Isotopes:

GLOBAL IMPORTANCE AND OPPORTUNITIES FOR CANADA

CANADIAN NUCLEAR ISOTOPE COUNCIL

Advancing human health. Saving lives.

Contents

Foreword

This publication highlights the importance of having a continuous and reliable supply of medical isotopes accessible to Canada and the rest of the world. It also describes the substantial efforts taken by all supply chain partners towards breakthroughs for future nuclear health care services and treatment of patients. This was compiled as a summary of a range of studies and information from members of the CNIC with the goal of framing this key strategic area for Canada and the need for strong leadership moving forward.

Canada has a unique position that is recognized internationally: it is the world's largest supplier of Cobalt-60 and Iodine-125, it hosts mostly all supply chain partners within its borders, it has a long tradition in supply chain collaboration, and it is renowned around the world for developing new applications.

Message from the Chair

James Scongack
Chair, Canadian Nuclear Isotope Council

For more than 60 years, Canada has been a leader globally in the research, development and production of medical isotopes and radiopharmaceuticals. This has meant that Canada has been a global leader in the fight against cancer and keeping our hospitals clean and safe. The world has always counted on Canada and it's for this reason the Canadian Nuclear Isotope Council was created to ensure we continue and expand on this leadership position.

Today, more than 10,000 hospitals around the world use medical isotopes for sterilization, diagnostic imaging and cancer treatment. Canada's nuclear isotope program pioneered a number of medical applications that are used widely today, and much of that work has been focused on the diagnosis and treatment of cancer.

Investments in cancer control, including prevention, early detection and treatment, have all played a role in increasing the overall survival rate in cancer patients from about 25 per cent in 1940s to 60 per cent today. Continuing to make those investments is critical at a time when the Canadian Cancer Society predicts that one in two Canadians will be diagnosed with cancer in their lifetime. There is an even larger number of people all around the world that will be touched directly or indirectly by cancer and these people are counting on Canada.

Medical isotopes also provide a pathway for health-care professionals to improve lives through targeted imaging and therapy that will deliver a specific medical diagnosis and treatment to an individual. They provide the foundation to advance research for improved drug discovery and development.

Canada is a leader in the fight against cancer and disease, but our work isn't nearly done. It's a time to make a renewed commitment to finding new programs, products and procedures to improve people's lives.

That's what this report is all about. It's designed to fully articulate our role in a simple, clean manner while outlining some key steps our policymakers across Canada can take to build on the capacity and leadership position people all over the world are counting on us to play.

About the CNIC

DID YOU KNOW?

Canadian isotopes are used for:

- Sterilization
- Diagnostic imaging
- Cancer treatment
- Insect sterilization
- Food irradiation
- Research & Development

The Canadian Nuclear Isotope Council (CNIC) is an independent organization consisting of representatives from various levels within the Canadian health sector, nuclear industry and research bodies, convened specifically to advocate for our country's role in the production of the world's isotope supply.

A secure supply of a diverse portfolio of isotopes is essential to maintaining and improving our standard of living. Isotopes are used every day to verify the safety of our roadways, discover and develop natural resources, test industrial products, and support research in mental health and aging. They are also a major source of clean energy. Isotopes are critical in the health care sector, where they are used not only to diagnose and treat disease, but also to sterilize medical supplies.

The CNIC serves as a voice in safeguarding the continued availability of isotopes, ensuring our public policies are risk-informed and science-based, and support the highest levels of public health and safety. Leveraging existing infrastructure and expertise will have a significant positive impact on human health across the globe, keeping hospitals clean and safe while expanding Canada's leadership role in the global community by supporting new and innovative treatments.

We thank our members for their commitment to the CNIC.

"This potential for growth in the isotope space provides an invaluable opportunity to leverage Ontario's established Nuclear supply chain that has developed over the past several years in support of the ongoing reactor refurbishments at OPG's Darlington site and the Major Component Replacement program at Bruce Power. This provides an invaluable opportunity to sustain our ongoing prosperity, which in turn leads to continued investment in our local economy, and the increased employment of long-term, well-paying jobs within our community. "

Darryl Spector, President, Promation

QUICK FACTS ABOUT

Isotopes in Canada

Nuclear technology saves lives through use of isotopes for screening, diagnosis and therapy of a wide variety of medical conditions.

The Canadian Nuclear Safety Commission licenses the use and production of

over 250 isotopes in Canada.

In industrial radiography, nuclear substances are used for the **non-destructive examination** and testing of new materials. Radiation from the substances passes through the material and allows defects in welds or constituency to be recorded on film or a digital imager.

Technetium-99m

accounts for approximately 80% of nuclear medicine diagnostic procedures in Canada. According to the National Research Council of Canada, almost 5,500 diagnostic procedures are carried out every day with Tc-99m.

Canadian scientists were the pioneers in a number of nuclear applications.

In 1951, the world's first cancer treatment with Co-60 took place in **London, Ontario**. This marked an important milestone for both the fight against cancer and Canada's emergence as a leader in the field of nuclear power.

Irradiation technology is increasingly being used to

preserve food

— spices, grains, fruit, vegetables and meat. It avoids the use of potentially harmful chemical fumigants and insecticides.

According to the Canadian Medical Imaging Inventory there were

1,444,651 diagnostic imaging procedures

in Canada in 2017.

Worldwide there are over

40 million nuclear medicine procedures

performed each year using isotopes, with approximately 36 million for diagnostic nuclear medicine and four million for therapy.

Currently, Lutetium-177 (Lu-177) accounts for

16% of the beta emitters

in the Canadian therapeutic product market.

^{125}I

60%

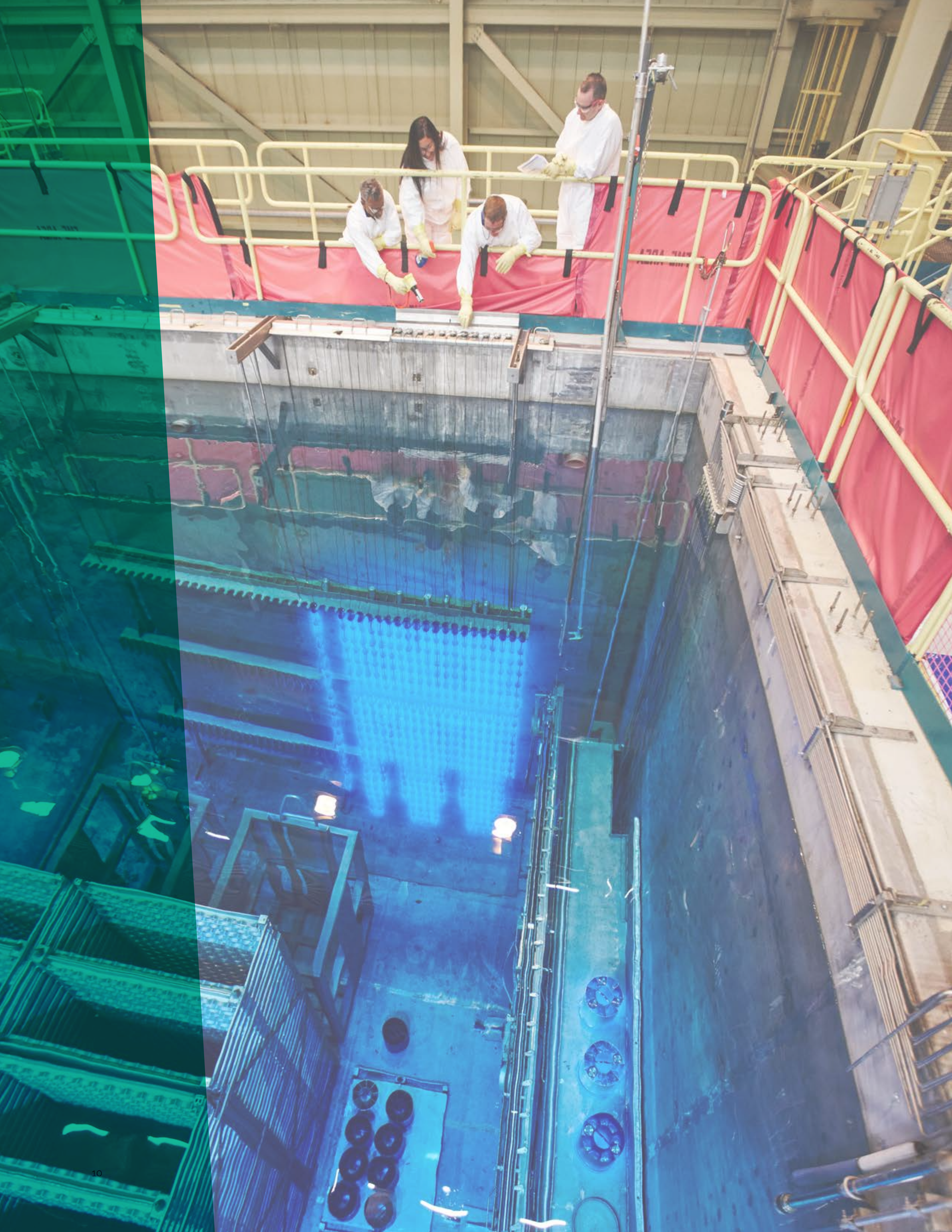
of the world's market of Iodine-125 is produced at The McMaster Nuclear Reactor at McMaster University.

"Canada has been a pioneer in the development of radioisotopes, saving millions of lives in more than 80 countries for over six decades. We have demonstrated world-class nuclear expertise and achievements, leading to significant advancements in medical imaging, cancer therapy, sterilization, food and water safety, and disease prevention."

John Gorman, President and CEO, Canadian Nuclear Association

Key Learnings

- People in Canada and around the world rely on the continuous availability of medical isotopes, and see the potential for market growth in this industry. The entire supply chain is working hard on innovations that will ensure patients receive even better care in the future.
- The changing landscape of medical isotope production and utilization represents a tremendous opportunity for innovation through coalition building. By re-engaging with advanced medical isotope technologies, Canada has an opportunity to solidify itself as a global leader in this field.
- The global market for medical isotopes is experiencing a period of significant change. The commercialization of disruptive new technologies is altering the landscape for the production of the most widely distributed isotope, Molybdenum-99. At the same time, new therapeutic agents containing Lutetium-177, for example, are arriving in clinical trials both in Canada and around the world, and will soon be driving commercial demand for this and other medical isotopes.
- In Canada, four nuclear sites across two provinces house 19 operational commercial reactors and one research reactor. In addition, slow-poke reactors spread across the country are all reasons why Canada has been at the forefront of medical isotope research, development, and technology for more than 60 years. Today, Canadians are engaged in a full spectrum of medical isotope research and development, from devising new ways to generate isotopes, to designing and testing new diagnostic and therapeutic agents, and finally toward deploying these agents in clinical trials and the marketplace. Canada is also the world's leading supplier of two of the top 10 isotopes in medicine, namely Cobalt-60 and Iodine-125.
- Canada is host to over two dozen low- to high-capacity cyclotrons, each with their own set of medical isotope production capabilities. Canadian accelerator technology is also widely regarded as world leading, as are the accelerator-based innovations in isotope production that are emerging in response to medical community uses and demands for various medical isotopes.
- The size of the global isotope market was estimated to be $9.6 billion (US) in 2018. A major driver for the market growth of isotopes is its application in accurate diagnosis, imaging and treatment solutions. While diagnostic pharmaceuticals are the largest revenue-generating segment in the market, targeted therapeutics like Lu-177 is a fast-developing market where key challenges include scaling up production, improving availability and recycling of target materials.
- The size of the Canadian medical isotope market was estimated to be $508.4 million (US) in 2018 and is projected to grow to $925.4 million by 2023, at a CAGR of 12.7 per cent. Emerging markets, increasing demand for oncology treatment, and the improving reimbursement scenario surrounding insurance coverage are expected to present a wide range of opportunities and demand for key isotopes under consideration.
- Two-thirds (66 per cent) of Canadians are concerned about ceding their leadership position in isotope production and research and development.
- 63 per cent of Canadians support the development of a national strategy for isotopes to ensure Canada remains at the forefront of this sector.
- To ensure that Canadians benefit from recent advances in nuclear medicine, Canada must build and maintain a domestic supply of both established and emerging medical isotopes, and strengthen its ability to convert the raw isotopes into clinical quality products. Canada continues to have a strategic advantage in medical isotopes, but the challenge is clinical demand is changing and Canadian infrastructure is aging. Co-ordinated investment is required to maintain Canada's long-term global leadership into the future is paramount.
- If Canada is to maintain its standing as a leading force in global science — and enjoy the associated economic and societal benefits — the country must invest in its physical infrastructure, knowledge base and support clinical trials in Canada. Such investments demonstrate a commitment to Canada's role as a leader in nuclear medicine, and dramatically bolster our capacity to innovate and deliver substantial economic and societal benefits to both Canadians and patients around the globe.



Recommendations

The Canadian Nuclear Isotope Council recognizes the opportunity presented by continued Canadian leadership in isotope development and is therefore calling on federal and provincial government officials to take the following important steps:

- **Develop a Pan-Canadian Strategy for Isotopes**
  There's an opportunity with the support of the federal and provincial governments, through a forum such as the Council of the Federation, to adopt a Pan-Canadian strategy which integrates and supports Canada's leading role in the supply, distribution and development of isotopes for medical and industrial applications. This strategy should also address inter-provincial barriers and how to leverage Canada's position to lead in global research and manufacturing.

- **National Supply Infrastructure Framework**
  Designate the supply of isotopes as a key element of strategic national infrastructure for domestic and international use, allowing the same access to funding and other tools as is the case with roads, bridges, energy projects and many other initiatives. Encourage more of the international value chain to be located in Canada through initiatives such as using the Canada Infrastructure Bank and/or similar provincial and federal mechanisms to enable public/private partnerships.

- **Federal Strategic Innovation Fund**
  Designate Canada's isotope community as a key focus area within the SIF to help Canada leverage its infrastructure advantage and strong network of researchers, clinicians and entrepreneurs to position our country as a global leader in medical isotope innovation. We can build a network to leverage specialized isotope production capacity, connect a Canadian medical research and clinical trials network, and advance new drug development pipelines with established industry partners and entrepreneurs to create new companies, jobs and better health outcomes for cancer patients.

- **Break down barriers within Canada and abroad**
  As a world leader in the supply of two key medical isotopes, we must allow Canada to be a place where trials and new innovative cancer diagnostics and treatments are more easily advanced to the benefit of cancer patients and researchers who are on the front line of fighting cancer every day. Removing regulatory red tape will help to accommodate new treatments and new clinical trials to give patients easier access and support the interprovincial trading and international export of critical isotopes.

- **Technology Applications for Rural, Northern and Remote Regions**
  Deploy new technologies accessible to Canadians in rural, northern and remote communities that will reduce travel requirements, improve outcomes and equality around the standard of care.

- **Promote Canadian isotope leadership abroad and continue with international co-ordination**
  We recommend that the government work with other countries to better co-ordinate worldwide efforts around isotope production and distribution through the removal of trade and export barriers. Canada's focus should be on the promotion of exporting our products, allowing for affordable and reliable cancer care..

- **Secure Canadian talent and expertise by supporting our medical isotope research institutions**
  Canada must build on existing expertise within industry to drive future innovation in medical isotope production capabilities. At the same time, it must invest in the next generation of experts by supporting educational initiatives that bring bright young minds into the field, and support funding initiatives that enable researchers to develop and translate new medical isotope based agents from the laboratory bench to the patient's bedside.

Isotope Background

ISOTOPES AND MEDICAL ISOTOPES

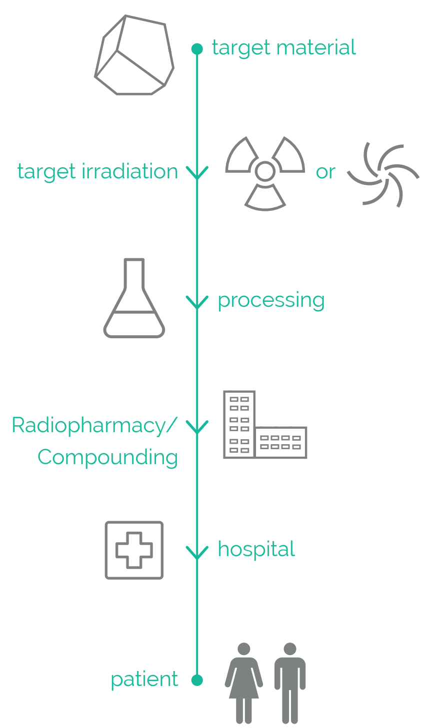
Isotopes are atoms that have the same number of protons as each other, but different numbers of neutrons. There are both stable and non-stable isotopes, of which the unstable forms exhibit characteristic radioactive decay via electromagnetic (gamma) or particulate (alpha, beta, Auger, etc.) emission.

A "medical isotope" is simply a isotope that is used in the practice of medicine. Medical isotopes are the cornerstone of nuclear medicine, a branch of medical science that uses radioactive sources, atoms, and molecules to diagnose, characterize, and treat disease. Nuclear medicine encompasses the imaging techniques Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET), as well as the therapeutic interventions brachytherapy, radioembolic therapy, and Targeted Internal Radionuclide Therapy (TIRT). Some types of External Beam Radiation Therapy (EBRT) also use medical isotopes. Nuclear medicine physicians rely on access to more than a dozen different isotopes, which are matched to different applications depending on their chemical and radioactive decay properties.

WHAT IS HALF-LIFE?

Each isotope also has its own unique "half-life": the time it takes for half of the atoms to undergo radioactive decay. A radioactive half-life (t½) can range in duration from nanoseconds to hundreds of thousands of years.

Isotopes Production Chain

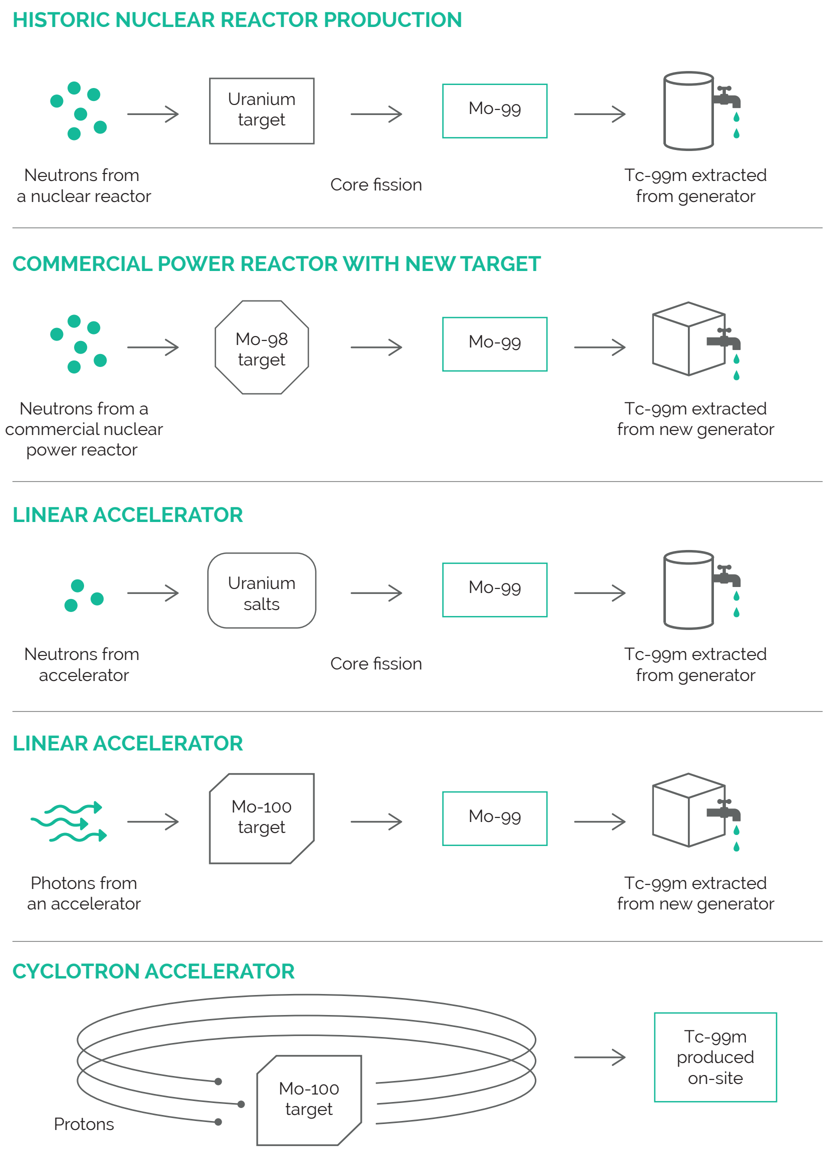


“Every day, 27 Canadians are diagnosed with a brain tumour and (they) all face limited treatment options. This is why the Brain Tumour Foundation of Canada is so encouraged to be participating as part of the CNIC. It will provide more hope in the form of innovative treatments for brain tumour patients in the future.”

Susan Marshall, CEO, Brain Tumour Foundation of Canada.

Isotopes are essential components of modern health care, natural resource development, and infrastructure management. Isotopes are used to characterize human disease, to detect contraband at international borders, to sterilize medical equipment, and to power batteries for space exploration. Isotopes also enable research in agriculture, astronomy, biology, chemistry, materials science, medicine, and nuclear safety (Figure 2). Canada has historically been a world leader in isotope production — a multi billion-dollar global industry — and has the physical and knowledge infrastructure necessary to make a major contribution to this important field on the international stage.

FIGURE 1: Process For Making Isotopes
(Mo-99 is used as an example to demonstrate the process)



HOW DO WE PRODUCE ISOTOPES IN CANADA ?

The production of medical isotopes is achieved using two overarching technologies: i) nuclear reactors, and ii) particle accelerators. Both reactor and accelerators/cyclotrons production methods rely on various chemical processes to separate, purify and prepare isotopes for medical use.

i. *Nuclear reactors embody neutron-based production by using fission of a fuel material (typically uranium-235) to produce neutrons that are used to bombard target materials to form unstable products.*

ii. *Accelerators/cyclotrons utilize charged particles (proton, electron, neutron alpha, etc.) to accomplish the same.*

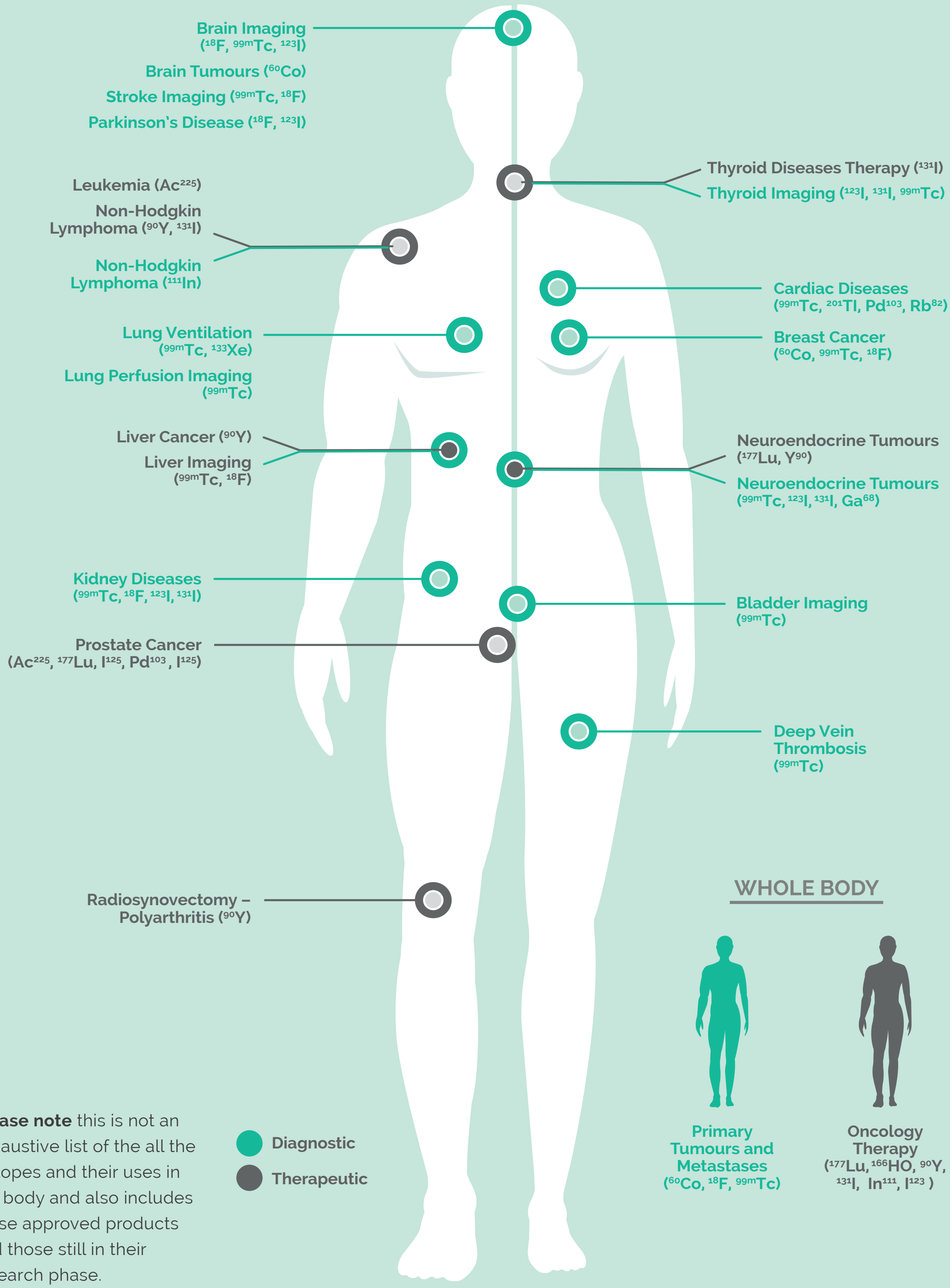
DO ACCELERATORS AND REACTORS PRODUCE THE SAME ISOTOPES?

Particle accelerators and nuclear reactors are complementary technologies. Radioisotopes generated in a particle accelerator are typically neutron-poor, meaning that they are unstable because they have too few neutrons. Radioisotopes generated in a nuclear reactor are typically neutron-rich – unstable because they have too many neutrons.

ISOTOPES IN MEDICINE

There is widespread awareness of the use of radiation and isotopes in medicine, particularly for diagnosis and therapy of various medical conditions. Medical isotopes are very important, particularly for diagnostic purposes in oncology; cardiology and neurology. Therapeutic applications, however, are quickly growing in use and will be a potential driver of market demand in the coming years. In therapeutics, by linking the correct medical isotope to a suitable tracer, the nuclear medicine specialist is able to deliver the medical isotopes to the correct site in the body. This significantly minimizes the damage to healthy cells while effectively killing the diseased cells.

FIGURE 2: Isotopes in the Body



Please note this is not an exhaustive list of the all the isotopes and their uses in the body and also includes those approved products and those still in their research phase.

A Brief History of Medical Isotopes and Nuclear Medicine

1901
The first use of a medical isotope was reported, only five years after the discovery of radioactivity. Using the naturally occurring isotope radium-226, physicians successfully cured a tuberculosis patient of previously untreatable skin lesions.

1931
Invention of the cyclotron — a small, circular particle accelerator.

Aug 18, 1944
Chalk River site officially chosen for the new National Research Council of Canada (later transferred to AECL) nuclear laboratory.

1946
Iodine-131 halted the growth of thyroid cancer and was found to be a useful tool in diagnosing thyroid diseases. This new method of organ imaging was invaluable and marked the beginning of a new era in medical history.

1947
The NRX reactor at Chalk River, Ontario began operating providing an ongoing supply of radioisotopes.

1948
Canadian radioisotopes were exported to the United States for the first time — radium needles used to treat cancer.

July 15, 1949
Cobalt-60 cancer therapy first proposed.

October 27, 1951
The world's first cancer treatment with Cobalt-60 radiation took place at Victoria Hospital in London, ON. This marked an important milestone for both the fight against cancer and Canada's emergence as a leader in the field of radiotherapy. To date, approximately 35-million cancer patients worldwide have benefited from this ground-breaking technology.

Nov. 8, 1951
First cancer patient treated with Co-60 in Saskatoon, Sask., with Harold Johns' beam therapy unit. [I&I]

1954
Government approval for the first Canadian power reactor.

April 10, 1959
McMaster University reactor officially opened.

September 1959
Official announcement of the construction of the Douglas Point reactor.

1968
TRIUMF founded. TRIUMF is a national university-owned and operated multidisciplinary facility with decades of experience in medical isotope research, development and production.

May 1, 1970
NRU production of molybdenum-99 began.

1971
Ontario Power Generation (previously Ontario Hydro) produces Co-60 first Cobalt-60 (Co-60) at Pickering NGS.

1978
Collaboration between TRIUMF and AECL-CP establishes isotope laboratory facilities.

1980s
Cardiac imaging using isotopes becomes prominent.

1981
First commercial cyclotron CP42 officially commissioned.

1990s
McMaster begins production of I-125.

1990
Ontario Power Generation (previously Ontario Hydro) produces Tritium (H-3) for commercial sale.

1991
NRU began conversion from high-enriched (HEU) to low-enriched (LEU) fuel. Completed in 1992.

May 18, 2009
NRU leak causes extended outage (>1 month). This is an interruption of a major supplier of medical isotopes (esp. Mo-99 for Tc-99m imaging diagnostics).

Nov. 30, 2009
Report of the Expert Review Panel on Medical Isotopes Production released.

June 9, 2014
Canadian team with members from TRIUMF, BC Cancer, the Centre for Probe Development & Commercialization, and Lawson Health Research Institute announced that they have dramatically advanced technology for addressing the medical isotope crisis. The key medical isotope, Technetium-99m (Tc-99m), can now be produced in meaningful quantities on the world's most popular cyclotrons, many of which are already installed across Canada and around the world.

August 2015
Canada is a signing member of the Joint Declaration on the Security of Supply of Medical Isotopes. *"WE, the Ministers and representatives of Australia, Belgium, Canada, France, Germany, Japan, the Republic of Korea, the Netherlands, Poland, the Russian Federation, South Africa, Spain, the United Kingdom and the United States of America, SHARE a common interest in ensuring the (99Mo)(99mTc) security of supply of the most widely used medical isotope, Molybdenum-99 and its decay product, Technetium-99m which is used in approximately 40-million medical diagnostic imaging procedures per year worldwide enabling precise and accurate, early detection and management of diseases such as heart conditions and cancer, in a non-invasive manner."*

December 2015
The Government of Canada and the bipartisan Standing Committee on Natural Resources declares Ontario's nuclear innovations a success story, recognizing the critical role that medical isotopes play in the global community and stated its intention to work with industry, the national health-care community and provincial/territorial governments to ensure that the Canadian supply of isotopes is brought to the next level.

October 31, 2016
Canadian Nuclear Laboratories' routine production of Molybdenum-99 at Chalk River Laboratories (CRL) draws to a close.

April 2018
Canadian Nuclear Isotope Council established.

March 31, 2018
The National Research Universal Reactor at Chalk River, ON is turned off.

Nov. 1, 2018
Prime Minister Justin Trudeau announced $10.23 million in federal funding to build a new nuclear medicine hub — the first of its kind in Canada — at TRIUMF to be named The Institute for Advance Medical Isotopes (IAMI). The construction of IAMI is valued at $31.8 million. Other contributors include the province of British Columbia with a contribution of $12.25 million, TRIUMF with $5.35 million, and BC Cancer and UBC each contributing $2 million. The IAMI facility will become a national hub of innovative cancer therapeutic research and development to find new solutions and to change outcomes for those facing an advanced cancer diagnosis.

March 2019
Bruce Power completes first successful harvest of High Specific Activity (HSA) Cobalt.

April 2019
McMaster/CPDC spinoff Fusion Pharmaceuticals financing for US$105M announced to support innovation and research. They have raised over US$150M for innovative Ac-225 based therapeutic for cancer treatment.

Canadian Views on Isotopes

While Canada has been a world leader in the production of medical isotopes for decades due to world-leading research reactors like the NRU at Chalk River and McMaster's research reactor, many Canadians are unaware of our leadership role in this field.

Nearly half of Canadians are unaware of the critical role isotopes play in health care. Even less Canadians are aware of the storied history of Canada regarding isotopes and their usage. Of those who are aware, their knowledge exists primarily through their use in medical sterilization.

These results, generated from a survey of n=1804 adult Canadians, was conducted online by Innovative Research between July 26-31, 2019. The results are weighted to n=1,200 based on Census data from Statistics Canada.

Question 1: *Canada has been a world leader for decades in the supply of essential isotopes used to sterilize medical equipment used by doctors and hospitals and also to diagnose and treat cancer worldwide. Before this survey, how familiar were you with this?*

When provided more information about Canada's current and historical role as a lead supplier of life-saving isotopes, two-thirds of Canadians say that they are concerned about Canada ceding its leadership position. Notably, only four per cent of Canadians are not concerned at all. This suggests that as more information is provided about Canada's role, the importance of the industry and Canada's role to support it will increase.

Total	100%
Very familiar	13%
Somewhat familiar	34%
Not very familiar	23%
Not at all familiar	25%
Don't know	4%
FAMILIAR	47%
NOT FAMILIAR	49%

Question 2: *Canada currently produces 50 per cent of the base isotope material globally that is used in both medical and commercial applications. There is also a growing global demand for medical isotopes at the same time that supply is shrinking. How concerned would you be if Canada were to cede its leadership position?*

Not only are Canadians concerned about losing its position, another 63 per cent support provincial and federal governments working together to adopt a pan-Canadian strategy to secure a global supply of isotopes. These echo the recommendations made by the joint panel on isotopes report which was released in 2009 and demonstrates that Canadians feel this is an important public policy issue that requires action by both the provincial government and the federal government.

Total	100%
Very concerned	27%
Somewhat concerned	40%
Not very concerned	15%
Not concerned at all	4%
Don't know	14%
CONCERNED	66%
NOT CONCERNED	19%

Question 3: *Would you support or oppose provincial and federal governments adopting a Pan-Canadian strategy to secure the global supply of isotopes from Canada and promote their development, export, and use fighting cancer?*

Total	100%
Strongly support	31%
Somewhat support	32%
Neither support nor oppose	17%
Somewhat oppose	3%
Strongly oppose	1%
Don't know	15%
SUPPORT	63%
OPPOSE	4%

KEY TAKEAWAYS

Canadians want to remain at the forefront of research and development, commercializing and supply of medical isotopes. Two-thirds of respondents expressed concern if Canada were to lose its leadership position in isotope supply with nearly one-third of respondents being seriously concerned. This support goes so far that a further 63 per cent of Canadians support the provincial and federal governments adopting a Pan-Canadian strategy to secure the global supply of isotopes from Canada. Taken together, these two indicators clearly demonstrate that isotope leadership is important to Canadians, and are largely in favour of government playing a critical role in helping to shape this.

Canadian policymakers should be acutely aware of the previous challenges Canadians and global citizens faced during an alarming isotope supply shortage. These potential vulnerabilities can be overcome through creating redundancy in supply and supporting Canada's isotope industry by developing policies and a strategy that aim to fosters competitiveness, and supports the promotion and development of isotopes both for export and use in fighting cancer.

Canadian Isotope Landscape

The year 2018 marked the end of an era for medical isotope production in Canada, as the NRU reactor was taken out of services after six decades of supplying medical isotopes to the world. Nevertheless, Canada continues to play an important role on the global stage as a large scale producer and exporter of several key medical isotopes including Cobalt-60, Palladium-103, and Iodine-125. At home, new cyclotron facilities across the nation are increasing Canadians' access to PET imaging, while active clinical and laboratory research programs are working with world-class GMP production facilities to bring new medical isotopes – and medical isotope-based diagnostics and therapies – to patients in Canada and around the world.

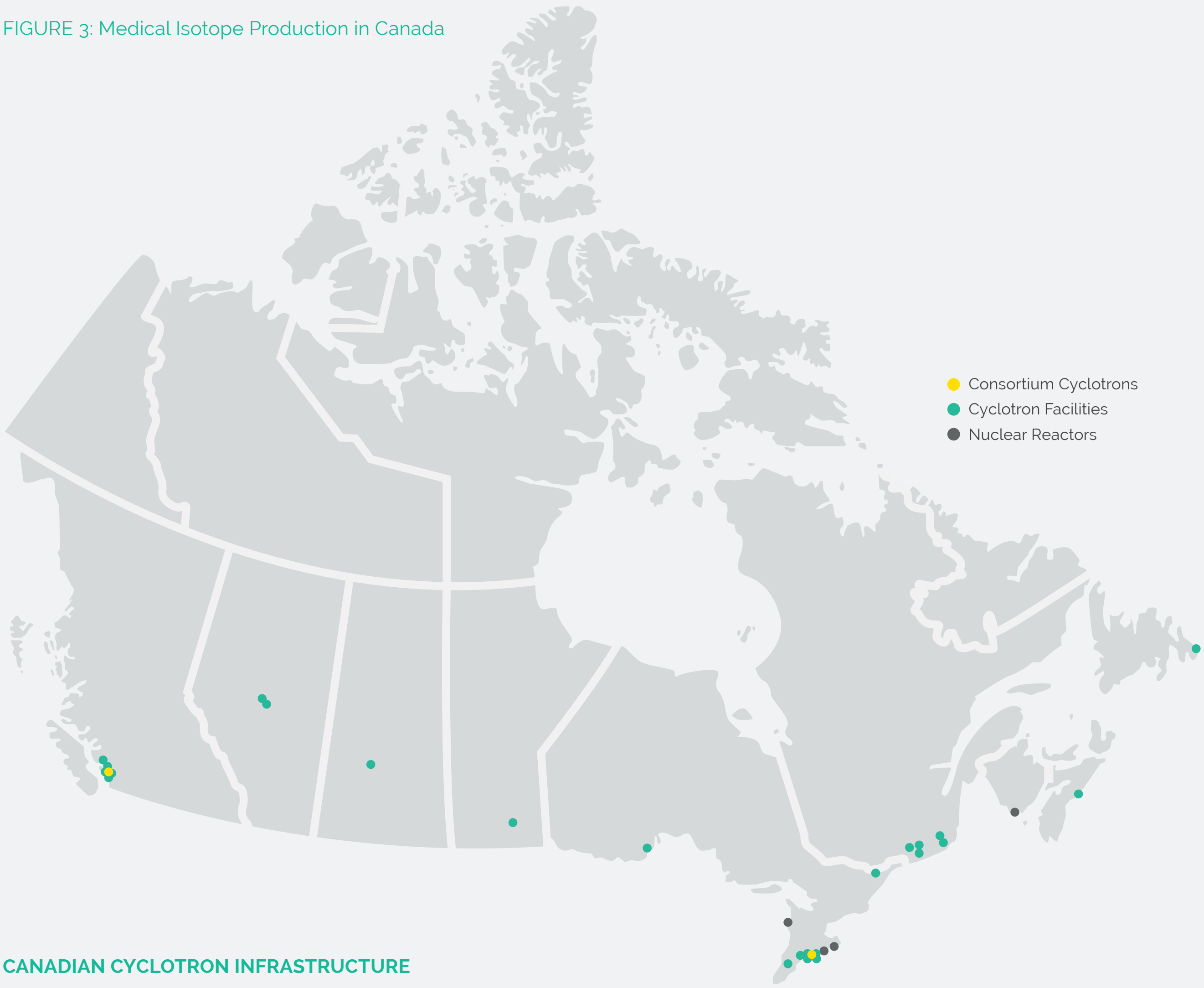
There are various reactor designs used globally, but they typically fall into two categories — research reactors, such as the NRU reactor found at Chalk River, ON., and McMaster University; and power reactors, such as those used by Bruce Power and Ontario Power Generation to produce electricity. Reactor production capabilities are defined by their neutron energy and flux. Accelerators fall into several categories that are defined by the type of particle (i.e. proton vs electron), the method (circular or linear), energy (in millions of electron volts, MeV) and intensity (in ampheres) of particle acceleration. In Canada, there are two primary types of accelerators used for medical isotope production — proton cyclotrons and electron linear accelerators (elinacs). Proton cyclotrons operate at low (<16 MeV, <100 µA), medium (16-24 MeV, 100 to 500 µA), intermediate (29-70 MeV, 100 to 1000 µA) and high (>100 MeV, >100 µA) capacity. All can be used to produce various medical isotopes. Hospital-based machines are typically low to medium capacity.

The landscape of medical isotope production in Canada is diverse, due in part, to the long-standing and world-class research into reactor and accelerator research. Canada is a leader in reactor construction and application for the production of medical isotopes that have been used globally for the past several decades. Canada relies on both domestic production and the global supply chain to provide medical isotopes to our hospitals. Some of the key players in the current Canadian medical isotope supply chain are listed in Figure 3.

"As Canada's nuclear university and home to the country's only research reactor, McMaster is a leader in radioisotope R&D and innovation, and the world's largest supplier of Iodine-125 — one of the top 10 medical radioisotopes. Our integrated suite of research facilities enables discoveries in medicine, clean energy, nuclear safety, materials and environmental science."

Karen Mossman, Vice-President, Research, McMaster University

FIGURE 3: Medical Isotope Production in Canada



CANADIAN CYCLOTRON INFRASTRUCTURE

25 Cyclotrons in Canada:

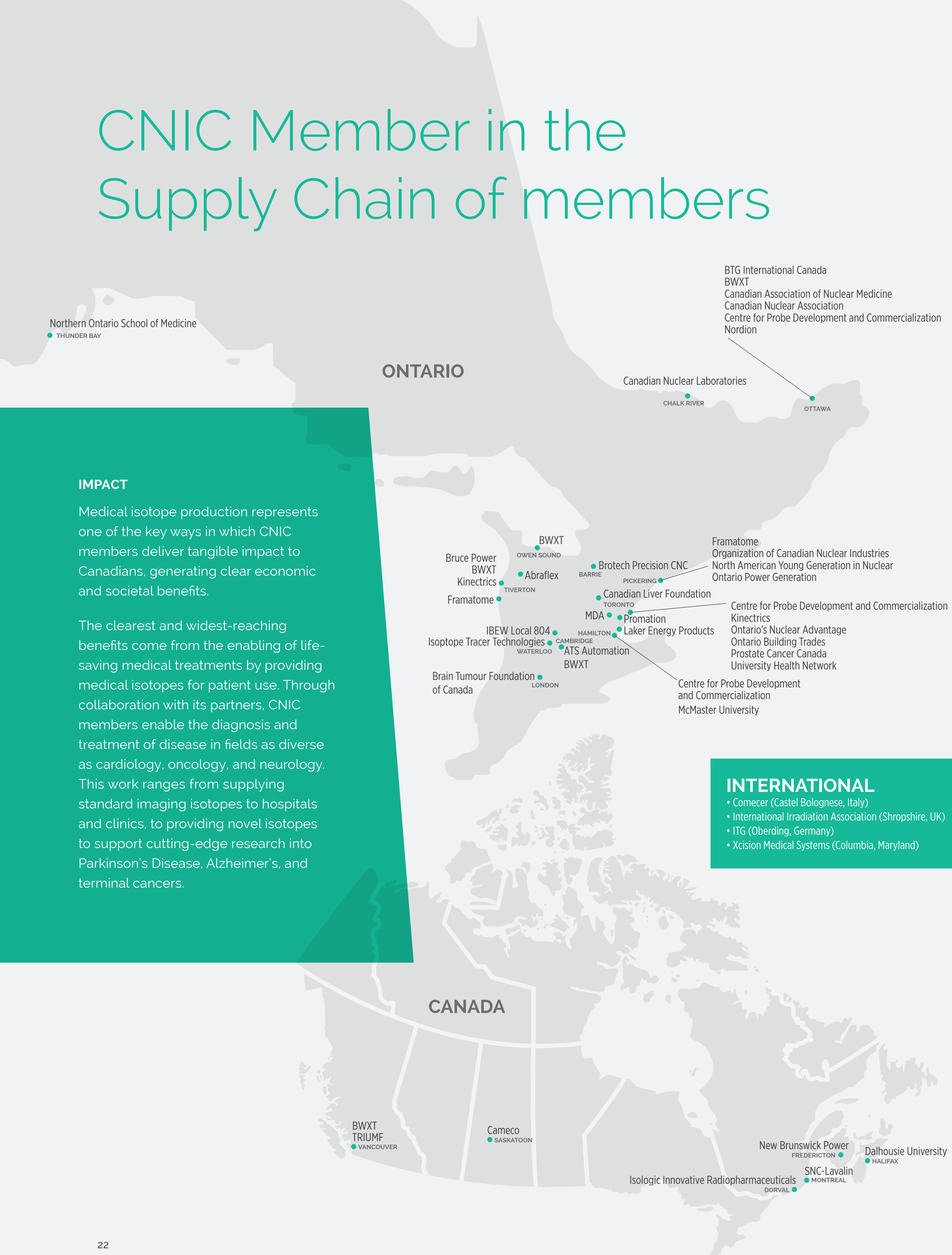
- 6 in Vancouver.
- 3 in Toronto and Montreal.
- 2 in Hamilton, Edmonton, Sherbooke, Que.
- 1 in Winnipeg (MB), London (ON), Ottawa (ON), Saskatoon (Sask), Thunder Bay (ON), Saint John's (NL), Halifax (NS).

CNIC Member in the Supply Chain of members

IMPACT

Medical isotope production represents one of the key ways in which CNIC members deliver tangible impact to Canadians, generating clear economic and societal benefits.

The clearest and widest-reaching benefits come from the enabling of life-saving medical treatments by providing medical isotopes for patient use. Through collaboration with its partners, CNIC members enable the diagnosis and treatment of disease in fields as diverse as cardiology, oncology, and neurology. This work ranges from supplying standard imaging isotopes to hospitals and clinics, to providing novel isotopes to support cutting-edge research into Parkinson's Disease, Alzheimer's, and terminal cancers.



INTERNATIONAL

- Comecer (Castel Bolognese, Italy)
- International Irradiation Association (Shropshire, UK)
- ITG (Oberding, Germany)
- Xcision Medical Systems (Columbia, Maryland)

Present and Future for Canada's Isotope Supply Chain

For more than 30 years, the four reactors at **Bruce Power's** Bruce B station have been a reliable Cobalt-60 supply for Nordion, an Ottawa-based company. Bruce Power's supply of Cobalt-60 helps to sterilize 40 per cent of the world's single-use medical devices, including sutures, syringes, masks, gloves and more. The company recently began producing medical-grade Cobalt-60 with the first harvest being completed in March 2019.

BWXT Isotope Technologies provides its customers, who conduct life-saving medical procedures for patients around the world, the benefit of decades of experience in the development, manufacturing, packaging and delivery of medical isotopes and radiopharmaceuticals. Headquartered in Kanata, Ontario, BWXT Isotope Technologies employs over 150 highly skilled people in Kanata and Vancouver, British Columbia. BWXT Isotope Technologies is part of the BWXT nuclear power segment (NPG) of BWX Technologies, Inc.

Though it no longer directly produces significant quantities of isotopes, the Chalk River site of **Canadian Nuclear Laboratories** is actively involved in researching the processing and application of isotopes for medical purposes. It is well positioned to contribute to the advancement of isotope processing and finding new applications, as well as the design of new isotope production facilities.

Centre for Probe Development and Commercialization (CPDC) operates three cyclotron facilities in Ontario, located in Hamilton, Toronto (CanProbe, a joint venture between the University Health Network and the CPDC), and Ottawa (at the University of Ottawa Heart Institute).

CPDC has established a robust and reliable global supply of innovative diagnostic and therapeutic radiopharmaceuticals used daily for the detection and treatment of human diseases such as cancer. To date, CPDC manufactures and supplies 15 radiopharmaceuticals for clinical and commercial supply, and CPDC's products collectively have helped with the diagnosis and treatment of more than 80,000 patients. These products include F-18, Lu-177, In-111, Ac-225, Ga-68, Tc-99m, Zr-89 and I-131.

McMaster University is Canada's pre-eminent nuclear research institution. The Hamilton-based post-secondary institution is home to a unique suite of world-class nuclear research facilities that are anchored by the five-megawatt McMaster Nuclear Reactor (MNR). With the closure of Chalk River's National Research Universal (NRU) reactor, MNR is now Canada's only major neutron source and therefore a key national research resource. Medical Isotopes from McMaster treat more than 70,000 patients globally per year.

For decades, **Ontario Power Generation's** (OPG) nuclear stations have not only provided clean, low-cost power for Ontarians, they have also been a world-leading source of life-saving medical isotopes. Since the 1970s, OPG has been successfully harvesting Cobalt-60 from reactors at its Pickering Nuclear GS. The Darlington Nuclear Generating Station east of Toronto is poised to become a major producer of a nuclear isotope used in the detection of heart disease and cancer. Ontario Power Generation announced that, pending regulatory approval, the facility would begin generation of Molybdenum-99 in 2021.

TRIUMF is a national university-owned and operated multidisciplinary facility with programs in particle and nuclear physics, accelerator science, quantum materials and life sciences. With 20 Canadian member universities, as well as dozens of collaborators and partners across the country and around the world, TRIUMF is a global hub for accelerator-based science. A critical component of the national isotope network, TRIUMF provides Canada with strategic advantage over growing global competition. Presently, approximately two-million doses of life-saving medical isotopes produced at TRIUMF each year are distributed to more than a dozen countries around the world.

The Canadian Situation

Canada has existing significant core infrastructure investments at Bruce Power (reactor based), Chalk River (waste handling and disposal), TRIUMF (accelerator based) and coupled with a strong research/clinical network and private sector investments Canada a very good base in the field of medical isotopes both in production and in their use.

Nearly the complete supply chain for the production, processing and delivery of medical isotopes is represented in Canada. In addition, we have a very well-equipped nuclear medicine infrastructure.

Canadians have identified that guarding and supporting our nuclear knowledge infrastructure is important for both our health care and safety. Canadian nuclear and medical infrastructure is ideal for performing fundamental and applied scientific research in the field of medical isotopes. All steps in the chain are present in order to perform our own research, but also to contribute to international developments and clinical trials.

In addition to sterilization, **Cobalt-60** is also used for medical procedures including the Gamma Knife. There are about 1,200 Cobalt-60 therapy machines operating throughout the world.

3900+ diagnostic imaging procedures with radioisotopes every day.

Canada has 45 approved radiopharmaceuticals: 23 currently approved radioisotopes, and is the world's leading supplier of two key medical isotopes.

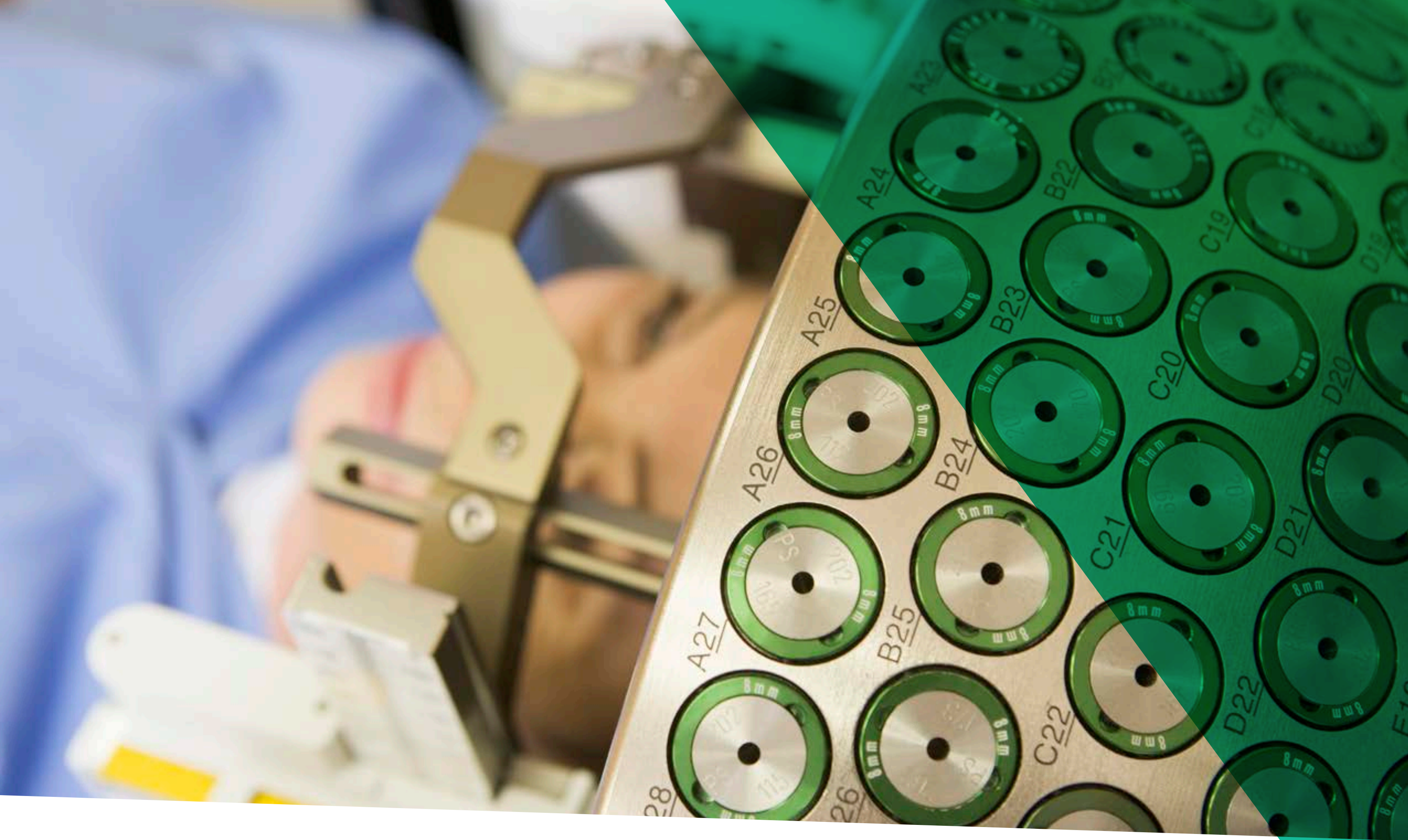
More than 40 per cent of all **single-use medical devices** produced globally are sterilized with Cobalt-60.

More than half of the global supply is produced within Canada from the **Bruce Power and Pickering reactors**. When including additional supply from global sources, **Canada refines more than 90 per cent of the Cobalt-60 market globally**.

With nearly 600 SPECT and SPECT-CT scanners at **336 hospital sites** distributed across the 10 provinces, a total of **1.35 million SPECT imaging procedures** were carried out in Canada in 2017 alone. This equates to **37 SPECT scans for every 1,000 Canadians**.

McMaster produces over 60% of the world's market of Iodine-125 which is used commonly in treating more than 200 brachytherapy patients per day, and over 70,000 per year globally.

***TheraSphere** is a radiotherapy treatment for hepatocellular carcinoma (HCC) that consists of millions of microscopic, radioactive glass microspheres (20-30 micrometres in diameter) being infused into the arteries that feed liver tumours. The product is manufactured in Canada for world-wide distribution.*

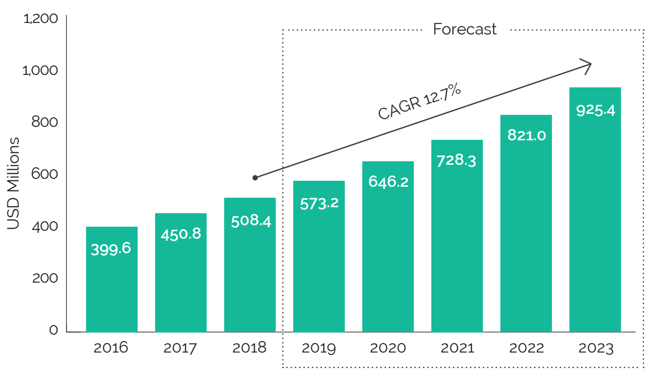


Canadian Market Trends

People in Canada and around the world rely on the continuous availability of medical isotopes, and see the potential for market growth in this industry. The entire supply chain is working hard on innovations that will ensure patients receive even better care in the future. The development of new therapeutic isotopes is a good example.

In 2018, the size of the Canadian medical isotope market was estimated to be $508.4 million (US) in 2018 and is projected to grow to $925.4 million by 2023, at a CAGR of 12.7 per cent. (Figure 4). Emerging markets, increasing demand for oncology treatment, and the improving reimbursement scenario surrounding insurance coverage, are expected to present a wide range of opportunities and demand for Canadian isotopes. Additionally, in Canada, key growth drivers include aging populations, the ongoing modernization of health care facilities, and growing demand from from both patients and doctors.

FIGURE 4: Canadian Medical Isotope Market



"An average of 11 Canadian men die from prostate cancer every day. We're working with our partners to change that statistic (by) developing innovative isotope treatments. Isotopes play a crucial role from diagnosis to treating advanced forms of the disease for which there is no cure."

Peter Coleridge, President and CEO, Prostate Cancer Canada

CANADIAN LUTETIUM-177

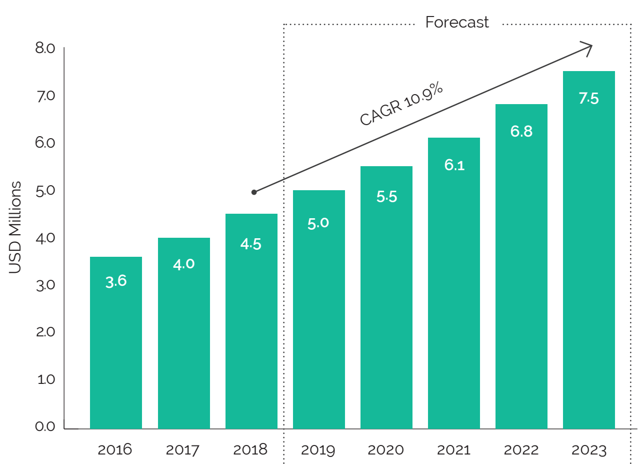
Lu-177 is used in targeted radionuclide therapy to treat conditions like neuroendocrine tumours and advanced prostate cancer. The medical grade isotope is used to destroy cancer cells while leaving healthy cells unaffected. Currently, Lu-177 accounts for 16 per cent of the beta emitters in the Canadian therapeutic product market.

Canada's supply of Lu-177 is mainly sourced from McMaster University's reactor. In June 2018, Bruce Power partnered with Isotopen Technologien München (ITM) to examine the production of Lu-177 at the Bruce Power site. Together, both through both Bruce Power and McMaster, Canada has the ability to meet global supply needs.

By leveraging our infrastructure, Canada can both support, new emerging isotopes as well as supply the current ones.

Lu-177 demand is projected to grow at a CAGR of 10.9 per cent over the 2018-23 forecast periods, owing to its increasing usage in treating cancer and other disease (Figure 5).

FIGURE 5: Canada Lutetium-177 Market Size, 2016-2023

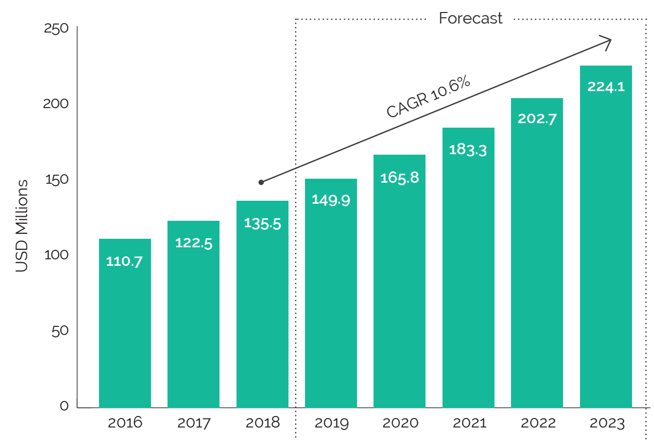


CANADIAN MOLYBDENUM-99/TECHNETIUM-99M

The domestic and world supply of Mo-99 was disrupted after Canada's National Research Universal (NRU) reactor in Chalk River ended production in 2016, requiring increased production by reactors in Europe, Africa and Australia. Due to this challenge, private sector companies like OPG and BWXT are working to neutron capture Mo-99 from a power reactor. Additionally cyclotron-based production pioneered in Canada has been critical in helping to meet demand. In fact with several TR24 and PET Trace machines in Canada, cyclotrons could produce enough Tc-99m for hundreds of thousands of patients per year.

Tc-99m usage in medical imaging is expected to rise at a CAGR of 10.6 per cent, where it is anticipated to increase to $224.1million in 2023 (Figure 6).

FIGURE 6: Canada Technetium-99m market size, 2016-2023



To ensure that Canadians benefit from recent advances in nuclear medicine, Canada must build and maintain a domestic supply of both established and emerging medical isotopes, and strengthen its ability to convert the raw isotopes into clinical quality products. Canada continues to have a strategic advantage in medical isotopes, but the challenge is clinical demand is changing, Health Canada has a slow approvals process and Canadian infrastructure is aging. Focusing on co-ordinated investment is required to maintain Canada's long-term global leadership into the future. Additionally, increasing reliable supply will help lower the price of isotopes, making it more affordable for patients in Canada and around the world.

Note: MOLYBDENUM-99/TECHNETIUM-99M and LUTETIUM-177 are featured in this section for various reasons including but not limited to their historical importance and/or current importance to Canada as well as their future importance and growth potential for the Canadian isotope supply chain.

The Future of Medical Isotopes in Canada

"Alpha and beta emitting isotopes attached to cancer targeting molecules can work in cases where nothing else works to treat patients who have failed conventional chemotherapy and radiotherapy,"

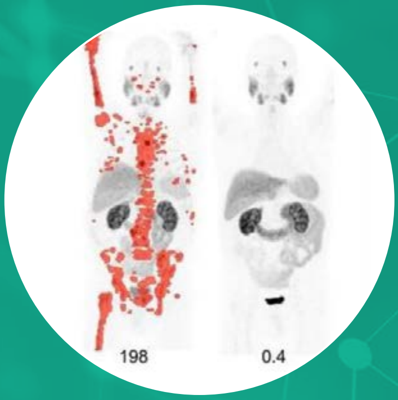
Dr. Paul Schaffer, a researcher at TRIUMF, Canada's Particle Accelerator Centre.

The future of medical isotopes in Canada looks bright. As we move into a new decade, medical isotope-based technologies are being developed and exported from Canada, while other new therapies arrive from Europe. At home, medical isotope-based therapies and treatment regimens are entering clinical trials — the final verification and validation process that is required by Health Canada before they become available to physicians for routine prescription. Canadian researchers continue to develop innovative targeting molecules, radiolabelling strategies, and medical isotope production methodologies to ensure that the pipeline to clinical trials remains full. Finally, target irradiation capacity for both cyclotron and nuclear reactor-generated isotopes is on the rise in Canada.

Also, nuclear medicine is rapidly following the trends in personalized medicine. One example is the combination of therapy and diagnostics, called "theranostics", which is an emerging application of medical isotopes. In theranostics, the radiopharmaceutical tracks down the tumour and, once it has been absorbed properly, the same molecule is labelled with a therapeutic substance (an alpha or beta emitter). This allows the treatment to be targeted and modified for maximum effectiveness and the fewest possible side effects.

Examples of this are diagnostics and therapy using the molecule PSMA. For example, when PSMA is linked to Lutetium-177, it then irradiates only those sites that are visible on the scan. When PSMA is linked to Actinium-225, the energy released by the isotope is strong enough to break DNA bonds in cancer cells, destroying their ability to repair and multiply, thus killing tumor cells. If the molecule is targeted with high specificity, you kill only the cells around the targeted cell without damaging the surrounding tissue that is healthy.

The combination of therapy and diagnostics means that nuclear medicines will make an even greater contribution to personalized medicine.



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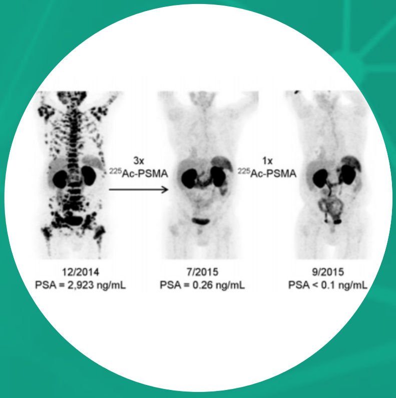


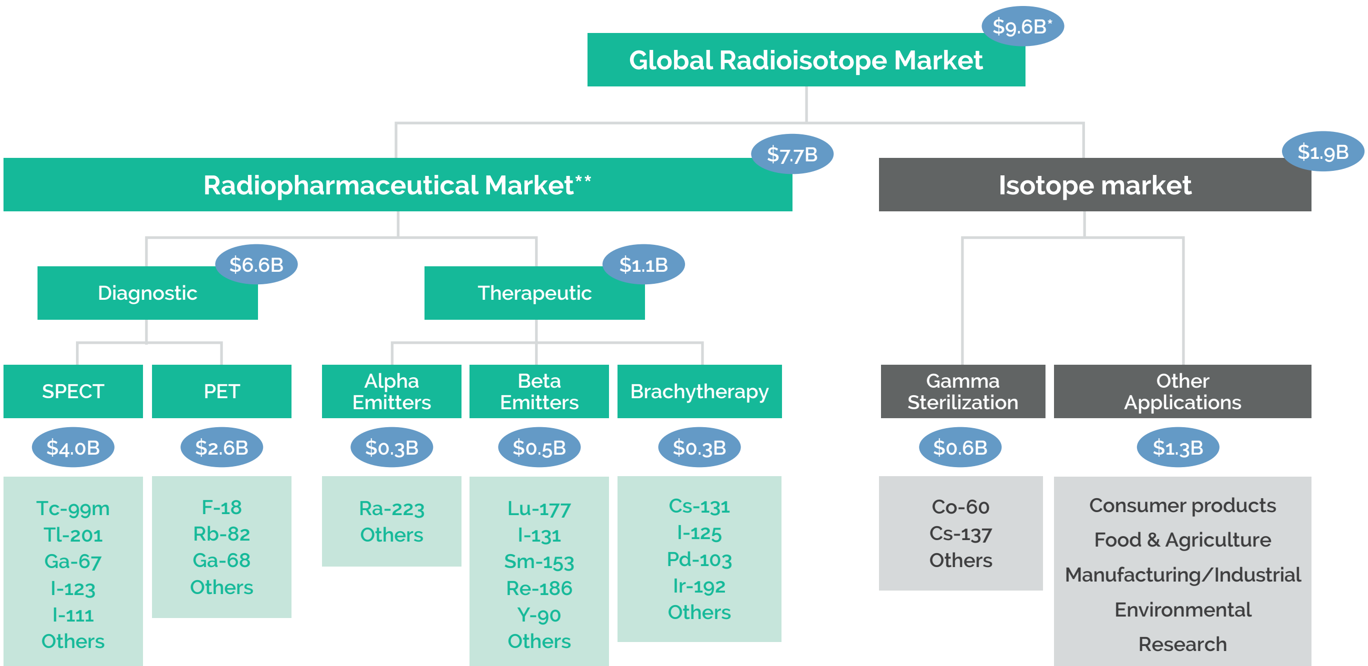
New targeted radiotherapy Reference: C Kratochwil et al, J Nuc Med (2016) doi:10.2967/ jnumed.116.178673

Global Business Analysis

GLOBAL MEDICAL ISOTOPE MARKET

The size of the global isotope market is estimated to be $9.6 billion (US) in 2018. As shown in Table 3 the global radiopharmaceutical (diagnostic and therapeutic) market accounted for approximately 80 per cent of the overall medial isotope market in 2018 ($7.7 billion US) with the radio non-pharmaceutical market accounting for 20 per cent ($1.98 billion US).

FIGURE 7: Global Isotope Market

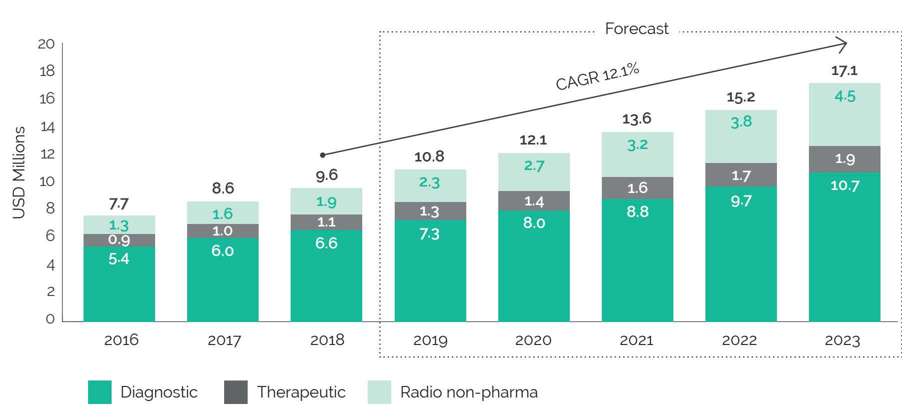


*Numbers may not sum due to rounding
**Note: As per World Nuclear Association, medical isotopes account for 80% of the global isotope market

Source: Grandview Research, World Nuclear Association, American Nuclear Society, Deloitte Analysis

While the global isotope market was valued at $9.6 billion US in 2018, all signs over the next five years indicate this will be a growing industry in Canada and worldwide. The global medical isotope market, comprised of radiopharmaceutical and radio non-pharmaceutical markets, is projected to grow at a CAGR of 12.1 per cent from 2018 to 2023 to a total of $17.1 billion in 2023 (Figure 8).

FIGURE 8: Global Isotope Market, 2016-2023



In 2018, North America accounted for the largest market share with approximately 40 per cent of the global market. However, globally, Asia-Pacific was estimated to register the fastest CAGR of 10.8 per cent through the 2018-23 forecast periods, with Japan, India and China at the forefront of that surge. The main drivers include an aging population, urbanization, and increasing health care expenditures in low and middle-income countries (Figure 9).

FIGURE 9: Medical Isotopes Global Business Analysis

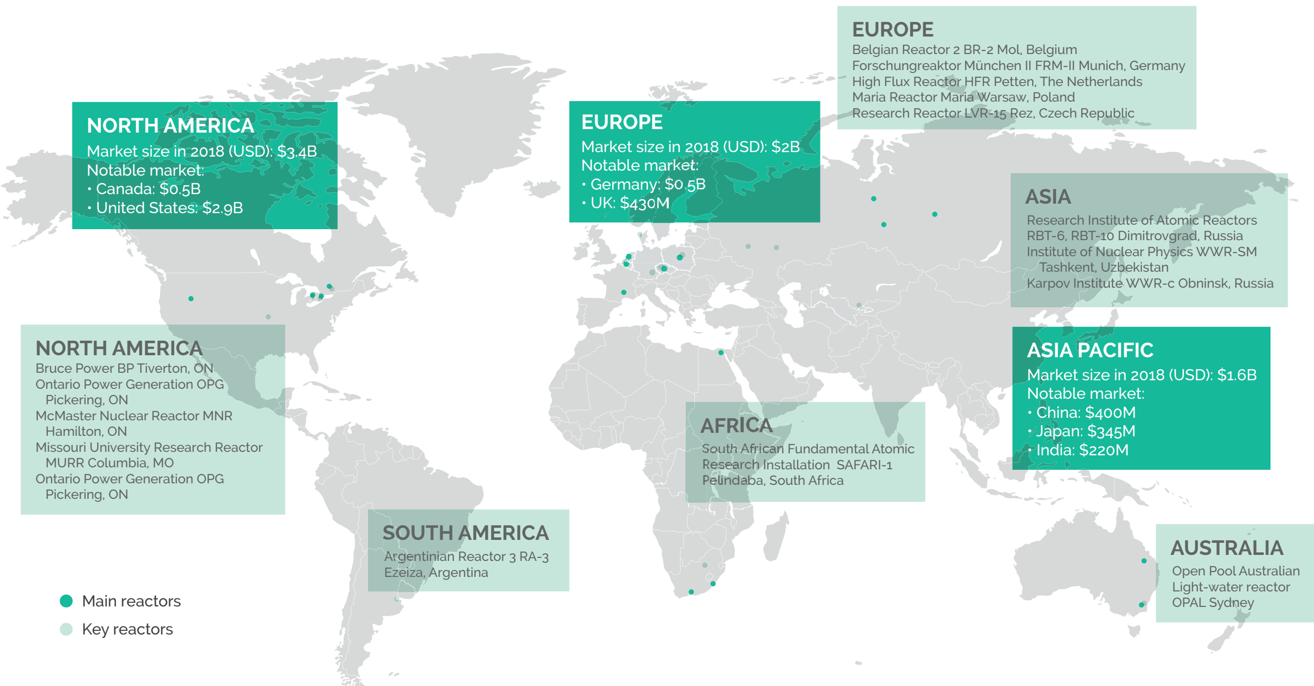


FIGURE 10: Global Isotope Needs

A major driver for the market growth of isotopes is its application in accurate diagnosis, imaging and treatment solutions. While diagnostic pharmaceuticals are the largest revenue generating segment in the market, targeted therapeutics, like Lu-177 and Ac-225, is a fast-developing market where key challenges include scaling up production, including improving availability and recycling of target materials.

What follows is examples of a subset of isotopes the demonstrate Canada's strategic advantage in the global market place.

ISOTOPE	Number of procedures using medical isotopes worldwide in 2017	Expected trend in the next 10 years
Tc-99m	35 million	+
I-131	1 million	=
Ra-223	10,000	++
Xe-133	100,000	--
Y-90	20,000	+
Ho-166	400	++
Lu-177	15,000	+++
Alpha emitters (Ac-225, Ra-223 etc.)	2,000	+++
Sr/Re/Sm	10,000-20,000	---
I-125	120,000-140,000	+
I-123	1,000,00	+
I-111	100,000	+

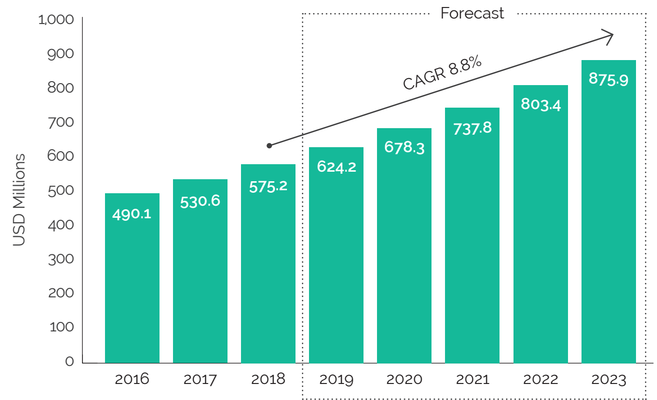
Drafted based on data from the OECD, IAEA and RG

GLOBAL GAMMA STERILIZATION AND COBALT-60 MARKET SIZE

Cobalt-60 is heavily used in gamma sterilization, encompassing more than 98 per cent of the isotope's demand. Over half of global supply is produced within Canada from the Bruce Power and Pickering reactors, and, when including additional supply from global sources, Canada refines more than 90 per cent of the Cobalt-60 market globally. Beyond medical sterilization, Cobalt-60 is the key component of the Sterile Insect Technique (SIT). This process aims at eliminating or suppressing diseases spread by insect populations, such as Zika, West Nile and dengue. At present, SIT is applied across six continents.

Over the 2018-23 forecast periods, global use of gamma sterilization is projected to grow at a CAGR of 8.8 per cent (Figure 11). Key growth factors for Cobalt-60 over this term are due to the fact that gamma radiation provides the ability to sterilize both the packaging as well as the product. The approval of gamma radiation as an industrial standard is expected to increase its adoption and make it the most preferred nuclear sterilization method.

FIGURE 11: Gamma Sterilization Market Size, 2016-2023

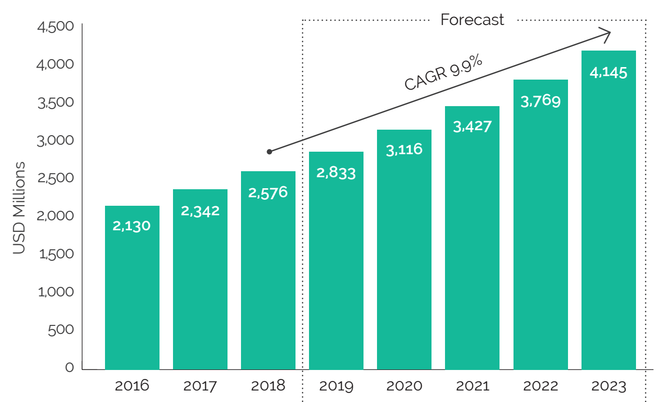


GLOBAL MOLYBDENUM-99/TECHNETIUM-99M MARKET SIZE

Production was increased at HFR, BR2, OPAL, SAFARI-1, LVR-15 and MARIA research reactors to bridge the gap left by the shutdown of the NRU reactor in Canada. Globally, the major suppliers of Mo-99 are Curium, IRE, NTP and ANSTO respectively. Tc-99m demand is anticipated to grow at a CAGR of 9.9 per cent during the 2018-23 forecast period, to reach a value of $4.145 million (US) in 2023 (Figure 12).

The demand for Mo-99 is anticipated to remain high over the forecast period. Cold kits used in the formulation of the final solution have a long shelf life and hence the demand for Tc-99m is expected to remain high over the next decade. The Tc-99m market was valued at $2.6 billion in 2018 and is expected to grow at a CAGR of 9.9 per cent during the 2018-23 forecast periods, reaching a value of $4.145 billion in 2023.

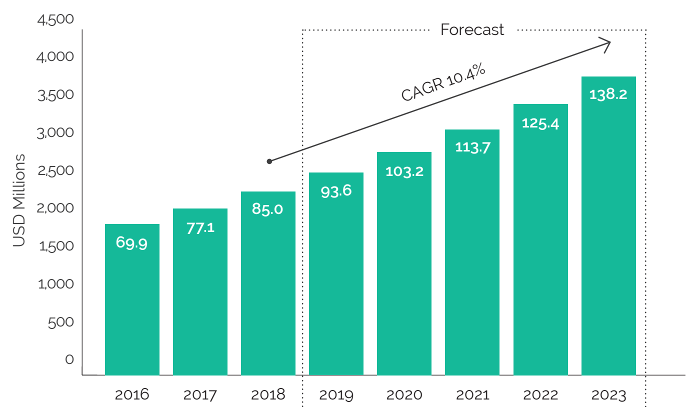
FIGURE 12: Technetium-99m Market Size



GLOBAL LUTETIUM-177 MARKET SIZE

The Lu-177 market was valued at $85 million (US) in 2018 and is expected to grow at a CAGR of 10.4 per cent during the 2018-23 forecast periods to reach a value of $138.2 million in 2023 (Figure 13). Lu-177 is a fast-developing market where key challenges include scaling up production, and improving availability and recycling of target materials. Lu-177 is included as one of the most widely used beta-emitting therapeutic isotopes. Beta emitters in particular have gained popularity in the past decade due to holding advantages such as effective treatment, low side effects and easy administration. In addition, the half-life of Lu-177 is 6.64 days, aiding in transport.

FIGURE 13: Lutetium-177 Market Size



Conclusion

As this report has demonstrated, Canadians support the need for a Pan-Canadian strategy on isotopes to ensure Canada **does not cede its** leadership position. The strategy should establish a framework for co-operation in which governments and stakeholders, **owners and operators** can work together to prevent, mitigate, prepare for, respond to, and recover from disruptions of critical infrastructure, and most importantly, continue to move forward with research and development of critical isotopes to improve people's lives.

If Canada is to maintain its standing as a leading force in global science — and enjoy the associated economic and societal benefits — the nation must invest in the isotope infrastructure. Investments that support Canada's isotope research and production to have a lasting impact on the outlook and promise of a cure for cancer. Canada's isotope innovations continue to serve as a model for delivering tangible impact, using science to find solutions to real world challenges. Canada has a long and successful history of developing new radiopharmaceuticals and medical isotope-based devices. If Canada is to continue to innovate on the global stage, this work must be supported. Bringing a new medical isotope device from the design phase through to a Phase I clinical trial takes years or even decades, and requires interdisciplinary collaboration across many fields. Canada has a roster of experts in translational medical isotope research: in universities from coast to coast; research organizations like BC Cancer, Canadian Nuclear Laboratories, the McMaster Nuclear Reactor, and TRIUMF, not--for-profit centres such as the Centre for Probe Development; and clinical trial sites in university hospitals and provincial cancer care agencies. Their work provides direct benefits to Canadians by bringing branches of multi-national clinical trials to Canada, providing Canadians with timely access to new radiopharmaceuticals.

While we celebrate the contributions of Canada's innovative nuclear scientists, we are focused on working together to build a better tomorrow.

ACKNOWLEDGMENT

The CNIC would like to thank the following organizations for their support and without whose contributions this report would not have been possible.

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