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Canadian Medical Imaging Inventory Service Report

The Role of PET-CT in Drugs Targeting Amyloid-Beta in Alzheimer Disease: Part 2

Context

Alzheimer disease (AD) is a neurological condition in which brain cell dysfunction and death causes memory loss and cognitive decline.[1] It is a form of dementia, as well as the most common cause of it.[2] The main pathological characteristics of the disease are believed to be the widespread accumulation of amyloid plaques and neurofibrillary tangles in the brain.[3] Together, these proteins reduce the capacity of neural circuits to work properly, leading to memory dysfunction and cognitive impairment.[4]

The emergence of new amyloid-targeted therapies are intended to modify or stop the course of AD by targeting and removing amyloid plaques from the brain.[5] Of the 126 drugs currently in clinical trials for AD, 83% are disease modification therapies and most are amyloid- and tau protein-targeted radiopharmaceuticals for the treatment of the progression of AD.[6]

Patient eligibility for amyloid-targeted therapies is confirmed with a PET-CT exam.[7] An amyloid PET-CT scan demonstrates the presence of amyloid in the brain[7] to estimate the density and distribution of aggregated tau neurofibrillary tangles.[6] This exam may predict the conversion of at-risk individuals 10 years before the onset of AD symptoms.[8]

PET-CT imaging requires the use of radiopharmaceuticals. These are injected into the patient's bloodstream and produce a radioactive signal detectable with a PET-CT unit[8] and used to visualize, characterize, and quantify physiological activity at the molecular and cellular levels.[9] Amyloid radiopharmaceuticals measure amyloid deposition in the brain.[10] The production of radiopharmaceuticals requires a particle accelerator known as a cyclotron.[11] Due to the short half-life of commercial amyloid radiopharmaceuticals, cyclotrons must be located close to PET-CT sites.[12]

An alternative means of diagnosing AD is via cerebrospinal fluid (CSF) collection by lumbar puncture. While this is a less expensive means of evaluating the presence of amyloid, the method carries the risks of adverse effects, including headache, infection, bleeding, cerebral herniation, minor neurologic symptoms such as radicular pain or numbness, late onset of epidermoid tumours of the thecal sac and back pain,[13] as well as patient discomfort.[9] Also, while these 2 methods may be considered interchangeable, in some instances an amyloid PET-CT exam is requested after performing CSF biomarkers with inconclusive findings[14,15] and amyloid PET-CT positivity is frequently used as an enrolment criterion for AD clinical trials.[16]

To ensure that patients with amyloid burden are identified before the appearance of AD symptoms, the health care system's capacity to conduct this testing must be assessed. From a neuroimaging perspective, potential barriers to the optimal delivery of patient care must be

identified, such as the availability of PET-CT equipment, including radiopharmaceuticals and cyclotrons, and the cost of this equipment.

Objective

The purpose of this report is to assess the infrastructural readiness of the health care system for the potential introduction of amyloid-targeted drugs for the treatment of Alzheimer disease from the perspective of PET-CT services in Canada. The key objectives are, as follows:

- outline considerations for future planning for PET-CT capacity
- identify the radiopharmaceuticals required to detect the presence of amyloid plaque and potential access challenges
- identify cyclotron capacity and barriers to use.

This document builds upon work published on November 1, 2021, The Role of Neuroimaging in Drugs Targeting Amyloid-Beta in Alzheimer Disease: Part 1. The focus of that report was to determine system readiness for MRI and PET-CT, with consideration to the number of units, volume of exams, types of use, hours of use, wait times, human resources, and the age of equipment.

About This Document

This document summarizes information identified through the collection of data for the Canadian Medical Imaging Inventory (CMII)[17] and a limited literature search. The methods for this analysis have been previously described in the CMII report published in 2021[18] and are based on a web-based survey that was distributed to 455 sites with MRI, PET-CT, CT, single-photon emission computed tomography (SPECT), and SPECT-CT units. As well, data from a survey distributed among the Canadian nuclear medicine community is described here.[19]

Results

PET-CT

PET-CT is becoming an indispensable imaging modality — not just for cancer, but also for neurology, cardiology, and infectious diseases.[20] Its use in these clinical areas continue to expand and are the source of PET-CT's rapid adoption.[20] The provision of PET-CT for the detection of AD must be viewed within the context of an overall competing demand for the service, as it is now, and with consideration to trends over time, as well as the anticipated future growth.

The future growth of PET-CT will be influenced by numerous factors, including an increasing aging population whereby 25% of Canadians will be seniors by 2030.[21] In addition, technological innovations with PET-CT that improve diagnostic confidence by enhancing image quality, as well as the regulatory approval of novel radiopharmaceuticals, will further expand the uses of PET-CT beyond traditional diagnostic capabilities.[19]

Current Use

Across Canada's 57 PET-CT units, approximately 2,220 clinical exams were conducted per unit in the fiscal year 2019–2020 for a total of 125,775 exams. This is in keeping with the annual patient throughput that is considered reasonable for a PET-CT unit — i.e., between 2,000 to 2,500 exams.[22]

Currently, less than 6% of all PET-CT use in Canada is for neuroimaging, particularly for the diagnosis of dementia and epilepsy.[18] The most common application and overall priority for PET-CT is oncology, accounting for 79% of the entire volume of clinical PET-CT exams in Canada[18] and representing 11 different types of cancer approved for public funding across all provinces.[20]

It has recently been reported that there are insufficient PET-CT resources to manage the current standard of care for oncology indications in Canada,[19] with a limited numbers of units, wait times that are longer than clinically recommended targets, and inadequate human resource capacity.[19] Wait lists for oncology exams are longer than recommended targets and take priority over all other indications. Indeed, some Canadian clinicians often consider PET-CT unavailable within clinically relevant timelines for non-oncologic indications.[19] Wait lists for a PET brain scan can be longer than 1 year and some patients have waited up to 3 years for an amyloid PET-CT before exam requisitions were finally cancelled.[19]

Trends Over Time

Overall, capacity in PET-CT has not kept pace with the growth in demand for the service. While the number of PET-CT units in Canada has risen by more than 43% over the past 10 years, from 40 to 57 units,[18] Canada has fewer PET-CT units per capita than most OECD — Organisation for Economic Co-operation and Development — countries.[18]

PET-CT units increased from 1.2 per million people in 2010 to 1.5 per million people in 2019–2020, representing a 25% increase over the time period. Seven provinces experienced a slight growth in the number of PET-CT units per million people over the last 10 years, while 3 jurisdictions experienced a slight decline.[18]

As for growth in the volume of publicly funded PET-CT exams, the number of exams has increased by 39% from 90,530 to 125,775 between the last 2 iterations of the CMII (the 2017–2018 to 2019–2020 fiscal years).

Anticipated Future Use

There are numerous new indications that are anticipated to be introduced into clinical practice in Canada in the near future. If these expanded indications are adopted in routine clinical practice, they will likely double existing PET-CT exam volumes.[19]

Oncologic Indications

On the oncological front, which is the current priority for PET-CT, it is anticipated that this expansion will be led by increasing the number of publicly funded indications, as well as increasing PET-CT use beyond diagnosis.[19] PET-CT is progressively being used for follow-up to assess disease response during treatment (e.g., to determine if a tumour is responding to chemotherapy).[19]

A commonly anticipated new indication for the use of PET-CT in Canada is for the diagnosis of prostate cancer using 18F-fluorodeoxyglucose (^{18}FDG) prostate-specific membrane antigen (PSMA) and/or gallium-68 (^{68}Ga) PSMA.[19] Gallium-68 PSMA is approved by the US FDA and the European Medicines Agency (EMA).[23] The volume of exams per PET-CT unit is anticipated to be medium to high (medium volume: 6 to 10 patients per week, per scanner; or high volume: more than 10 patients per week, per scanner).[19] Assuming a moderate scenario, where 10 patients per unit receive an exam per week, an additional 29,640 exams per year may be required across Canada, representing a 23% increase in overall PET-CT exam capacity for prostate cancer imaging.

Another anticipated used of PET-CT is for neuroendocrine tumours, using ^{68}Ga-labelled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-tyrosine-3-octreotate (^{68}Ga-DOTATATE). This radiopharmaceutical has also been approved by the FDA and the EMA for this indication.[23] In Canada, the volume of exams per PET-CT unit is anticipated to be low to medium (low volume: less than 5 patients per week, per scanner; medium volume: 6 to 10 patients per week, per scanner).[19] Assuming a moderate scenario whereby 6 patients per unit receive an exam per week, an additional 17,784 exams per year may be required across Canada, representing a 14% increase in overall PET-CT exam capacity for neuroendocrine tumours. Table 1 indicates the anticipated future volume of some new PET-CT indications.

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

Indication	Radioisotope	Moderate anticipated exam volume	Percentage increase from existing PET-CT capacity
Prostate cancer	^{18}FDG PSMA, ^{68}Ga PSMA	29,640	23
Neuroendocrine cancer	^{68}Ga-DOTATATE	17,784	14
Cardiac — myocardial perfusion imaging	^{82}Rb, ammonia	29,640	23
Alzheimer disease — amyloid plaque	^{18}FDG fluorine	29,640	23

^{18}FDG = 18F-fluorodeoxyglucose; PSMA = prostate-specific membrane antigen; ^{68}Ga-DOTATATE = ^{68}Ga-labelled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-tyrosine-3-octreotate; ^{82}Rb = 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 (^{82}Rb) and also using ammonia to detect ischemic heart disease.[19] The volume of exams is anticipated to be high — i.e., more than 10 patients per week, per scanner.[19]

The most commonly anticipated expansion of use for PET-CT for neurodegenerative indications is AD using amyloid plaque imaging. The volume of exams is anticipated to be high — i.e., more than 10 patients per week, per scanner.[19] Indeed, it is reported that there is the potential for dementia-related imaging to significantly impact overall PET-CT volumes.[19] Assuming a moderate 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 capacity for amyloid plaque imaging.

Other non-oncologic indications that will expand the use of PET-CT included inflammatory and infectious conditions, and bone scans for arthritis.[19]

Radiopharmaceuticals

Amyloid PET-CT

Amyloid imaging with PET-CT uses fluorine-based radiopharmaceuticals that allow for the quantification of amyloid deposition in the brain. Amyloid radiopharmaceuticals bind to fibrillar beta-amyloid plaques and are able to estimate neuritic amyloid plaque burden,[10] and may predict the conversion of at-risk subjects 10 years before the onset of AD symptoms.[8]

The most commonly used amyloid PET-CT radiopharmaceuticals are florbetaben, florbetapir, and futemetamol.[7]

Administration

Amyloid radiopharmaceuticals are injected intravenously and require approximately a 30 to 50 minute uptake time,[8] with a PET-CT image acquisition time of between 10 to 20 minutes.[24] The half-life of these amyloid radiopharmaceuticals is approximately 110 minutes.[25] This may be long enough for an amyloid radiopharmaceutical to be produced commercially at offsite cyclotrons and shipped to imaging centres within a local radius. However, access to a reliable and uninterrupted source of radiopharmaceuticals is a prerequisite for the successful implementation of PET-CT because its radioactivity decreases by half every 2 hours[26] and locating a PET-CT further than 4 hours away from a cyclotron is impractical.[27] Table 2 shows the characteristics of amyloid radiopharmaceuticals that influence patient throughput.

Table 2: Time-Limiting Characteristics of Amyloid PET-CT Radiopharmaceuticals.

Radiopharmaceutical	Half-life	Expiry time after uptake (after injection)	Image acquisition time
Florbetaben[25]	110 minutes	Up to 130 minutes	20 minutes
Florbetapir[28]	110 minutes	Up to 60 minutes	10 minutes
Flutemetamol[29]	110 minutes	Up to 90 minutes	20 minutes

Regulatory Approvals

Florabetaben is the only Health Canada-approved amyloid-targeted radiopharmaceutical. It was approved in 2017[30] and is produced at 1 site in Canada.[19]

As mentioned previously, 3 amyloid radiopharmaceuticals have been approved both by the FDA and the EMA: florbetapir, florbetaben, and flutemetamol.[9]

Potential Service Barriers

There are numerous barriers that may limit the availability of radiopharmaceuticals. Some of the main barriers are described in more detail here.

Access

Proximity to a cyclotron may be one of the biggest factors that has thwarted the more widespread adoption of PET-CT.[31] Within the context of amyloid PET-CT, because florabetaben is produced at 1 cyclotron in Toronto, Canada,[19] logistical complications (short half-life and short

expiry time compounded by ground and air transport delays) can render amyloid PET-CT as effectively unavailable in areas outside a local travel radius of the site where it is produced.

Regulatory

Health Canada's regulatory practices regarding the approval of radiopharmaceuticals for clinical use may act as a barrier to the efficient use of PET-CT.[19] Producers are required to file a Health Canada Notice of Compliance (NOC) for a novel radiopharmaceutical to be considered for routine clinical use.[32] Their willingness to do so will depend on business or economic imperatives, if it is a strategic priority to distribute the novel tracer outside of their institutions, and if they have adequate human resource capacity to support a NOC submission.[19]

Supply

For PET-CT sites that rely on a single supplier, there is more vulnerability to service disruptions in the supply chain when there are radiopharmaceutical production issues. In some instances, supply interruptions may impact the availability or cost of radiopharmaceuticals for weekend or extended-hour use. As well, PET-CT facilities can find it challenging to source radiopharmaceuticals from alternative vendors, particularly at short notice. In some instances, suppliers are less willing to supply services for short-term needs, which may result in the cancellation of exams.[19]

The number of radiopharmaceutical suppliers in Canada is low and limited to larger commercial central radiopharmacies.[33] An environment where only a small number of radiopharmaceutical suppliers operate may promote monopolistic practices, which can lead to inflated prices.[19,33]

The packaging requirements of some suppliers prevent the extraction of more than 1 dose from a single vial, which could potentially be used for up to 14 patients.[19] As well, PET-CT facilities that rely on the shipment of radiotracers usually order twice the amount of radiopharmaceuticals required to account for in-transit decay due to the short half-life of radiotracers.[19] In some instances, only 25% of a shipment can be used for patient imaging,[34] thereby intensifying the demand for radiopharmaceuticals.[19]

Cyclotrons

The production of radiopharmaceuticals requires a particle accelerator known as a cyclotron.[11] Radioisotopes are created in the cyclotron and converted into radiopharmaceuticals through chemistry techniques that are mostly conducted in hot cells (a shielded nuclear radiation containment chamber where chemical reactions take place to manufacture the radiopharmaceutical).[35] Some hospitals house their own cyclotrons and produce radiopharmaceuticals onsite. Other cyclotrons are privately owned and operated near PET-CT units, and transport radiopharmaceuticals in shielded containers and cases from the facility to hospitals.[35] All cyclotrons require licensing through the Canadian Nuclear Safety Commission and Health Canada.[19]

Capacity

While the number of isotope production accelerators, such as cyclotrons, has doubled in the last 10 years in Canada,[35] the existing inventory of cyclotrons may not have the capacity to meet the growing demand for radiopharmaceutical quotas with expected increases in PET-CT exam volume.[19]

The short half-lives of radiopharmaceuticals means that they cannot be stored for future use and must be produced daily. Batch production for ^{18}FDG takes approximately 1 to 2 hours.[36] For

facilities that have a single hot cell, cyclotron production may be limited to a single product per day.[19] As well, PET-CTs that do not have a local cyclotron may not be able to conduct as many exams per day, reducing the volume of 12 to 13 exams down to 8 or 9.[12]

Number of Cyclotrons

Currently, there are 25 cyclotrons in Canada licensed to produce radiopharmaceuticals for nuclear medicine exams (source data provided by the Canadian Nuclear Safety Commission, Ottawa, Ontario, October 14, 2021). All provinces with a PET-CT are within proximity to at least 1 cyclotron within provincial jurisdictional boundaries, apart from 1 province — New Brunswick — which does not have its own cyclotron. Table 3 shows the distribution of PET-CTs and cyclotrons per province.

Table 3: Number of PET-CT Units and Cyclotrons Per Province

Province	PET-CT	Cyclotron
Alberta	4	2
British Columbia	4	6
Manitoba	1	1
New Brunswick	2	0
Newfoundland and Labrador	1	1
Nova Scotia	1	1
Ontario	20	8
Quebec	23	5
Saskatchewan	1	1
Total	57	25

Cyclotron licensing in Canada is mostly focused on the production of 4 radiopharmaceuticals, with virtually all cyclotrons producing ^{18}FDG, at least 14 producing nitrogen-13 (^{13}N), at least 13 sites producing carbon-11 (^{11}C), and 9 producing ^{68}Ga (source data provided by the Canadian Nuclear Safety Commission, Ottawa, Ontario, October 14, 2021). Although ^{68}Ga is only used for research purposes, supply constraints are already an issue and the supply chain is considered to be inefficient, of high cost, and at constant risk for interruption.[37]

Continuity of Service

One of the main concerns with provinces having access to only 1 cyclotron is the continuity of service. Cyclotrons experience more down time than PET-CT scanners and unplanned down time, which is more common with older equipment, can create a single point of failure, requiring the cancellation of patient appointments for a province.[19]

PET-CTs that rely on radiopharmaceuticals produced offsite must coordinate with an external cyclotron's production schedules. As well, because most PET-CT services purchase more radiopharmaceuticals than needed, actual demand is inflated to account for losses from transportation delays. At 1 PET-CT site in Canada, prior to setting up their own cyclotron, the users shipped in 1,200 to 1,300 millicuries (unit of radioactivity) of radioisotopes to assure they would have 300 millicuries per day. Now, they are able to run their own cyclotron for an hour to get their daily 300 millicuries' requirement.[12]

It has been noted that Health Canada-approval of ^{68}Ga and PSMA drugs would put pressure on existing capacity. As well, at 1 centre, insufficient staffing resources have already reduced production capacity to 4 days per week.

Costs

The high cost of PET-CT equipment is regarded as a significant barrier to its more widespread adoption, especially when considering infrastructural, installation, operating, and ongoing maintenance costs. Initial equipment costs are outlined here.

PET-CT

The cost of installing a PET-CT is approximately $7 M, with approximately $3 M for the PET-CT unit, and an additional $4 M for construction and installation costs.[38] If an existing PET-CT facility has space for an additional unit, the cost would be much lower and mostly limited to the expense of the scanner itself.

Cyclotron

The cost of building a cyclotron facility can range from $2.5 M to $6.6 M.[11,39] A new cyclotron and radiopharmaceutical facility is planned for Calgary at a cost of $18 M.[34] The broad range of costs is partially linked to investment in cutting edge research facilities for the development of new radiopharmaceuticals and radioisotopes, for which Canada is recognized as a global leader.[40]

Conclusion

Canada's inventory of imaging equipment, as well as the availability of and access to radiopharmaceuticals, and cyclotrons, may not be sufficient to sustain current use. This is more acute in areas that have fewer PET-CT units and/or local access to a cyclotron for radiopharmaceutical production.

The introduction of new indications for PET-CT, particularly those that are anticipated to require a high volume of exams — such as amyloid PET-CT for AD — may not be possible without investment in the entire PET-CT infrastructure. The health system readiness for the accelerated use of PET-CT services will need to be made with consideration to future demand for PET-CTs, so that the necessary equipment, including PET-CT units and cyclotrons, as well as essential supplies such as radiopharmaceuticals, are available and readily accessible. As pointed out in The Role of Neuroimaging in Drugs Targeting Amyloid-Beta in Alzheimer Disease: Part 1, maximizing imaging capacity must also be considered within the context of health system constraints such as human resource shortages and education and training requirements. Failure to consider each of these elements will likely act as a bottleneck to the optimal treatment of patients.

As cancer is the current priority for PET-CT, the use of this equipment for other indications will most likely require policy development to support its use for clinical conditions that may not be considered as immediately urgent.

References

1. Lee JC, Kim SJ, Hong S, Kim Y. Diagnosis of Alzheimer's disease utilizing amyloid and tau as fluid biomarkers. *Exp Mol Med.* 2019;51(5):1-10.
2. Valotassiou V, Malamitsi J, Papatriantafyllou J, et al. SPECT and PET imaging in Alzheimer's disease. *Ann Nucl Med.* 2018;32(9):583-593.
3. Uddin MS, Kabir MT, Rahman MS, et al. Revisiting the Amyloid Cascade Hypothesis: From Anti-Aβ Therapeutics to Auspicious New Ways for Alzheimer's Disease. *Int J Mol Sci.* 2020;21(16):5858.
4. McKinnon C, Gros P, Lee DJ, et al. Deep brain stimulation: potential for neuroprotection. *Ann Clin Transl Neurol.* 2019;6(1):174-185.
5. Mullard A. Landmark Alzheimer's drug approval confounds research community. *Nature.* 2021;594(7863):309-310.
6. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. *Alzheimers Dement (N Y).* 2021;7(1):e12179.
7. Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: Appropriate Use Recommendations. *J Prev Alzheimers Dis.* 2021;8(4):398-410.
8. Suppiah S, Didier M-A, Vinjamuri S. The Who, When, Why, and How of PET Amyloid Imaging in Management of Alzheimer's Disease-Review of Literature and Interesting Images. *Diagnostics (Basel, Switzerland).* 2019;9(2):65.
9. Uzuegbunam BC, Librizzi D, Hooshyar Yousefi B. PET Radiopharmaceuticals for Alzheimer's Disease and Parkinson's Disease Diagnosis, the Current and Future Landscape. *Molecules.* 2020;25(4):977.
10. Yeo JM, Waddell B, Khan Z, Pal S. A systematic review and meta-analysis of (18)F-labeled amyloid imaging in Alzheimer's disease. *Alzheimers Dement (Amst).* 2015;1(1):5-13.
11. Nuclear medicine profile. Ottawa: Canadian Medical Association; 2018: https://www.cma.ca/sites/default/files/2019-01/nuclear-e.pdf. Accessed 2020 Sep 30.
12. Clarke P. The QEII's Cyclotron. *QEII Times.* 2014. https://www.qe2times.ca/the-qeiis-cyclotron-71. Accessed 2021 Nov 29.
13. Johnson KS, Sexton DJ. Lumbar puncture: Technique, indications, contraindications, and complications in adults. 2021 Oct 7; https://www.uptodate.com/contents/lumbar-puncture-technique-indications-contraindications-and-complications-in-adults#H7. Accessed 2021 Dec 7.
14. Muñoz I, Cueva L, Fábrega J, et al. PET-Amyloid After Inconclusive Cerebrospinal Fluid Biomarkers in Clinical Practice. Is it Necessary to Duplicate Procedures? *Current Alzheimer Research.* 2020;17.
15. Reimand J, Groot C, Teunissen C, et al. Why Is Amyloid-β PET Requested After Performing Cerebrospinal Fluid Biomarkers? *Journal of Alzheimer's Disease.* 2019;73:1-11.
16. Therriault J, Benedet AL, Pascoal TA, et al. Determining Amyloid-β Positivity Using (18)F-AZD4694 PET Imaging. *J Nucl Med.* 2021;62(2):247-252.
17. The Canadian Medical Imaging Inventory. Ottawa (ON): CADTH; 2021: https://cadth.ca/canadian-medical-imaging-inventory-0. Accessed 2021 Oct 18.
18. Chao YS, Sinclair A, Morrison A, Hafizi D, Pyke L. The Canadian Medical Imaging Inventory 2019-2020. *(CADTH health technology review)*. Ottawa (ON): CADTH; 2021: https://cadth.ca/sites/default/files/ou-tr/op0546-cmii3-final-report.pdf. Accessed 2021 Feb 17.
19. Vu T. The future of PET-CT in Canada. Ottawa (ON): CADTH; 2021: https://www.cadth.ca/sites/default/files/pdf/public_funded_pet_ct_pan_canadian.pdf. Accessed 2021 Oct 08.
20. Morrison A. Publicly funded PET-CT indications: A pan-Canadian comparison. Ottawa (ON): CADTH; 2021: https://www.cadth.ca/sites/default/files/pdf/public_funded_pet_ct_pan_canadian.pdf. Accessed 2021 Oct 08.
21. Government of Canada — Action for Seniors report. Ottawa (ON): Government of Canada; 2014: https://www.canada.ca/en/employment-social-development/programs/seniors-action-report.html. Accessed 2021 Nov 29.
22. A framework for the development of positron emission tomography (PET) services in England. London: Department of Health 2005: https://www.inahta.org/wp-content/uploads/2014/09/PET_A_framework_for_development_of_PET_services_in_England.pdf. Accessed 2021 Nov 29.
23. Hennrich U, Benešová M. [(68)Ga]Ga-DOTA-TOC: The First FDA-Approved (68)Ga-Radiopharmaceutical for PET Imaging. *Pharmaceuticals (Basel).* 2020;13(3):38. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151717/. Accessed 2021 Nov 29.
24. Koslowsky I. Radiopharmaceuticals for imaging Alzheimer's disease. 2014; https://www.canm-acmn.ca/resources/Documents/2014%20Speaker%20Presentations/2014_Ingrid%20Koslowsky%20April%2011th%20PM.pdf. Accessed 2021 Nov 29.

25. Summary of product characteristics: Neuraceq. Amsterdam: European Medicines Agency; 2021: https://www.ema.europa.eu/en/documents/product-information/neuraceq-epar-product-information_en.pdf. Accessed 2021 Nov 29.
26. Diagnostic imaging network capital equipment planning guide. London (UK): NHS England; 2021: https://www.england.nhs.uk/wp-content/uploads/2021/04/B0030-Capital-equipment-planning-guide-April-2021.pdf. Accessed 2021 Sep 29.
27. Cyclotron facility design. Vienna: Internatioanl Atomic Energy Agency; 2009: https://www-pub.iaea.org/MTCD/publications/PDF/Pub1457_web.pdf#page=68. Accessed 2021 Dec 7.
28. Summary of product characteristics: Amyvid. Amsterdam: European Medicines Agency; 2021: https://www.ema.europa.eu/en/documents/product-information/amyvid-epar-product-information_en.pdf. Accessed 2021 Nov 29.
29. Summary of product charactertistics: Vizamyl. Amsterdam: European Medicines Agency; 2021: https://www.ema.europa.eu/en/documents/product-information/vizamyl-epar-product-information_en.pdf. Accessed 2021 Nov 29.
30. Piramal imaging SA and Isologic Innovative Radiopharmaceuticals annouce commercial approval of Neuraceq™ by Health Canada. 2017; https://www.isologicradiopharm.ca/early-diagnosis-of-alzheimers-disease-approved-in-canada. Accessed 2021 Nov 29.
31. Dash A, Chakravarty R. Radionuclide generators: the prospect of availing PET radiotracers to meet current clinical needs and future research demands. *Am J Nucl Med Mol Imaging.* 2019;9(1):30-66.
32. Regulatory roadmap for radiopharmaceutical (Schedule C) drugs in Canada. *Health Canada* 2021; https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/regulatory-roadmap-schedule-c.html. Accessed 2021 Nov 29.
33. Ross A. Radiopharmaceutical regulations: Changing the tide: International nuclear medicine community collaboration. 2018; https://canm-acmn.ca/resources/Documents/2018%20Speaker%20Presentations/Saturday%20Presentations/180324-1500-Andrew%20Ross-GMP%20Harmonization.pdf. Accessed 2021 Nov 29.
34. Calgary to build cyclotron for radiopharmaceuticals. *Canadian Healthcare Technology* 2021; https://www.canhealth.com/2021/07/21/calgary-to-build-cyclotron-for-radiopharmaceuticals/. Accessed 2021 Nov 29.
35. Facility disclosure: about ISOLOGIC. 2020; https://www.isologicradiopharm.ca/wp-content/uploads/2020/02/Facility-Disclosure-.pdf. Accessed 2021 Nov 29.
36. Yu S. Review of F-FDG Synthesis and Quality Control. *Biomed Imaging Interv J.* 2006;2(4):e57-e57.
37. Canada's ARTMS registers cyclotron production of gallium-68. *Nuclear Engineering International* 2021; https://www.neimagazine.com/news/newscanadas-artms-registers-cyclotron-production-of-gallium-68-9189609. Accessed 2021 Nov 29.
38. Tollinky N. Quebec continues leadership in PET/CT. *Canadian Healthcare Technology*2020: https://www.canhealth.com/2020/10/29/quebec-continues-leadership-in-pet-ct/. Accessed 2021 Nov 29.
39. Corner Brook's PET scanner: a white elephant or a golden goose? 2021; https://www.saltwire.com/halifax/news/canada/corner-brooks-pet-scanner-a-white-elephant-or-golden-goose-551147/. Accessed 2021 Nov 29.
40. CARI Blog #2: Discover the Medical Isotope & Radiopharmaceutical Landscape in Canada. 2021; https://www.imagingprobes.ca/news/cari-blog-2-discover-the-medical-isotope-radiopharmaceutical-landscape-in-canada/. Accessed 2021 Nov 29.

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