1 Health care systems require Tc-99m to maintain patient care

Nuclear medicine diagnostic procedures support diagnoses of disease in a broad range of medical specialties, organ systems and clinical indications. Prior experience illustrates that substitutes are available for some Technetium-99m-based scans. Cardiac and bone scans, which are a large share of all diagnostic scans, are notable examples of where substitution is possible. In some areas, alternatives to Tc-99m, such as PET scans in myocardial perfusion imaging, may in fact offer improved diagnostic performance. However, even where substitution is possible from a clinical point of view, it might not be easy to achieve in practice. For example, the current base of PET, CT and MRI equipment and workforce may not be able to absorb the additional volume of scans necessary to substitute for the use of Tc-99m. Substitution may also imply cost increases for health systems. No comparable substitutes are available in indications such as breast, melanoma and head/neck cancer sentinel lymph node studies, and in a range of diagnostics in children. In some areas Tc-99m-based scans also continue to be the preferred standard of care, such as whole-body bone scans to screen for skeletal metastases. Tc-99m will therefore continue to be an essential product for health systems.

1.1. Introduction

This Chapter provides an overview of the utility of nuclear medicine (NM) diagnostics from a clinical perspective. The Chapter also situates NM within a range of other diagnostic imaging modalities and outlines the main alternatives to Tc-99m-based procedures. It shows that NM diagnostics are used for a wide range of purposes. Although substitution would be clinically possible in some areas, it is not without challenges. There are also a number of uses of Tc-99m-based scans for which no alternatives are available. Finally, the Chapter provides an outlook on the future of NM.

1.2. Clinical overview of NM and other diagnostic imaging modalities

This Section summarises the main clinical uses of NM diagnostics, and of Tc-99m-based scans in particular, and situates NM within a range of other diagnostic imaging modalities.

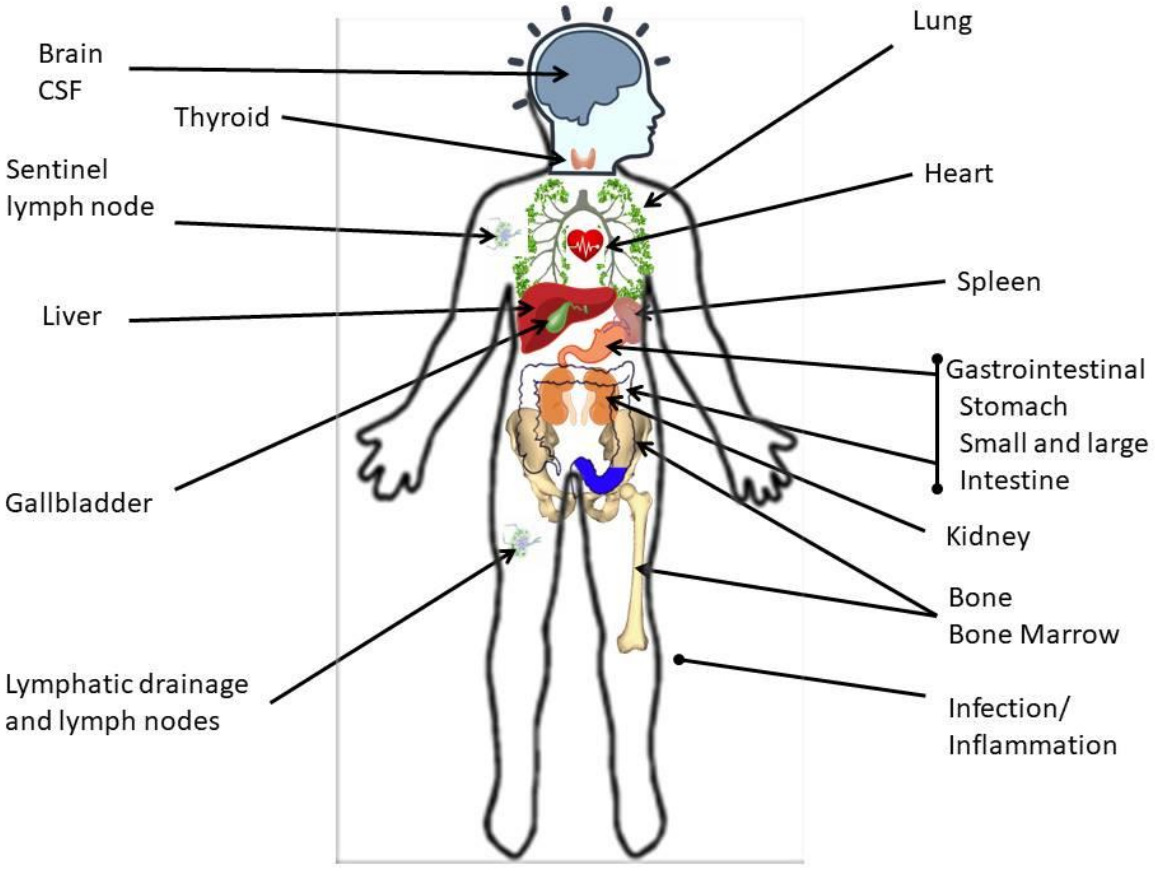
1.2.1. NM diagnostics are used for a wide range of indications

Nuclear medicine (NM) is a distinct clinical speciality that includes both diagnostic and therapeutic procedures. These involve the administration of radiolabelled materials and compounds known as *radiopharmaceuticals*, which are used for imaging, sample counting and therapy. The NM diagnostic imaging modalities are part of a broader set of imaging modalities including: x-ray plain film, x-ray fluoroscopy, x-ray computed tomography (CT), ultrasound (US) and magnetic resonance imaging (MRI). Therapeutic and interventional procedures are possible with all these modalities save for simple x-ray.

NM involves the administration of trace amounts of radiopharmaceuticals, through injection into veins (intravenous), skin (intradermal) or tissues (intraparenchymal) as well as breathing in (inhalation) or eating/drinking (ingestion).

After intake, the function, or physiology, of various tissues, organs or organ systems can be demonstrated and quantified relative to the pharmacological properties of the specific radiopharmaceutical used. NM can image and demonstrate function in many organ systems as is illustrated in Figure 1.1. Table 1.1 provides a list of Tc-99m-based radiopharmaceuticals and their use by organ system. It should be noted that there may be regional, national and international variation in the availability and utilisation of various NM radiopharmaceuticals and, as such, Figure 1.1 and Table 1.1 are for general reference only.

Figure 1.1. Major organ systems imaged with Tc-99m-based radiopharmaceuticals



Note: There may be regional, national and international variation in the availability and utilisation of various NM radiopharmaceuticals. This Figure is for general reference only.
Source: authors.

Technetium-99m (Tc-99m) is the most commonly used diagnostic NM radioisotope with Molybdenum-99 (Mo-99) being its parent isotope (i.e. Mo-99 undergoes radioactive decay to Tc-99m). Tc-99m was first proposed as a NM radioisotope in 1958 and since the 1980s Mo-99 has been sourced as a fission product from high enriched uranium (HEU) targets irradiated in nuclear research reactors. With the aging of nuclear research reactors, along with global policies concerning nuclear non-proliferation, there has been a phase-out in HEU target usage for Mo-99 production, and several alternate sources of bulk Mo-99 have been developed. These include fission production from low enriched uranium (LEU) targets; a return to neutron activation using natural or enriched Mo-98 targets in existing research reactors (e.g. Mo-98 + neutron = Mo-99) utilising new separation technologies; and particle accelerator production (e.g. linear accelerator production of Mo-99 and cyclotron direct production of Tc-99m) (Pillai, Dash and Knapp Jr., 2013[1]).

Table 1.1. Tc-99m-based radiopharmaceuticals and clinical indications by organ system

Organ System	Radiopharmaceutical -Indication	Comment	Alternate Modalities
Brain	^{99m}Tc ECD dementia/movement disorders, seizure disorders, brain death	Declining use of ECD with increasing use of MRI and FDG PET/CT for dementia/movement and seizure disorders. Clinical assessment and cerebral CT angiography are now most commonly used for the diagnosis of brain death.	MRI CT PET/CT – FDG PET/CT – growing list of specific neuro-tracers SPECT – ^{123}I-Datscan used for dopamine transporter imaging
CSF	^{99m}Tc DTPA Assessment of CSF flow in shunts between the brain and abdomen/heart	Low volume indication for which longer lived radioisotopes, such as ^{111}In, are being used as product sterility can be confirmed prospectively versus retrospectively, especially for procedures requiring lumbar punctures.	CT MRI NM-^{111}In-DTPA
Thyroid	^{99m}Tc (as Pertechnetate) to assess thyroid function in patients who may have overactive thyroid glands. To assess the function of thyroid nodules to help differentiate normal thyroid tissue from thyroid cancer.	^{123}I offers superior imaging and functional analysis but is generally more expensive which may influence relative utilisation of pertechnetate versus ^{123}I depending on economic and other circumstances.	NM-^{123}I PET-^{124}I NM-^{131}I (normally a thyroid therapy or uptake isotope which can also be used for imaging, most commonly in patients with thyroid cancer)
Parathyroid	^{99m}Tc (as Pertechnetate) ^{99m}Tc MIBI	In patients with biochemical evidence (i.e. elevated serum calcium and parathyroid hormone) of hyperparathyroidism, this test is used to help determine if a parathyroid adenoma is the cause. Usually done as SPECT/CT to help surgeons plan the least invasive approach to removing an identified parathyroid adenoma (e.g. in the past a surgeon may surgically explore both sides of the neck but with this study they will only need to operate on the side of the adenoma).	US – neck Other biochemical tests to rule other causes of non-primary hyperparathyroidism (e.g. renal failure, vitamin D deficiency) PET-CT-^{11}C-Methionine (generally only available in research centres) PET-CT-^{18}F-Fluorocholine (availability varies within and across jurisdictions) Selective venous sampling
Salivary Glands	^{99m}Tc (as Pertechnetate) salivary gland function, e.g. post head and neck radiation therapy.	An uncommon indication.	
Lung Perfusion and Ventilation (V/Q scans)	^{99m}Tc MAA quantify regional lung perfusion (e.g. prior to major lung surgery), to rule out pulmonary embolism (PE), or to quantify the impact of congenital anomalies such as pulmonary artery stenosis.	Untreated PE has a high fatality rate and is one of the main causes of maternal death during pregnancy in developed nations (Simcox et al., 2015[2]; Yazdani et al., 2015[3]). Diagnostic pathways for the diagnosis of PE are complex and have undergone considerable review and evolution (CADTH, 2018[4]; CADTH, 2018[5]). Multiple options exist for risk stratification through: clinical prediction rules (e.g. Geneva	CTPA NM – ^{133}Xe gas (less commonly used) NM – ^{85}Kr gas (historic)

Organ System	Radiopharmaceutical -Indication	Comment	Alternate Modalities
	^{99m}Tc as Technegas or various aerosolised ^{99m}Tc products for assessment of lung ventilation in conjunction with perfusion agents most commonly to rule out PE.	score, Wells and modified Wells criteria), PE rule-out criteria (e.g. D-dimer blood tests) and diagnostic imaging tests (e.g. VQ and CT pulmonary angiography or CTPA) (CADTH, 2018[4]; CADTH, 2018[5]). Depending on the jurisdiction, practice patterns vary widely between using NM V/Q scans versus CTPA to rule out PE. In jurisdictions which offer both V/Q and CTPA services clinical practice algorithms may be stratified by different patient characteristics (e.g. age, pregnancy, normal chest radiographs, presentation during regular working hours or afterhours, etc.).	
Cardiac Perfusion	^{99m}Tc MIBI or ^{99m}Tc Tetrofosmin to rule out myocardial ischemia or infarction as well as to quantify cardiac function.	One of the most utilised NM tests with high levels of evidence for utility in risk stratification of intermediate cardiac risk individuals, pre-operative cardiac risk assessment and follow-up post coronary artery intervention (Cremer and Hachamovitch, 2014[6]). The risk of significant cardiac event (e.g. myocardial infarction) can be stratified based on SPECT myocardial perfusion imaging (MPI) results as follows -: normal study < 1%, mildly abnormal up to 3%, moderately abnormal ~ 3% and severely abnormal ~ 4%. In diabetic patients, who are at increased cardiac risk, these numbers rise to: normal study 1%, mildly abnormal up to 4%, moderately/severely abnormal 8% (Berman et al., 2003[7]; Hachamovitch et al., 1998[8]). Standard of care myocardial perfusion imaging protocols have been established by the European Association of Nuclear Medicine (EANM 2015) and by a combination of: The Society of Nuclear Medicine (SNMMI), American Society of Nuclear Cardiology (ASNC) and the Society of Cardiovascular CT (SCCT) (Dorbala et al., 2013[9]). The ISCHEMIA trial[1] (ISCHEMIA Trial Research Group et al., 2018[10]) is an ongoing prospective multicentre (i.e. more than 400 centres globally) trial which has enrolled over 5000 participants. It utilises MPI risk stratification, along with other options (e.g. PET MPI, MR, exercise stress testing and ECG results), to determine inclusion into the study. The study randomises those at increased risk into medical versus interventional treatment arms to help determine the best course of action.	CTCA MRI, including adenosine / dobutamine stress MRI PET/CT ^{18}F-FDG (myocardial viability) PET/CT ^{82}Rb NM-^{201}Tl US – dobutamine stress echocardiography
Cardiac – MUGA	^{99m}Tc labelled RBC	A standard of care test for assessing cardiac function in various patient populations including pre-chemotherapy in cancer patients. Cardiac echocardiography (a form of US) is a reasonable alternate noting MUGA scans are more accurate in estimating left ventricular ejection fraction.	US – echocardiography MRI Ventriculogram post cardiac catheterisation – fluoroscopy
Sentinel Node and Lymphatic System	^{99m}Tc Sulfur colloid (North America), ^{99m}Tc Nanocolloids (Europe) to identify the first lymph node that drains the body area that has an identified cancer.	Sentinel lymph nodes (SNL) studies are a standard of care procedure for breast cancer and are also commonly used for melanoma and head and neck cancers. There is also growing use in patients with vulvar cancer. SNL studies, in combination with intraoperative blue dye injection, assist surgeons in demonstrating the first lymph node(s) that drain the tissues around the identified cancer. The pathological status of the sentinel lymph nodes drives patient management (e.g. if	Intraoperative blue dye infusion which is commonly done as a complementary procedure. New developments with optical and magnetic nanobeads are currently being assessed and are largely investigational

Organ System	Radiopharmaceutical -Indication	Comment	Alternate Modalities
		positive: further lymph node harvesting, addition of chemotherapy or radiation therapy etc.). For women with breast cancer this has resulted in significantly reduced morbidity (e.g. swelling and pain) associated with extensive axillary (i.e. armpit) lymph node dissection and removal (Buscombe et al., 2007[11]). The sentinel lymph node can be identified by imaging, most commonly via SPECT/CT, and intra-operatively, as a non-imaging procedure, by the surgeon using a gamma probe to detect accumulated radiation in the lymph node. Assessing lymphatic drainage is an uncommon test. It is an option to help manage patients with leg or arm oedema of unknown aetiology.	at present.
Liver and gallbladder	^{99m}Tc Mebrofinin, ^{99m}Tc HIDA, ^{99m}Tc DISIDA, ^{99m}Tc Sulfur colloid, ^{99m}Tc labelled red blood cells ^{99m}Tc-MAA used to detect shunting prior to therapeutic interventions such as SIRT.	Most commonly used to assess bile drainage patterns from the liver and to confirm drainage of the gallbladder (e.g. to rule out gallbladder outlet obstruction from gallstones). In specific circumstances US and MRI cholangiograms are equally effective alternates, and use will depend on the jurisdiction. Considered a standard of care study to rule out biliary atresia (i.e. the lack of a biliary drainage system) in jaundiced neonatal patients. Less commonly used to characterise liver lesions of indeterminate aetiology on CT or MRI.	CT MRI – general MRI – cholangiography US
Gastrointestinal tract, stomach, small bowel and colonic transit	^{99m}Tc labelled foods for gastric emptying studies (e.g. in diabetic patients whose stomachs may empty slowly).	Variable practice with lack of consensus on standard solid or liquid meals. Growing interest in the evaluation of dyspepsia and gastroparesis.	Some MRI procedures currently being assessed. Breath tests- ^{13}C or ^{14}C urea breath tests used to diagnose for *helicobacter pylori* related gastritis.
Bone/Bone Marrow	^{99m}Tc MDP, ^{99m}Tc HDP used in the most common indications for bone scans to detect tumour, trauma/fractures or infection in bones. ^{99m}Tc Sulfur colloid/nano-colloid used to distinguish bone marrow redistribution, versus infection, especially in the setting of bone trauma or prior orthopaedic interventions such as joint replacements (i.e. to increase the specificity of a combination WBC/marrow or bone/marrow scan).	Whole body bone scanning is standard of care for staging cancers such as prostate or breast. Bone scans are more efficient and less costly versus whole body CT or MRI for assessing metastatic bone involvement. ^{18}F(NaF) PET/CT bone scans are an alternative but PET/CT is more expensive and may not be as available for this relatively high volume indication. Standard of care bone scanning imaging protocols have been established by the EANM (Van Den Wyngaert et al., 2016[12]) and by the SNMMI (2003[13]).	CT MRI PET/CT-^{18}F NaF PET/CT – FDG – to detect marrow infiltration or tumour presences in bone
Spleen	^{99m}Tc Sulfur colloid or heat damaged ^{99m}Tc labelled RBC can be used to assess for splenic function (i.e. to rule out functional asplenia) or the presence of splenic remnants post splenectomy.	Uncommon but a relatively specific test to determine the function of the spleen which may be anatomically present but clinical assessment suggests splenic dysfunction. Patients who have had a splenectomy but still have undefined soft tissue nodules on their CT scan or who have persistent symptoms related to possible splenic remnants may benefit from this test.	CT MRI

Organ System	Radiopharmaceutical -Indication	Comment	Alternate Modalities
Renal	^{99m}Tc MAG3, ^{99m}Tc DTPA, ^{99m}Tc DMSA used to assess for renal function in native and transplanted kidneys and to assess for blockages in urine flow between the kidney and the bladder. ^{99m}Tc DMSA scans are also used to confirm renal scarring.	NM renography has long been used to assess renal function and to detect renal outflow obstruction (Taylor et al., 2018[14]). This is especially important in children where surgical interventions (e.g. pyeloplasty) are largely predicated on renal functional status (Gordon et al., 2011[15]). The referral base is largely related to investigating prenatal US findings (e.g. prenatal hydronephrosis). ^{99m}Tc DTPA is also used for the assessment of GFR as a non-imaging study. This is especially valuable in work up of paediatric patients undergoing chemotherapy, where the amount of administered chemotherapy drug is based on renal function. (This is even more critical as production of ^{51}Cr-EDTA has been discontinued in early 2019). Post renal transplant assessment of function, renal blood flow and possible leakage. Doppler US has generally become the DI modality of choice with NM being used selectively to monitor function in impaired transplant kidneys or to demonstrate a urine leak. NM is the standard of care for assessing renal function and for obstruction although MRI protocols are being developed (Zhang et al., 2013[16]; Ebrahimi, Textor and Lerman, 2014[17]).	Angiography CT MRI US
Infection	^{99m}Tc HMPAO labelled WBC to localise infection/inflammation. Tc-99m-labeled antibodies in a scan of bone marrow or to localise infection/inflammation.	Largely replaced with ^{111}In labelled WBC or FDG PET/CT.	PET/CT-^{18}F-FDG NM-^{111}In-WBC
Other	^{99m}Tc Labelled RBC to detect for the presence and location of gastrointestinal (GI) bleeding	^{99m}Tc Labelled RBC is the most sensitive test to detect the presence of GI (e.g. small intestine and colon) bleeding and is about 10 times more sensitive than CTA. The disadvantages are that the patient has to be actively bleeding at the time of imaging, and imaging times can be as long as two hours. Anatomic identification of the source of bleeding is less specific than for angiography/CTA.	

Notes: There may be regional, national and international variation in the availability and utilisation of various NM radiopharmaceuticals. This Table is for general reference only. CSF... cerebrospinal flow, CT... computed tomography, CTA... computed tomography angiograpy. CTCA... CT coronary angiogram, CTPA... computed tomography pulmonary angiography, DTPA... diethylenetriamine-pentacetate, DMSA... dimercaptosuccinic acid, ECD... ethyl cysteinate dimer, Echo...echocardiography, EDTA… **e**thylenediaminetetraacetic acid, FDG... flurodeoxyglucose, GFR… glomerular filtration rate, ^{85}Kr gas…Krypton-85 gas as a ventilation imaging agent, MAA... macro aggregated albumin, HDP... hydroxymethylene diphosphonate, MAG3... Mercaptoacetyltriglycine, MDP... methylene diphosphonate, MIBI...sestimibi, NM...Nuclear Medicine, MUGA... multi-unit gated acquisition, NaF... sodium fluoride, PE...pulmonary emboli, PET... positron emission tomography, RBC...red blood cells, SIRT…selective internal radiation therapy, US...ultrasound, V/Q... ventilation perfusion, WBC...white blood cells, ^{133}Xe gas…Xenon-133 gas as a ventilation imaging agent.
Source: Author based on sources cited in the Table.

NM diagnostic imaging is used in a broad range of fields. Figure 1.2 shows relative levels of utilisation of NM (SPECT/CT and PET/CT) by organ system or medical specialty compared to other imaging modalities in Canada, with the highest colour density indicting an important leading use, the lighter colour density indicating secondary or more limited use and no colour indicating no use. Is it notable that NM is used across a broader range of purposes than CT and MRI. In some areas, only NM diagnostics are used. In the leading areas of use of diagnostic imaging, i.e. oncology and to a lesser extent neurology and cardiology, all of the technology types are used. The Figure represents the recent usage pattern in Canada, the relative usage patterns in other countries may differ.

Figure 1.2. Relative use of NM (SPECT/CT and PET/CT) diagnostics and other imaging modalities by organ systems

Note: The Figure represents the recent usage pattern in Canada, the relative usage patterns in other countries may differ.
Source: Adapted by the authors from Table 27 of the Canadian Medical Imaging Inventory (CADTH, 2018[18])

Once radiopharmaceuticals are administered and internalised by the patient, they are “physiologically” distributed within the body. NM is called a “functional” imaging modality as it reflects both normal, and abnormal, organ and tissue physiology based on the resulting bio-distribution of the various radiopharmaceuticals. The time between radiopharmaceutical administration and imaging is variable depending on the route of administration and the specific NM study being conducted. Imaging times (i.e. the amount of time that a patient is under the NM camera) are also variable depending on the specific protocol.

Other imaging modalities are generally thought of as “anatomical” imaging modalities as they characterise the detailed body anatomy and structure but not necessarily the functions. For example, a kidney US may demonstrate that there is fluid held up in the renal collecting systems (i.e. hydronephrosis) but US will not quantify the degree of functional impairment, if any, in the affected kidney. A NM renal scan will be able to demonstrate whether there is a physiologically significant obstruction in the renal collecting system.

As an example of NM imaging, Figure 1.3 demonstrates normal (a) and abnormal whole-body bone scans (b). These Figures demonstrate the convenience of visualising the whole skeleton in one set of images. Subtle or equivocal findings in these images can be further interrogated or supplemented with additional cross-sectional images (e.g. SPECT/CT).

There are also technological differences in how images are acquired between NM and other imaging modalities.

For x-ray, fluoroscopy and CT, x-rays are produced and transmitted through the patient and registered on a detector producing a tissue density “shadow” image. These can be static images, such as in x-ray, or cross-sectional images, as in CT. CT images can also be reformatted to produce three-dimensional representations of the anatomy.

For US, high frequency sound waves are transmitted through tissues and their reflected waves are collected to form images.

The physics of MRI imaging is complex. In brief, patients are put into a strong pulsing magnetic field, which causes atoms, predominately hydrogen, to line up in an orderly fashion. The alignment and relaxation of atoms with each pulse release signals which are collected and converted into detailed images. There is abundant hydrogen present to facilitate MRI imaging because tissues predominately consist of water.

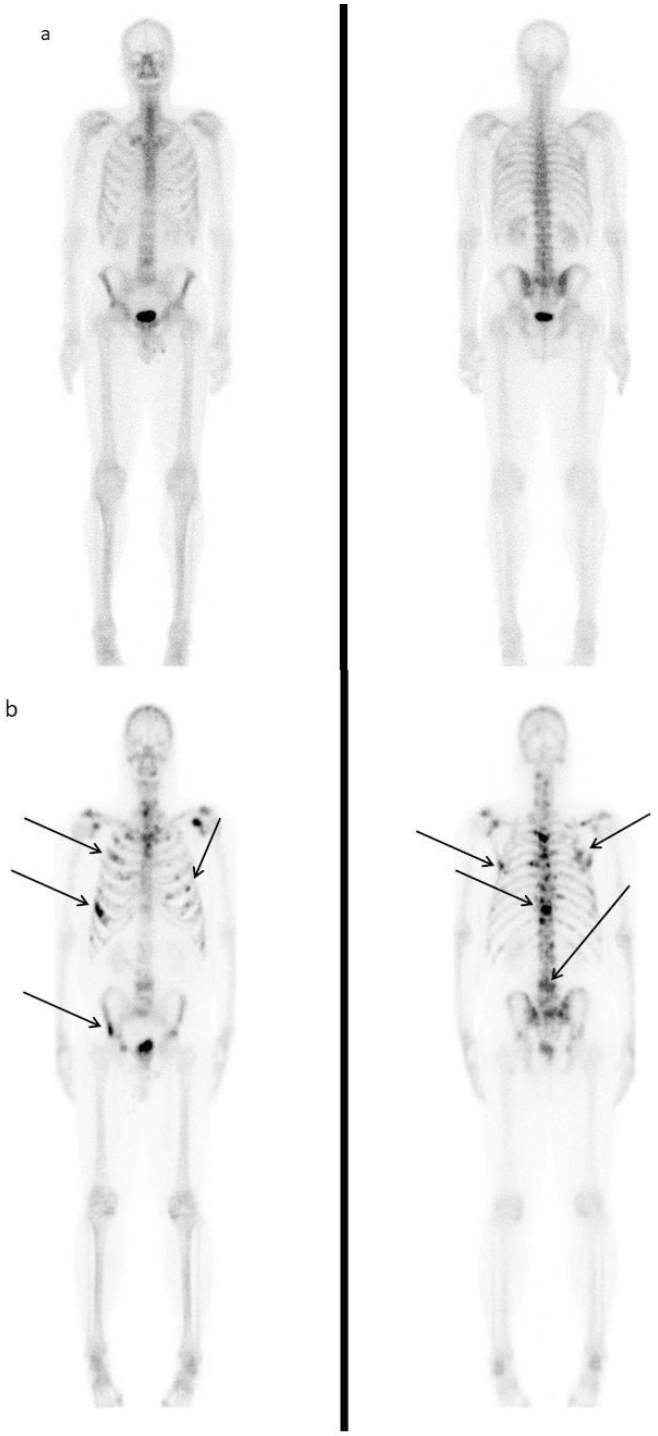
In NM diagnostic imaging, diagnostic radiopharmaceuticals undergo radioactive decay and emit gamma photons which are registered on detectors in gamma cameras. Each detected photon is registered as a “point” and, during scanning, hundreds of thousands of points are collected to form a final image. This is similar to how artists, such as Paul Signac, painted point by point (i.e. “pointillism”).

NM imaging can be in the form of static pictures, moving pictures (e.g. cine), cross-sectional images and three-dimensional images. Cross-sectional images are referred to as single photon emission computed tomography (SPECT). The majority of NM cameras have two gamma detector heads on a rotating axis and many are now combined with a CT unit to allow the production of combined functional and anatomical fused image sets (so-called hybrid imaging – see Section 1.2.2).

Some medical radioisotopes undergo positron decay resulting in the simultaneous emission of two photons that move in opposite directions. These isotopes require specialised NM cameras called “positron emission tomography – computed tomography” (PET/CT) cameras for imaging. Fluorine-18 (F-18) is the most common PET isotope and is most commonly used in the form of sugar (i.e. ^{18}F-Fluro-deoxy-glucose or FDG). F-18 has a relatively short half-life of approximately two hours. PET isotopes are produced by low energy medical cyclotrons that are often located on-site in hospitals or in nuclear pharmacies. FDG PET/CT has become the standard of care in oncology imaging (e.g. for disease staging, response to therapy and recurrence assessment).

Figure 1.3. Whole body Tc-99m methylene diphosphonate bone scan

Normal (a) and abnormal (b)



Note: a. illustrates a normal bone scan with expected excreted activity in the kidneys (arrow) and bladder (white arrow head), b. illustrates an abnormal bone scan in a patient with multiple skeletal metastatic deposits, some of which are marked with arrows.
Source: Images Courtesy of Dr Sandor J. Demeter, Health Sciences Centre, Winnipeg, Manitoba.

1.2.2. Hybrid imaging techniques have improved diagnosis

The advent of hybrid imaging technologies, such as SPECT/CT and PET/CT began in the early 1990s (Patton, Townsend and Hutton, 2009[19]) and revolutionised the practice of NM (Bockisch et al., 2009[20]; Even-Sapir, Keidar and Bar-Shalom, 2009[21]). Figure 1.4 illustrates a typical SPECT/CT NM camera. More recently, circa 2010, some whole-body clinical PET/MRI units have been installed in Europe[1] and North America (Muzic and DiFilippo, 2014[22]), primarily in research settings.

There are many benefits of hybrid technologies, which allow functional imaging to be fused with detailed anatomic imaging. For example, this significantly improves the sensitivity and specificity of diagnosis, especially for oncology patients (Bockisch et al., 2009[20]; Jadvar and Colletti, 2014[23]). In another example, a recent retrospective study by Pazhenkottil et al. (2018[24]) demonstrated that combining data from CT (i.e. CT coronary angiography) and SPECT (i.e. myocardial perfusion) is valuable in predicting major adverse cardiac events (MACE).

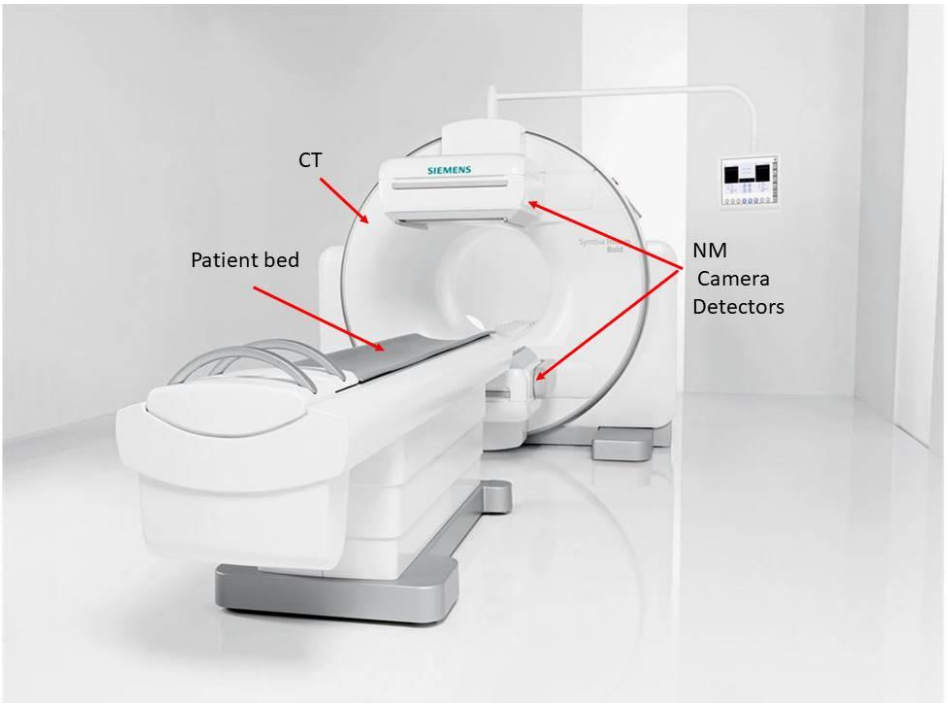
1.2.3. The evidence base for traditional Tc-99m-based NM diagnostics is relatively weak

There have been significant historical advances in all diagnostic imaging modalities and this has resulted in changes in the standards of care for many clinical indications. This is the environment in which NM must compete to remain relevant.

Radiopharmaceuticals were unregulated in many countries during the early days of NM and were only subjected to pharmaceutical regulation later, which increased evidence requirements. The term “evidence-based medicine” was first published in 1990 (Eddy, 1990[25]). This was after the development and introduction of many conventional Tc-99m-based radiopharmaceuticals, which became standard of care based on historical use and expert opinion. In contrast with newer Tc-99m-based and PET radiopharmaceuticals, which have generally undergone full prospective clinical trials, the strength of evidence for most conventional Tc-99m based radiopharmaceuticals is relatively weak compared to standard level of evidence frameworks[2] and falls into “observational studies” and “expert opinion” categories. Tc-99m based myocardial perfusion imaging agents (e.g. MIBI and Tetrofosmin) are an exception, where high levels of evidence of their utility exist.

Figure 1.4. SPECT/CT Camera

The patient bed moves patients into the camera for sequential CT and NM imaging



Source: © 2018 Siemens Healthcare GmbH. All Rights Reserved. Product photo provided courtesy of Siemens Healthcare GmbH.

1.3. There are alternatives to Tc-99m but substitutability may be limited

The effect of shortages of Tc-99m in 2009 and 2010 illustrated the need for Tc-99m in health care and hold a number of lessons on possible responses to future shortages, including substitution with alternative imaging modalities or NM radioisotopes. This Section summarises responses to the 2009 and 2010 shortage in Canada and the United States and collates existing information on substitutability of Tc-99m.

1.3.1. Substitution of Tc-99m-based scans is possible for some indications but may encounter practical difficulties

While there is scope for substitution in the face of severe Mo-99/Tc-99m shortages, substitution is not without practical challenges and may increase the cost to health care systems.

Table 1.2 outlines the pros and cons of alternate approaches for common Tc-99m-based procedures: bone, cardiac perfusion and pulmonary embolism imaging. These scans constitute a large share of all NM diagnostic procedures (see Chapter 2). Some can be replaced with PET/CT and CT pulmonary angiography, which generally have equal or superior diagnostic accuracy. However, one of the greatest hurdles to achieving this transition, especially during a Tc-99m shortage, would be to gain access to the smaller installed base of PET/CT scanners, which is already heavily relied upon for oncology indications. Although an analysis of the cost of alternatives is not in scope of this report, PET procedures are generally more expensive than Tc-99m-based procedures so that substitution would likely increase costs.

Tc-99m-based scans continue to be the preferred standard of care for some indications (e.g. whole-body bone scanning to screen for metastatic cancer spread to bones). There are some Tc-99m-based studies for which there are no comparable substitutes, for example NM sentinel node studies in breast, melanoma

and head and neck cancer. There are also no ideal substitutes for Tc-99m-based NM renal studies, especially to assess function and blockages in paediatric populations. Parathyroid imaging to rule out a parathyroid adenoma is another example of a currently unique role for NM. Although that F-18 Choline is a promising alternative parathyroid imaging agent, availability varies within and between jurisdictions.

An individual national view was summarised in 2014, when the French National Academy of Medicine published a communiqué in response to a government request outlining the possible effects of a sustained shortage of Tc-99m.[3] The document pointed out the lack of alternatives to Tc-99m-based scans in studies of the sentinel lymph node, in particular for breast cancer patients; in diagnosis of pulmonary embolism in pregnant women to avoid CT with contrast injection, which can pose risks to the development of the thyroid gland of the foetus; on patients with a contraindication to contrast media, such as diabetic patients with renal insufficiency or treated with metformin; in detection of the origin of hyperparathyroidism; on most paediatric patients, in particular mainly bone and renal scans; and in studies to assess separate function of the two kidneys. The document also noted that substitution of Tc-99m, for example with PET and Tl-201-based scans, was clinically possible in bone and myocardial scans, albeit at a higher cost to the French health care system and only with additional investments in PET scanner infrastructure.[3]

Historically all NM myocardial perfusion tests used Tl-201. As outlined in Table 1.2, there are some advantages and disadvantages to using Tl-201 versus Tc-99m-based myocardial perfusion agents. Major disadvantages of using Tl-201 is less flexible patient imaging logistics and increased patient radiation dose.

Radiation dose may be another consideration in substitutability of NM scans with other diagnostic imaging modalities. Especially in paediatric populations, the level of radiation dose continues to receive a high level of attention. Diagnostic imaging appropriateness guidelines[4] include radiation dose as a consideration of what imaging modality to choose. There have been some advances made in reducing NM doses through guidelines (e.g. by EANM and SNMNI) or through advances in image reconstruction, which allow for either lower dose or faster imaging with the conventional dose (e.g. allowing higher patient throughput). MRI and US have do not expose patients to ionising radiation.

While relative dose reduction for CT has generally outpaced dose reduction in NM, minimising radiation dose is a moving target because new generations of equipment have the potential for additional dose reduction. In addition, advances are being made in dose reduction for CT and NM via both hardware (e.g. solid-state NM detectors) and software development (e.g. iterative image reconstruction). Further information on radiation doses is presented in Section 1.4.1.

Table 1.2. Alternatives to common Tc-99m-based diagnostic procedures in the setting of severe Tc-99m shortages

In the setting of severe Tc-99m shortages.

Tc-99m Procedure	Alternate	Pro	Con
Bone Scan (99mTc MDP)	^{18}F as NaF (Sodium Fluoride)	Easily produced in medical cyclotrons. Similar radiation dose. Superior diagnostic performance (Bastawrous et al., 2014[26]; Langsteger et al., 2016[27])	SPECT/CT has a larger installed base. The current installed PET/CT base may not be able to accommodate bone imaging demand without significant investment due to existing demands from oncology, neurology and cardiac indications.
Myocardial Perfusion Imaging (99mTc Sestimibi or Tetrofosmin)	^{82}Rb (Rubidium-82) (PET Tracer)	^{82}Rb has a short half life (75 seconds) allowing serial rest and stress studies to be done in one appointment. ^{89}Sr/^{82}Rb is generator produced and does not require a local medical cyclotron. Lower radiation dose. Superior diagnostic performance (Ghotbi, Kjær and Hasbak, 2014[28]; Knight et al., 2018[29]).	SPECT/CT has a larger installed base and cardiac PET is generally provided only in dedicated centres. The current general installed PET/CT base may not be able to accommodate MPI imaging demand without significant investment to also accommodate existing oncology, neurology and cardiac indications. The economics of cost per case will vary by jurisdiction depending on relative costs of the ^{99m}Tc radiopharmaceuticals and the ^{89}Sr/^{82}Rb generator. Can only be used for pharmacological cardiac stress tests (i.e. not for exercise MPI protocols). Not presently licensed in all jurisdictions.
Myocardial Perfusion Imaging (99mTc Sestimibi or Tetrofosmin)	^{201}Tl (Thallium-201)	Established myocardial perfusion imaging protocols as it pre-dated ^{99m}Tc based myocardial perfusion agents. Easy to re-establish use. Cyclotron produced and not impacted by fluctuations in reactor based medical isotope production. Slightly better at identifying viable myocardium and identifying defect related to less sever coronary artery stenosis. Some centres use a ^{201}Tl/^{99m}Tc (i.e. for rest/stress phases) protocol which can be efficient and increase throughput and takes advantage of the desirable aspects of both agents (Pagnanelli and Basso, 2010[30]).	Higher radiation dose. Slightly poorer spatial resolution for imaging. Less convenient imaging protocols due to relatively tight timelines between injection and imaging. For stress protocols the treadmill has to be in close proximity to the NM camera. Loss of working experience with ^{201}Tl in some departments.
MUGA scans	Echocardiography	Provides additional information related to heart valve function and cardiac muscle disease (i.e. cardiomyopathies). Possible to combine with a dobutamine infusion (i.e. a dobutamine stress echo) which can assess wall motion under rest/stress condition to detect myocardium at risk (e.g. ischemia) (Senior et al., 2005[31]; Takagi, 2017[32]). No radiation dose to patient.	ECHO calculated ejection fractions require geometrical assumptions which are not required by MUGA. MUGA ejection fractions, especially at the low end, may be more accurate (Bellenger et al., 2000[33]). Patient body habitus can significantly interfere with echo image quality (transthoracic approach); more so than with MUGA scans. Transesophageal approach is much less comfortable for patients.
Lung Scans for PE	CTPA	Slightly better diagnostic performance with pooled	Contraindicated in patients with CT contrast allergies or hypersensitivities.

Tc-99m Procedure	Alternate	Pro	Con
99mTc MAA – perfusion 99mTc – various ventilation agents		sensitivity/specificity (CADTH, 2018[5]). CT has a larger install base than SPECT/CT. Shorter procedure time. More timely access as CT departments which serve acute care centres and are generally staffed 24/7 which may not be the case for NM departments.	Relative contraindication for patients in renal failure. Higher nominal radiation dose.

Note: CTPA: computed tomography pulmonary angiography, MAA: Macroaggregated albumin, MDP: methyl diphosphonate, MPI: myocardial perfusion imaging, MUGA: multi-unit gated acquisition, PE: pulmonary embolus, SPECT: single photon computed tomography, VQ: ventilation perfusion.
Sources: Author and sources cited in the Table.

1.3.2. Strategies to respond to shortages

This Section briefly summarises strategies related to substitution of Tc-99m-based NM diagnostic scans that were developed in response to Mo-99/Tc-99m shortages in Canada and the United States in 2009 and 2010. Additional background on responses to shortages is provided in the Annex.

Canada

There was major global shortage of medical isotope between 2009 and 2010 due in part to the unplanned shut down of the National Research Universal (NRU) reactor in Chalk River, Ontario that produced a variety of essential medical isotopes, primarily for cancer diagnosis and treatment, including Mo-99.

Canada had been pre-sensitised to the potential problem of disrupted NM radioisotope supply because of an earlier event at the National Research Universal Reactor (NRU). The government had already initiated some work prior to 2009-2010 events and, therefore, Canada was better prepared than most countries to respond to a shortage and has continued to actively investigate the area.

The decentralisation of health care to the provincial/territorial level in Canada (also see Chapter 3) resulted in different approaches to manage the isotope shortage crises based on population distribution and health care system/emergency response structures in each province and territory. The role of the Canadian federal government was to facilitate and co-ordinate responses between all key stakeholders (e.g. irradiators, processors, generator manufacturers, nuclear pharmacies, other suppliers, clinical end-users, government agencies etc.).

In response to an earlier medical isotope shortage associated with an unplanned shutdown of the NRU in 2007 an ad-hoc expert working group, referred to as the "Ad-Hoc Group", had already been organised to advise Health Canada on,

"measures to minimize the potential for future shortages, to mitigate patient care consequences should shortages occur and to establish a nation-wide plan to co-ordinate the supply, distribution and management of medical isotopes." (Ad Hoc Health Experts Working 2008 in Forward page v).

The Ad-Hoc Group's report included a list of suggested operational strategies to mitigate the impact of shortages, which included substitution of Tc-99m-based procedures. Their strategies are summarised below:

- Extend the use of generators,
- Use of alternate radiopharmaceuticals,
- Use of alternate imaging modalities, and,
- Use of alternate forms of therapy noting that for thyroid cancer, especially if it has spread, I-131 is the ideal form of therapy

The Ad Hoc Group used a SWOT (i.e. strengths, weaknesses, opportunities and threats) framework to guide a broader set of recommendations, which are summarised in Appendix A.

In addition, Health Canada hosted a Federal/Provincial/Territorial workshop on managing medical isotope shortages on 13 February 2009.[1] The workshop offered insights as to how medical isotope shortages were managed at different levels. It was, however, apparent that there were no "one size fits all" solutions across all Provinces and Territories. The variability in medical isotope service delivery models even within one country, i.e. Canada, is magnified manifold across other different countries. Strategies presented at this workshop are summarised in Appendix A.

Substitution was also the subject of a project commissioned by the Canadian Agency for Drugs and Technologies in Health (CADTH), which investigated strategies to mitigate shortages. The project was overseen by a panel of content experts, key stakeholders, CADTH staff, and government representatives.

It resulted in a final report (CADTH, 2012[34]) and a web based tool for end users to assist them in making decision on the best use of limited supply of isotopes and which alternate diagnostic imaging modality was optimal by clinical indication.[2]

United States

In 2016, the National Academies of Sciences, Engineering, and Medicine (NAS) released a report mandated by the America Medical Isotope Production Act (AMIPA 2012) related to concerns that there would be severe shortages of Tc-99m starting in 2016. The NAS made several recommendations, including increased Medicare provider payment for non-HEU sourced Mo-99 described in Chapter 3, the support of alternate non-HEU Mo-99 production and possible imposition of financial deterrents on continued importation of HEU produced Mo-99 (National Academies of Sciences, 2016[35]).

1.4. The future of Tc-99m-based nuclear medicine procedures

This Section provides a brief outlook on the future of NM in comparison with other diagnostic imaging modalities.

1.4.1. Radiation dose

Keeping radiation doses to patients as low as reasonably achievable (referred to as the ALARA principle) is increasingly a consideration in justifying the choice of diagnostic imaging modalities and in formulating appropriate use guidelines.[3] ALARA is deeply entrenched in international radiation protection guidelines.[4]

Despite controversies about the health effects of low-dose radiation (i.e. the dose ranges experienced in diagnostic imaging), the linear non-threshold (LNT) dose model remains the dominant model used by regulators. According to the LNT model there is no *safe* level of radiation relative to cancer induction or adverse heredity effects, which are stochastic events, but the probability of adverse outcomes are very low at low doses, as are generally used in medical imaging. The LNT model is the driving force behind ALARA, with the result that other diagnostic imaging modalities may be preferentially chosen if they offer comparable diagnostic and prognostic value at lower radiation doses than NM. Table 1.3 compares patient radiation dose between NM and CT for selected procedures.

Between the early 1980s and 2006, the increased use of x-ray, fluoroscopy, CT and NM doubled the estimated collective radiation dose of the population in the United States (NCRP, 2009[36]). It is interesting to note that the radiation dose contribution from NM, as a proportion of all medical exposure in the United States, remained constant at 26% over this period, whereas the contribution of CT and fluoroscopy rose from 3% each to 49% and 14% respectively, with fluoroscopy primarily used in interventional procedures.

As such, the overall rise in population radiation dose related to medical imaging and interventional procedures is not unexpected, and not without clinical benefit. The relative increase in utilisation rates for CT and fluoroscopy are a result of a trend towards confirming diagnoses prior to surgery (e.g. appendicitis) and of reduced morbidity/mortality related to less invasive procedures to achieve comparable results (e.g. interventional coronary artery angioplasty versus open heart coronary artery bypass graft (CABG) surgery).

Prior to the advent of SPECT/CT and PET/CT in the early 2000s, radiologists and NM specialists would review SPECT and PET images side by side with prior diagnostic CT studies and “fuse” the images with their eyes. Ordering an additional CT scan specifically for comparison with the SPECT or PET images was uncommon. Increased use of SPECT/CT and PET/CT have the potential to increase the overall patient dose as the CT portion may contribute a net additional dose. Some centres mitigate this by adjusting protocols and using the CT portion as a replacement for a pre-hoc diagnostic CT.

Table 1.3. Adult Dose Comparisons for select studies NM versus CT*

For reference, typical background radiation to the general population is approximately 2 to 3 mSv/year.

Anatomical area or organ system	NM diagnostic scan and radiation dose	(mSv)	CT scan and radiation dose	(mSv)
Head	ECD brain	5.7	Standard brain	2.0
			Brain and neck+ CTA	16.4
Cardiac	MIBI/Tetrofosmin for each study** double for a rest/stress combo	10	Coronary CTA	16.0
	^{201}Tl for each study	15	Coronary calcium scoring	3.0
	^{82}Rb (PET) for each study	1.8		
Thorax	VQ	1.4 -1.6	Standard chest	7.0
	Perfusion	1.2	Low dose screening	2.0
	Ventilation – Technegas	0.4	CT PE study	15.0
	DTPA aerosol	0.2	(chest x-ray 2 view)	0.1
Abdomen	GI Bleed RBC	6.5	Standard abdomen	8.0
	Liver/Biliary	2.5	Virtual colonoscopy	10.0
			Abdominal Angiogram (non CT)	12.0
Pelvis	Renal MAG3	1.3	Standard pelvis	6.0
Bone	Bone scan -MDP	5.3	Thoracic spine	10.0
	NaF-^{18}F	7.5	Lumbar spine	5.6

Notes: * Doses are approximate and for standard exams in adults. Doses will vary from patient to patient depending on age, gender and body habitus. In addition, continued advances in dose reduction, especially for CT technologies, will tend to make these conservative estimates which will probably come down through time.
** The dose in this Table would need to be doubled as the study is usually done in two separate parts, i.e. separate rest and stress studies.
Source: SNMMI NM Radiation Dose Tool (2018) using ICRP 128 tables for nuclear medicine studies; X-Ray Risk (2018) for non-nuclear medicine studies.

1.4.2. Innovation in Tc-99m-based products lags behind other fields of NM

Although some NM procedures are standard of care, there is continuous evolution of diagnostic imaging practices.

As NM diagnostics compete with other modalities, and Tc-99m with other non-Tc-99m-based NM scans, innovation in Tc-99m-based radiopharmaceuticals has generally lagged behind. Research investment has primarily been directed at other modalities and much of the research performed takes place at academic institutions, rather than in commercial organisations. A new generation of clinically approved Tc-99m-based radiopharmaceuticals will be needed for SPECT to keep up with advances made using non-Tc-99m-based products and other diagnostic imaging modalities.

As an example, within NM there has been significant basic and applied research and clinical trials with non-Tc-99m agents. By performing a simple OVID® search for “positron emission tomography” (heading and subheadings) AND “novel” (keyword) AND “radiopharmaceutical” (heading and subheading), more than 1 050 articles can be identified in 2018, whereas the same search using “technetium” (heading and subheadings) or “99mTc” (keyword) in place of “positron emission tomography” results in only 287 articles.

Two notable areas of new development in PET are prostate cancer and Alzheimer’s disease.

In prostate cancer, diagnostic and therapeutic agents have been linked to prostate-specific membrane antigens (PSMA). Typical prospective diagnostic and therapeutic agents (a theranostic pair) are Ga-68-PSMA (a PET labelled radiotracer) and Lu-177-PSMA (the same radiotracer labelled with a beta emitting isotope). These two agents may revolutionise the diagnosis and treatment of prostate cancer. However, the development of a Tc-99m-based PSMA agent is also possible. Pre- and post-treatment PSMA images

in a patient with widespread but a very treatment responsive prostate cancer was declared the 2018 SNMMI "image of the year" based on an original article by Hofman et al. (2018[37]).

In 2012 the FDA approved a new F-18 labelled imaging agent (florbeapir being marketed as Amyvid) for Alzheimer's disease. This agent targets beta-amyloid plaque, a hallmark of Alzheimer's disease. As progress is made on dementia therapy the use of such agents will likely increase.[5]

1.5. Conclusion

Nuclear medicine (NM) diagnostic procedures support diagnoses of disease in various organ systems and medical specialties and a broad range of clinical indications. Current patterns of practice in NM diagnostics, as well as in the use of alternative imaging modalities, have developed in a context of sequential technological advancements and changing regulatory environments that dictate evidence requirements. As a result, practice patterns vary between countries and a limited body of rigorous evidence is available to analyse comprehensively the substitutability of Tc-99m-based scans.

However, experience with prior shortages of radioisotopes illustrates that substitutes are available for some Tc-99m-based scans. Cardiac and bone scans, which represent a large share of all diagnostic scans (see Chapter 2), are notable examples of where substitution is possible. In some areas, alternatives to Tc-99m, such as PET scans in myocardial perfusion imaging, may in fact offer improved diagnostic performance. However, even where substitution is possible from a clinical point of view, it might not be easy to achieve in practice. For example, additional capital investments would be necessary because the current installed base of PET, CT and MRI equipment may not be able to absorb the additional volume of scans necessary to substitute for the use of Tc-99m. Although an analysis of the cost of alternatives is not in scope of this report, in particular PET scans tend to be more expensive than Tc-99m-based scans, so that substitution would imply overall cost increases for health care systems.

On the other hand, no comparable substitutes are available in indications such as breast, melanoma and head/neck cancer sentinel lymph node studies. Ferrous-based MRI agents and optical agents are being investigated as alternates for these purposes but are not currently part of standard practice. A range of diagnostics in children, in particular for paediatric bone and renal scans, rely exclusively on Tc-99m. There are also some areas in which Tc-99m-based scans continue to be the preferred standard of care, such as whole-body bone scans to screen for skeletal metastases. Tc-99m will therefore continue to be a product that is essential to health systems to ensure accurate diagnoses and effective patient care. The broad utility of Tc-99m will continue to support the development of new applications.

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