

CADTH Health Technology Review

Prostate-Specific Membrane Antigen PET-CT Imaging for the Staging of Prostate Cancer in Canada

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Key Messages

- Health Canada approved the first prostate-specific membrane antigen (PSMA)-PET radiopharmaceutical in October 2022 for the staging of PSMA-positive lesions in those with prostate cancer. Health Canada also approved a lutetium-177 PSMA-617 therapy for patients with advanced PSMA-positive metastatic castration-resistant prostate cancer in September 2022, a therapy for which patient eligibility is identified with a gallium-68 PSMA-PET exam.
- With 57 PET-CT units in 9 provinces, access to PET-CT may be limited by the health care system's capacity to conduct these exams due to wait lists, competing clinical priorities, and staff shortages.
- It is anticipated that the public funding of PSMA-PET across Canada will increase existing demand for PET-CT by a minimum of 23%.
- The provision of PSMA-PET would occur within the context of managing competing new demands for this service that could double existing exam volume.
- Sufficient staffing is needed to ensure sustainable operation and development of PET-CT services, supported by investment in the workforce through education and training opportunities.
- There is potential to increase the hours of operation of PET-CT units in many facilities, with consideration to the many dependencies, including staffing and the fact that the operating times of PET-CT units are closely tied to the operating times of the cyclotrons that supply the radiopharmaceuticals used in PET-CT exams.
- The upfront capital and ongoing operational costs of PET-CT, radiopharmaceutical products, and equipment may act as barriers to the further adoption of this technology.
- A combination of both generator-produced and cyclotron-produced PSMA-PET radiopharmaceuticals will likely be needed to meet the geography of Canadian jurisdictions and to secure a reliable and resilient supply chain.

Context

Prostate cancer is the most common cancer among men, except for skin cancer.¹ One in 9 men living in Canada will be diagnosed with prostate cancer over their lifetimes.² The estimated number of new cases in men in Canada for 2022 is almost 25,000.¹ Around 60% of cases are diagnosed in men aged 65 years or older. The average age at the time of diagnosis is 66 years.³

Around 90% of prostate cancers overexpress prostate-specific membrane antigen (PSMA) — a protein that is found in high levels on the surface of prostate cancer cells.⁴ Expression is low in normal prostate tissue but increases in both localized and metastatic prostate cancer. PSMA expression correlates directly with tumour grade and is significantly upregulated in castrate-resistant prostate cancer.⁵ PSMA is also expressed in the blood vessels of many solid tumours.⁵

Both gallium-68 (68Ga) and fluorine-18 (18F)-labelled PSMA-specific radiopharmaceuticals are clinically used to stage prostate cancer tumour cells with PET-CT.⁶ A growing body of evidence⁶⁻⁹ suggests that PSMA-directed PET (PSMA-PET) radiopharmaceuticals can determine different stages of cancer in the prostate with more specificity than conventional

imaging such as CT, MRI, and bone scan,¹⁰ and can detect spread to pelvic nodal or distant metastatic sites.¹¹

Accurate staging of prostate cancer before primary therapy can help guide treatment decisions, such as choices between surgery and radiation therapy, use of adjuvant hormone therapy, and design of therapeutic approaches, such as targeting suspicious lymph nodes for node dissection or radiotherapy. Additionally, in the setting of biochemical failure after primary treatment, accurate restaging can identify those with recurrence limited to the prostate, prostate bed, and/or pelvic lymph nodes where salvage therapies may still be potentially curative and where integration of local salvage surgery, radiotherapy, or other ablative techniques may avoid the need for lifelong palliative androgen deprivation therapy. In selected patients with limited metastatic disease (i.e., oligometastases) lesion-directed therapy with surgery or radiotherapy as an androgen deprivation deferral strategy or as an adjunct to hormone therapy has shown promise in clinical trials and is under ongoing investigation.¹² Imaging with PSMA-PET may also reduce adverse events by preventing unnecessary treatment and ultimately improve the quality of life and overall survival of patients.¹¹

Gallium-68 PSMA may also play a role in selecting patients who may benefit from targeted systemic radionuclide therapy; for example, Lutetium-177 PSMA-617,¹³ which was approved by Health Canada in September 2022.¹⁴ This therapy delivers beta-particle radiation to PSMA-expressing cells and the surrounding microenvironment and is intended to extend progression-free survival and overall survival when added to the standard of care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer.¹³ To qualify for this therapy, patients are required to undertake a 68Ga PSMA-PET exam.¹³ As well, therapy response can be evaluated with 68Ga PSMA-PET. Thus, there are several potential diagnostic and therapeutic applications of PET-PSMA radiopharmaceuticals for the selection and follow-up of patients after targeted radiotherapy procedures.⁵

With Health Canada's approval of the first PSMA radiopharmaceutical in Canada in October 2022,¹⁵ an assessment of the infrastructural readiness of the health care system can support the optimal delivery of patient care. The availability of PET-CT may be limited by the health care system's capacity to conduct these exams, due to factors such as high capital and operational costs of PET-CT equipment,¹⁶ challenges with accessibility, wait times, and competing clinical priorities.¹⁷ The production and delivery of the PSMA radiopharmaceuticals and the availability of cyclotrons or generators may act as a bottleneck to the availability of this imaging modality, and may further limit patient access to this important diagnostic tool.

Objective

This report summarizes information on the infrastructural readiness of Canada's health care system for the adoption of PSMA-PET for the staging and restaging of prostate cancer. It is intended to help inform decisions about the potential adoption of this novel technology into clinical practice.

About This Document

This document summarizes information mainly identified through the 2019–2020 iteration of the Canadian Medical Imaging Inventory (CMII)¹⁷ and a limited literature search. The methods for this analysis are described in the 2019–2020 CMII report and are based on a web survey that was distributed to 455 sites with MRI, PET-CT, CT, single-photon emission CT (SPECT), and SPECT-CT across Canada. As well, data from other CMII-related reports were used to inform aspects of this discussion of the infrastructural readiness of Canada's health care system, particularly a survey drawing on the opinions of 18 PET-CT experts in all provinces with PET-CT capacity.¹⁸ The main CMII Service reports that informed the findings of this report are linked here:

- [The Canadian Medical Imaging Inventory 2019–2020](#)
- [The Future of PET-CT in Canada](#)
- [The Implementation Considerations of PET-CT](#)
- [PET-CT Exam Volumes: Comparison of Canada With Other Countries.](#)

Results

The approval of PSMA-PET in Canada for the staging and restaging of prostate cancer will have numerous implications for the health care system. To ensure health system infrastructural readiness, consideration to the current inventory of PET-CT units across Canada, the anticipated future uses of PET-CT, the production and distribution of PSMA radiopharmaceuticals, access to equipment, human resource capacity, costs, and regulatory requirements may be beneficial. Each of these considerations are discussed here with regard to some of the implications for the delivery of optimal patient care within the Canadian health care system.

PET-CT in Canada

PET-CT has become an indispensable imaging modality – primarily for cancer, but also for neurology, cardiology, and some infectious diseases. The ongoing adoption of PET-CT is largely due to its continued expansion in new clinical areas.¹⁹

The provision of PET-CT for the detection of PSMA would occur within the context of other current competing demands for the service and with consideration to trends over time and to the anticipated future growth of PET-CT – which will be influenced by numerous factors, including an increasing aging population. In addition, technological innovations with PET-CT that enhance image quality, as well as the regulatory approval of other novel radiopharmaceuticals, may further expand the uses of PET-CT beyond traditional diagnostic capabilities.¹⁸ It is anticipated that continued technical improvements in PET-CT units may offset some of the growing demand through increased patient throughput and decreased exam times.¹⁸

Number of Units

Canada ranks 21st in PET-CT units per million population among 32 other Organisation for Economic Co-operation and Development (OECD) countries.¹⁷ Currently, there are 57 PET-CT units in Canada (including 7 PET-CT units that operate in the private sector), representing 1.5 units per million population. Prince Edward Island and the territories do not have PET-CT units and people living in those places are sent to provinces with PET-CT capacity for these scans.²⁰ [Figure 1](#) shows the geographical distribution of PET-CT units across Canada, mapped to the level of city or town, with the circle diameter proportional to the number of units. Counts for all sites within a city were aggregated. [Table 3](#) in [Appendix 1](#) provides details on the number of units per province.¹⁷

Access to PET-CT

Not all provinces and territories have access to PET-CT; for those that do, access is mostly limited to densely populated urban centres. Travel burden may be a barrier for some patients, particularly for those who are too sick to travel, have mobility limitations, or are unwilling or unable to travel long distances.²¹ Populations in rural and remote communities incur out-of-pocket travel expenses when travelling to urban centres for imaging.²² Costs are also incurred by patients and their caregivers through work absenteeism and other incidentals, and may present a disincentive to seeking a diagnosis.¹⁹ A PET-CT expert noted anecdotally that even in sites with PET-CT units, for investigational radiopharmaceuticals like PSMA-PET, imaging may be limited to a subset of centres where trials are conducted.

Health care systems around the world are increasingly using mobile imaging equipment as a means of expanding imaging capacity to underserved locations. The extension of PET-CT to these settings – such as rural and remote communities, and long-term care facilities – through mobile imaging may help to reduce disparities in the delivery of health care.²³ There are currently no publicly funded mobile PET-CT units operating between communities in Canada.¹⁷

Volume of Exams

The volume of publicly funded PET-CT exams across Canada in the fiscal year ending March 31, 2020, was 125,775, which represents 3.3 exams per thousand population.¹⁷ The average number of exams per unit was 2,206. According to a framework developed by the UK's Department of Health, this is in keeping with the annual patient throughput that is considered reasonable for a PET-CT unit (i.e., between 2,000 and 2,500 exams).²⁴

It has been anecdotally reported that the addition of multiparametric MRI for castration-resistant prostate cancer may further increase demand for PSMA-PET as more tumours will potentially be imaged and biopsied within this program, adding to current volumes. Increasingly, multiparametric MRI is being implemented to diagnose prostate cancer.²⁵ This special type of MRI scan is specific for diagnosing prostate cancer and provides insight into the potential transformation of the tumour by assessing certain key parameters such as diffusion restriction.²⁶

Type of Use

Approximately 80% of PET-CT's overall use is dedicated to oncology exams, with some variation from province to province. For prostate cancer, there is variability across Canadian provinces and territories in accessing PET-CT.^{11,17} As of 2021, 4 provinces do not currently

fund the use of PET-CT in prostate cancer for any purpose, and 1 province funds the use of PET-CT in prostate cancer upon discussion with a nuclear medicine specialist. At least 5 provinces fund PSMA-PET as part of clinical trials.²⁷

Hours of Operation

The average PET-CT unit in Canada operates for 9 hours per day. Almost half of PET-CT units operate between 8 to 12 hours a day, 38% of units operate for less than 8 hours a day, 12% for between 12 to 18 hours, and no units are used for more than 18 hours a day. Most PET-CT units do not operate on weekends, although at least 3 sites reported that at least 1 unit operates at their site on weekends if staffing and radiopharmaceuticals are available.¹⁷ There is the potential to increase the hours of operation of PET-CT units in many facilities, with consideration to the many dependencies, including staffing and the fact that the operating times of PET-CT units are closely tied to the operating times of the cyclotrons that supply the radiopharmaceuticals used in PET-CT exams.¹⁷

Wait Times

While the average wait time for a PET-CT exam is unclear, according to some professionals in Canada who work with PET-CT, they are beyond provincial targets for oncology exams in some provinces.¹⁸

Trends Over Time

Overall, capacity in PET-CT has not kept pace with the growth in demand for the service. Demand for PET-CT may be driven by the introduction of new indications, as well as greater awareness among patients and clinicians of the role of this modality in the diagnosis and

Figure 1: Geographic Distribution of PET-CT Units in Canada



monitoring of disease. The number of publicly funded exams has increased by 39%, from 90,530 to 125,775, between the 2017–2018 and 2019–2020 fiscal years (i.e., between the last 2 iterations of the CMII report). While the overall number of PET-CT units in Canada has risen by more than 43% over the past 10 years, from 40 to 57 units,¹⁷ Canada has fewer PET-CT units per capita than most OECD countries.¹⁷ PET-CT units per capita have increased from 1.2 per million people in 2010 to 1.5 per million people in 2019 to 2020, representing a 25% increase over the time period. Six provinces have experienced a slight growth in the number of PET-CT units per million people over the past 10 years, while 3 provinces have experienced a slight decline.¹⁷

Current Standard of Care

While there is evidence to support the use of PSMA-PET as the gold standard for imaging of biochemical recurrent prostate cancer,²⁸ and emerging evidence supporting PSMA-PET for primary staging of high-risk cancer,²⁹ PET-CT is not a standard test for prostate cancer³⁰ in Canada and, for this indication, is used mostly in clinical trials in at least 5 provinces.¹⁹

Clinical trials are under way in British Columbia, Ontario, and Saskatchewan to determine the accuracy of PSMA-PET in detecting prostate cancer recurrence and/or remission. A clinical trial is being prepared in Alberta to combine PSMA-PET (18F PSMA-1007) with MRI for initial staging in prostate cancer. As well, clinical trials are under way in Quebec and Ontario to determine the clinical effectiveness of PSMA-PET–guided radiation therapy.^{27,31} As of October 22, 2022, there are 22 clinical trials incorporating PSMA-PET for prostate cancer actively recruiting patients in Canada, as listed in ClinicalTrials.Gov.³²

While PSMA-PET has demonstrated promise in the clinical trials setting, the current standard of care in imaging techniques for prostate cancer are CT abdomen and pelvis and technetium-99m methylene diphosphonate bone scans³⁰ and systematic transrectal ultrasound.²⁵ Many clinical guidelines identify PSMA-PET as an emerging imaging modality that is rapidly becoming part of standard practice.^{33,34}

Anticipated Future Use of PET-CT

There are numerous new indications anticipated to be introduced into clinical practice in Canada over the next decade, according to participants of the CMII survey on the anticipated future of PET-CT in Canada. If these expanded indications are adopted in routine clinical practice, this could double current demand for PET-CT exams,¹⁸ as elaborated in the following. The introduction of PSMA-PET would occur within the wider context of other competing PET-CT priorities.

Oncologic Indications

In the oncology field, which is a health system priority and where PET-CT is currently most commonly used, it is anticipated that an increase in demand will be led by growing the number of publicly funded indications, as well as increasing PET-CT use beyond diagnosis.¹⁸ PET-CT is progressively being used for follow-up to assess disease response during and following treatment (e.g., to determine if a tumour is responding to chemotherapy).¹⁸

PSMA-PET is 1 of the most commonly anticipated new indications for the use of PET-CT in Canada for the diagnosis of prostate cancer using both 18F PSMA and/or 68Ga PSMA.¹⁸ According to the participants of a CMII survey on the anticipated future of PET-CT in Canada over the next 10 years, it is estimated that the volume of exams per PET-CT unit will be

medium to high (medium volume meaning 6 to 10 patients per week, per scanner; high volume meaning more than 10 patients per week, per scanner).¹⁸ Assuming a conservative scenario, where 10 patients per unit receive 1 exam per week, an additional 29,640 exams per year may be required across Canada – representing a 23% increase in overall PET-CT exam demand ([Table 1](#)).

Another anticipated use of PET-CT in oncology is for neuroendocrine tumours, which would use 68Ga-labelled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-tyrosine-3-octreotate (68Ga-DOTATATE), a radiopharmaceutical recently approved by Health Canada.³⁵ According to the participants of a CMII survey on the anticipated future of PET-CT in Canada over the next 10 years, the volume of exams per PET-CT unit is anticipated to be low to medium (low volume meaning fewer than 5 patients per week, per scanner; medium volume meaning 6 to 10 patients per week, per scanner).¹⁸ Assuming a conservative scenario whereby 6 patients per unit receive 1 exam per week, an additional 17,784 exams per year may be required across Canada – representing a 14% increase in overall PET-CT exam demand for neuroendocrine tumours. [Table 1](#) indicates the anticipated future demand by volume of PET-CT exams for some new and emerging PET-CT indications.

Table 1: PET-CT Exam Volume Growth, With Anticipated New Indications, as Identified by Survey Participants, Across Canada Over a 10-Year Period

Indication	Radiopharmaceutical	Conservative anticipated exam volume ⁴ (current exam volume: 125,775) ¹¹	Percentage increase from existing PET-CT capacity ⁴
Prostate cancer	18F PSMA, 68Ga PSMA	29,640	23
Neuroendocrine cancer	68Ga-DOTATATE	17,784	14
Cardiac – myocardial perfusion imaging	82Rb, ammonia	29,640	23
Alzheimer disease – amyloid plaque	18FDG fluorine	29,640	23
Total exams with new indications	–	106,704	–

¹⁸FDG = fluorine-18-fluorodeoxyglucose; 68Ga-DOTATATE = gallium-68-labelled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-tyrosine-3-octreotate; PSMA = prostate-specific membrane antigen; 82Rb = rubidium-82.

Non-Oncologic Indications

Non-oncologic indications for PET-CT are also anticipated to expand. This will likely be led by myocardial perfusion imaging for cardiac indications, particularly using rubidium-82 and ammonia to detect ischemic heart disease.¹⁸ The volume of exams is anticipated to be high (i.e., more than 10 patients per week, per scanner).¹⁸ Assuming a conservative scenario whereby 10 patients per week receive a PET-CT exam, an additional 29,640 exams per year may be required, representing a 23% increase in overall PET-CT exam demand.

The most commonly anticipated expansion of use for PET-CT for neurodegenerative indications is for Alzheimer disease using amyloid plaque imaging. The volume of exams is anticipated to be high (i.e., more than 10 patients per week, per scanner).¹⁸ Assuming a conservative scenario whereby 10 patients per week receive a PET-CT exam, an additional 29,640 exams per year may be required, representing a 23% increase in overall PET-CT exam demand for amyloid plaque imaging.

Other non-oncologic indications may contribute to an increase in demand for and use of PET-CT in the future, including inflammatory and infectious conditions, and bone scans for arthritis.¹⁸

Overall, when considering system readiness for the introduction of PSMA-PET, decision-makers may need to consider the anticipated future expansion of other PET-CT indications. For the 4 indications reported in [Table 1](#), which includes PSMA-PET radiopharmaceuticals, it is assumed, based on conservative estimates, they will almost double existing exam volumes (i.e., from the 125,775 exams reported in the last iteration of the CMII report to 232,479 exams).¹⁷

Age of Imaging Equipment

According to life cycle guidance, imaging equipment, including PET-CT units, older than 10 years should be considered for replacement^{36,37} because, compared to newer equipment, they may be less operationally reliable and have reduced diagnostic capabilities.³⁸ Currently, approximately 40% of PET-CT units in Canada are older than 10 years.³⁹ Older imaging equipment may also be more likely to break down and may be more challenging to maintain and repair.⁴⁰

Replacing PET-CT units may also be considered within the context of technology advances that have led to improvements, including lower radiation exposure to patients and staff, clearer images, and faster image acquisition times.⁴¹ A PET-CT expert noted anecdotally that when an older PET-CT was replaced with a newer digital PET-CT unit at their facility, the patient volume doubled, from 7 to 14 patients per day. When considering Canada's future PET-CT capacity needs, the age of existing imaging equipment may need to be taken into account.

Equipment Planning Cycles

Many equipment procurement cycles across Canadian jurisdictions are for 5 years.⁴² An anecdotal comment from a PET-CT professional noted that 5-year planning cycles may need to be revised to assist with health system readiness for the introduction of new technologies, with consideration to additional sites for PET-CT in new geographic locations.

PSMA Radiopharmaceuticals

While 18F fluorodeoxyglucose is the most widely used cancer imaging radiopharmaceutical overall,¹⁸ it may not be as adept as other radiopharmaceuticals at locating prostate cancer cells in the body.^{43,44} Several radiolabelled PSMA inhibitors have been developed, with 68Ga and 18F recognized for their clinical relevance for the diagnosis of prostate cancer.

The most commonly used PSMA-PET radiopharmaceutical is 68Ga,⁴⁵ which can be used diagnostically when paired with PSMA-11.⁴⁶ It can also be used therapeutically when paired with lutetium-177 or actinium-225.^{46,47} Due to the short half-life of 68Ga, there has been increased interest in the development of other PSMA-labelled radiopharmaceuticals, particularly 18F PSMA.⁴⁵

In Canada, PSMA-labelled radiopharmaceuticals, including 68Ga PSMA-11, 18F DCFPyL, and 18F PSMA-1007, are used in the research setting for detecting recurrent prostate cancer.⁴⁸ With the recent approval of a 68Ga PSMA radiopharmaceutical in Canada, its

adoption into clinical use is anticipated. Current guidelines support the use of any of these radiopharmaceuticals, subject to jurisdictional approval and supply issues.⁴⁹

Administration Considerations

The time-limiting characteristics of PSMA-PET radiopharmaceuticals can impact the throughput of patients, the management of radiopharmaceuticals, and the PET-CT process. The half-life of 68Ga is 68 minutes, while the half-life of 18F is 110 minutes.⁶ This means that the synthesis of these radiopharmaceuticals must be carefully coordinated with the arrival of patients to the nuclear medicine department. Patients are initially directed to an uptake room, where the radiopharmaceutical is administered. The uptake time (i.e., the time it takes for the radiopharmaceutical to circulate through the body after it is administered to the patient), is 60 to 90 minutes for 68Ga, and 60 to 120 minutes for 18F. The patient remains in the uptake room for the duration of the uptake period.⁶ A PET-CT exam is then performed in the imaging room, with an image acquisition time of between 20 and 40 minutes (Table 2).⁵⁰ Typically, 1 exam is required,¹¹ and the entire procedure takes approximately 2.5 hours.

Production of PSMA-PET Radiopharmaceuticals

PSMA radiopharmaceuticals can be produced in 2 main ways – using decentralized generators or centralized cyclotrons – and each method is associated with strengths and weaknesses.⁵¹

Generator Production of 68Ga PSMA-PET

Gallium-68 PSMA is predominantly available by the elution (the process of extracting one material from another) of a table top generator, although it can also be produced in a cyclotron.⁵² A generator is a device for the radiochemical separation of a daughter radionuclide, in this instance 68Ga, which is formed by the decay of the parent radionuclide, germanium-68.⁵³

A generator can be procured from an approved manufacturer in different capacities and grades for research and/or clinical purposes. A generator is delivered to the nuclear medicine department of a health care facility, where it can be prepared.⁵³ The generator can be eluted, manually or automatically, and the radiopharmaceutical is then transferred to a synthesis module (synthesizer) where it is further formulated, purified, and tested.⁵² This process may be time consuming, requires highly qualified staff (as discussed in the Human Health Resources section of this report) and expensive synthesis and sampling equipment, in addition to high-grade purity of consumables and reagents.⁵⁴ As well, the handling of 68Ga requires specific radioprotection equipment, which may be heavy and have a large footprint.⁵⁴

Table 2: Time-Limiting Characteristics of PSMA-PET Radiopharmaceuticals

Radiopharmaceutical	Half-life	Expiry time after uptake (after injection)	Image acquisition time
68Ga PSMA	67.71 minutes ⁶	60 to 90 minutes ⁶	20 to 40 minutes ⁵⁰
18F PSMA	110 minutes ⁶	60 to 120 minutes ⁶	

18F = fluorine-18; 68Ga = gallium-68; PSMA = prostate-specific membrane antigen.

Most ⁶⁸Ga generators can be eluted, on demand, for a maximum of 3 patient doses per day⁵⁵ and require approximately 4 hours of regeneration time between elutions before the next elution can produce a full yield,⁵⁶ although this may depend on the initial activity of the generator and its age.⁵⁵ Because the eluted activity of a generator continuously declines, to ensure a regular clinical supply of ⁶⁸Ga PSMA, in some instances, and depending on patient volume, multiple sequential and overlapping generators must be purchased throughout the year.⁵² Typically, a generator may be used for up to 6 to 12 months, or for 250 to 400 elutions before a replacement generator is required.⁵¹ Ongoing technological advancements in generators are intended to facilitate additional doses from a single generator elution and increase the number of daily elutions.⁵⁷

Cyclotron Production of PSMA-PET Radiopharmaceuticals

While ⁶⁸Ga is most commonly produced in a generator,⁶ both ⁶⁸Ga and ¹⁸F can be produced with a cyclotron. A cyclotron is a specialized, large-scale particle accelerator that creates radionuclides through nuclear reactions for use in nuclear medicine diagnosis and treatment. The resulting radionuclides are then radiochemically processed in synthesis modules to produce radiopharmaceuticals.⁵⁸ One-third of sites with PET-CT units in Canada have access to a local cyclotron.⁵⁵ A cyclotron can produce a variety of different radiopharmaceuticals; for example, in addition to ⁶⁸Ga and ¹⁸F, the cyclotron operated by BC Cancer in Vancouver produces numerous radiopharmaceuticals such as nitrogen-13, carbon-11, and technetium-99m.⁵⁹

The addition of cyclotron-produced ⁶⁸Ga may help increase ⁶⁸Ga supply and help address reported shortages with generators due to increased demand around the world.^{17,51} Cyclotron-produced ⁶⁸Ga may be a more cost-effective and faster method of producing this radiopharmaceutical, when relying on existing cyclotron capacity, compared to the ongoing costs of replacing generators. A cyclotron produces a higher yield of ⁶⁸Ga compared to that produced in a generator,⁶⁰ and its quality is reported to be comparable to that of its generator-produced equivalent.⁶⁰ As well, the production yield of cyclotron-produced ¹⁸F is higher than that of a ⁶⁸Ga generator,⁶ allowing for around 25 PET-CT exams a day.³⁴

While centralized production of PSMA radiopharmaceuticals using cyclotrons may provide greater production efficiency and cost-effectiveness when compared to generator-produced radiopharmaceuticals,⁶¹ for provinces with PET-CT that rely on a single cyclotron (which is the case in 6 provinces), unplanned downtime due to technical problems or unanticipated maintenance can create a “single point of failure,” which results in the cancellation of patient appointments.¹⁸ Generators allow sites that do not have access to cyclotrons to have a supply of ⁶⁸Ga PSMA.⁵¹

Current Capacity Challenges

Numerous shortages in the supply of generators have been reported.⁵¹ Until recently, in the US, the procurement of a ⁶⁸Ga good manufacturing practices (GMP)-grade generator could take up to 18 months. Increased production capacity and a more competitive landscape have reduced the procurement period to around 3 months in the US.⁵¹ Nonetheless, from a Canadian perspective, production and supply issues may be challenging to circumvent once PSMA radiopharmaceuticals become reimbursable, and demand correspondingly increases.⁵¹

Cyclotron scalability is noted as a potential factor that may present a barrier to the production of PSMA-PET radiopharmaceuticals.¹⁸ It is possible that existing cyclotrons may not have the capacity to meet new demand, due to the demand already created from newly installed

PET-CT units across Canada that may already be challenging cyclotron capacity.¹⁸ As well, cyclotron production cycles may already be stretched to accommodate the public funding of new clinical indications.¹⁸ Furthermore, cyclotrons with a single hot cell (a shielded nuclear radiation containment chamber where the chemical reaction takes place to manufacture the radiopharmaceutical) may limit cyclotron production to a single product per day.¹⁸ From this perspective, the use of both generators and cyclotrons for the production of PSMA-PET radiopharmaceuticals may be the optimal solution to ensure continuous supply to patients.

Regulatory Approval of Radiopharmaceuticals

Health Canada approved the first PSMA-PET radiopharmaceutical for a 68Ga product in October, 2022, for the diagnosis of prostate cancer that is suspected of having spread to other parts of the body.¹⁵ Both 68Ga PSMA and 18F PSMA products have been approved by the FDA⁶² and the European Medicines Agency (EMA).^{63,64} With these approvals, the demand for PSMA radiopharmaceuticals rapidly increased worldwide.⁴⁸ Health Canada's approval of 68Ga PSMA may put pressure on existing PET-CT capacity and could, as mentioned previously, increase the overall annual exam volume by a minimum of 23% from existing PET-CT capacity.⁶⁵

A Health Canada drug establishment licence is required for a facility to produce radiopharmaceuticals. In particular, Health Canada's Food and Drug Regulations require conformity to GMP, which is a set of international practices intended to provide a traceable process to ensure that radiopharmaceutical products are consistently produced and controlled to quality standards intended for their use.⁶⁶ The length of time it takes before a fully operational cyclotron receives a licence may vary, and has been reported to take up to 5 years in Canada.¹⁸

The Canadian Nuclear Safety Commission (CNSC) requires a licence for the use, storage, possession, production, import, export, and service of nuclear substances and devices. The use of nuclear substances and devices for diagnostic nuclear medicine is considered a medium risk activity, while the use of radiopharmaceuticals may require a high-risk licence.¹⁸

For the human applications of radiopharmaceuticals, a lack of harmonization between international regulatory frameworks has previously been described as a barrier to widespread access to radiopharmaceuticals.^{67,68}

Supply Monopoly

In some settings, monopolization of radiopharmaceutical production has been observed over the past 10 years due to substantial industry consolidation.⁶⁹ Dependency on a single supplier can impact radiopharmaceutical accessibility when there are disruptions in the supply chain and fewer suppliers to source radiopharmaceuticals from,¹⁸ which can result in the cancellation and rebooking of appointments.¹⁸

When supply disruptions occur with radiopharmaceuticals, facilities may need to secure replacement radiopharmaceuticals from other, typically more distant, locations. These radiopharmaceuticals may be more expensive, and due to a short half-life may require more complex transportation plans.¹⁸ It can be challenging to source radiopharmaceuticals from alternative vendors, particularly with short notice, and some vendors may be less willing to supply service for short-term needs. In a monopoly situation, market prices may rise and,

in some situations, purchase limitations may be imposed to customers (e.g., limiting doses per patient).⁴¹

Costs

The high cost of PET-CT equipment is recognized as a major component of health expenditure, and subsequently is a significant barrier to the further adoption of this imaging modality, including for prostate cancer staging. Costs include infrastructural, installation, operating, licensing, and ongoing maintenance costs, which would vary depending on the context in which PSMA-PET is being adopted and whether a facility requires a new installation or is adding to existing capacity. The upfront capital investment for installing a new PET-CT is approximately CA\$7 million, with around CA\$3 million for the PET-CT unit and an additional CA\$4 million for construction and installation.⁷⁰ If an existing PET-CT facility has space for an additional unit, the cost would be less as it would be mostly limited to the expense of the PET-CT unit itself.

A generator for the production of ⁶⁸Ga costs around US\$100,000 and requires replacement approximately every 12 months.⁵¹ The cost of building a cyclotron facility can range from CA\$2.5 million to CA\$6.6 million.⁴¹ A new cyclotron and radiopharmaceutical facility planned for Calgary has an estimated cost of CA\$18 million.⁷¹ The broad range of costs is, in part, due to the investment made into creating cutting-edge research facilities for the development of new radiopharmaceuticals and radioisotopes.

Potential cost savings with PSMA-PET, as compared with conventional imaging for the detection of metastatic disease in people with high-risk prostate cancer, include those related to more accurate testing and subsequently better-informed treatment decisions.¹¹ A recent Australian economic evaluation of PSMA-PET indicated that it is likely to be considered more cost-effective compared with conventional imaging, with savings also garnered in the accurate detection of nodal disease.¹¹ As well, the cost of PSMA-PET varies considerably by geographical region, likely due to transportation-related costs, and may vary depending on the production method.¹¹

Human Health Resources Considerations

Staffing

The availability of trained personnel to conduct, read, and interpret imaging exams is an ongoing concern in Canada.⁷² As of 2018, there are 271 nuclear medicine specialists, 25,033 technologists, and 47 imaging medical physicists across Canada. Increasing imaging capacity will require an investment in imaging staff ([Table 4](#) in [Appendix 1](#) provides details on the number of radiologists, nuclear medicine specialists, technologists, and imaging medical physicists per province and territory).

Shortages in nuclear medicine technologists, particularly those with experience in PET-CT, is common across provinces with PET-CT capacity.¹⁸ In some jurisdictions, staff shortages with medical physicists, radiochemists, and medical physicists have been reported.¹⁸ It has been noted that when PSMA-PET radiopharmaceuticals are approved, the expertise needed to manufacture and handle them may not be available.¹⁸

Challenges have also been reported related to recruiting physicians who are dual-trained in nuclear medicine and radiology. This skill is in high demand across Canada (except Quebec, where single-specialty nuclear medicine is still predominant). As well, the retention of trained

physicians can be challenging. In some cases, it has been observed that if a centre does not use a particular technology that physicians were trained on, they may relocate to centres where the technology they were trained on is in use and where there is availability and capacity for expanded clinical indications.¹⁸

Staff shortages have been reported in Canada with cyclotron operators and radiochemists, radiopharmacists (particularly those with experience in synthesizing novel radiopharmaceuticals), and radiotechnologists, likely linked to a limited number of funding and training programs. It has been noted that many cyclotron operators are trained in-house, and losing 1 such staff member can put an entire program in jeopardy.¹⁸ A qualified person, such as a radiopharmacy operator, is needed to process PSMA-PET radiopharmaceuticals. This person will require formal training in GMP and ideally 2 years of practical experience working in an authorized GMP-licensed facility involved in radiopharmaceuticals. This level of experience in setting up a GMP radiopharmacy would help to navigate the numerous compliance and authorization procedures with speed and efficiency. Other staff may also require additional training to meet GMP standards for radiopharmaceutical production.

Other positions with reported shortages are support staff such as clinical trial coordinators, clerical staff, clinical trial nurses, and clinical trial technologists. As well, support staff are needed for regulatory affairs and requirements for current products, novel tracer development, and new drug submissions (e.g., Notice of Compliance [NOC], Drug Identification Number [DIN]).¹⁸

It has been anecdotally reported that radiation oncologists have training in the use of external beam and sealed radiation sources (brachytherapy) and have experience in image interpretation, treatment design, dosimetry, toxicity management, and radiation safety. There may be opportunities for collaboration with this specialty on the therapeutic radiopharmaceutical side that could augment both existing and developing nuclear medicine capabilities. Similar opportunities may exist among radiation therapy technologists.

Education and Training

Overall, limited funding for training has been reported in Canada, and this may partially be linked to the limited number of PET-CT units – which may limit the number of sites at which training opportunities may exist.¹⁸ While nuclear medicine residencies and fellowship training programs now often include PET as part of standard training, there are few training sites overall for accredited nuclear medicine residencies and fellowships.¹⁸

Many physicians will require additional training for this new indication and for other novel radiopharmaceuticals, as well as training for managing spills and contamination events.^{18,73} It has been anecdotally reported that clinical trials using PSMA-PET are operated in a limited number of centres, and that there will be a steep learning curve for the interpretation of these exams. Most technologists are trained in nuclear medicine but require additional training for PET-CT. As well, the expansion of PET-CT to new radioisotopes will create further education and training needs. Currently, there are limited programs in Canada that provide PET-CT training for technologists.¹⁸

Equipment Considerations

Supply Chain Fragility

The COVID-19 pandemic exposed vulnerabilities in global supply chains.⁷⁴ From an imaging perspective, this was most recently demonstrated with global shortages with iodinated contrast media that resulted in the cancellation of many exams.⁷⁵ Reductions in commercial flights, as seen during the pandemic when travel restrictions led to reduced traffic volume, can hinder access to radiopharmaceuticals and drive up their costs.⁷⁶ As well, geopolitical sensitivities, wars, natural disasters, or other disruptions (e.g., due to climate change) are exposing weaknesses in supply chains that may occur in 1 country but reverberate throughout the supply chain in other countries.⁷⁷

To better mitigate disruptions and create resilient supply chains that have an ability to recover, procurers may consider alternative supply chain principles focused on implementing dual or multiple sourcing strategies for critical materials (including selecting suppliers with more than 1 manufacturing site⁷⁸) and shifting from global to regional markets.⁷⁴

PET-MRI

Prostate cancer imaging using a hybrid modality that combines PET and MRI into a single unit is an emerging technology.¹⁷ A systematic review and meta-analysis by Ling et al. suggests that the overall diagnostic accuracy of 68GA PSMA-PET-MRI compared to 68GA PSMA-PET-CT may be equivalent in primary prostate cancer staging.⁴⁸ The use of PET-MRI would expose patients to less radiation than with PET-CT.⁴⁸ Currently, there are 3 PET-MRI units in Canada: 2 in Ontario and 1 in Alberta. Because PET-MRI is only used for research purposes in Canada at this time, it is unlikely that this new hybrid modality will play a meaningful role in the diagnosis of prostate cancer in the foreseeable future. Given the increased incorporation of multiparametric MRI into diagnostic and treatment pathways for prostate cancer in Canada, opportunities to leverage existing PET-MRI for prostate cancer may require further exploration.⁷⁹

Implications for Decision-Making

PSMA-PET is becoming the worldwide gold standard for staging prostate cancer, particularly in primary, high-risk prostate cancer and in recurring disease. It can be useful for guiding biopsies to improve sample accuracy, guiding surgery, confirming eligibility for treatment, and monitoring treatment response to therapy. Gallium-68 PSMA is playing a role in selecting patients who may benefit from targeted systemic radionuclide therapy, lutetium-177 PSMA-617.

It is anticipated that the diagnostic use of PSMA-PET will, minimally, increase the existing PET exam volume by 23%. This increase does not consider other competing demands for this imaging modality. With 57 units in Canada, patient access to PET is limited, and as such, it is unlikely that all eligible patients with prostate cancer will be able to receive a PSMA-PET exam in a reasonable time frame.

Implementing new PET-CT programs will be necessary, and this will require investment in new equipment (e.g., PET-CT units, radiochemistry units, cyclotrons, and generators) and access to a variety of PSMA radiopharmaceuticals. A combination of both generator-produced

and cyclotron-produced PSMA-PET radiopharmaceuticals will likely be needed to meet the geography of Canadian jurisdictions and to secure a reliable and resilient supply chain.

In addition to investing in new equipment, decision-makers may look for opportunities to maximize the use of existing imaging capacity. This may involve extending hours of operation of equipment, particularly for evening and weekend use, and ensuring accompanied production capabilities for radiopharmaceuticals. Wider adoption of tools, such as clinical decision-support software, artificial intelligence, and centralized order entry systems, all intended to promote appropriate equipment use and support efficiencies in imaging equipment management and workflow, may also help to maximize existing imaging capacity. As well, as evidence continues to emerge, continued consideration should be given to the optimal clinical role of ¹⁸F fluorodeoxyglucose in detecting prostate cancer.

Sufficient staffing is needed to ensure sustainable operation and development of PET-CT services. Investment in the workforce through education and training opportunities may help to ensure that staffing shortages do not get in the way of delivering the best quality of care to patients. This can be achieved, at least in part, through the provision of mentorship and tailored education programs. As well, collaborative endeavours with radiation oncologists and radiation therapy technologists may help to accelerate learning opportunities related to therapeutic radiopharmaceuticals.

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Appendix 1: Supplementary Summary Tables for the 2019–2020 Canadian Medical Imaging Inventory

Note that this appendix has not been copy-edited.

Table 3: Summary of Available of PET-CT Units by Province in 2019 to 2020

Province	Sites with availability	Total units (free standing facilities)
Alberta	3	4 (0)
British Columbia	3	4 (1)
Manitoba	1	1 (0)
New Brunswick	2	2 (0)
Newfoundland and Labrador	1	1 (0)
Nova Scotia	1	1 (0)
Ontario	16	20 (3)
Quebec	18	23 (3)
Saskatchewan	1	1 (0)
Canada	46	57 (7)

Table 4: Number of Radiologists, Nuclear Medicine Specialists, Medical Radiation Technologists, and Imaging Medical Physicists in Canada in 2018

Province or territory	Radiologists ⁸⁰		Nuclear medicine specialists ⁸¹		Medical radiation technologists ⁸²		Imaging medical physicists ^a	
	Count	Per million population	Count	Per million population	Count	Per million population	Count	Per million population
Alberta	294	65.7	28	6.3	2,416	540.2	7	1.6
British Columbia	314	61.5	29	5.7	2,128	417.0	9	1.8
Manitoba	88	63.6	6	4.3	841	608.6	5	3.6
New Brunswick	57	73.5	3	3.9	595	767.1	0	0.0
Newfoundland and Labrador	52	99.6	5	9.6	396	758.2	1	1.9
Nova Scotia	85	87.9	8	8.3	609	629.7	2	2.1
Ontario	939	64	79	5.4	10,720	730.3	18	1.2
Prince Edward Island	9	57.2	0 ^b	0.0	113	718.0	0 ^c	0.0
Quebec	661	77.8	107	12.6	6,587	775.4	5	0.6
Saskatchewan	83	69.5	6	5.0	628	525.0	0	0.0
Territories	0	0	0	0.0	NR	0.0	0	0.0

Province or territory	Radiologists ⁸⁰		Nuclear medicine specialists ⁸¹		Medical radiation technologists ⁸²		Imaging medical physicists ^a	
	Count	Per million population	Count	Per million population	Count	Per million population	Count	Per million population
Canada	2,582	68.2	271	7.2	25,033	661.0	47	1.2

NR = not reported.

^a(Gisele Kite, Administrator, COMP–Canadian Organization of Medical Physicists, ON: personal communication, Sept 17, 2020).

^bAlthough not reported by the Canadian Medical Association, there is one radiologist practising in Prince Edward Island who is fellowship trained in nuclear medicine (Grant McKenna, Health PEI, Queen Elizabeth Hospital, PE: personal communication, Oct 20, 2020).

^cThere is 1 imaging medical physicist practising in Prince Edward Island who is certified in mammography (Grant McKenna: personal communication, Oct 20, 2020).