while the product goes through the various public review stages).

Although there have been efforts to create joint cross-agency agreements and mechanisms to eliminate duplication and accelerate the start of reviews or shorten the review times, for the most part, the system remains fragmented, sequential, and non-binding for agencies down the line (i.e., payors). Furthermore, criteria for prioritizing or accelerating access are based on different definitions of “value”. Of major concern noted by informants was continued spending on ineffective treatments, which was viewed as an opportunity lost for other promising breakthrough therapies. The current system does not accommodate reassessments or outcomes-based funding adjustments. All stakeholders shared the view that system flexibility with built-in mechanisms to reassess and adjust the funding terms for a drug based on new evidence, including de-funding if the expected value has not been realized is critically important.

It was noted that such flexibility will require changes in policy and a mindset shift for many stakeholders, given that uncertainty is common with many breakthrough treatments. Ultimately, what will be required is a conditional approval and reassessment process, whereby breakthrough therapies that do appear very promising are funded, while patient-level real world evidence (RWE) is being collected, and a re-negotiation of funding terms for that drug follows based on the reassessment according to pre-defined criteria at an agreed upon time.

One area deserving of attention to enable earlier approval of breakthrough treatment innovations is the evolution of evidence requirements both in terms of outcome measures utilized, but also in the benchmark against which to compare the evidence. For example, some of our key informants highlighted the need to evolve the types of clinical data and endpoints that are being used for assessment of the potential value of promising new breakthrough treatments. In recognition of better responses and longer survival durations, the gold standard “overall survival” measure may no longer be feasible for some studies, both for ethical and for timeliness reasons. In clinical trials, for some of the therapies discussed in our quantitative model, for example, median overall survival still had not been reached after 5 years. Some of the newer end points developed to overcome these challenges include metastasis-free survival, progression-free survival, progression-free survival on subsequent therapy, molecular end points for response, minimal residual disease end points, time before next therapy, or time on treatment. All the aforementioned may indeed be a surrogate of clinical end points. With some

of the newer immunotherapies, there are immune related end points that are different than conventional end points used in clinical trials.[349] Using conventional criteria of disease progression would label these patients' disease as having progressed ("pseudoprogression") when in reality the drug is effectively inducing a response and extending survival in a different way.[350] Hence, moving to accepting these newer end points, particularly with the immune therapies, which work in this manner, was seen as very important. Other types of outcomes and study types viewed as valuable were patient reported outcomes and single-arm studies (where drugs have very small patient populations, and a control group may not be possible). It was also noted that non-traditional breakthrough treatments such as tumour agnostic drugs, which target a specific genetic or molecular alteration and are therefore not specific to the anatomical location of the tumour, will require different approaches to testing and reviewing. Currently, many HTA systems still maintain an organ-specific approach in reviewing cancer drugs.[351]

It was noted that Health Canada is moving forward, albeit cautiously, and looking at the newer end points and accepting some of them, which was viewed very positively. The changes needed to improve the current regulatory environment require progressive thinking in a balanced fashion.

In summary, early approval and reassessment mechanisms should be established to:

- Set up streamlined pathways across different review agencies (including payers) and criteria to expedite access on a conditional basis during data collection
- Create conditions for reassessments tied to data collected
- Accept new and different types of evidence and judge on the merit of measured outcomes using data collected

Funding Reform

The changes required for the regulatory/HTA reform described above need to be accompanied by the following funding reform elements:

- Risk sharing
- Alternative Funding Sources and Policies

Risk Sharing

Our key informants noted that risk-sharing strategies are used around the world, though to a much lesser degree in Canada. This approach addresses the uncertainty of promising breakthrough therapies and prevents delays. Risk-sharing strategies can also be leveraged in the context of early conditional approvals to implement the terms of data collection, reassessment, and funding renegotiation.

[349] Anagnostou and others, "Immuno-Oncology Trial Endpoints: Capturing Clinically Meaningful Activity."
[350] Chiou and Burotto, "Pseudoprogression and Immune-Related Response in Solid Tumors."
[351] Angelis, Lange, and Kanavos, "Using Health Technology Assessment to Assess the Value of New Medicines."

Risk-sharing agreements are based on the principle of risk sharing between manufacturers and payors and can either be outcomes-based (also known as value-based or performance-based agreements), or not outcomes-based - in which case they are more generally known as managed-access or managed-entry agreements.[352] Specifically, under an outcomes-based agreement the manufacturer agrees to "issue a refund or rebate to the payer based on how well the therapy performs in a real-world patient population, when measured against an agreed-upon, pre-defined set of benchmarks".[353] The UK Cancer Drug Fund and Patient Access Scheme (Figure 4) offers a leading example.

Although there are examples of outcome-based agreements in Canada, our key informants noted they are not very common. This is due, in part, to the complexity of their implementation. For example, they would require appropriate data collection and reporting according to specific criteria, at specific time intervals, usually carried out by physicians and administrators, to determine whether the therapy met the criteria in patients receiving it. One key informant cited an example where a managed agreement around a breakthrough therapy for multiple myeloma became a legal matter due to the disagreement on how the effectiveness in patients was being assessed. All these extra processes and potential liabilities led to resistance to their widespread implementation.[354]

One of the best examples of managed access is the Cancer Drugs Fund in UK.[11] It was originally established by the government of UK in 2010, as a safety net for allowing clinicians to give patients promising drugs that were being rejected by National Institute for Health and Care Excellence (NICE), which is an equivalent of Canadian pCODR. Unfortunately, the fund kept growing year to year until it had to be changed. In 2016, it became a money-centric, managed-entry type of agreement, whereby approval is granted for temporary reimbursement, while more data is collected to address clinical uncertainty. In the meantime, patients get access to promising new treatments many months earlier than before.

In addition, companies may submit a patient access scheme proposal for any technology going through NICE appraisal process.[1] There are "simple discount schemes", which may offer either a fixed pricing agreement that is lower than the list price of the treatment or a percentage discount from the list price. There are also "complex schemes" which can offer outcomes-based dose caps, or rebates, or upfront free stock. The proposals are evaluated by the Patient Access Schemes Liaison Unit, part of the Centre for Health Technology Evaluation, which advises NICE on the feasibility of implementation of patient access scheme proposals within the National Health Service (NHS).

Figure 4: The UK Cancer Drug Fund and Patient Access Scheme

[352] 20Sense, *Outcomes-Based Agreements in Canada, The 20Sense Report*.
[353] Ibid.
[354] In those provinces that implemented managed access under product listing agreements, nobody is free to talk about what these agreements look like or what was their experience with them, since they are confidential. Literature shows that there were 16 known 'innovative access contracts' in Canada as of late 2017; only two outcome-based agreements had some publicly available information. The province of Alberta has been recognized for future-oriented thinking in this area, with its Institute for Health Economics leading the work on creating tools and resources to support these agreements. See: 20Sense. 20Sense, *Outcomes-Based Agreements in Canada, The 20Sense Report*.

Concern was also expressed by some key informants that if each province comes up with different criteria for implementing risk-sharing agreements, this could potentially lead to further inequity across the country. One solution would be to develop a pan-Canadian framework within which the provinces could operate and harmonize their own approaches accordingly. This would mean employing centralized standards, resources and supports, and structural reorganization to operate in a more efficient, harmonized way.

A suggestion was also made that these risk-sharing agreements should be integrated within HTA reviews, so that the evaluation and recommendations could be informed by the negotiated terms. This idea is similar to the Patient Access Scheme in the UK.[355] These are innovative pricing agreements proposed by pharmaceutical companies in an attempt to improve cost-effectiveness measures and enable patients to gain earlier access to higher-cost treatments in situations where clinical effectiveness is uncertain. To do so would require the agreement term negotiations to occur in parallel with the HTA process. Such an option provides the opportunity to further streamline processes and cut down on review timelines.

In summary, risk-sharing agreements need to:

- Form the basis of funding agreements and be integrated into the HTA process, including but not limited to early conditional access
- Be founded on outcomes, which determine value
- Be subject to harmonized criteria and collaboration inter-provincially

Alternative Funding Sources and Policies

While participants mentioned several types of funding models, one stood out as unique: the amortization model. This model is being proposed (internationally)[356] for potentially curative gene and cell therapy products, which are expected to provide "durable and profound long-term treatment effects with a single administration."[357] Because of their curative potential, their upfront high price reflects the assumed potential avoidance of costs that would be otherwise incurred on more chronic treatments that have to be given throughout the remainder of a patient's life. In addition to the high up-front costs of these therapies, there are other costs to consider, for example, costs of setting up highly specialized facilities, with appropriately skilled resources, which may not available across Canada's vast geographic regions. At the same time, it has been argued that the traditional reimbursement models based on cost-per-unit of product or per-procedure are not appropriate to support the adoption of these potentially curative innovations or to facilitate patient access to them.[358]

Under the amortization model, payment for these one-time therapies could be amortized on a per patient basis over multiple years, thereby reducing large up-front costs and budget impacts to the payor. This, in turn, would eliminate the cost barrier for eligible patients to access these treatments. It is also argued that amortizing costs of these therapies would be more aligned with the length of time over which their single administration is expected to produce benefits to

[355] National Institute for Health and Care Excellence, "Patient Access Schemes Liaison Unit."
[356] Slocomb and others, "New Payment And Financing Models For Curative Regenerative Medicines."
[357] Ibid.
[358] Ibid.

the patient.[359] A criticism of this model includes the fact that amortization will take the payor into subsequent budget cycle(s), and in some provinces it may not be feasible or even legal to accommodate a funding source that extends beyond a budget approved by a legislature for the current year. That, in turn, could magnify the already existing inequities in coverage (and therefore access) observed in different provinces.

There was recognition by informants that these inequities are due in part to the different models of cancer care delivery and related budget allocations across provinces. While centralization of funding is rarely seen as a desirable option in provincial health care, a need for more standardization across the country was expressed. For example, a need to share or centralize resources and eliminate duplication, by encouraging specialization via centres of excellence, and creating interprovincial collaborative processes and relationships. Some examples were described for diagnostic testing (see Diagnostic testing section), data collection and reporting (see data reform section), and implementation of some complex treatments like CAR-T-cell therapies, which due to their complexity are offered only in three Canadian provinces (Ontario, Quebec, and Alberta). In Ontario, certain hospitals are funded to deliver CAR-T-cell therapy to eligible patients from Ontario and from provinces or territories where it is not yet available.[360] Out-of-province eligible patients may be able to access this through provincial out-of-province or out-of-country programs.[361]

In considering alternative models of procurement and harmonized standards, stakeholders acknowledged the importance of ensuring the presence of mechanisms to reward innovation. Recognizing and adopting value by measuring outcomes is the foundation of proposed funding reform; however, how this gets translated into funding allocations, or more simply in reimbursement prices and revenue potential for manufacturers of breakthrough innovative therapies, is an important consideration for our nation and society. To continue to encourage investments in biotechnology research, drug discovery and development (including attracting clinical trials), Canadian governments and clinician leaders at all levels are called upon to unify a common vision, align objectives, and structure transparent and effective mechanisms to course-correct when mandates contradict.

In terms of funding models that prioritize and reward innovation, the UK and Scotland have current initiatives that highlight specific provisions, such as end of life or magnitude of benefit. The UK's National Institute for Health and Care Excellence (NICE) includes factors in decision-making, such as the severity of a condition and the ability of a new technology to reduce health inequalities.[362] NICE is also considering the role of real-world evidence and refining its approach to measuring health-related quality of life in different circumstances. Evolution of NICE's evaluation methods alongside advances in medicines and data synthesis reflects the UK's commitment to "ensuring rapid access to clinically and cost-effective health technologies".[363]

Informants were in agreement that all stakeholders ultimately desire the same outcome, which is to increase and improve access to breakthrough cancer treatments for Canadian patients.

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[359] Ibid.
[360] Cancer Care Ontario, "Chimeric Antigen Receptor (CAR) T-Cell Therapy Enrolment Process."
[361] Ibid.
[362] National Institute for Health and Care Excellence, "Changes We're Making to Health Technology Evaluation."
[363] National Institute for Health and Care Excellence, "NICE's Processes of Technology Evaluation - Presenting a Case for Change."

However, it was also noted that the public and the government are not sufficiently aware of the issues and challenges in this area and innovation in this context is not presently seen as a priority. They emphasized a strong need to raise awareness, through educating the public and lobbying the government, to bring focus and attention to both policy and funding commitments.

When it comes to funding agreement models and sources, our key informants noted that "one size fits all" is an unlikely approach suitable to the Canadian context. Instead, the variety of forthcoming breakthrough treatment innovations will necessitate more adaptive and flexible approaches, perhaps even a combination of multiple options. For example, amortization and managed access outcome-based financing.

In summary, funding sources need to:

- Enable out-of-the-box solutions such as the amortization model
- Address inequities by centralizing resources and standardizing processes through greater inter-provincial collaboration
- Reward and prioritize innovation as a policy (increase funding commitments)

Diagnostic Testing Reform

Regulatory/HTA reform and funding reform cannot be discussed without including diagnostic testing, which is a key enabler of the adoption of precision medicine. The following diagnostic testing reform elements were identified:

- Create a national strategy and standards for provinces to adapt and adopt
- Specialization and inter-provincial collaboration

National Strategy and Standards for Provinces to Adapt and Adopt

The need for a national strategy to help address the existing inequities in access to diagnostic testing (and therefore treatments) due to inconsistencies in implementation and reimbursement processes was expressed. It was recognized that deep characterization of tumours is becoming more common as it relates to targeted therapeutics, and hence there has been a proliferation of molecular tests in recent years. It is no longer a one-test-one-drug environment, hence our systems and processes that review individual drug-test combinations need to evolve accordingly.[364] A need for more consistent standards for assessment of clinical utility and economic impact of diagnostic testing was expressed to address some of the challenges related to reimbursement decisions and making these tests and associated-treatments available to patients.

One informant proposed a distinct technology appraisal of the diagnostic tests through a pan-Canadian HTA process and adjudication structures, noting that currently, there is nothing comparable to the Common Drug Review (CDR) or pan-Canadian Oncology Drug Review (pCODR) for molecular testing. Other stakeholders believe that any HTA diagnostic testing

[364] CADTH assesses companion diagnostics in the context of a single drug/indication-test pair. See: 4th Appendix — Specific guidance for treatments with companion diagnostics. Ottawa: CADTH; 2019 Sep. Available at: https://www.cadth.ca/sites/default/files/pdf/CADTH_Consult_Proposed_Process_Companion_Diagnostics.pdf

assessments should continue to be conducted at the provincial level to reflect the local context and health system considerations. It was also noted that there is a need to define more broadly which diagnostic tests are valid to be used in Canada for which approved drugs and indications.

The inconsistencies in reimbursement processes across the provinces were attributed, in part, to the fact that *"there is no unified funding body"* and funding allocated for drugs is separate from funding allocated to diagnostic testing (which falls under lab services) in the provinces.

The dichotomy of who pays for the drug versus who pays for the diagnostic testing often results in the patient having to pay for the test out of pocket. There is also a private-public disconnect for funding tests. For a drug that is not funded publicly, a person with a private insurance plan that would cover this drug can't get tested unless they pay for it out of pocket. This is because most private insurers don't cover testing services as they view such services as a public expenditure. Some informants believed that savings may be realized if diagnostic testing was publicly funded improving care standardization across the provinces.

Significant provincial/territorical-level policy changes will be required to make the necessary changes with respect to how diagnostic testing is assessed, reimbursed and made available to patients in Canada. Jurisdictions need to better coordinate the public approach to assessing, implementing and funding diagnostic tests. A national strategy can set the standards for the provinces to adopt and adapt.

In summary, a national strategy for diagnostics testing would:

- Establish clear technology appraisal and reimbursement processes for diagnostic tests and set pan-Canadian standards for provinces to adapt and adopt

Specialization and Inter-provincial Collaboration

It was recognized that some diagnostic tests are so specialized, particularly the more extensive molecular profiling or next generation sequencing, that they can only be done in a limited number of centres across Canada. In some cases, they must be sent to the United States if a very sophisticated diagnostic profile of the patient's tumour is required.

Streamlining diagnostic testing at Centres of Excellence is one solution. These typically are high volume centres, which have the necessary experience, expertise, capacity, resources, and quality assurance processes in place. This approach was seen as more cost-effective, more equitable, and more coordinated. It was noted, however, that there is no system to designate centres where these tests should be done. Having a provincial/territorial mechanism to determine this would be advantageous. One key informant cautioned that even though some tests are specialized right now, the technology is evolving rapidly and there are and will be ways to provide point-of-care testing. Furthermore, centralization efforts may disturb a patient's care trajectory. UK experience serves as an example of detrimental impacts of molecular testing centralization on patients within the NHS England, where increases in turn-around times forced some hospitals to perform certain time-sensitive tests in-house to prevent treatment delays.[365]

Given the investment in infrastructure and training which is necessary to establish such Centres of Excellence, collaboration across provinces will be necessary to address potential inequities in

[365] Article25 Capital Partners, "Impact of Testing Centralisation on Patients in the UK."

access. For example, a province like Prince Edward Island may align with a pathology department in Halifax, Nova Scotia, and have their samples sent there. Such arrangements will require modernization of interprovincial billing and relationships and could be defined in the national strategy.

In summary, specialization and inter-provincial collaboration involves:

- Designating specialized labs to conduct diagnostic tests and genomic profiling
- Investing in infrastructure and training for those specialized centres of excellence
- Sharing that investment and those resources between provinces

Data Infrastructure Reform

The structural reform, funding reform, and diagnostic testing reform all rest on appropriate and reliable data being made available for decision making and implementation. The following Data infrastructure elements were identified:

- Broader value capture through Real World Evidence (RWE)
- Data sharing and integration

Broader Value Capture Through Real World Evidence (RWE)

It was recognized that the adaptations to the regulatory/HTA and reimbursement pathways proposed above (namely to address the uncertainty of clinical evidence related to the value of the new innovations), will require ongoing evidence collection in the form of real world evidence (RWE). RWE refers to data that are obtained outside the context of randomized controlled trials and is necessary for long-term assessment of how well drug is performing in the population of eligible patients. This type of data can be derived from various sources including Electronic Medical Records (EMRs), provincial administrative databases tracking healthcare utilization (claims and billing), disease registries, and additional research studies (not necessarily RCTs). The goal is to track patient outcomes over the long term to determine whether the treatment they received resulted in expected outcomes or presented disproportionate adverse patient or system level effects.

It was noted that at this point, there are no processes in place in Canada to conduct RWE studies or to efficiently to use that information to assess value needed to support decision making. Addressing these gaps were viewed as a priority.

Defining and supporting the data infrastructure for various decisions was acknowledged as the primary question facing health systems. The decision matrix includes early access approvals, HTA, outcome-based agreements, other managed-entry agreements, as well as diagnostics testing evaluations. It was noted that cooperation of various stakeholders, including patients, clinicians and industry will be needed to collect the required data. It was also noted that substantive data and evidence are already being collected in separate databases, by different parties, and for different purposes (e.g., clinical versus research). Despite this “fragmentation”, advanced data science approaches and partnerships may be leveraged to realize progress.

One of the elements noted as important to track systematically was RWE quality of life data. It was noted that there are no current systems in place to collect quality of life data effectively,

though some efforts are being made. For example, Edmonton symptom assessment scales (ESAS) are being implemented in cancer centres in Ontario, where patients are expected at each visit to go to an electronic kiosk and complete the assessment. Examples of information collected through ESAS include physical symptoms like pain, shortness of breath, and psychological symptoms like depression, anxiety, and restlessness. It was believed that there will be increasing calls for prospective capture of quality of life within RWE studies, hence it is necessary to create processes and systems for capturing of these data. It was also noted that quality of life data could be linked to administrative data by prescribed research entities, for a comprehensive assessment of value of innovative breakthrough therapies.

Finally, it was recognized that RWE collection will have additional costs as it requires proper infrastructure and additional resources. This was viewed as a worthy investment. Collection of this data is critical for adapting funding models and for supporting decisions based on the actual value and population benefit of breakthrough cancer innovations in the real world. Eventually, it was believed that a database of RWE across Canada could support decision making to ensure greater value for the public.

In summary, RWE value capture depends on:

- A process for conducting RWE studies in the context of value assessments for reimbursement decision-making and implementation of agreements
- A data infrastructure connecting existing fragmented evidence and adding new evidence and patient-reported quality of life data
- Additional dedicated investment

Data Sharing and Integration

> *"…the whole idea of data sharing and data sharing networks needs to be sorted out in Canada. It's a Canadian problem, we silo data really badly" (health policy researcher)*

Our key informants noted that health data in Canada is siloed on several levels: province to province, institution to institution, research and clinical, etc. One of the biggest challenges identified was sharing and interoperability of systems.

For example, even though health data for a given patient are captured across a person's lifespan, it is provincially based. There is no national database. Some provinces are more advanced in access to secondary data and patient specific data than others. In general, a substantial amount of funding has been invested in point-of-care electronic medical records (EMRs) and jurisdictional electronic health records systems (EHRs) across Canada. Value from these systems may be realized if interprovincial data sharing were feasible. In this regard, data sharing regulations and privacy related policies as well as system interoperability were brought up as barriers to sharing research and clinical data. It was believed collectively by informants that the cancer care system can benefit from data coming out of research activities and cancer care clinics if electronic systems could "talk to each other" and privacy and data standards requirements were federated.

A shift in mindset and policy leadership is required to view research and clinical data as being related to each other rather than independent. This was emphasized particularly with respect to genomic testing data. For example, data collected by academic settings or industry is not

shared beyond the investigator, or research team, or the healthcare organization. In clinical settings, some institutions are doing 100 gene panel test, and other centres do 200 gene panel testing, and these data are not sharable. The implication for patients who are tested in one centre versus the other is that they're getting different access testing that may potentially evolve or be relevant to future treatments. Having the infrastructure required to support a model of 'open data' was viewed as critical to advance access. See 'data sharing' examples below (Figures 5 and 6).

Considerations for the future were raised around data ownership and eventually patients controlling their own data (similar to Estonia). It was also noted that when it comes to genetic data, policy-level barriers around privacy will need to be examined as they may be preventing collection, sharing, and using these data for clinical decision making.

In summary, data sharing and integration requires:

- Leveraging inter-provincial relations to increase capacity for data sharing
- Addressing data sharing and privacy regulations as well as systems interoperability
- Connecting research and clinical data and leveraging it for clinical use

Estonia was given as an example of a small country (population of 1.3 million people) with a national health care system, considered to be the first fully digitized country in the world.[1] They built a single health record, where more than 95% of the data generated by hospitals and physicians has been digitized. This enables patients to have access and be in control of their own health records. It also facilitates generation of data for policy decision making. Since 2000, they have also completed genetic profiling of close to 200,000 Estonian adults.[1] This genetic data is incorporated into their digital health record and is used to guide personalized, genetic risk-based diagnosis, treatments as well as preventative life-style choices. It is also used for population-based genetic and public health research.

Figure 5. Data sharing in Estonia

In Ontario, the Ontario-wide Cancer TArgeted Nucleic acid Evaluation (OCTANE) trial supported by the Ontario Institute for Cancer Research (OICR) was given as an example of an effort to establish a network of cancer sites offering molecular profiling through next generation sequencing (NGS) and sharing their data. It allows for deeper molecular characterization of advanced tumours and for using the results to inform the choice of appropriate treatment. It also provides an opportunity to collect province-wide real world data which will be used to evaluate outcomes and costs of NGS for patients with advanced cancer. Finally, it presents an opportunity to develop a province-wide repository of genomically and clinically characterized samples, which can accelerate the development novel genomic tests for clinical use

Figure 6. Data sharing - Ontario's Octane trial

Part 3: How to Move Forward

Achieving the regulatory/HTA, price negotiation, funding, diagnostic testing and data infrastructure reforms proposed above is no small task. Other countries are facing similar challenges and are actively formulating policy changes to improve access to breakthrough cancer treatments.[366] The UK has already undertaken processes to evolve their technology appraisal evaluation methods in order to enable rapid access to clinically and cost-effective health technologies.[367] The COVID-19 pandemic has exacerbated existing gaps and worsened access issues for patients across Canada, but also represents an opportunity to enable and reinforce the domains of a stronger, resilient healthcare system.[368] Strong partnerships and collaboration grounded in the following elements are needed:

- Common vision, guiding principles, and accountability
- Trust and meaningful participation of all stakeholders

Common Vision, Guiding Principles, and Accountability

Improving access to breakthrough cancer treatments in Canada's publicly funded healthcare system will require policy advancements in several areas described above. This can only be achieved via collective effort of all stakeholders coming together and being willing to move away from working in silos into a more collaborative and transparent patient-centred venture. It is necessary to ensure that a multitude of perspectives, including patients, providers, governments, health technology assessors, industry, healthcare administrators, and

[366] OECD, "Addressing Challenges in Access to Oncology Medicines."
[367] National Institute for Health and Care Excellence. "NICE's processes of technology evaluation - presenting a case for change."
[368] Resilient Healthcare Coalition, "Building Resilient Healthcare Systems for a Post-Crisis Era."

researchers, are captured when formulating the vision for what the system will look like and defining the guiding principles upon which it can be achieved and deliver results.

A multi-stakeholder forum was suggested for ongoing discussions and consensus-building with regards to the common goals, defining what "value" means from different perspectives and identifying opportunities for collaborations. This forum and its participants will be well served to enter discussions with a deep understanding of the current policy challenges, willingness to find solutions from an outcomes perspective, and an understanding that compromises will have to be made to reform the system for forthcoming treatment innovations. Transparency and accountability were identified as critical:

> *"…if you really want to change…you have to undergo structural change. And that includes a forum. A selection of stakeholders who are going to be in that room and work without preconceived notions, and without preconceived outcomes, but understanding what the policy challenges are and really not looking at it from an academic or an industry, or a public policy perspective, but from a Canadian health care outcome perspective, which should include all those components." (former payor)*

Accountability to a public policy mandate that reaches over and above any individual jurisdiction, stakeholder or ministry is crucial for continued sustainable success. This mandate should be accompanied by a budget commitment, as this would send a strong signal of political will and momentum that this is a cross-government priority.

Trust and Meaningful Participation of all Stakeholders

Willingness of payors and industry to align was highlighted as crucial, recognizing that all parties would understand that collaboration and partnership requires a lot of energy and initiative. It was recognized that trust issues exist and will have to be overcome to gain and build a unified momentum. For example, a renewed partnership between industry that brings breakthrough treatment innovations to market, clinicians, healthcare payors and system stakeholders in these reforms (e.g., digital health sector) would be helpful to establish solutions for sustainability to create an enabling environment for forthcoming breakthrough treatment innovations.

Strengths and Limitations

We had broad representation of different stakeholders from across Canada, which allowed for integration of multiple perspectives into this analysis. Despite this broad representation, generalizability can be considered limited given the complexities of the Canadian healthcare system and inter-provincial differences. The views expressed by key informants were largely high-level, hence further discussions are warranted to define the specific details behind the proposed reforms. Given the individual context of the interviews, assigning priority to recommendations above have not been proposed.

Conclusions and Key Takeaways

Canada's healthcare systems face a golden opportunity to evolve and create an enabling environment for forthcoming breakthrough cancer care treatments. Moreover, the massive backlog in cancer diagnoses and accentuated care disparities resulting from the COVID-19 pandemic compels the collective of all stakeholders: governments (all levels), industry, researchers, and patients respond and accelerate change. Structural level regulatory/HTA, funding, price negotiation, diagnostic testing and data infrastructure reforms are needed to catch up with the tremendous advancements achieved to-date and those on the horizon. The outlined policy reforms must be tackled collaboratively, with all stakeholders aligning to a unified vision and guiding principles, and a clear mandate from the government with dedicated funding commitment.

In summary:

1) Measuring the value that breakthrough cancer therapies bring to society at large, as illustrated in this report is a complex undertaking that goes beyond assessment of the clinical benefit.
2) We are at a critical juncture and there is an urgent need to transform Canada's cancer care system of approval and reimbursement and funding to accelerate and broaden access to promising breakthrough treatment innovations for Canadians.
3) Investments in innovative risk sharing agreements, RWE infrastructure and diagnostic genetic testing framework are essential.
4) Processes and systems require integration; data sharing and interoperability are critical levers to monitor outcomes and agile decision making; accountability and control must be shared; and compromises will need to be made to achieve harmonization and equity.
5) All stakeholders will have to take more risks and be adaptable to change.
6) New ways of working together are needed to develop and implement a strategy, supported by a renewed commitment from governments and backed by dedicated funding.

Appendices

A.1 Detailed Quantitative Model Methodology

This report quantifies the clinical benefits and economic value of a select group of breakthrough cancer treatments over the 2011-2021 period.

Selection Criteria for Oncology Innovations

Time Period

The time horizon of 2011-2021 was chosen as breakthrough therapies selected for this analysis were approved by CADTH for at least one indication during this time period, and patients were included up to the current year.

Patient Estimates

Estimated target population pools were calculated from the sum of annual cancer incidence data provided by Statistics Canada (annual) and estimated progression to the relevant stage (based on rates identified through a literature review).

Clinical Value Estimates

In a quantitative sense, the clinical value of an innovation is defined as the years of progression-free (or metastatic-free, or overall) survival added to patients' lives by the breakthrough treatment innovation (beyond the standard of care). Based on expert guidance, median progression-free survival (PFS) was chosen as a suitable metric of ability to work or ability to contribute to society in retirement while maintaining a reasonably sound quality of life. Some exceptions were made, as described in the paper and further below.

Each breakthrough treatment's PFS (or other relevant) metric was identified using the pivotal clinical trials used to inform that innovation's CADTH approval, with a further literature review to identify any up-to-date results of the clinical trials. These metrics were then validated through expert working groups. Where multiple treatments were considered for a given tumour type, the relevant survival metrics were weighted according to utilization rates reported by IQVIA claims data (Pharmastat).[369] Where treatments were used in multiple lines of therapy or indications, PFS data in the model changed in accordance with the timeline of CADTH approvals being reflected in the utilization data. With regard to melanoma, an existing working group of experts have created a new set of immunotherapies Response Evaluation Criteria in Solid Tumours criteria for disease progression (iRECIST), to acknowledge delayed response or "pseudoprogression" that is common to patients taking immunotherapies.[370,371]

[369] Ontario unique monthly patients averaged over one year of data across both public and private drug claims (Pharmastat); for the IV medications which are not available in Pharmastat data, a 50/50 split was assumed (pembrolizumab and nivolumab in melanoma). Myeloma had only 1 product.
[370] Gyawali, Hey, and Kesselheim, "A Comparison of Response Patterns for Progression-Free Survival and Overall Survival Following Treatment for Cancer With PD-1 Inhibitors."
[371] Seymour and others, "IRECIST: Guidelines for Response Criteria for Use in Trials Testing Immunotherapeutics."

To estimate the clinical value, annual patient cohorts (separated by age) were tracked for the duration of their PFS under two scenarios – innovative breakthrough treatment and standard of care. For each tumour type, patients first entered the model when the treatment was first approved for an indication by CADTH. The difference in PFS/MFS/OS between treatment scenarios is used to represent the benefit of breakthrough treatment. Overall PFS/MFS/OS years gained (due to breakthrough treatment) is the sum of years gained across all annual patient cohorts.

Economic Value Estimates

For the purposes of this study, the economic value of a breakthrough treatment innovation is its positive effect due to lowering lost production. In this analysis, this is quantified by estimating the income that treated individuals would have been able to earn during the extended period of years gained and subsequent time spent working. This approach follows a modified human capital method (HCM) – one of two methods identified in Public Health Agency of Canada publications, such as the *Economic Burden of Illness in Canada* reports. The HCM was chosen in favour of the friction cost method given data limitations on patient labour market outcomes. However, use of the HCM requires some strong assumptions including zero involuntary unemployment. Estimates should therefore be considered as the *upper bound* of the value of lost production.[372]

To estimate economic value, annual patient cohorts (separated by age) were tracked for the duration of their PFS under both breakthrough treatment and standard of care. PFS/MFS/OS-years, per annual patient cohort – for breakthrough treatment and for standard of care – were multiplied by appropriate annual employment rates and median income data (varying by age group) reported by Statistics Canada. Patients are assumed to remain on treatment and to continue working until progression. The analysis assumes the same employment rates between the standard of care and breakthrough treatment groups; however, we know this is not likely to be true. For non-working individuals over the age of 39, median age-appropriate retirement income is utilized as a proxy to capture the lost economic output of premature mortality.

The difference in averted lost production between the two treatment scenarios is used to represent the benefit of breakthrough cancer treatment(s). The overall gain in production is the sum of income gained across all annual patient cohorts.

Median income data was derived from Statistics Canada Table 11-10-0239-01. The median income data used in a given model was chosen to reflect the biological sex most commonly diagnosed with that cancer type. For example, the prostate cancer models used median income data for Canadian males, and the breast cancer models used median income for Canadian females. Mixed tumour models use the combined totals.

Differences in treatment rates or in ability to work while receiving treatment (i.e. reduced incidence of absenteeism) between the two interventions are not quantified in our model. Including each of these would lower the overall population estimates in both treatment groups but may increase or decrease the magnitude of difference between the two arms.

Rationale for Using MFS or OS as Marker of Benefit

[372] The Public Health Agency of Canada, *Economic Burden of Illness in Canada, 2010*.

The use of PFS as a surrogate efficacy marker for survival outcomes has long been controversial (as explained in our General Approach and Methods section). However, in recent years the use and relevance of OS has become increasingly challenging as a primary efficacy outcome measure due to length of trials required (with improving duration of responses, treatment in earlier stages of disease, and increasing number of subsequent treatments), and for data contamination reasons from cross-over effects (for ethical reasons patients in the control treatment arm who progress or do poorly cross-over to the intervention arm). In most breakthrough targeted therapies PFS has been shown to have better outcomes, but this does not always translate to better OS.[373] This is why in part we have relied on PFS as a measure of better quality of life and ability to work or otherwise contribute to society.

Two exceptions were made to using PFS as the primary efficacy marker to estimate economic value. In the indication for non-metastatic castration-resistant prostate cancer, the primary outcome was metastasis-free survival while progression-free survival was a secondary outcome. The FDA, Health Canada, and other regulators, as well as CADTH and other international reimbursement decision-making agencies based their approval decisions on primary outcome measures, in this case accepting metastatic-free survival as an appropriate measure of survival benefit. The second exception was in the indication for metastatic or unresectable melanoma, where overall survival was identified in the literature as a more appropriate measure of survival benefit for immunotherapies specifically. As noted above, a working group created a new set of Response Evaluation Criteria in Solid Tumours criteria for disease progression that apply to immunotherapies (iRECIST), to acknowledge delayed response or "pseudoprogression" that is common to patients taking immunotherapies.[374,375]

[373] Gyawali, Hey, and Kesselheim, "A Comparison of Response Patterns for Progression-Free Survival and Overall Survival Following Treatment for Cancer With PD-1 Inhibitors."
[374] Ibid.
[375] Seymour and others, "IRECIST: Guidelines for Response Criteria for Use in Trials Testing Immunotherapeutics."

Breakthrough Cancer Treatment Innovations for Modelling

Table A.1.1. Verified List of Active Ingredients (and Brand Names) of Selected Therapeutic Classes

Tumour type	Type of innovation	Mechanism of action	Modelling data analysis	Outside modelling inclusion criteria. Qualitative data analysis
Melanoma	Immunotherapy	**Anti PD-1/PD-L1**	Pembrolizumab (Keytruda)[1] Nivolumab (Opdivo)[1] - in combination with Ipilimumab (Yervoy)	
Lung	Targeted therapy	**EGFR inhibitors** **&** **ALK inhibitors**	Afatinib (Giotrif) Erlotinib (Tarceva + generics) Gefitinib (Iressa + generics) Osimertinib (Tagrisso) Crizotinib (Xalkori) Ceritinib (Zykadia) Alectinib (Alecensaro)	Dacomitinib (Vizimpro)[2] Brigatinib (Alunbrig)[2]
Heme	Immunotherapy	**mAb targeting CD38**	Daratumumab (Darzalex)[1]	Darzalex (Subcutaneous) [2] Isatuximab (Sarclisa) [2]
Breast	Targeted therapy	**CDK4/6**	Palbociclib (Ibrance) Ribociclib (Kisqali)	Abemaciclib (Verzenio) [2]
Prostate	Targeted therapy	**ARAT therapy**	Abiraterone acetate (Zytiga) Enzalutamide (Xtandi) Apalutamide (Erleada)	Darolutamide (Nubeqa) [2]

[1] IV therapy. (All other therapies are oral therapies); [2] Outside modelling criteria as not publicly funded (incomplete/unsuccessful pCPA negotiations) or not publicly funded prior to 2021.

References for Modelling Incidence and Progression Rates

Tumour	Epidemiology Metric	Sources
Prostate	**Incidence:** new cases metastatic – 8%	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics
	Progression to metastatic: [1] New cases non-metastatic – 89% * Rate of progression – 50%	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics - Martha K Terris (MD, FACS). Metastatic and Advanced Prostate Cancer. Medscape eMedicine, Dec 29, 2020
	Progression to NMCR: [1] New cases non-metastatic – 89% * 5-year rate of developing castration-resistance – 10-20%)[2]	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics - M Kirby, C Hirst, E D Crawford. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract, 2011 Nov.
Lung	**Incidence:** NSCLC: 85% * *EGFR*+: 15% *ALK*+: 5% * new cases Stages 3-4 – 58%	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics - American Cancer Society: What is Lung Cancer? - American Cancer Society: Treating Non-Small Cell by Stage - Melosky B, Banerji S, Blais N, Chu Q, Juergens R, Leighl NB, Liu G, Cheema P. Canadian consensus: a new systemic treatment algorithm for advanced EGFR-mutated non-small-cell lung cancer. - pERC, Initial Recommendation for Osimertinib (Tagrisso) for Advanced or Metastatic Non-Small Cell Lung Cancer - Melosky B, Cheema P, Agulnik J, Albadine R, Bebb DG, Blais N, Burkes R, Butts C, Card PB, Chan AM, Hirsh V. Canadian perspectives: update on inhibition of *ALK*-positive tumours in advanced non-small-cell lung cancer. Current Oncology. 2018 Oct;25(5):317-28 - CADTH Technology Review: Anaplastic Lymphoma Kinase Inhibitors for Advanced Non-Small Cell Lung Carcinoma - Hisayuki Shigematsu et al. Clinical and biological features associated with epidermal growth factor

		receptor gene mutations in lung cancers. J Natl Cancer Inst. 2005 Mar 2. - Charles N. Prabhakar. Epidermal growth factor receptor in non-small cell lung cancer. Transl Lung Cancer Res. 2015 Apr
	Progression to advanced/metastatic: [1] New cases non-metastatic (Stages 1-3) * Rate of progression to advanced: 30% of Stage 1, 50% of stage 2, 70% of stage 3	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics - Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res. 2014;3(4):242-9. - Sasaki H, Suzuki A, Tatematsu T, et al. Prognosis of recurrent non-small cell lung cancer following complete resection. Oncol Lett. 2014;7(4):1300-4.
Breast	**Incidence:** ER+/HER-: 71% * new cases Stages 3-4: 16%	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics - American Society of Clinical Oncology. 2007 Update of recommendations for the use of tumour markers in breast cancer. J. Oncol. Pract. 3, 336–339 (2007)
	Progression to advanced/metastatic: [1] New cases non-metastatic (Stages 1-3): 88% * Rate of progression to advanced/metastatic: 30%	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics - Joyce O'Shaughnessy. Extending Survival with Chemotherapy in Metastatic Breast Cancer. The Oncologist. 01 October 2005. - Angela B Mariotto et al. Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. Cancer Epidemiol Biomarkers Prev. 2017 Jun
Melanoma	**Incidence:** new cases Stages 3 unresectable: 15%[3] of stage 3 (8%) + New cases Stage 4 (metastatic): 4%	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics - Emanuela Romano et al. Site and Timing of First Relapse in Stage III Melanoma Patients: Implications for Follow-Up Guidelines. J Clin Oncol. 2010 Jun 20.
	Progression to advanced/metastatic: 1	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics

	New cases non-metastatic (Stages 1-2): 72% * Rate of recurrence to stage 3 unresectable or metastatic: 10% stage 1, 30% stage 2, 70% stage 3 resectable[4] * Rate of systemic relapses (vs local or regional): 50%	- Hematology Oncology Associates of Fredericksburg. Stage III Melanoma. Omni Health Media 2016. (review of literature) - Emanuela Romano et al. Site and Timing of First Relapse in Stage III Melanoma Patients: Implications for Follow-Up Guidelines. J Clin Oncol. 2010 Jun 20. - Piotr Rutkowski et al. Follow-up in melanoma patients. Magazine of European Medical Oncology. 24 June 2014.
Myeloma	Progression: [1] New cases Myeloma: 100% [5] * Rate of relapse: 85% [6]	- Statistics Canada (Canadian Cancer Registry Database); and NIH Seer Cancer Statistics - N Majithia et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. Leukemia. 2016 Nov.

[1] Progression rates are applied to applicable incidence rates 3-5 years prior depending on data availability.

[2] Higher end was selected (20%) to align with objective of estimating “potential” eligible population.

[3] No specific number provided, but surgical resection in stage 3 is the norm. Assumed 15% are unresectable.

[4] Stages 1 & 2 were not differentiated, so 20% assumed between the two of them. Stages 3a, 3b and 3c had 27%, 68% and 89% recurrence rates, respectively, so 70% (the middle one) was taken to represent all Stage 3 recurrence rates.

[5] Myeloma by definition is “multiple” or distant so all new cases are included.

[6] Specific number not provided, only “frequently” is used. Assuming 85%.

Appendix A2. Detailed Qualitative Methodology

Objective

Our objective was to identify the most pressing challenges and priorities for action to support the adoption of breakthrough cancer treatments in Canada over the next decade.

Research Question

What will it take to optimize access to (and impact of) forthcoming breakthrough cancer treatments on the Canadian population into the next decade?

Approach

The approach taken included the following components:

- Key informant interviews
- Qualitative content analysis
- Literature review

Policy Topics Selection

Prior to conducting the key informant interviews, the study team conducted a brief survey of an Advisory Committee established for the project and among the IMC/BIOTECanada – Joint Oncology Project Team (JOPT) members to identify specific topics to address as part of the qualitative policy analysis. The survey asked respondents to indicate interest in several pertinent policy topics. A total of 13 individuals responded to the survey. Figure A2.1 below shows the level of interest in each of the proposed topic.

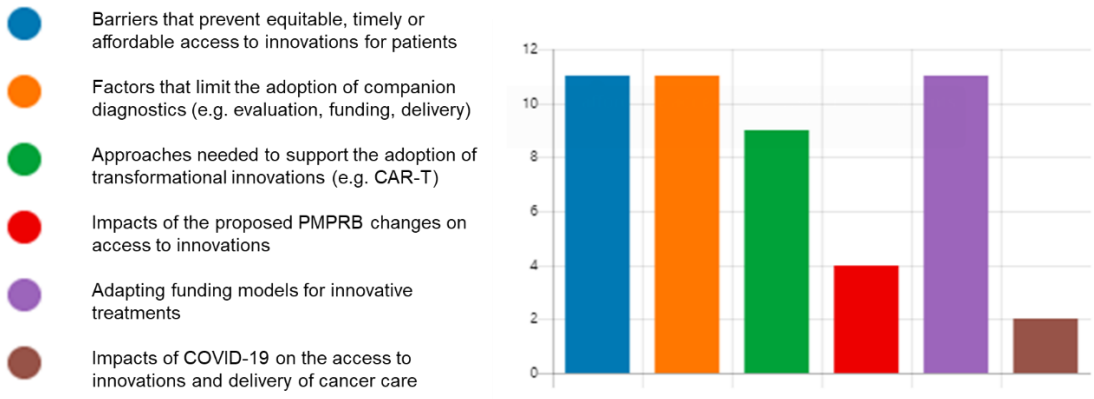

Figure A2.1 Interest in Specific Policy Topic (Frequency, n=13).

The survey results informed development of the interview questions. All participants were asked to express their opinion to the following questions:

1. What are the most pressing challenges facing patients, clinicians, or decision makers with regards to oncology innovations in Canada?
2. What changes to the policy and/or regulatory environment are needed to better support the access to, or adoption of, oncology innovations in Canada?

In addition, the following topics were raised:

- Barriers to equitable, timely, and affordable access to treatment (including early access);
- Factors that limit the adoption of precision medicine and diagnostic testing;
- Adapting funding models for innovations;
- Approaches needed to support transformational innovations (such as CAR-T); and
- The potential impacts of the proposed PMPRB changes on access to innovations (note: the interviews were conducted prior to January 2021).

Participants

A total of eighteen key informants agreed to participate in the interviews. They represented different stakeholder groups: clinicians (n=3), patient advocates (n=3), former payors (n=4), health technology assessors (n=4), and health policy researchers (2). All participants were recognized Canadian experts in this topic area. These individuals were chosen (convenience sample) from the Advisory Committee established for the project, the IMC/BIOTECanada Joint Oncology Project Team (JOPT), and a few other experts recommended by our advisors. Our key informants represented ten members of the Advisory Committee, two members of the JOPT committee, and 6 invited experts.

Interview Format

Semi-structured interviews, approximately one hour in duration, were conducted with the key informants in December 2020. Every key informant received the interview questions in advance.

Data Collection

Two interviews were exploratory in nature and were not recorded. Notes were made and included in the analysis. All other interviews were audio-recorded, yielding a total of 13 recordings. One of these interviews was a group interview with 4 individuals. Detailed notes were taken during the interviews and later transcribed. The resulting transcripts were imported into NVivo 12 software to aid in qualitative content analysis.

Analysis

The Framework for Applied Policy Research[376] was used to guide the content analysis. Figure A2.2 shows the key steps in the analysis: familiarization, identification of a thematic framework, indexing, charting, and mapping and interpretation.

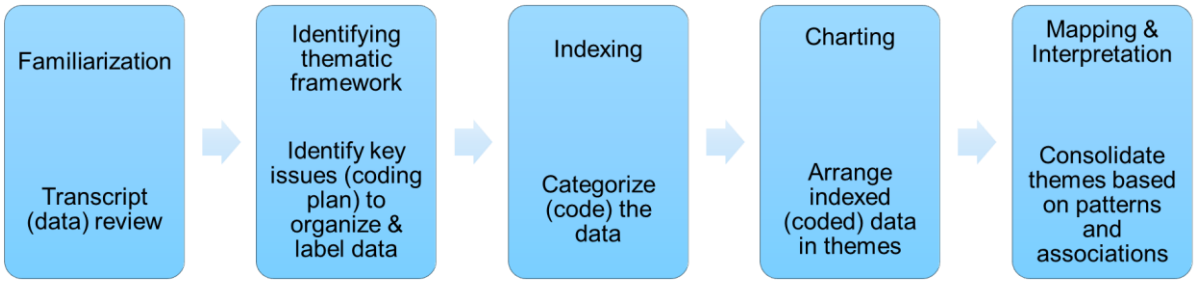

Figure A2.2. Key Steps Undertaken in the Qualitative Analysis.

Two reviewers (The Conference Board of Canada) meet regularly to discuss the transcripts and their coding. They started by reviewing 5 transcripts, coding as per the initial framework based on the member survey, discussed any discrepancies until consensus was reached, and revised the coding accordingly. This process was repeated until all transcripts were analyzed. Major themes in the data were derived by condensing the data into simpler categories and synthesizing the findings accordingly. Measures were taken to assure methodological rigour and trustworthiness.[377] For example, in addition to research team discussions of the data until consensus was reached, preliminary results (while coding was in progress) and final results were shared with the Advisory committee during update meetings. Since several members of the committee served as key informants, this process provided an opportunity for discussion and for obtaining participant validation of the themes and interpretation. The feedback of the committee was carefully considered and incorporated into the analysis. The qualitative analysis has been supplemented by a selective and non-systematic literature review, including open-access and grey literature, pertaining to the issues raised by the key informants.

[376] Srivastava and Thomson, “Framework Analysis: A Qualitative Methodology for Applied Policy Research.”
[377] Korstjens and Moser, “Series: Practical Guidance to Qualitative Research.”

Appendix A2.2 How Oncology Drugs get Funded in Canada

How Oncology Drugs get Funded in Canada

Step 1 – Authorization for sale - Health Canada

A new cancer drug must first receive approval from Health Canada. The review process focuses on evaluation of data reflecting the safety, efficacy, and quality of the product. If approved, a notice of compliance (NOC) is issued and authorizes the manufacturer to market the drug. Two additional pathways for approval of new active substances can be utilized to enable Canadians to have a timely access to promising therapies for serious, life-threatening or debilitating illnesses.[378] These include: i) a priority review that involves the company submitting a New Drug Submission (NDS) with an expedited review period of 180 days; and, ii) issuing the Notice of Compliance with conditions (NOC/c), to give earlier market access to drugs with limited evidence (e.g. phase II clinical trials or trials with surrogate markers only) for "serious, life-threatening or severely debilitating diseases." This is on the condition that the manufacturer will conduct additional studies to demonstrate efficacy. Note: Health Canada's approval of a drug for sale in Canada does not necessarily mean that government drug plans in individual provinces will fund it.

Step 2 – Determining maximum non-excessive price - the Patented Medicine Prices Review Board (PMPRB)

PMPRB has a regulatory mandate to determine if a patentee is selling patented medicines to its customers at an "excessive price". [379] The PMPRB regulates price ceilings according to a complex set of rules outlined in the Patented Medicines Regulations the PMPRB's Guidelines. [380] These protocols are currently undergoing fundamental changes. Many stakeholders are concerned about the negative impacts some of these changes are expected to have on further delaying patient access to breakthrough treatments across Canada.[381] Further price adjustments are made to determine Maximum Rebated Price ceiling for some medicines (high costs and high market size) after taking into account therapeutic effects (according to the Therapeutic Criteria Levels), pharmacoeconomic value and market size of the medicine.

Step 3 – Recommendation for funding by the provinces - the Canadian Agency for Drugs and Technologies in Health's (CADTH) pan-Canadian Oncology Drug Review (pCODR) and the Institut national d'excellence en santé et services sociaux (INESSS) in Quebec

A health technology assessment is conducted to assess the drug's value based on clinical effectiveness, cost of the drugs, patient values, and any implementation considerations that can impact access. The recommendations are developed by expert advisory committees based on clinician and cost-effectiveness information along with input from patients and clinicians in order to make a reimbursement recommendation to the provinces. pCODR can make one of three types of recommendations: "Reimburse" or "Reimburse with clinical criteria and/or conditions" or "'Do not reimburse."[382] After recommendations are made, CADTH provides implementation support (distinct from reimbursement review) to jurisdictions related to implementation of CADTH recommendations and making provincial/territorial reimbursement decisions.

Note: CADTH recommendations are non-binding to the drug plans of individual provinces and territories.

Step 4 – Negotiating price with manufacturer – pan-Canadian Pharmaceutical Alliance (pCPA)

[378] Lexchin, "Health Canada's Use of Expedited Review Pathways and Therapeutic Innovation, 1995–2016."
[379] Government of Canada, "Patented Medicines Prices Review Board."
[380] Government of Canada, "PMPRB Guidelines."
[381] Government of Canada, "Consultations/Submissions Received"
[382] Canadian Agency for Drugs and Technologies in Health, "Procedures for the CADTH Pan-Canadian Oncology Drug Review."

pCPA, which is an alliance of the provincial, territorial and federal governments, conducts joint provincial/territorial price negotiations for innovative and generic drugs in Canada being considered for reimbursement through participating public drug plans. The objective is to achieve greater value for these programs. Interested provinces and territories participate in the confidential negotiations.

Step 5 - Decision to fund – Provincial and territorial ministries of health and cancer agencies
Following pCPA negotiation, it is the provincial and territorial ministries of health and cancer agencies that use the recommendations from pCODR to decide whether to fund a drug or not. This is usually done in consultation with their own expert committees and based on provincial priorities and budgets.

Appendix A2.3 Representative Quotes

Representative quotes organized by major themes

Themes and subthemes	Quotes
Pressing Challenges • Delays due to fragmentation of regulatory and reimbursement processes • Costs of innovations and limited funding • Proliferation of innovations and uncertainty in the evidence • Lack of consistency in implementation and reimbursement processes for diagnostic testing	"We continue to have a fragmented system, both in terms of decision making and in terms of value evaluation of the technology. Specifically, you've got a regulator, you've got HTA, you have a pricing body, and you have a reimbursement body at a provincial level, which actually executes it. And nobody's connected." (FP3, former payor) "Health Canada's approval generally means at least five to six months before you get health technology assessment recommendation, which the majority are conditional on cost effectiveness being improved. And then after that you have another period of time, maybe six to nine months, maybe up to a year, before national price is negotiated. And then, all of that, leads to this huge amount of time where public access through funded public access is not available" (FP1, former payor) "A lot of it [barriers to make things more timely] is resources and public sector not having necessarily enough manpower to get through files more quickly than they do now. Things are better, but even then people would still argue it takes a long time to get through the reimbursement pathways and even time to listing varies across the country" (FP2, former payor) Certainly the costs [are a challenge], so not only the costs of technology but the costs of the whole administration or impact to the patients…[…] …and paperwork from the regulatory space and about also how do they actually manage to utilize or get access to these technologies, and there could be significant kinds of indirect kinds of costs associated with that." (HTA1, health technology assessor) "…[there is lack of awareness] on how money flows, how priorities are made, and what we're willing to pay. Not that we don't care about the patients, we do, but we also care about all of them, with all of these diseases and have to balance multiple myeloma with this drug for pancreatic cancer". (FP1, former payor). "I think we forget that in our universal health care system not everything is paid for. And so the cost of cancer care out-of-pocket [expenses] to patients is substantial. Then, there's differences across Canada." (C1, clinician) "One of the most difficult aspects of day-to-day treatment of patients is determining what's funded, what can we get funded, where can

	we get funding from, are there compassionate programs, does the patient have insurance, how can we position the drug [eligibility-wise] to get the therapy? Even strategies of sequencing drugs are based upon funding." (C2, clinician) "I think it's just the volume issue. I mentioned the tsunami of new drugs and I think for those who are managing CADTH, pCODR, or common drug review, there's just a large volume of drugs to process and treatment strategies. And knowing how to priority set, and how to sequence new drugs is very challenging. (C1 clinician) "The complexity of ordering innovative drugs is becoming really challenging… And so sometimes it's hard to get the treatments you feel would be most appropriate for your patient because they don't exactly meet the criteria that have been defined through the drug approval process. And if you try to get it, it is actually often extremely time consuming and complex, and may not even lead to success and getting the drug that you want. And there are differences between the provinces, even though we have an approval mechanism with one indication approved." (C1, clinician) "And so, the decision maker is faced with a product that looks promising and wants to get it to patients because they might benefit from that, but the data is flimsy and it makes a high degree of uncertainty, making decision making difficult." (C1, clinician) "…the big problem for both payors and clinicians and possibly even patients is that we really don't have that much information on whether the drug works and how good it works. And so drugs have been approved on the kind of evidence that has never been approved in the past. And it's leaving the people who make the purchasing decisions in a lot of trouble because it's not clear to them what they're buying in terms of extra benefit." (MD, health policy researcher) ""…a lot of the modern innovative products come with a companion diagnostic and we do a terrible job in this country of approving them, funding them, and evaluating them." (C1 clinician) It's, it's a disaster, and usually it seems to fall to the pharmaceutical company to provide the funding to set up diagnostic tests, and they often are obligated to keep funding it for a long time before the ministries of health or departments of health finally kick in and provide the necessary funding. And some things are so specialized, particularly the molecular profiling, next generation sequencing, and so on, it's only done in in limited numbers of centres, and sometimes has to be sent out of the country […] if you want a very sophisticated profile of the patient's tumour." (C1 clinician) "I think both public and private payers are really afraid, a lot of these diagnostics are very expensive, I heard some of them could potentially be more expensive than drugs and biologics themselves,

	so we kind of resisted the need to bundle things together in terms of providing an overall solution for a particular patient. This is partly to do with reimbursement but is also to do with the procurement side, the listing side of a decision." (FP4, former payor) "…[who pays for the test] is different province by province, centre by centre, because we work so differently across this country. It does make it hard because there's really no unified funding body. […] in BC, the cancer treatment would come out of one budget, the diagnostic treatment or testing would come out of another. And even those two bodies probably don't talk." (PA1 patient advocate) "…there's all the questions about who develops the diagnostic, who pays for the diagnostic, if there's value added by adding the diagnostic, who gets that added value, is it the company who makes the drug or the company with a diagnostic." (HP1, health policy researcher). "…we as Canadians, in most jurisdictions, we still have ways to go on having a strong lab services models, particularly that support precision medicine genetic treatment, etc. I do think there is a lot of work there. (HTA2, health technology assessor) "Our diagnostic testing review processes are non transparent, fragmented, and not linked up with the drug review processes." (IR1, industry representative) "…fear is that precision medicine will triple and quadruple the costs, because all of the sudden you have access to everything. But in the end of the day, it means the treatment that will work for me is the only one I need, I don't need anything else. You don't need a budget envelope to cover patient population, its more understanding how you provide treatment or care based on individual genetic profile."
Regulatory/HTA reform • Pan-Canadian policy framework prioritizing value based on outcomes • Early approval and reassessment mechanisms	"What's needed more than anything is a nimble transparent framework for assessing innovations." (HP2, health policy researcher) "We also have to have the mechanisms not just to say yes based on incomplete data or pending evaluation, but to stay no or to say STOP when a therapy is clearly ineffective" (FP4, former payor) "It [value] is more than just the price. It's more than the technology. It's actually talking about health outcomes and measuring what the value proposition at large to what actually is achieved." (FP3, former payor) "And most of all, we have to move away from just a cost perspective, or a value perspective only. We have to get to a cost-benefit-risk perspective, rather than just a cost-benefit perspective, it has to be both". (FP3, former payor)

	"…there are always going to be difficult choices but some of the choices that have to be made can be made for real innovation versus one more treatment in some type of treatment protocol where there is already many accesses." (HTA2, health technology assessor) "…something that is innovative, but not maybe as far along the spectrum [as CAR-T] and new should not necessarily be lumped with all the standard stuff" (IR1, industry representative) "He [doctor] always said that I was the example of where medicine was going to go because they'll never know which one of my, my four treatments was my lifesaver. Or was it a little combination of all." (PA1 patient advocate) "Ultimately, I think what will be required is that we need a process whereby innovative therapies that do appear very promising are given a provisional approval, some level of funding in the timeframe in which to collect real world evidence, and a reassessment after some number of years probably three to five. And then a re-negotiation of price for that drug assuming that the real world evidence supports its benefits." (C1 clinician)
Funding reform • Risk sharing • Alternative funding sources and policies	"There are some examples of having these outcome-based agreements, but that needs to become not the exception, but probably looking more maybe not to a rule, but making them more common place. And having this idea of If you've got a very promising therapy but for whatever reason, if it is a targeted therapy, you've got a very small population, we need to find a way to provide access for patients if this is a promising therapy and these patients have very few other options, and we need to find a way to collect evidence, and also find a way to share some of that risk. (IR2, industry representative) "…we don't do managed entry agreements. Everybody else in the developed world seems to do that. We don't even do performance agreements. So I think that that's partly because they're more complicated to do and when you've got 10 provinces three territories, and each has to have its own agreement with the manufacturer, it does get complicated to implement." (C1 clinician) "It has potential to be more work to have these outcomes based agreements. It's much easier to put something on a formulary and just let it sit there in perpetuity than trying to have these outcome-based agreements, where you actually had to go back and re-visit a funding decision." (IR2, industry representative) "Uncertainty [about long-term effects] isn't necessarily the kind of uncertainty you can quantify because it [the therapy] is either a cure or it isn't. And if it was a cure, it would be worth a lot of money. And if it isn't a cure, it probably wouldn't be worth a lot of money. So, the

	only way you can deal with that kind of uncertainty is through your payment model. So you might have an agreement, kind of an outcome based agreement for five years, and then it might be renewed based on the information that we now have about the long term durability of that therapy. It's really impossible to have an outcome-based agreement lasting 20 years, but you may be able to pass through a series of outcome based agreements that would change in their nature as more and more information became available about the long term effect of the therapy." (HP1, health policy researcher) "To change the [funding] models you have to be able to find a way to manage and predict risks. Because the biggest issue with funding models is knowing the predictability of your budget. […]…you need to change the way people measure risk and you need to create a new set of not guidelines, but look at it from much more long term, or a vision: you can spend more upfront but save more down the road." (PA2 patient advocate) "For adapting funding models, I think this should encompass the need for conditional HTA review pathways, use of RWE and ongoing evidence generation, and performance-based risk sharing. (PA3 patient advocate) "I think one starting point for discussion about new funding models is determining a defined aliquot of funding and how do we live within it and add new products within it. It grows but there are choices rather than it being what feels like sometimes free-for-all with every manufacturer." (HTA2, health technology assessor) "One thing that's going to come up is a possibility of drugs that will actually cure cancer, those will be very expensive. Some manufacturers are suggesting we should amortize the costs of these therapies on a per patient basis over multiple years, and there's a lot of fear and skepticism amongst public payers at least in even talking about that. Because it takes you into subsequent budget cycles and the current one that you're budgeting for within your government. But on the other hand the costs are so huge, [that] people may well be losing access to drugs because the amounts are just too large to deal with within a current fiscal year, within one fiscal year or even 3 fiscal years. […] some provinces probably don't even have the ability or provincial legislation to consider a funding model that's anything beyond a budget approved by their legislature for the current year. So we have to think that one through." (FP4, former payor) "…perhaps some of the treatments will never belong to every jurisdiction; there is a modernization of interprovincial billing and relationships that probably needs to be examined." (HTA2, health technology assessor)

	"In Scotland, for some time now, the reimbursement authority, the Scottish Medicines Consortium, have had a list of six or seven explicit modifiers, meaning factors that directly translate to a higher price or have a higher cost effectiveness threshold. Many of those would apply to cancer drugs I think. The only modifier we pay a premium for in England was for end of life care. But NICE is currently having a renewal of these methods and is having a more general discussion about modifiers and what kinds of factors would mean that you could pay a little bit extra, like severity of the condition, where there is a higher unmet need, or some notion of equity maybe." (HP1, health policy researcher) "If we had more funding, we could invest in more biotechs that might bring more innovative treatments, with the understanding and recognition that they're not all going to pan out. And that's fine. Right now we're on the other side of that equation, there are many that would likely turn out to be valuable or develop useful products, but they're not getting the funding to move forward. (C2, clinician)
Diagnostic testing reform • national strategy with well-defined standards for provinces to adopt and adapt • Specialization and inter-provincial collaboration	"…the answer [to] should this [diagnostic] test be reimbursed, or that test for universities, it's easier to say no. Because we don't know what evidence we need and we don't even know how to evaluate that, and we certainly don't know how to do it quickly. So, to me there's a whole framework that's required to make this process work more effectively. I think that's one of the big policy regulatory changes that needs to happen and it's going to be complex. It has to be done provincially, but there's no reason that you couldn't develop a framework that could be adopted or slightly modified by each of the provinces." (HP2 health policy researcher) "…when we look at a new innovation coming, a new diagnostic test, a new drug, a new imaging modality, whatever it is, our biggest challenge is knowing what to do with it. And we're seeing this played out particularly in the molecular genetics space where there is all kinds of molecular tests, whether they're companion diagnostics for drugs or they're their prognostic indicators. We're doing deep characterization of tumours which is becoming more and more targeted and related to targeted therapeutics." (HP2 health policy researcher) "…some of these tests still continue to evolve, it's not just a simple test, and some require quite a bit of expertise, need to be validated, so if it's a test that's not that common, especially in a small province, they can't actually do the testing, they have to send it somewhere else. So having some kind of strategy, national strategy on how to deal with this, would probably be helpful. (FP2, former payor) "…there seems to be a lack of any kind of consistent process or strategy. I know there's some work happening in some provinces, around some kind of strategy around testing, so hopefully it helps,

	but I think some kind of national work and some kind of process, particularly as it's linked to treatments whether its drugs or otherwise, I think would be helpful." (FP2, former payor) "Diagnostic testing for sure, I think there is a huge opportunity for us. And from a policy side, I think we need to have far more clear transparent testing review processes within provinces, and basically a shift in mindset from a one drug one test approach to an NGS approach of looking across biomarkers." (IR1, industry representative) "It may be that we can no longer treat a comprehensive oncology formulary as strictly drugs and biologics. I believe that we shouldn't be providing access to a therapy for which we do not support, at least in public plans, the diagnostic testing that determines whether therapy is appropriate. So that could mean the need for innovation and a rethink of how manufacturers contract with drug programs, so may be coming under the heading of the product listing agreement, this we should've caught up on before now and we haven't. (FP4, former payor) "…some of these [diagnostic] tests still continue to evolve, its not just a simple test, and some require quite a bit of expertise, need to be validated, so if it's a test that's not that common, especially in a small province, they can't actually do the testing, they have to send it somewhere else. So having some kind of strategy, national strategy on how to deal with this, would probably be helpful. (FP2, former payor) "It would be cheaper, more equitable, and more coordinated if a greater emphasis on diagnostic testing was placed at designated Centres of Excellence that streamline testing." (PA3 patient advocate) "…there's no system to sort of rationalize where companion diagnostics should be done. And they can't be done everywhere. […] There has to be a provincial mechanism to determine who does what when, …[…]… the number of drugs requiring these companion diagnostic diagnostics is going up exponentially so it's time that ministries of health go and address the issue." (C1 clinician)
Data Reform • Broader value capture through Real World Evidence (RWE) • Data sharing and integration	"There has to be also an awareness, when we have these new technologies that are complex and uncertain, about any of the value. We need an infrastructure also for some of that value generation beyond the regulatory approval. […] There is actually no infrastructure established to do some of that work, to continue to look at some of the value, or generate data that will actually support a value of these." (HTA1, health technology assessor)

	"Right now, we don't have processes in Canada in place to do real world effectiveness studies efficiently and to use that information to support the decision making." (C1 clinician) "… we have to find a way to provide both infrastructure to support the data collection to do that, to make decisions based on real world evidence" (FP4, former payor) "I think the other big challenge related to regulatory environment is anything to do with data sharing. So, we're only going to get benefit from all of the data that's coming out of research and data that's coming out of the clinic if we have electronic systems that will talk to each other. (HP2 health policy researcher) "…the whole idea of data sharing and data sharing networks needs to be sorted out in Canada. It's a Canadian problem, we silo data really badly" (HP2 health policy researcher) "[…] lots of good innovations are out there, whether they are from the industry or academic perspective, but the results […] are not available to be shared beyond that investigator or that team or that organization." HTA1, health technology assessor)
Partnerships and collaboration • Common vision, guiding principles, and accountability • Trust and meaningful participation of all stakeholders	"One in two Canadians will have cancer in their lifetime, one in four will die of it. Right now, as the key demographic group ages, that may go up. So are we really prepared to think of oncology as public issue as opposed to disease specific basis?" (FP4, former payor) "For early access, there is recognition that needs to happen and it can happen with the right initiatives, and right partnerships. There's no single group alone who can create early access, there has to be a collaboration and that can be a challenge depending on who you're working with and willingness to work with different people (IR2, industry representative) "At a policy level, I don't think we have a framework that actually spells out nationwide objectives around early access to the most promising new therapies, or our competitiveness, not as provinces, but as a country on attracting R&D investment, attracting clinical trials, that sort of thing." (FP4, former payor) "I think that payors don't believe that they can align themselves with industry so I don't know how that that can happen or where it can go but it requires one or two people on both sides of the fence to step up and make it work." (FP1, former payor) "You need a forum to actually engage in dialogue with policy makers, so that we're all rowing in the same way. And nobody says you have to be all aligned but we need a safe forum for people to actually advance policy, which is not happening right now. Everybody's in their own silos. (FP3, former payor)

	"…it starts with having intelligent policy discussions, rather than one way dialogue. And policy discussion is about evidence and value. And I think all participants in the equation need to have a very serious discussion, there is no right or wrong. It's really about evaluating what we're paying for and making decisions on what that framework looks like, and being transparent about that evaluation process. And by the way, that's not a knock on the HTA or the payors alone, or the clinicians. It's also on industry." (FP3, former payor) "Obviously, industry, there's reputation of not the most trustworthy place, hesitation and trust issues. But that's something we need to figure out how to overcome." (IR2, industry representative) "I think there needs to be a better partnership between the industry that brings the innovations to market and the healthcare payors and the health care system. I don't think that there is a very good relationship there. I don't think there's a trustful relationship there. I think that needs to be worked on because both parties need to come to the table to bring solutions for sustainability. (FP1, former payor) "I am hopeful that we can collectively engage in meaningful dialogue that advances it and makes the system better. […] We can only make it better by a) shining a light on it, b) being balanced in how we look at the issue. And then deciding those things that are good to keep and those things that need fixing. But hold us all accountable in that process." (FP3, former payor) I really do think the industry has proven itself to be very critical and responsive when we have a challenge, such as covid, it could be a real moment to reestablish relationships and solve problems differently. And not start with cost driving the discussion […] but really have a conversation where it fits in the care of the patient. (HTA2, health technology assessor)

Bibliography

Ahmed, S, and R K Shahid. “Disparity in Cancer Care: A Canadian Perspective.” *Current Oncology (Toronto, Ont.)* 19, no. 6 (December 2012): e376–82.

American Cancer Society. “Drug Therapy for Multiple Myeloma.” Accessed September 22, 2021. https://www.cancer.org/cancer/multiple-myeloma/treating/chemotherapy.html.

American Cancer Society. “Hormone Therapy for Prostate Cancer,” Accessed September 25, 2021. https://www.cancer.org/cancer/prostate-cancer/treating/hormone-therapy.html.

American Cancer Society. “Stem Cell Transplant for Multiple Myeloma.” Accessed October 11, 2021. https://www.cancer.org/cancer/multiple-myeloma/treating/stem-cell-transplant.html.

American Cancer Society. “Treatment Choices for Non-Small Cell Lung Cancer, by Stage.” Accessed October 12, 2021. https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/by-stage.html.

American Cancer Society. “Treatment of Melanoma Skin Cancer, by Stage.” Accessed September 26, 2021. https://www.cancer.org/cancer/melanoma-skin-cancer/treating/by-stage.html.

American Cancer Society. “What Is Multiple Myeloma?” Accessed October 11, 2021. https://www.cancer.org/cancer/multiple-myeloma/about/what-is-multiple-myeloma.html.

Ammazzalorso, Alessandra, Mariangela Agamennone, Barbara De Filippis, and Marialuigia Fantacuzzi. “Development of CDK4/6 Inhibitors: A Five Years Update.” *Molecules* 26, no. 5 (2021): 1488.

Anagnostou, Valsamo, Mark Yarchoan, Aaron R Hansen, Hao Wang, Franco Verde, Elad Sharon, Deborah Collyar, Laura QM Chow, and Patrick M Forde. “Immuno-Oncology Trial Endpoints: Capturing Clinically Meaningful Activity,” 2017. *Clinical cancer research: an official journal of the American Association for Cancer Research* 23, no. 17: 4959–4969.

Angelis, Aris, Ansgar Lange, and Panos Kanavos. “Using Health Technology Assessment to Assess the Value of New Medicines: Results of a Systematic Review and Expert Consultation across Eight European Countries.” *The European Journal of Health Economics* 19, no. 1 (2018): 123–52.

Armstrong, Andrew J, Ping Lin, Bertrand Tombal, Fred Saad, Celestia S Higano, Anthony M Joshua, Teresa Parli, Brad Rosbrook, Steve van Os, and Tomasz M Beer. “Five-Year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer from the PREVAIL Trial.” *European Urology* 78, no. 3 (2020): 347–57.

Arndt, Volker, Lena Koch-Gallenkamp, Heike Bertram, Andrea Eberle, Bernd Holleczek, Ron Pritzkuleit, Mechthild Waldeyer-Sauerland, Annika Waldmann, Sylke Ruth Zeissig, and Daniela Doege. “Return to Work after Cancer. A Multi-Regional Population-Based Study from Germany.” *Acta Oncologica* 58, no. 5 (2019): 811–18.

Article25 Capital Partners. “Impact of Testing Centralisation on Patients in the UK.” Accessed September 25, 2021. https://www.art25capital.com/en/news/impact-of-testing-centralisation-on-patients-in-the-uk.

Ascierto, Paolo A, Michele Del Vecchio, Mario Mandalá, Helen Gogas, Ana M Arance, Stephane Dalle, C Lance Cowey, Michael Schenker, Jean-Jacques Grob, and Vanna Chiarion-Sileni. “Adjuvant Nivolumab versus Ipilimumab in Resected Stage IIIB–C and Stage IV Melanoma (CheckMate 238): 4-Year Results from a Multicentre, Double-Blind, Randomised, Controlled, Phase 3 Trial.” *The Lancet Oncology* 21, no. 11 (2020): 1465–77.

AstraZeneca Canada Inc. *Tagrisso (Osimertinib), Product Monograph*. AstraZeneca Canada Inc., 2021. https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/tagrisso-product-monograph-en.pdf.

AstraZeneca Canada Inc. *Iressa (Gefitinib), Product Monograph.* AstraZeneca Canada Inc., 2021. https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/iressa-product-monograph-en.pdf.

Attal, Michel, Paul G Richardson, S Vincent Rajkumar, Jesus San-Miguel, Meral Beksac, Ivan Spicka, Xavier Leleu, Fredrik Schjesvold, Philippe Moreau, and Meletios A Dimopoulos. “Isatuximab plus Pomalidomide and Low-Dose Dexamethasone versus Pomalidomide and Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma (ICARIA-MM): A Randomised, Multicentre, Open-Label, Phase 3 Study.” *The Lancet* 394, no. 10214 (2019): 2096–2107.

Awad, Mark M, and Alice T Shaw. “ALK Inhibitors in Non–Small Cell Lung Cancer: Crizotinib and Beyond.” *Clinical Advances in Hematology & Oncology: H&O* 12, no. 7 (2014): 429.

Bahlis, Nizar J, Meletios A Dimopoulos, Darrell J White, Lotfi Benboubker, Gordon Cook, Merav Leiba, P Joy Ho, Kihyun Kim, Naoki Takezako, and Philippe Moreau. “Daratumumab plus Lenalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Extended Follow-up of POLLUX, a Randomized, Open-Label, Phase 3 Study.” *Leukemia* 34, no. 7 (2020): 1875–84.

Bayer Inc. “Health Canada Approves VITRAKVI® (Larotrectinib), the First Tumour Agnostic Cancer Treatment for Advanced Solid Tumours Harbouring an NTRK Gene Fusion Français.” *Newswire*, July 30, 2019. https://www.newswire.ca/news-releases/health-canada-approves-vitrakvi-r-larotrectinib-the-first-tumour-agnostic-cancer-treatment-for-advanced-solid-tumours-harbouring-an-ntrk-gene-fusion-880379419.html.

Beck, JT, P Neven, FJ Esteva, A Bardia, N Harbeck, S Hurvitz, J O’Shaughnessy, S Verma, B Lanoue, and J Alam. “Patient-Reported Outcomes with Ribociclib-Based Therapy in Hormone

Receptor-Positive, HER2-Negative Advanced Breast Cancer: Results from the Phase III MONALEESA-2,-3, and-7 Trials." *Amer Assoc Cancer Research* 79, no. 4 (2019): P6-18.

Beer, Tomasz M, Andrew J Armstrong, Dana E Rathkopf, Yohann Loriot, Cora N Sternberg, Celestia S Higano, Peter Iversen, Suman Bhattacharya, Joan Carles, and Simon Chowdhury. "Enzalutamide in Metastatic Prostate Cancer before Chemotherapy." *New England Journal of Medicine* 371, no. 5 (2014): 424–33.

Beer, Tomasz M, Andrew J Armstrong, Dana Rathkopf, Yohann Loriot, Cora N Sternberg, Celestia S Higano, Peter Iversen, Christopher P Evans, Choung-Soo Kim, and Go Kimura. "Enzalutamide in Men with Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study." *European Urology* 71, no. 2 (2017): 151–54.

Bhatia, Shailender, Scott S Tykodi, and John A Thompson. "Treatment of Metastatic Melanoma: An Overview." *Oncology* 23, no. 6 (2009): 488.

Blackhall, Fiona, Dong-Wan Kim, Benjamin Besse, Hiroshi Nokihara, Ji-Youn Han, Keith D Wilner, Arlene Reisman, Shrividya Iyer, Vera Hirsh, and Alice T Shaw. "Patient-Reported Outcomes and Quality of Life in PROFILE 1007: A Randomized Trial of Crizotinib Compared with Chemotherapy in Previously Treated Patients with ALK-Positive Advanced Non–Small-Cell Lung Cancer." *Journal of Thoracic Oncology* 9, no. 11 (2014): 1625–33.

Boehringer Ingelheim (Canada) Ltd. *Giotrif (afatinib), Product Monograph*. Boehringer Ingelheim (Canada) Ltd., 2019. https://www.boehringer-ingelheim.ca/sites/ca/files/documents/giotrifpmen.pdf.

Bonter, Katherine, and Rachael Manion. *Companion Diagnostics (CDx) Policy Discussion Paper: Issues, Gaps and Opportunities for Change in Canada.* BioCanRx, 2017. https://biocanrx.com/wp-content/uploads/2018/05/Companion-Diagnostics-CDx-Discussion-Paper-Jun-23-2017.pdf.

Brenner, Darren R, Hannah K Weir, Alain A Demers, Larry F Ellison, Cheryl Louzado, Amanda Shaw, Donna Turner, Ryan R Woods, and Leah M Smith. "Projected Estimates of Cancer in Canada in 2020." *Canadian Medical Association Journal* 192, no. 9 (2020): E199–205.

Brezden-Masley, Christine, Kelly E Fathers, Megan E Coombes, Behin Pourmirza, Cloris Xue, and Katarzyna J Jerzak. "A Population-Based Comparison of Treatment Patterns, Resource Utilization, and Costs by Cancer Stage for Ontario Patients with Hormone Receptor-Positive/HER2-Negative Breast Cancer." *Breast Cancer Research and Treatment* 185, no. 2 (2021): 507–15.

Bristol-Myers Squibb Canada Co. *OPDIVO, Nivolumab, Product Monograph*. Bristol-Myers Squibb Canada Co., 2021. https://pdf.hres.ca/dpd_pm/00062198.PDF.

Cancer Connect. “Understand ALK Inhibitor Treatment of ALK Positive Lung Cancer.” Accessed October 13, 2021 https://news.cancerconnect.com/lung-cancer/understand-alk-inhibitor-treatment-of-alk-positive-lung-cancer.

Camidge, D Ross, Hye Ryun Kim, Myung-Ju Ahn, James CH Yang, Ji-Youn Han, Maximilian J Hochmair, Ki Hyeong Lee, Angelo Delmonte, DW Kim, and F Griesinger. “Brigatinib versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial.” *Journal of Clinical Oncology*, 2020.

Canadian Agency for Drugs and Technologies in Health. *Anaplastic Lymphoma Kinase Inhibitors for Advanced Non-Small Cell Lung Carcinoma*. CADTH, 2019. https://www.cadth.ca/sites/default/files/pdf/he0017-alk-inhibitors-nsclc-report.pdf.

Canadian Agency for Drugs and Technologies in Health. *Final Recommendation for Apalutamide (Erleada) for Metastatic Castration-Sensitive Prostate Cancer*. CADTH, 2020. https://www.cadth.ca/sites/default/files/pcodr/Reviews2020/10200ApalutamidemCSPC_fnRec_ChairApproved_EarlyConv_22Apr2020_final.pdf.

Canadian Agency for Drugs and Technologies in Health. *Initial Recommendation for Osimertinib (Tagrisso) for Advanced or Metastatic Non-Small Cell Lung Cancer*. CADTH, 2019. https://www.cadth.ca/sites/default/files/pcodr/pcodr_osimertinib_tagrisso_nsclc_1stln_in_rec.pdf.

Canadian Agency for Drugs and Technologies in Health. “Isatuximab.” Accessed September 20, 2021. https://www.cadth.ca/isatuximab.

Canadian Agency for Drugs and Technologies in Health. “Isatuximab (Sarclisa) for Multiple Myeloma - Details.” Accessed September 20, 2021. https://www.cadth.ca/isatuximab-sarclisa-multiple-myeloma-details.

Canadian Agency for Drugs and Technologies in Health. *Procedures for the CADTH Pan-Canadian Oncology Drug Review*. CADTH, 2020. https://www.cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pcodr-procedures.pdf.

Canadian Agency for Drugs and Technologies in Health, *Pan-Canadian Oncology Drug Review Pre-Submission, Submission and Resubmission Guidelines.* CADTH, 2019. https://www.cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pcodr-presub_submission_resub-guidelines.pdf.

Canadian Agency for Drugs and Technologies in Health. “Reimbursement Review Reports.” Accessed September 25, 2021. https://www.cadth.ca/reimbursement-review-reports.

Canadian Cancer Society. “Cancer Statistics at a Glance.” Accessed September 25, 2021. https://action.cancer.ca/en/research/cancer-statistics/cancer-statistics-at-a-glance.

Canadian Cancer Society. “Hormone Therapy for Prostate Cancer.” Accessed September 25, 2021. https://cancer.ca/en/cancer-information/cancer-types/prostate/treatment/hormone-therapy.

Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, Statistics Canada and the Public Health Agency of Canada. Canadian Cancer Statistics 2021. Toronto: Canadian Cancer Society, 2021. Available at: cancer.ca/Canadian-Cancer-Statistics-2021-EN.

Canadian Cancer Society. “Stem Cell Transplant.” Accessed October 11, 2021. https://cancer.ca/en/treatments/treatment-types/stem-cell-transplant.

Canadian Cancer Society. "Survival Statistics for Breast Cancer.” Accessed September 26, 2021. https://cancer.ca/en/cancer-information/cancer-types/breast/prognosis-and-survival/survival-statistics.

Canadian Cancer Society. “Survival Statistics for Melanoma Skin Cancer.” Accessed October 7, 2021. https://cancer.ca/en/cancer-information/cancer-types/skin-melanoma/prognosis-and-survival/survival-statistics.

Canadian Cancer Society. “Survival Statistics for Prostate Cancer.” Accessed September 25, 2021. https://cancer.ca/en/cancer-information/cancer-types/prostate/prognosis-and-survival/survival-statistics.

Canadian Cancer Statistics Advisory Committee. *Canadian Cancer Statistics 2018: A 2018 Special Report on Cancer Incidence by Stage.* Toronto, ON: Canadian Cancer Society, 2018. https://cdn.cancer.ca/-/media/files/research/cancer-statistics/2018-statistics/canadian-cancer-statistics-2018-en.pdf.

———. *Canadian Cancer Statistics 2019.* Toronto: Canadian Cancer Society, 2019. https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2019-EN.pdf?la=en.

———. *Canadian Cancer Statistics: A 2020 Special Report on Lung Cancer.* Toronto: Canadian Cancer Society, 2020. https://cdn.cancer.ca/-/media/files/cancer-information/resources/publications/2020-canadian-cancer-statistics-special-report/2020-canadian-cancer-statistics-special-report-en.pdf?rev=15c66a0b05f5479e935b48035c70dca3&hash=3D51B0D0FB5C3F7E659F896D66495CE8&_ga=2.189265003.1710992694.1624651248-951630869.1614365710.

Cancer Care Ontario. “Chimeric Antigen Receptor (CAR) T-Cell Therapy Enrolment Process and Forms.” Accessed October 13, 2021. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/hematologic/car-t-cell-therapy-enrolment.

Canadian Partnership Against Cancer. *The 2018 Cancer System Performance Report.* Toronto: Canadian Partnership Against Cancer, 2018. https://s22457.pcdn.co/wp-content/uploads/2019/01/2018-Cancer-System-Performance-Report-EN.pdf.

Canadian Institute for Health Information. *Prescribed Drug Spending in Canada*. CIHI, 2020. https://www.cihi.ca/sites/default/files/document/prescribed-drug-spending-in-canada-2020-report-en.pdf.

Canadian Institute for Health Information. *National Health Expenditure Trends*. CIHI, 2020. https://www.cihi.ca/sites/default/files/document/nhex-trends-2020-narrative-report-en.pdf.

Canadian Task Force on Preventive Health Care. "Recommendations on Screening for Breast Cancer in Average-Risk Women Aged 40–74 Years." *Canadian Medical Association Journal,* 183, no. 17 (2011): 1991–2001.

CanREValue Collaboration Data Working Group. *Mapping Canadian Provincial Data Assets to Conduct Real-World Studies on Cancer Drugs: CanREValue Collaboration Data Working Group Interim Report 2020.* 2020. https://cc-arcc.ca/wp-content/uploads/2020/04/The-CanREValue-Data-WG-Interim-Report-Revision_Final_v1.pdf.

Cardoso, F, S Paluch-Shimon, E Senkus, G Curigliano, MS Aapro, F André, CH Barrios, J Bergh, GS Bhattacharyya, and L Biganzoli. "5th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 5)." *Annals of Oncology* 31, no. 12 (2020): 1623–49.

Caswell-Jin, Jennifer L, Sylvia K Plevritis, Lu Tian, Christopher J Cadham, Cong Xu, Natasha K Stout, George W Sledge, Jeanne S Mandelblatt, and Allison W Kurian. "Change in Survival in Metastatic Breast Cancer with Treatment Advances: Meta-Analysis and Systematic Review." *JNCI Cancer Spectrum* 2, no. 4 (2018): pky062.

Chan, Kelvin KW, Matthew C Cheung, Dean A Regier, Annette Hay, Alexander V Louie, Winson Y Cheung, Jean-Eric Tarride, Suji Udayakumar, and Nicole Mittmann. "The Past, Present, and Future of Economic Evaluations of Precision Medicine at the Committee for Economic Analyses of the Canadian Cancer Trials Group." *Current Oncology* 28, no. 5 (2021): 3649–58.

Chan, Kelvin, Seungree Nam, Bill Evans, Claire de Oliveira, Alexandra Chambers, Scott Gavura, Jeffrey Hoch, Rebecca E Mercer, Wei Fang Dai, and Jaclyn Beca. "Developing a Framework to Incorporate Real-World Evidence in Cancer Drug Funding Decisions: The Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) Collaboration." *BMJ Open* 10, no. 1 (2020): e032884.

Chang, Yoon Soo, Chang-Min Choi, and Jae Cheol Lee. "Mechanisms of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Resistance and Strategies to Overcome Resistance in Lung Adenocarcinoma." *Tuberculosis and Respiratory Diseases* 79, no. 4 (2016): 248–56.

Cheema, PK, S Gavura, M Migus, B Godman, L Yeung, and ME Trudeau. "International Variability in the Reimbursement of Cancer Drugs by Publically Funded Drug Programs." *Current Oncology* 19, no. 3 (2012): 165–76.

Chiou, Victoria L, and Mauricio Burotto. "Pseudoprogression and Immune-Related Response in Solid Tumors." *Journal of Clinical Oncology* 33, no. 31 (2015): 3541.

ClinicalTrials.gov. “LDK378 Versus Chemotherapy in ALK Rearranged (ALK Positive) Patients Previously Treated With Chemotherapy (Platinum Doublet) and Crizotinib.” May 2021. https://clinicaltrials.gov/ct2/show/results/NCT01828112?view=results.

Connor, Kris. “What Are CDK4/6 Inhibitors?” Accessed September 25, 2021. https://www.breastcancer.org/treatment/targeted_therapies/cdk46-inhibitors.

Cowan, Andrew J, Shasank R Chennupati, Yuan Xu, Ang Li, David A Garcia, Edward Libby, Catherine Fedorenko, Scott D Ramsey, Veena Shankaran, and Winson Y Cheung. “Comparison of Outcomes and Utilization of Therapy in Multiple Myeloma Patients in the USA and Alberta, Canada.” *Blood* 136 (2020): 20–21.

Dai, Wei Fang, Jaclyn M Beca, Ruth Croxford, Wanrudee Isaranawatchai, Ines B Menjak, Teresa M Petrella, Nicole Mittmann, et al. “Real-World Comparative Effectiveness of Second-Line Ipilimumab for Metastatic Melanoma: A Population-Based Cohort Study in Ontario, Canada.” *BMC Cancer* 20, no. 1 (April 2020): 304–304. https://doi.org/10.1186/s12885-020-06798-1.

DeMichele, Angela, Massimo Cristofanilli, Adam Brufsky, Xianchen Liu, Jack Mardekian, Lynn McRoy, Rachel M Layman, Birol Emir, Mylin A Torres, and Hope S Rugo. “Comparative Effectiveness of First-Line Palbociclib plus Letrozole versus Letrozole Alone for HR+/HER2− Metastatic Breast Cancer in US Real-World Clinical Practice.” *Breast Cancer Research* 23, no. 1 (2021): 1–10.

Dimopoulos, Meletios A, Philippe Moreau, Evangelos Terpos, María-Victoria Mateos, Sonja Zweegman, Gordon Cook, Michel Delforge, Roman Hájek, Fredrik Schjesvold, and Michele Cavo. “Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up.” *Annals of Oncology* 32, no. 3 (2021): 309–22.

Economist Intelligence Unit, The. *Assessing Innovation: How Health Technology Assessment Can Adapt to Improve the Evaluation of Novel Cancer Therapies in Europe.* The Economist Intelligence Unit, 2021. https://impact.economist.com/perspectives/healthcare/assessing-innovation-health-technology-assessment-europe.

Eggermont, Alexander MM, Christian U Blank, Mario Mandala, Georgina V Long, Victoria G Atkinson, Stéphane Dalle, Andrew M Haydon, Andrey Meshcheryakov, Adnan Khattak, and Matteo S Carlino. “Longer Follow-up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results from the EORTC 1325-MG/KEYNOTE-054 Trial,” *Journal of Clinical Oncology* 38, no. 33 (2020): 3925.

Eldridge, Lynne. “What Is Lung Cancer Recurrence?” Accessed October 12, 2021. https://www.verywellhealth.com/lung-cancer-recurrence-treatment-and-prognosis-2249264.

Ellison, Larry F. *The Cancer Survival Index: Measuring Progress in Cancer Survival to Help Evaluate Cancer Control Efforts in Canada.* Statistics Canada, 2021. https://www150.statcan.gc.ca/n1/en/pub/82-003-x/2021009/article/00002-eng.pdf?st=oXeBIDKD.

Falzone, Luca, Salvatore Salomone, and Massimo Libra. “Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium.” *Frontiers in Pharmacology* 9 (2018): 1300.

Fasching, PA, FJ Esteva, X Pivot, A Nusch, JT Beck, A Chan, A Pieris-Gunatilaka, Y Wang, B Lanoue, and D Chandiwana. “Patient-Reported Outcomes (PROs) in Advanced Breast Cancer (ABC) Treated with Ribociclib+ Fulvestrant: Results from MONALEESA-3.” *Annals of Oncology* 29 (2018): viii90.

Fizazi, K, N Shore, TL Tammela, et. al. *Supplement to: Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer*. *New England Journal of Medicine*, 2019. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1815671/suppl_file/nejmoa1815671_appendix.pdf.

Fizazi, Karim, Howard I Scher, Arturo Molina, Christopher J Logothetis, Kim N Chi, Robert J Jones, John N Staffurth, Scott North, Nicholas J Vogelzang, and Fred Saad. “Abiraterone Acetate for Treatment of Metastatic Castration-Resistant Prostate Cancer: Final Overall Survival Analysis of the COU-AA-301 Randomised, Double-Blind, Placebo-Controlled Phase 3 Study.” *The Lancet Oncology* 13, no. 10 (2012): 983–92.

Fizazi, Karim, Neal Shore, Teuvo L Tammela, Albertas Ulys, Egils Vjaters, Sergey Polyakov, Mindaugas Jievaltas, Murilo Luz, Boris Alekseev, and Iris Kuss. “Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer.” *New England Journal of Medicine* 380, no. 13 (2019): 1235–46.

———. “Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide.” *New England Journal of Medicine* 383, no. 11 (2020): 1040–49.

Gatopoulou, X, K Bardenheuer, S Van Hoorenbeeck, and A Kempel. “Treatment Patterns of Relapsed and Refractory Multiple Myeloma in Europe (EU-28).” *Value in Health* 19, no. 7 (2016): A715–16.

Gibson, Amanda JW, Adrian Box, Michelle L Dean, Anifat A Elegbede, Desiree Hao, Randeep Sangha, and D Gwyn Bebb. “Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors.” *JTO Clinical and Research Reports* 2, no. 4 (2021): 100157.

Godman, Brian, Anna Bucsics, Patricia Vella Bonanno, Wija Oortwijn, Celia C Rothe, Alessandra Ferrario, Simone Bosselli, Andrew Hill, Antony P Martin, and Steven Simoens. “Barriers for Access to New Medicines: Searching for the Balance between Rising Costs and Limited Budgets.” *Frontiers in Public Health* 6 (2018): 328.

Gotfrit, Joanna, John JW Shin, Ranjeeta Mallick, David J Stewart, and Paul Wheatley-Price. “Potential Life-Years Lost: The Impact of the Cancer Drug Regulatory and Funding Process in Canada.” *The Oncologist* 25, no. 1 (2020): e130.

Government of Canada. *Appendix A: Funding of Oncology Medicines in Canada, by Province and Delivery of Care.* Government of Canada, 2021. https://www.canada.ca/en/patented-medicine-prices-review/services/npduis/analytical-studies/formularies-part2-oncology-medicines.html#appendix-a.

Government of Canada. *Canada's Health Care System*. Government of Canada, 2019. https://www.canada.ca/en/health-canada/services/health-care-system/reports-publications/health-care-system/canada.html.

Government of Canada. *PMPRB Guidelines*. Government of Canada, 2021. https://www.canada.ca/en/patented-medicine-prices-review/services/legislation/about-guidelines/guidelines.html#app-e.

Government of Canada. Patented Medicine Prices Review Board, Consultations/Submissions Received. January 24, 2022. https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/notice-comment-references-comparator-countries/submissionsreceived.html.

Government of Canada, "Project Orbis." Accessed October 2021. https://www.canada.ca/en/health-canada/services/drugs-health-products/international-activities/project-orbis.html.

Government of Canada, "Notice of Compliance (NOC) Database." Accessed September 25, 2021. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/database.html.

Government of Canada. *Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making.* Health Products and Food Branch Notice, 2019. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html.

Government of Canada, "Patented Medicines Prices Review Board." Accessed September 30, 2021. https://www.canada.ca/en/patented-medicine-prices-review.html.

Gyawali, Bishal, Spencer Phillips Hey, and Aaron S Kesselheim. "A Comparison of Response Patterns for Progression-Free Survival and Overall Survival Following Treatment for Cancer With PD-1 Inhibitors: A Meta-Analysis of Correlation and Differences in Effect Sizes." *JAMA Network Open* 1, no. 2 (June 2018): e180416–e180416.

Han, Yanyan, Dandan Liu, and Lianhong Li. "PD-1/PD-L1 Pathway: Current Researches in Cancer." *American Journal of Cancer Research* 10, no. 3 (2020): 727.

Harbeck, N, S Iyer, N Turner, M Cristofanilli, J Ro, F André, S Loi, S Verma, H Iwata, and H Bhattacharyya. "Quality of Life with Palbociclib plus Fulvestrant in Previously Treated Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer: Patient-Reported Outcomes from the PALOMA-3 Trial." *Annals of Oncology* 27, no. 6 (2016): 1047–54.

Helwick, Caroline. *Overall Survival Benefit With Upfront Daratumumab Plus Lenalidomide/Dexamethasone for Newly Diagnosed Transplant-Ineligible Patients With Multiple Myeloma.* The ASCO post, 2021. https://ascopost.com/news/june-2021/overall-survival-benefit-with-upfront-daratumumab-plus-lenalidomidedexamethasone-for-newly-diagnosed-transplant-ineligible-patients-with-multiple-myeloma/.

Hematology Oncology Associates of Fredericksburg, “Stage III Melanoma.” Accessed October 18, 2021. https://www.hoafredericksburg.com/stage-iii-melanoma/.

Ho, Cheryl, Shilo Lefresne, Moishe Liberman, Anna McGuire, David Palma, Alexandra Pender, Stephanie Snow, Alain Tremblay, and Renelle Myers. “Lung Cancer in Canada.” *Journal of Thoracic Oncology* 14, no. 7 (2019): 1128–33.

Hoffmann-La Roche Limited. *Tarceva (Erlotinib), Product Monograph.* Hoffmann-La Roche Limited, 2018. https://www.rochecanada.com/PMs/Tarceva/Tarceva_PM_E.pdf.

Hortobagyi, Gabriel N, Salomon M Stemmer, Howard A Burris, Yoon-Sim Yap, Gabe S Sonke, S Paluch-Shimon, Mario Campone, Katarina Petrakova, Kimberly L Blackwell, and Eric P Winer. “Updated Results from MONALEESA-2, a Phase III Trial of First-Line Ribociclib plus Letrozole versus Placebo plus Letrozole in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer.” *Annals of Oncology* 29, no. 7 (2018): 1541–47.

Hotte, Sebastien J, Antonio Finelli, Kim N Chi, Christina M Canil, Neil Fleshner, Anil Kapoor, Michael Paul Kolinsky, Shawn Malone, Chris Morash, and Tamim Niazi. “Real-World Management of Advanced Prostate Cancer: A Canadian Comparison of Academic Specialists and Community-Based Prostate Cancer Physicians.” 2020.

Houghton, Katherine, Meletios A Dimopoulos, Peggy Lin, Sophie Guillonneau, Denise Bury, Michel Attal, Paul G Richardson, and Michel Delforge. “Health-Related Quality of Life in Patients with Relapsed/Refractory Multiple Myeloma Treated with Isatuximab plus Pomalidomide and Dexamethasone: ICARIA-MM Study.” 2019: 1850-1850.

Huff, Carol Ann, and William Matsui. “Multiple Myeloma Cancer Stem Cells.” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 26, no. 17 (2008): 2895.

Hungria, Vania, Meral Beksac, Katja C Weisel, Ajay K Nooka, Tamas Masszi, Ivan Spicka, Markus Munder, María-Victoria Mateos, Tomer M Mark, and Ming Qi. “Health-related Quality of Life Maintained over Time in Patients with Relapsed or Refractory Multiple Myeloma Treated with Daratumumab in Combination with Bortezomib and Dexamethasone: Results from the Phase III CASTOR Trial.” *British Journal of Haematology* 193, no. 3 (2021): 561–69.

Hurlbert, Marc. “2020 Melanoma Mortality Rates Decreasing Despite Ongoing Increase in Incidence.” Accessed October 18, 2021. https://www.curemelanoma.org/blog/article/2020-melanoma-mortality-rates-decreasing-despite-ongoing-increase-in-incidence-rates.

Hussain, Maha, Karim Fizazi, Fred Saad, Per Rathenborg, Neal Shore, Ubirajara Ferreira, Petro Ivashchenko, Eren Demirhan, Katharina Modelska, and De Phung. “Enzalutamide in Men with

Nonmetastatic, Castration-Resistant Prostate Cancer." *New England Journal of Medicine* 378, no. 26 (2018): 2465–74.

Innovative Medicines Canada. *Oncology Clinical Trials: Canada within the International Context*. Innovative Medicines Canada, 2021. http://innovativemedicines.ca/wp-content/uploads/2021/11/20211115_Research_Note_Oncology_CTs_CA_Int_EN_Final.pdf

Islami, Farhad, Elizabeth M Ward, Hyuna Sung, Kathleen A Cronin, Florence K L Tangka, Recinda L Sherman, Jingxuan Zhao, et al. "Annual Report to the Nation on the Status of Cancer, Part 1: National Cancer Statistics." *Journal of the National Cancer Institute*, no. djab131 (July 2021). https://doi.org/10.1093/jnci/djab131.

Jenei, Kristina, Stuart Peacock, Michael Burgess, and Craig Mitton. "Describing Sources of Uncertainty in Cancer Drug Formulary Priority Setting across Canada." *Current Oncology* 28, no. 4 (2021): 2708–19.

Kaufman, Peter A, Masakazu Toi, Patrick Neven, Joohyuk Sohn, Eva-Maria Grischke, Valerie Andre, Clemens Stoffregen, Sarah Shekarriz, Gregory L Price, and Gebra Cuyun Carter. "Health-related Quality of Life in MONARCH 2: Abemaciclib plus Fulvestrant in Hormone Receptor-positive, HER2-negative Advanced Breast Cancer after Endocrine Therapy." *The Oncologist* 25, no. 2 (2020): e243.

Kirby, M., C. Hirst, and E. D. Crawford. "Characterising the Castration-Resistant Prostate Cancer Population: A Systematic Review." *International Journal of Clinical Practice* 65, no. 11 (2011): 1180–92.

Knop, Stefan, Maria-Victoria Mateos, Meletios A Dimopoulos, Kenshi Suzuki, Andrzej Jakubowiak, Chantal Doyen, Paulo Lucio, Zsolt Nagy, Ganna Usenko, and Ludek Pour. "Health-Related Quality of Life in Patients with Newly Diagnosed Multiple Myeloma Ineligible for Stem Cell Transplantation: Results from the Randomized Phase III ALCYONE Trial." *BMC Cancer* 21, no. 1 (2021): 1–14.

Korstjens, Irene, and Albine Moser. "Series: Practical Guidance to Qualitative Research. Part 4: Trustworthiness and Publishing." *European Journal of General Practice* 24, no. 1 (2018): 120–24.

Kumar, Shaji K, Thierry Facon, Saad Z Usmani, Torben Plesner, Robert Z Orlowski, Cyrille Touzeau, Supratik Basu, Nizar J Bahlis, Hartmut Goldschmidt, and Michael E O'Dwyer. "Updated Analysis of Daratumumab plus Lenalidomide and Dexamethasone (D-Rd) versus Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): The Phase 3 Maia Study." *Blood* 136 (2020): 24–26.

Lackey, Adam, and Jessica S Donington. "Surgical Management of Lung Cancer." *Thieme Medical Publishers*, 30 (2013):133–40.

Larkin, James, Vanna Chiarion-Sileni, Rene Gonzalez, Jean-Jacques Grob, Piotr Rutkowski, Christopher D Lao, C Lance Cowey, Dirk Schadendorf, John Wagstaff, and Reinhard Dummer.

"Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma." *New England Journal of Medicine* 381, no. 16 (2019): 1535–46.

LeBlanc, Allana, Alain Demers, and Amanda Shaw. *Recent Trends in Prostate Cancer in Canada*. Statistics Canada, 2019. https://www150.statcan.gc.ca/n1/pub/82-003-x/2019004/article/00002-eng.htm.

Lee, Chee Khoon, Silvia Novello, Anna Rydén, A Templeton, K Rüdell, H Mann, S Ghiorghiu, and T Mok. "Patient-Reported Symptoms and Impact of Treatment with Osimertinib versus Chemotherapy in Advanced Non-Small-Cell Lung Cancer: The AURA3 Trial" (2018): 1853-1860.

Leigh, Jennifer, Daniel Qureshi, Ewa Sucha, Colleen Webber, Peter Tanuseputro, and Michael Ong. "Barriers to Access of Contemporary Treatment for Lethal Prostate Cancer: An Ontario Population-Based Study. 01_CAMO_2021 (Award Recipient)." University of Ottawa, 2021. https://www.mdpi.com/1718-7729/28/3/204/pdf.

Leighl, Natasha B, Nina Karaseva, Kazuhiko Nakagawa, Byoung-Chul Cho, Jhanelle E Gray, Tina Hovey, Andrew Walding, Anna Rydén, and Silvia Novello. "Patient-Reported Outcomes from FLAURA: Osimertinib versus Erlotinib or Gefitinib in Patients with EGFR-Mutated Advanced Non-Small-Cell Lung Cancer." *European Journal of Cancer* 125 (2020): 49–57.

Lexchin, Joel. "Health Canada's Use of Expedited Review Pathways and Therapeutic Innovation, 1995–2016: Cross-Sectional Analysis." *BMJ Open* 8, no. 8 (2018): e023605.

Li, Jinming, Xingfa Huo, Fuxing Zhao, Dengfeng Ren, Raees Ahmad, Xinyue Yuan, Feng Du, and Jiuda Zhao. "Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors with Survival in Patients with Hormone Receptor–Positive Metastatic Breast Cancer: A Systematic Review and Meta-Analysis." *JAMA Network Open* 3, no. 10 (2020): e2020312–e2020312.

Lung Cancer Canada. "Myths and Facts." Accessed October 17, 2021. https://www.lungcancercanada.ca/Lung-Cancer/Myths-and-Facts.aspx.

Luo, Jia, and Julie N Graff. "Impact of Enzalutamide on Patient-Related Outcomes in Metastatic Castration-Resistant Prostate Cancer: Current Perspectives." *Research and Reports in Urology* 8 (2016): 217.

Lussier Hoskyn, Sarah. "Explaining Public Reimbursement Delays for New Medicines for Canadian Patients." Accessed September 27, 2021. http://innovativemedicines.ca/wp-content/uploads/2020/06/20200630-CADTH-TTL-Poster-FINAL.pdf.

Lussier Hoskyn, Sarah, and Jason Field. "Early Signs of Negative Impacts for Patients of Health Canada Pharmaceutical Pricing Reforms." Accessed September 27, 2021. http://innovativemedicines.ca/wp-content/uploads/2020/06/20200630-CADTH-EarlySigns-FINAL.pdf.

Lye, Elizabeth, Louise Binder, and Martine Elias. *Improving Access to Innovative Cancer Therapies in Canada.* Lymphoma Canada, 2018. https://www.lymphoma.ca/wp-content/uploads/2018/03/lymphoma-canada-white-paper-web-reduced.pdf.

Mackenzie, Hugh. *The Canada Health Transfer Disconnect: An Aging Population, Rising Health Care Costs and a Shrinking Federal Role in Funding*. The Canadian Federation of Nurses Unions, 2015. https://nursesunions.ca/wp-content/uploads/2017/05/CFNU-Finance-Book-2015-final.pdf.

Majithia, N, SV Rajkumar, MQ Lacy, FK Buadi, A Dispenzieri, MA Gertz, SR Hayman, D Dingli, P Kapoor, and L Hwa. "Early Relapse Following Initial Therapy for Multiple Myeloma Predicts Poor Outcomes in the Era of Novel Agents." *Leukemia* 30, no. 11 (2016): 2208–13.

Mallick, Indranil. "The Role of T-Cells in Cancer." Accessed October 2021. https://www.verywellhealth.com/t-cells-2252171.

Mateos, Maria-Victoria. *Daratumumab Leads to PFS Improvement in Patients With Transplant-Ineligible Myeloma.* Targeted Oncology, 2019. https://www.targetedonc.com/view/krd-asct-improves-long-term-pfs-in-multiple-myeloma.

Mateos, Maria-Victoria, Michele Cavo, Joan Blade, Meletios A Dimopoulos, Kenshi Suzuki, Andrzej Jakubowiak, Stefan Knop, Chantal Doyen, Paulo Lucio, and Zsolt Nagy. "Overall Survival with Daratumumab, Bortezomib, Melphalan, and Prednisone in Newly Diagnosed Multiple Myeloma (ALCYONE): A Randomised, Open-Label, Phase 3 Trial." *The Lancet* 395, no. 10218 (2020): 132–41.

Mateos, Maria-Victoria, Pieter Sonneveld, Vania Hungria, Ajay K Nooka, Jane A Estell, Wolney Barreto, Paolo Corradini, Chang-Ki Min, Eva Medvedova, and Katja Weisel. "Daratumumab, Bortezomib, and Dexamethasone versus Bortezomib and Dexamethasone in Patients with Previously Treated Multiple Myeloma: Three-Year Follow-up of CASTOR." *Clinical Lymphoma Myeloma and Leukemia* 20, no. 8 (2020): 509–18.

Mavor, Meaghan E, Harriet Richardson, Qun Miao, Yuka Asai, and Timothy P Hanna. "Disparities in Diagnosis of Advanced Melanoma: A Population-Based Cohort Study." *Canadian Medical Association Journal Open* 6, no. 4 (2018): E502.

Mazieres, J, S Novello, J De Castro, MR Migliorino, Å Helland, R Dziadziuszko, F Griesinger, J Wolf, A Zeaiter, and A Cardona. "P1. 01-013 Patient-Reported Outcomes and Safety from the Phase III ALUR Study of Alectinib vs Chemotherapy in Pre-Treated ALK+ NSCLC." *Journal of Thoracic Oncology* 12, no. 11 (2017): S1897.

McDougall Scientific. *Clinical Trials in Canada: A Country Overview*. McDougall Scientific, 2020. https://www.mcdougallscientific.com/wp-content/uploads/2020-Clinical-Trials-in-Canada-an-Overview.pdf.

Medline Plus. "ALK Gene." Accessed October 17, 2021. https://medlineplus.gov/genetics/gene/alk/#conditions.

Melosky, B, S Banerji, N Blais, Q Chu, R Juergens, NB Leighl, G Liu, and P Cheema. “Canadian Consensus: A New Systemic Treatment Algorithm for Advanced EGFR-Mutated Non-Small-Cell Lung Cancer.” *Current Oncology* 27, no. 2 (2020): 146–55.

Melosky, B, P Cheema, J Agulnik, R Albadine, DG Bebb, N Blais, R Burkes, C Butts, PB Card, and AMY Chan. “Canadian Perspectives: Update on Inhibition of ALK-Positive Tumours in Advanced Non-Small-Cell Lung Cancer.” *Current Oncology* 25, no. 5 (2018): 317–28.

Merck Canada Inc. *Keytruda (Pembrolizumab), Product Monograph.* Merck Canada Inc., 2021. https://pdf.hres.ca/dpd_pm/00062141.PDF.

Mian, Hira S, Hsien Seow, Tanya M Wildes, C Tom Kouroukis, Gregory R Pond, Branavan Sivapathasundaram, and Jonathan Sussman. “Disparities in Treatment Patterns and Outcomes among Younger and Older Adults with Newly Diagnosed Multiple Myeloma: A Population-Based Study.” *Journal of Geriatric Oncology* 12, no. 4 (2021): 508–14.

Mikhael, Joseph, Nofisat Ismaila, Matthew C Cheung, Caitlin Costello, Madhav V Dhodapkar, Shaji Kumar, Martha Lacy, Brea Lipe, Richard F Little, and Anna Nikonova. “Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline.” *Journal of Clinical Oncology* 37, no. 14 (2019): 1228–63.

Mohideen, Shabna Iftikar, Piraveena Sabesan, Hussein EI-Khechen, and Julia Shen. *Identification of Gaps and Opportunities for Provincial Reimbursement of Oncology Companion Diagnostics in Canada.* Virtual ISPOR, 2021. https://www.pdci.ca/wp-content/uploads/2021/05/ISPOR_CDx_2021_PDCI.pdf.

Mok, Tony, DR Camidge, SM Gadgeel, R Rosell, R Dziadziuszko, D-W Kim, M Pérol, S-HI Ou, JS Ahn, and AT Shaw. “Updated Overall Survival and Final Progression-Free Survival Data for Patients with Treatment-Naive Advanced ALK-Positive Non-Small-Cell Lung Cancer in the ALEX Study.” *Annals of Oncology* 31, no. 8 (2020): 1056–64.

Mok, Tony S, Ying Cheng, Xiangdong Zhou, Ki Hyeong Lee, Kazuhiko Nakagawa, Seiji Niho, Alka Chawla, Rafael Rosell, Jesus Corral, and Maria Rita Migliorino. “Updated Overall Survival in a Randomized Study Comparing Dacomitinib with Gefitinib as First-Line Treatment in Patients with Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations.” *Drugs* 81, no. 2 (2021): 257–66.

Mok, Tony S, Yi-Long Wu, Myung-Ju Ahn, Marina C Garassino, Hye R Kim, Suresh S Ramalingam, Frances A Shepherd, Yong He, Hiroaki Akamatsu, and Willemijn SME Theelen. “Osimertinib or Platinum–Pemetrexed in EGFR T790M–Positive Lung Cancer.” *New England Journal of Medicine* 376, no. 7 (2017): 629–40.

Mok, TSK, G Scagliotti, TM Kim, L Crino, G Liu, C Gridelli, S Novello, K Kiura, A Bearz, and O Gautschi. “444PD Patient-Reported Outcomes (PROs) in ASCEND-5: A Randomized, Phase 3 Study of Ceritinib vs Chemotherapy (CT) in Patients (Pts) with Advanced Anaplastic Lymphoma Kinase Rearranged (ALK+) NSCLC Previously Treated with CT and Crizotinib (CRZ).” *Annals of Oncology* 27 (2016): ix142–43.

Morrell, Liz, Sarah Wordsworth, Howell Fu, Sian Rees, and Richard Barker. “Cancer Drug Funding Decisions in Scotland: Impact of New End-of-Life, Orphan and Ultra-Orphan Processes.” *BMC Health Services Research* 17, no. 1 (2017): 1–8.

Myeloma Canada, “Multiple Myeloma: Incidence and Prevalence in Canada.” Accessed October 2021. https://www.myelomacanada.ca/en/about-multiple-myeloma/what-is-myeloma-10/incidence-and-prevalence-in-canada.

National Cancer Institute at the National Institutes of Health, “Milestones in Cancer Research and Discovery.” Accessed September 28, 2021. https://www.cancer.gov/research/progress/250-years-milestones.

National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Onoclogy: Breast Cancer. Version 5.2020*. National Comprehensive Cancer Network, July 15, 2020. https://www2.tri-kobe.org/nccn/guideline/breast/english/breast.pdf.

National Cancer Institute. “Hormone Therapy for Prostate Cancer.” Accessed September 28, 2021. https://www.cancer.gov/types/prostate/prostate-hormone-therapy-fact-sheet.

National Cancer Institute. Surveillance, Epidemiology, and End Results Program, Recent Trends in Seer Age-Adjusted Incidence Rates, 2004-2018, Breast. Accessed September 2021. https://seer.cancer.gov/explorer/application.html?site=55&data_type=1&graph_type=2&compareBy=stage&chk_stage_104=104&chk_stage_105=105&chk_stage_106=106&chk_stage_107=107&hdn_rate_type=1&sex=3&race=1&age_range=1&advopt_precision=1&advopt_show_ci=on&advopt_display=2.

National Cancer Institute. Surveillance, Epidemiology, and End Results Program, Recent Trends in SEER Age-Adjusted Incidence Rates, 2004-2018, Melanoma of the Skin. Accessed September 2021. https://seer.cancer.gov/explorer/application.html?site=53&data_type=1&graph_type=2&compareBy=stage&chk_stage_104=104&chk_stage_105=105&chk_stage_106=106&chk_stage_107=107&hdn_rate_type=1&sex=1&race=1&age_range=1&advopt_precision=1&advopt_show_ci=on&advopt_display=2.

National Cancer Institute. Surveillance, Epidemiology, and End Results Program, Recent Trends in SEER Age-Adjusted Incidence Rates, 2004-2018, Myeloma. Accessed September 2021. https://seer.cancer.gov/explorer/application.html?site=89&data_type=1&graph_type=2&compareBy=stage&chk_stage_104=104&chk_stage_105=105&chk_stage_106=106&chk_stage_107=107&hdn_rate_type=1&sex=3&race=1&age_range=1&advopt_precision=1&advopt_show_ci=on&advopt_display=2.

National Cancer Institute, “What Is Cancer?” Accessed September 27, 2021. https://www.cancer.gov/about-cancer/understanding/what-is-cancer.

National Cancer Institute at the National Institutes of Health. *Advances in Breast Cancer Research*. National Cancer Institute, 2021. https://www.cancer.gov/types/breast/research.

National Institutes of Health. *About the All of Us Research Program: Precision Medicine Initiative.* National Institutes of Health, 2018. https://allofus.nih.gov/about.

National Institute for Health and Care Excellence. “Changes We’re Making to Health Technology Evaluation.” Accessed October 2021. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation.

National Institute for Health and Care Excellence. “NICE’s Processes of Technology Evaluation - Presenting a Case for Change.” Accessed October 2021. https://www.nice.org.uk/news/article/nice-s-processes-of-technology-evaluation-presenting-a-case-for-change.

National Institute for Health and Care Excellence. “Patient Access Schemes Liaison Unit.” Accessed October 2021. https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit.

Nooka, Ajay K, Jonathan L Kaufman, Craig C Hofmeister, Nisha S Joseph, Thomas L Heffner, Vikas A Gupta, Harold C Sullivan, Andrew S Neish, Madhav V Dhodapkar, and Sagar Lonial. “Daratumumab in Multiple Myeloma.” *Cancer* 125, no. 14 (2019): 2364–82.

Novartis Pharmaceuticals Canada Inc. *KISQALI (Ribociclib), Product Monograph*. Novartis Pharmaceuticals Canada Inc., 2020. https://pdf.hres.ca/dpd_pm/00059361.PDF.

Organisation for Economic Co-Operation and Development, The. Addressing Challenges in Access to Oncology Medicines. OECD, 2020. https://www.oecd.org/health/health-systems/addressing-challenges-in-access-to-oncology-medicines.htm.

O’Shaughnessy, Joyce. “Extending Survival with Chemotherapy in Metastatic Breast Cancer.” *The Oncologist* 10 (2005): 20–29.

pan-Canadian Oncology Drug Review. *Abiraterone Acetate (Zytiga) for Metastatic Castration-Resistant Prostate Cancer: Pan-Canadian Oncology Drug Review Final Clinical Guidance Report.* pCODR, 2013. https://www.cadth.ca/sites/default/files/pcodr/pcodr-zytiga-mcrpc-fn-cgr.pdf.

pan-Canadian Oncology Drug Review. *Final Clinical Guidance Report Apalutamide (Erleada) for Castration-Resistant Prostate Cancer.* pCODR, 2018. https://www.cadth.ca/sites/default/files/pcodr/pcodr_apalutamide_erleada_crpc_fn_cgr.pdf.

pan-Canadian Oncology Drug Review. *Final Recommendation for Alectinib (Alecensaro) for Metastatic Non-Small Cell Lung Cancer.* pCODR, 2018. https://www.cadth.ca/sites/default/files/pcodr/pcodr_alectinib_alecensaro_nsclc_2ln_fn_rec.pdf.

pan-Canadian Oncology Drug Review. *Final Recommendation for Ceritinib (Zykadia) Resubmission for Metastatic Non-Small Cell Lung Cancer.* pCODR, 2017. https://www.cadth.ca/sites/default/files/pcodr/pcodr_ceritinib_zykadia_nsclc_resub_fn_rec.pdf.

pan-Canadian Pharmaceutical Alliance. “Darzalex (Daratumumab).” Accessed September 29, 2021. https://www.pcpacanada.ca/negotiation/20979.

pan-Canadian Pharmaceutical Alliance. “Keytruda (Pembrolizumab): Non-Small Cell Lung Cancer.” Accessed September 29, 2021. https://www.pcpacanada.ca/negotiation/20927.

pan-Canadian Pharmaceutical Alliance. “Sarclisa (Isatuximab).” Accessed September 29, 2021. https://www.pcpacanada.ca/negotiations.

Papadimitrakopoulou, VA, TS Mok, J-Y Han, M-J Ahn, A Delmonte, SS Ramalingam, SW Kim, FA Shepherd, J Laskin, and Y He. “Osimertinib versus Platinum–Pemetrexed for Patients with EGFR T790M Advanced NSCLC and Progression on a Prior EGFR-Tyrosine Kinase Inhibitor: AURA3 Overall Survival Analysis.” *Annals of Oncology* 31, no. 11 (2020): 1536–44.

Patented Medicine Prices Review Board. *Alignment Among Public Formularies in Canada, Part 2: Oncology Medicines.* PMPRB, 2021. https://www.canada.ca/en/patented-medicine-prices-review/services/npduis/analytical-studies/formularies-part2-oncology-medicines.html#coverage.

Patented Medicine Prices Review Board, “New Patented Medicines Reported to PMPRB.” Last modified March 30, 2021. http://www.pmprb-cepmb.gc.ca/pmpMedicines.asp?x=611.

Pérol, Maurice, Nick Pavlakis, Evgeny Levchenko, Marco Platania, Julio Oliveira, Silvia Novello, Rita Chiari, Teresa Moran, Emmanuel Mitry, and Eveline Nüesch. “Patient-Reported Outcomes from the Randomized Phase III ALEX Study of Alectinib versus Crizotinib in Patients with ALK-Positive Non-Small-Cell Lung Cancer.” *Lung Cancer* 138 (2019): 79–87.

Perrot, Aurore, Thierry Facon, Torben Plesner, Saad Z Usmani, Shaji Kumar, Nizar J Bahlis, Cyrille Hulin, Robert Z Orlowski, Hareth Nahi, and Peter Mollee. “Health-Related Quality of Life in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma: Findings from the Phase III MAIA Trial.” *Journal of Clinical Oncology* 39, no. 3 (2021): 227–37.

Petrella, Teresa M, Caroline Robert, Erika Richtig, Wilson H Miller Jr, Giuseppe V Masucci, Euan Walpole, Celeste Lebbe, Neil Steven, Mark R Middleton, and Darcy Hille. “Patient-Reported Outcomes in KEYNOTE-006, a Randomised Study of Pembrolizumab versus Ipilimumab in Patients with Advanced Melanoma.” *European Journal of Cancer* 86 (2017): 115–24.

Plesner, Torben, Meletios A Dimopoulos, Albert Oriol, Jesus San-Miguel, Nizar J Bahlis, Neil Rabin, Kenshi Suzuki, Sung-Soo Yoon, Dina Ben-Yehuda, and Gordon Cook. “Health-related Quality of Life in Patients with Relapsed or Refractory Multiple Myeloma: Treatment with Daratumumab, Lenalidomide, and Dexamethasone in the Phase 3 POLLUX Trial.” *British Journal of Haematology*, 2021.

Rathkopf, Dana E, Matthew R Smith, Johann S De Bono, Christopher J Logothetis, Neal D Shore, Paul De Souza, Karim Fizazi, Peter FA Mulders, Paul Mainwaring, and John D Hainsworth. “Updated Interim Efficacy Analysis and Long-Term Safety of Abiraterone Acetate in

Metastatic Castration-Resistant Prostate Cancer Patients without Prior Chemotherapy (COU-AA-302).” *European Urology* 66, no. 5 (2014): 815–25.

Rausch, Matthew P, and Karen Taraszka Hastings. “Immune Checkpoint Inhibitors in the Treatment of Melanoma: From Basic Science to Clinical Application.” *Exon Publications*, 2017, 121–42.

Resilient Healthcare Coalition. *Building Resilient Healthcare Systems for a Post-Crisis Era*. Resilient Healthcare Coalition, 2021. https://www.resilienthealthcare.ca/.

ReThink Breast Cancer, “Breast Cancer Statistics in Canada.” Accessed September 2021. https://rethinkbreastcancer.com/breast-cancer-statistics-canada/.

Rendon, Ricardo A, Ross J Mason, Karim Marzouk, Antonio Finelli, Fred Saad, Alan So, Philippe D Violette, and Rodney H Breau. “Canadian Urological Association Recommendations on Prostate Cancer Screening and Early Diagnosis.” *Canadian Urological Association Journal* 11, no. 10 (2017): 298.

Richardson, Paul G, Aurore Perrot, Jesús F. San-Miguel, Meral Beksac, Ivan Spicka, Xavier Leleu, Fredrik Schjesvold, Philippe Moreau, Meletios A Dimopoulos, and Jeffrey SY Huang. “Updates from ICARIA-MM, a Phase 3 Study of Isatuximab (Isa) plus Pomalidomide and Low-Dose Dexamethasone (Pd) versus Pd in Relapsed and Refractory Multiple Myeloma (RRMM).,” 2021.

Robert, Caroline, Antoni Ribas, Jacob Schachter, Ana Arance, Jean-Jacques Grob, Laurent Mortier, Adil Daud, Matteo S Carlino, Catriona M McNeil, and Michal Lotem. “Pembrolizumab versus Ipilimumab in Advanced Melanoma (KEYNOTE-006): Post-Hoc 5-Year Results from an Open-Label, Multicentre, Randomised, Controlled, Phase 3 Study.” *The Lancet Oncology* 20, no. 9 (2019): 1239–51.

Roman, Viktoria, Alexandru Dobrescu, and SL Hoskyn. *How Would a Single-Payer Publicly Funded National Pharmacare Program Affect the Quality of Access to Medicines for Canadian Patients?* Innovative Medicines Canada, 2020. http://innovativemedicines.ca/resource/single-payer-publicly-funded-national-pharmacare-program-affect-quality-access-medicines-canadian-patients/.

Romano, Emanuela, Michael Scordo, Stephen W Dusza, Daniel G Coit, and Paul B Chapman. “Site and Timing of First Relapse in Stage III Melanoma Patients: Implications for Follow-up Guidelines.” *Journal of Clinical Oncology* 28, no. 18 (2010): 3042.

Rosell, Rafael, Enric Carcereny, Radj Gervais, Alain Vergnenegre, Bartomeu Massuti, Enriqueta Felip, Ramon Palmero, Ramon Garcia-Gomez, Cinta Pallares, and Jose Miguel Sanchez. “Erlotinib versus Standard Chemotherapy as First-Line Treatment for European Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer (EURTAC): A Multicentre, Open-Label, Randomised Phase 3 Trial.” *The Lancet Oncology* 13, no. 3 (2012): 239–46.

Rugo, HS, V Diéras, KA Gelmon, RS Finn, DJ Slamon, M Martin, P Neven, Y Shparyk, A Mori, and DR Lu. “Impact of Palbociclib plus Letrozole on Patient-Reported Health-Related Quality of Life: Results from the PALOMA-2 Trial.” *Annals of Oncology* 29, no. 4 (2018): 888–94.

Rugo, HS, RS Finn, V Diéras, J Ettl, O Lipatov, AA Joy, N Harbeck, A Castrellon, S Iyer, and DR Lu. “Palbociclib plus Letrozole as First-Line Therapy in Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer with Extended Follow-Up.” *Breast Cancer Research and Treatment* 174, no. 3 (2019): 719–29.

Ryan, Charles J, Matthew R Smith, Karim Fizazi, Fred Saad, Peter F A Mulders, Cora N Sternberg, Kurt Miller, et al. “Abiraterone Acetate plus Prednisone versus Placebo plus Prednisone in Chemotherapy-Naive Men with Metastatic Castration-Resistant Prostate Cancer (COU-AA-302): Final Overall Survival Analysis of a Randomised, Double-Blind, Placebo-Controlled Phase 3 Study.” *The Lancet Oncology* 16, no. 2 (February 2015): 152–60. https://doi.org/10.1016/S1470-2045(14)71205-7.

Saad, Fred, Armen Aprikian, Antonio Finelli, Neil E Fleshner, Martin Gleave, Anil Kapoor, Tamim Niazi, Scott A North, Frederic Pouliot, and Ricardo A Rendon. “2021 Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) Guideline: Management of Castration-Resistant Prostate Cancer (CRPC).” *Canadian Urological Association Journal* 15, no. 2 (2021): E81.

Saad, Fred, and Sebastien J Hotte. “Guidelines for the Management of Castrate-Resistant Prostate Cancer.” *Canadian Urological Association Journal* 4, no. 6 (2010): 380.

Salek, Sam, Sarah Lussier Hoskyn, Jeffrey Roy Johns, Nicola Allen, and Chander Sehgal. “Factors Influencing Delays in Patient Access to New Medicines in Canada: A Retrospective Study of Reimbursement Processes in Public Drug Plans.” *Frontiers in Pharmacology* 10 (2019): 196.

Salek, Sam M, Sarah Lussier Hoskyn, Jeffrey Johns, Nicola Allen, and Chander Sehgal. “Pan-Canadian Pharmaceutical Alliance (PCPA): Timelines Analysis and Policy Implications.” *Frontiers in Pharmacology* 9 (2019): 1578.

Schadendorf, Dirk, James MG Larkin, Jedd D Wolchok, Vanna Chiarion-Sileni, Fiona Taylor, Rachael Lawrance, Alejandro Moreno-Koehler, Jennifer Lord-Bessen, Jasmine I Rizzo, and Andriy Moshyk. “Patient-Reported Quality of Life (QoL) of Advanced Melanoma Patients in a Phase 3 Study of Nivolumab (NIVO) with or without Ipilimumab (IPI) versus IPI: CheckMate 067 4-Year Data.,” 2019.

Scher, Howard I, Karim Fizazi, Fred Saad, Mary-Ellen Taplin, Cora N Sternberg, Kurt Miller, Ronald De Wit, Peter Mulders, Kim N Chi, and Neal D Shore. “Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy.” *New England Journal of Medicine* 367, no. 13 (2012): 1187–97.

Scitable by Nature Education. “CDK.” Last modified in 2014. https://www.nature.com/scitable/topicpage/cdk-14046166/.

Seth, Rahul, Hans Messersmith, Varinder Kaur, John M Kirkwood, Ragini Kudchadkar, Jennifer Leigh McQuade, Anthony Provenzano, Umang Swami, Jeffrey Weber, and Krishna C Alluri. “Systemic Therapy for Melanoma: ASCO Guideline.” *Journal of Clinical Oncology* 38, no. 33 (2020): 3947–70.

Seung, S J, M Hurry, R N Walton, and W K Evans. “Real-World Treatment Patterns and Survival in Stage IV Non-Small-Cell Lung Cancer in Canada.” *Current Oncology* 27, no. 4 (August 2020): e361–67. https://doi.org/10.3747/co.27.6049.

Seymour, Lesley, Jan Bogaerts, Andrea Perrone, Robert Ford, Lawrence H Schwartz, Sumithra Mandrekar, Nancy U Lin, et al. “IRECIST: Guidelines for Response Criteria for Use in Trials Testing Immunotherapeutics.” *The Lancet. Oncology* 18, no. 3 (2017): e143–52. https://doi.org/10.1016/S1470-2045(17)30074-8.

Shah, Harsh, and Ulka Vaishampayan. “Therapy of Advanced Prostate Cancer: Targeting the Androgen Receptor Axis in Earlier Lines of Treatment.” *Targeted Oncology* 13, no. 6 (2018): 679–89.

Shah, Mirat, Maria Raquel Nunes, and Vered Stearns. “CDK4/6 Inhibitors: Game Changers in the Management of Hormone Receptor–Positive Advanced Breast Cancer?” *Oncology* 32, no. 5 (2018): 216.

Shields, Margot, and Kathryn Wilkins. *An Update on Mammography Use in Canad*a. Statistics Canada, 2009. https://www150.statcan.gc.ca/n1/en/pub/82-003-x/2009003/article/10873-eng.pdf?st=FhKGTDe-.

Slamon, DJ, P Neven, S Chia, G Jerusalem, M De Laurentiis, S Im, K Petrakova, G Valeria Bianchi, M Martín, and A Nusch. “Ribociclib plus Fulvestrant for Postmenopausal Women with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer in the Phase III Randomized MONALEESA-3 Trial: Updated Overall Survival.” *Annals of Oncology*, 2021.

Sledge, George W, Masakazu Toi, Patrick Neven, Joohyuk Sohn, Kenichi Inoue, Xavier Pivot, Olga Burdaeva, Meena Okera, Norikazu Masuda, and Peter A Kaufman. “The Effect of Abemaciclib plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2: A Randomized Clinical Trial.” *JAMA Oncology* 6, no. 1 (2020): 116–24.

Slocomb, Ted, Michael Werner, Ted Haack, Satish Valluri, and Beth Rader. *New Payment And Financing Models For Curative Regenerative Medicines*. In Vivo, 2017. https://alliancerm.org/wp-content/uploads/2018/05/ARM_Curative_Regenerative_IV1707_LRS.pdf.

Small, Eric Jay, Fred Saad, Simon Chowdhury, Stephane Oudard, Boris A Hadaschik, Julie N Graff, David Olmos, Paul N Mainwaring, Ji Youl Lee, and Hiroji Uemura. “Final Survival Results from SPARTAN, a Phase III Study of Apalutamide (APA) versus Placebo (PBO) in Patients (Pts) with Nonmetastatic Castration-Resistant Prostate Cancer (NmCRPC).” 2020.

Smith, Matthew R, Fred Saad, Simon Chowdhury, Stéphane Oudard, Boris A Hadaschik, Julie N Graff, David Olmos, Paul N Mainwaring, Ji Youl Lee, and Hiroji Uemura. “Apalutamide Treatment and Metastasis-Free Survival in Prostate Cancer.” *New England Journal of Medicine* 378, no. 15 (2018): 1408–18.

So, Alan I, Kim N Chi, Brita Danielson, Neil E Fleshner, Anil Kapoor, Tamim Niazi, Frederic Pouliot, Ricardo A Rendon, Bobby Shayegan, and Srikala Sridhar. “Canadian Urological Association-Canadian Urologic Oncology Group Guideline on Metastatic Castration-Naive and Castration-Sensitive Prostate Cancer.” *Canadian Urological Association Journal* 14, no. 2 (2020): 17.

Solomon, Benjamin J, Dong-Wan Kim, Yi-Long Wu, Kazuhiko Nakagawa, Tarek Mekhail, Enriqueta Felip, Federico Cappuzzo, Jolanda Paolini, Tiziana Usari, and Yiyun Tang. “Final Overall Survival Analysis from a Study Comparing First-Line Crizotinib versus Chemotherapy in ALK-Mutation-Positive Non-Small-Cell Lung Cancer.” *J Clin Oncol* 36, no. 22 (2018): 2251–58.

Sorin, M, EL Franco, and A Quesnel-Vallée. “Inter-and Intraprovincial Inequities in Public Coverage of Cancer Drug Programs across Canada: A Plea for the Establishment of a Pan-Canadian Pharmacare Program.” *Current Oncology* 26, no. 4 (2019): 266–69.

Southall, Jennifer. “Ipilimumab-Pembrolizumab Combination Appears Promising for Advanced Melanoma.” *Healio*, Accessed October 2021. https://www.healio.com/news/hematology-oncology/20200603/ipilimumabpembrolizumab-combination-appears-promising-for-advanced-melanoma.

Speer, Sean, and Ian Lee. *Toward a More Fair Medicare: Why Canadian Health Care Isn’t Equitable or Sustainable and How It Can Be*. Macdonald-Laurier Institute, 2016. https://www.macdonaldlaurier.ca/files/pdf/MLICanadasHealthcareCrisisSeries6_f_web.pdf.

Srikanthan, A, N Penner, KKW Chan, M Sabharwal, and A Grill. “Understanding the Reasons for Provincial Discordance in Cancer Drug Funding—a Survey of Policymakers.” *Current Oncology* 25, no. 4 (2018): 257–61.

Srivastava, Aashish, and S Bruce Thomson. “Framework Analysis: A Qualitative Methodology for Applied Policy Research,” 2009.

Statistics Canada. *Cancer Survival Statistics, 2020 Update*. Statistics Canada, 2020. https://www150.statcan.gc.ca/n1/en/daily-quotidien/201127/dq201127b-eng.pdf?st=K4oooA9F.

Statistics Canada. *Table: 13-10-0394-01: Leading Causes of Death, Total Population, by Age Grou*p. Accessed September 2021. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039401.

Statistics Canada. *Table 13-10-0761-01: Number and Rates of New Primary Cancer Cases, by Stage at Diagnosis, Selected Cancer Type, Age Group and Sex*. Accessed September 2021. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310076101.

Sternberg, Cora N, Karim Fizazi, Fred Saad, Neal D Shore, Ugo De Giorgi, David F Penson, Ubirajara Ferreira, Eleni Efstathiou, Katarzyna Madziarska, and Michael P Kolinsky. “Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer.” *New England Journal of Medicine* 382, no. 23 (2020): 2197–2206.

Stock-Martineau, Sophie, Katie Laurie, Mathieu McKinnon, Tinghua Zhang, and Paul Wheatley-Price. “Evolution of Systemic Treatment Uptake and Survival in Advanced Non-Small Cell Lung Cancer.” *Current Oncology* 28, no. 1 (2021): 60–68.

Terris, MK. “Metastatic and Advanced Prostate Cancer.” Medscape, 2020. https://emedicine.medscape.com/article/454114-overview#a2.

The Public Health Agency of Canada. *Economic Burden of Illness in Canada, 2010*. PHAC, 2017. https://www.canada.ca/en/public-health/services/publications/science-research-data/economic-burden-illness-canada-2010.html.

Tikkanen, R, R Osborn, E Mossialos, A Djordjevic, and GA Wharton. *International Health Care System Profiles: Canada.* The Commonwealth Fund, 2020. https://www.commonwealthfund.org/international-health-policy-center/countries/canada.

Tombal, Bertrand, Fred Saad, David Penson, Maha Hussain, Cora N Sternberg, Robert Morlock, Krishnan Ramaswamy, Cristina Ivanescu, and Gerhardt Attard. “Patient-Reported Outcomes Following Enzalutamide or Placebo in Men with Non-Metastatic, Castration-Resistant Prostate Cancer (PROSPER): A Multicentre, Randomised, Double-Blind, Phase 3 Trial.” *The Lancet Oncology* 20, no. 4 (2019): 556–69.

Turner, Nicholas C, Dennis J Slamon, Jungsil Ro, Igor Bondarenko, Seock-Ah Im, Norikazu Masuda, Marco Colleoni, Angela DeMichele, Sherene Loi, and Sunil Verma. “Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer.” *New England Journal of Medicine* 379, no. 20 (2018): 1926–36.

Uramoto, Hidetaka, and Fumihiro Tanaka. “Recurrence after Surgery in Patients with NSCLC.” Translational lung cancer research, August 2014. Accessed September 30, 2021. https://tlcr.amegroups.com/article/view/2053/3470.

Usmani, Saad Z, Hareth Nahi, Torben Plesner, Brendan M Weiss, Nizar J Bahlis, Andrew Belch, Peter M Voorhees, Jacob P Laubach, Niels WCJ van de Donk, and Tahamtan Ahmadi. “Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma: Final Results from the Phase 2 GEN501 and SIRIUS Trials.” *The Lancet Haematology* 7, no. 6 (2020): e447–55.

Villaruz, Liza C, and Mark A Socinski. “The Clinical Viewpoint: Definitions, Limitations of RECIST, Practical Considerations of Measurement,” 2013.

Wakelee, Heather, Karen Kelly, and Martin J Edelman. “50 Years of Progress in the Systemic Therapy of Non–Small Cell Lung Cancer.” *American Society of Clinical Oncology Educational Book* 34, no. 1 (2014): 177–89.

Weaver, CH. “In Depth Overview of Tyrosine Kinase Inhibitor Treatment of EGFR + Lung Cancer.” *Cancer Connect*, Accessed September 2021. https://news.cancerconnect.com/lung-cancer/in-depth-overview-of-tyrosine-kinase-inhibitor-treatment-of-egfr-lung-cancer.

Wolchok, Jedd D, Vanna Chiarion-Sileni, Rene Gonzalez, Jean-Jacques Grob, Piotr Rutkowski, Christopher D Lao, Charles Lance Cowey, Dirk Schadendorf, John Wagstaff, and Reinhard Dummer. “CheckMate 067: 6.5-Year Outcomes in Patients (Pts) with Advanced Melanoma.” 2021.

Woon, Dixon T S, Thenappan Chandrasekar, Lorne Aaron, Naveen S Basappa, Kim N Chi, Henry J Conter, Geoffrey Gotto, et al. “Disparity in Public Funding of Therapies for Metastatic Castrate-Resistant Prostate Cancer across Canadian Provinces.” *Canadian Urological Association Journal* 12, no. 10 (October 2018): 328–36. https://doi.org/10.5489/cuaj.5378.

World Health Organization, “Cancer.” Accessed September 27, 2021. https://www.who.int/news-room/fact-sheets/detail/cancer.

World Cancer Research Fund. “Worldwide Cancer Data.” Accessed September 27, 2021. https://www.wcrf.org/dietandcancer/worldwide-cancer-data/.

Yang, James Chih-Hsin, Yi-Long Wu, Martin Schuler, Martin Sebastian, Sanjay Popat, Nobuyuki Yamamoto, Caicun Zhou, Cheng-Ping Hu, Kenneth O’Byrne, and Jifeng Feng. “Afatinib versus Cisplatin-Based Chemotherapy for EGFR Mutation-Positive Lung Adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of Overall Survival Data from Two Randomised, Phase 3 Trials.” *The Lancet Oncology* 16, no. 2 (2015): 141–51.

Yang, JC, Vera Hirsh, Martin Schuler, Nobuyuki Yamamoto, Kenneth J O’Byrne, Tony Shu-kam Mok, Victoria Zazulina, Mehdi Shahidi, Juliane Lungershausen, and Dan Massey. “Symptom Control and Quality of Life in LUX-Lung 3: A Phase III Study of Afatinib or Cisplatin/Pemetrexed in Patients with Advanced Lung Adenocarcinoma with EGFR Mutations.” *J Clin Oncol* 31, no. 27 (2013): 3342–50.

Yi Lam, So, Wing Sze Liu, and Chung-Shien Lee. “A Review of CDK4/6 Inhibitors.” *US Pharm.* 2020;45(5)(Specialty&Oncology suppl):3-8.

Younis, T, and C Skedgel. “Timeliness of the Oncology Drug Review Process for Public Funding in Canada.” *Current Oncology* 24, no. 5 (2017): 279–81.

Yu Ko, Wellam F, John L Oliffe, and Joan L Bottorff. “Prostate Cancer Treatment and Work: A Scoping Review.” *American Journal of Men’s Health* 14, no. 6 (2020): 1557988320979257.

Yuasa, Akira, Naohiro Yonemoto, Michael LoPresti, and Shunya Ikeda. “Use of Productivity Loss/Gain in Cost-Effectiveness Analyses for Drugs: A Systematic Review.” *Pharmacoeconomics* 39, no. 1 (2021): 81–97.

20Sense. *Outcomes-Based Agreements in Canada, The 20Sense Report.* 20Sense, 2021. https://static1.squarespace.com/static/58fd16af1b631b1afffae9e0/t/60816e2a2980e13e08de1451/1619095083095/Issue_16_EN_The_20Sense_Report.pdf.

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