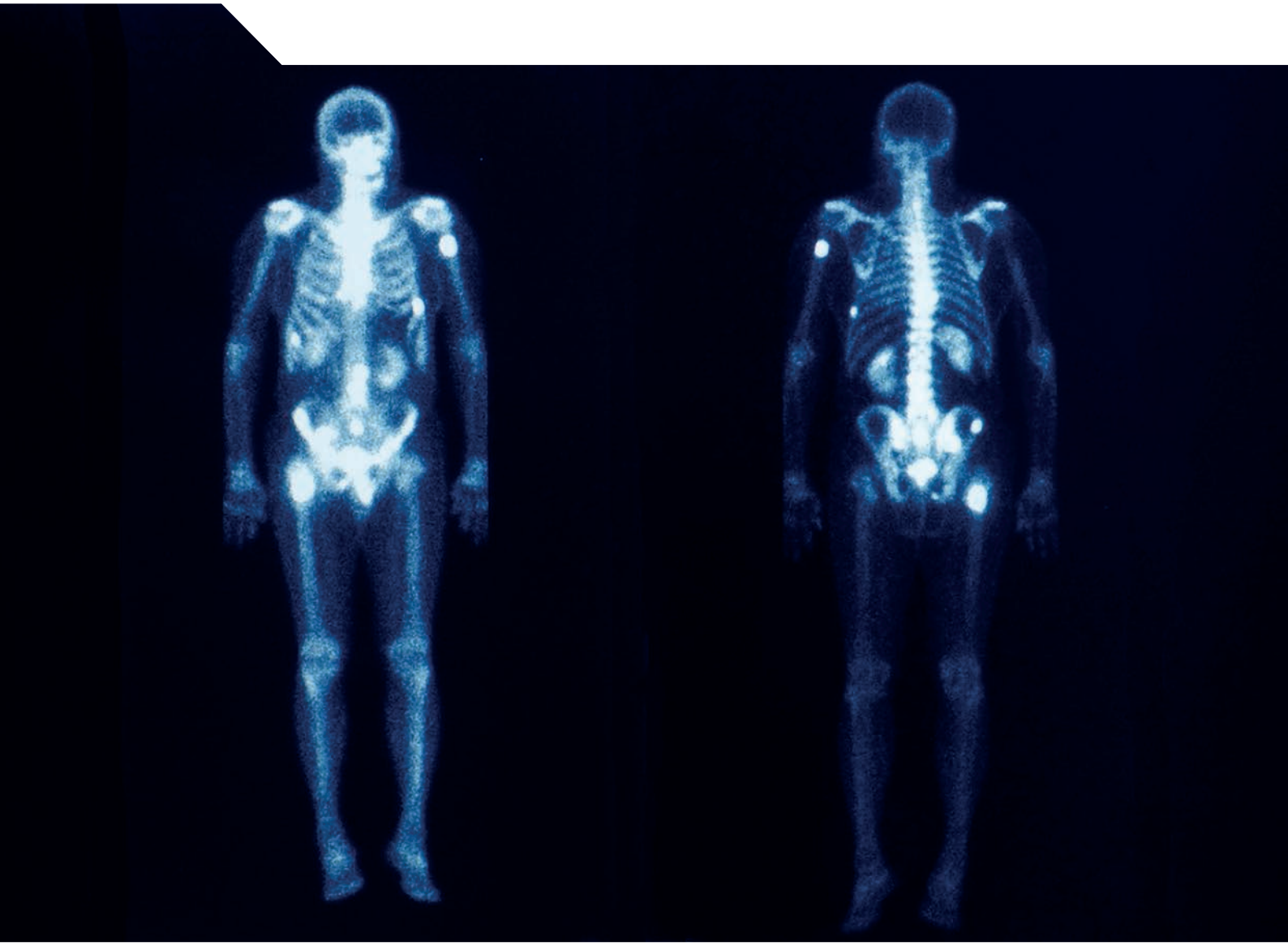
The Supply of Medical Isotopes

AN ECONOMIC DIAGNOSIS AND POSSIBLE SOLUTIONS



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Foreword

Technetium-99m (Tc-99m) is the most commonly used radioisotope in nuclear medicine (NM) diagnostic scans. It is essential for diagnostic scans of a broad range of body parts, and thus for accurate diagnoses of diseases, such as cancer, heart disease and neurological disorders including dementia and movement disorders, and effective patient care in health systems of OECD countries. It is also the most common diagnostic radioisotope, estimated to be used in approximately 85% of all NM diagnostic scans worldwide. The properties of Tc-99m, however, make its supply chain complicated. Tc-99m is obtained from radioactive decay of its parent isotope, Molybdenum-99 (Mo-99). Neither of these products can be stored for very long. Mo-99 has a half-life of 66 hours, that is, its radioactivity decreases by half in 66 hours, and the half-life of Tc-99m is only six hours. Therefore, supply is a just-in-time activity, combining a mix of governmental and commercial entities, and requires sufficient capacity for ongoing production of Mo-99 plus a reserve in case of unplanned outages.

Given this complexity, supply of Mo-99/Tc-99m to health care providers has often been unreliable over the past decade due to unexpected shutdowns and extended maintenance periods at some of the facilities that produce Mo-99, many of which are relatively old. These shutdowns have at times created extended global shortages. In particular in 2009-10, a series of unexpected outages of the nuclear research reactors (NRRs) required for Mo-99 production led to a global supply crisis and a severe shortage of Tc-99m. In response to the crisis, the OECD Nuclear Energy Agency (NEA) established the High-level Group on the security of supply of Medical Radioisotopes (HLG-MR) to help secure stable and economically sustainable supply of these products in the short and long-term. The HLG-MR developed a comprehensive policy framework to address supply chain issues based on six policy principles (see Annex A), which were endorsed by the NEA Steering Committee for Nuclear Energy.

During the HLG-MR meeting held on 21-23 January 2014, the NEA was asked to look at developing a more formal statement of commitment to the HLG-MR principles. Discussions were held with member countries and a consensus document, the Joint Declaration on the Security of Supply of Medical Radioisotopes was developed. On 17 December 2014, the OECD Council formally noted that eleven countries had officially signed up to the Joint Declaration; subsequently three more countries have confirmed their adherence. The Joint Declaration provided a co-ordinated political commitment by countries involved in the production and use of medical radioisotopes to bring about necessary changes across the whole supply chain and to encourage others to do likewise.

By 2017, supply had stabilised somewhat because of the actions of existing supply chain participants co-ordinated by the HLG-MR and the continued support of some governments. Many of the technical problems that led to the 2009-10 shortage had been solved. However, self-assessment by the HLG-MR indicated that considerable risks to the stability of the supply chain remained unaddressed. Full implementation of the six policy principles that were agreed upon was slow. Participants in the supply chain struggled to implement policy principles related to charging prices high enough to allow for full-cost recovery (FCR) and to keeping sufficient outage reserve capacity (ORC). Prices that do not reflect the full costs of medical isotope production and of their distribution throughout the supply chain pose risks of delay or cancellation of investments in existing or new facilities and could imply an increased risk of further supply disruptions

or shortages in the future. Further details on the 2009-10 crisis, the Mo-99/Tc-99m supply chain, and work by the NEA and the HLG-MR can be found in prior reports published by the NEA.[1]

At its meeting in July 2017, HLG-MR delegates requested the support of the OECD Health Committee to conduct a study from a health system perspective that describes the need for radioisotopes in national health systems and analyses the current market structure, identifying barriers to implementation of FCR, the first policy principle in the framework developed by the HLG-MR. This report is an answer to the request, and presents findings of the joint work between the NEA and the OECD Health Committee, which focused on NM diagnostic procedures that use Tc-99m. Geographically, the report focuses on Australia, Canada, Japan and the United States, the four non-European countries that are the largest end-users of Tc-99m, as well as countries of the European Union and Switzerland.

This report contains five main Chapters. Chapter 1 summarises the utility of NM diagnostic scans from a clinical perspective and outlines the main alternatives to Tc-99m-based procedures. Chapter 2 provides an overview of the volume of NM diagnostic scans conducted in the countries in scope. Chapter 3 summarises health care provider payment for NM diagnostic services and the financial incentives that arise from provider payment mechanisms. This particular analysis is limited to the United States and 17 countries that responded to the OECD Health Division Survey on Health Care Provider Payment for Nuclear Medicine Diagnostic Services: 13 of 23 countries that are members of the European Union and the OECD[2] as well as Australia, Canada, Japan and Switzerland. Chapter 4 analyses market structures in the Mo-99/Tc-99m supply chain. Chapter 5 identifies the main barriers to FCR and outlines possible measures governments could take to increase the reliability of Mo-99/Tc-99m supply.

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Abbreviations and acronyms

ALARA	As low as reasonably achievable
APC	United States Medicare Ambulatory Payment Classification
ATIH	French National Agency for Hospital Information (*Agence technique de l'information sur l'hospitalisation*)
Bq	Becquerel (unit of measure of radioactivity)
C-14	Carbon-14
CADTH	Canadian Agency for Drug and Technologies in Health
CCAM	French National Catalogue of Medical Services (*Classification commune des actes médicaux*)
CEPS	French National Economic Committee for Health Products (*Comité économique des produits de santé*)
Ci	Curie (unit of measure of radioactivity)
CMS	United States Centers for Medicare & Medicaid Services
Co-60	Cobalt-60
CT	Computed tomography
DKG	German National Association of Hospitals (*Deutsche Krankenhausgesellschaft*)
DRG	Diagnosis-related Group
EANM	European Association of Nuclear Medicine
EBM	German National Relative Value Scale of Medical Services (*Einheitlicher Berwertungsmaßstab*)
EC	European Commission
EOP	End of Processing
ERT	Emergency Response Team
F-18	Fluorine-18
FCR	Full-Cost Recovery
FFS	Fee-for-Service
Ga-68	Gallium-68
GHS	French version of diagnosis-related groups (*Groupes homogènes de séjours*)
GKV-SV	German National Association of Statutory Health Insurance Funds (*Spitzenverband Bund der Krankenkassen*)
HEU	High enriched Uranium
HHS	United States Department of Health and Human Services
HLG-MR	OECD Nuclear Energy Agency High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR)
HRG	Health Care Resource Groups (diagnosis-related groups used in the English NHS)
I-123	Iodine-123
I-131	Iodine-131
InEK	German Institute for Hospital Remuneration (*Institut für das Entgeltsystem im Krankenhaus*)
IPPS	United States Medicare Inpatient Prospective Payment System
KBV	German National Association of SHI-Affiliated Physicians (*Kassenärztliche Bundesvereinigung*)
LEU	Low enriched uranium
LNT	Linear Non-Threshold
Lu-177	Lutetium-177
Mo-99	Molybdenum-99
MBS	Australian Medicare Benefits Schedule
MFF	Market Forces Factor used in the English NHS to adjust hospital payments
MHLW	Japanese Ministry of Health, Labour and Welfare
MRI	Magnetic Resonance Imaging

MSC	British Columbia Medical Services Commission (Canada)
MSP	British Columbia Medical Services Plan (Canada)
NAS	United States National Academies of Sciences, Engineering, and Medicine
NEA	OECD Nuclear Energy Agency
NHS	English National Health Service
NM	Nuclear Medicine
NMEu-SoS	Nuclear Medicine Europe Security of Supply working group
NRR	Nuclear Research Reactor
NRU	Canadian National Research Universal Reactor (Chalk River, Ontario)
NTP	Nuclear Technology Products division of the South African Nuclear Energy Corporation
OPAL	Open-pool Australian Lightwater Reactor
OPPS	United States Medicare Outpatient Prospective Payment System
ORC	Outage Reserve Capacity
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography - Computed Tomography (hybrid imaging modality)
PET/MRI	Positron Emission Tomography – Magnetic Resonance Imaging (hybrid imaging modality)
PSMA	Prostate-Specific Membrane Antigens
RBRVS	Resource-based Relative Value Scale
RIZIV-INAMI	Belgian National Institute for Health and Disability Insurance (*Rijksinstituut voor Ziekte- en Invaliditeitsverzekering – Institut National d'Assurance Maladie-Invalidité*)
SHI	Social Health Insurance
SMER	Study on Sustainable and Resilient Supply of Medical Radioisotopes in the European Union
SNMMI	United States Society of Nuclear Medicine and Molecular Imaging
SPECT	Single Photon Emission Computed Tomography
SPECT/CT	Single Photon Emission Computed Tomography – Computed Tomography (hybrid imaging modality)
Tc-99m	Technetium-99m
Tl-201	Thallium-201
U-235	Uranium-235
UNCAM	French National Union of Social Health Insurers (*Union nationale des organismes d'assurance maladie*)
US	Ultrasound

Executive summary

This report explores the use and substitutability of Technetium-99m (Tc-99m) in health care and the main economic reasons behind its unreliable supply. It proposes policy options to help address the supply issue.

Tc-99m is an essential product for health systems that is used in 85% of nuclear medicine diagnostic scans performed worldwide, or around 30 million patient examinations every year, making it the most commonly used medical isotope. Tc-99m-based scans allow diagnoses of a broad range of diseases in many parts of the human body, including cancer, heart disease and neurological disorders such as dementia. Substitution of Tc-99m is difficult. No comparable substitutes are available for diagnoses of various cancers, such breast, melanoma and head/neck cancer, and for a range of diagnostics in children, in particular paediatric bone and renal scans. In some areas, Tc-99m-based scans are the preferred standard of care, such as whole-body bone scans to screen for skeletal metastases. Although substitution of Tc-99m is clinically possible for some of the most common types of diagnostic scans, notably cardiac and bone scans, effective substitution of these would imply cost increases and require significant long-term investments in alternative scanning equipment and human resources.

Medical isotopes are subject to radioactive decay and cannot be stored. For this reason, they have to be delivered just-in-time through a complex supply chain that requires sufficient capacity for ongoing production, plus a reserve in case of unplanned outages. However, ageing production facilities and low prices of Tc-99m have contributed to a lack of production capacity, which has made the supply of Tc-99m unreliable. The current structure of the supply chain leaves some participants unable to increase the prices of their services to levels that would cover all fixed and variable costs of the required production capacity for Tc-99m.

A phased and co-ordinated discontinuation of funding of the commercial production of Tc-99m by governments of producing countries would likely be necessary. This would compel producers to increase prices. Because a policy of withdrawing government funding of the production of medical isotopes could destabilise supply in the short-term, it would need to be accompanied, at least temporarily, by measures to help ensure that price increases are passed on through the supply chain. One way to achieve this would be to increase price transparency, to encourage supply chain participants to comply with commitments to increase prices. A temporary price floor could help ensure that producers are able to make up for the reduction of government funding through additional revenue. The establishment of a commodities trading platform could make prices more responsive to supply and demand and thus help ensure that the appropriate level of production capacity is available. Alternatively, governments could maintain funding of production but have end-user countries bear the costs in proportion to the share of total supply they consume. Governments could also aim to reduce the reliance on the current supply chain, through substituting Tc-99m with alternative isotopes or diagnostic modalities where possible, or by investing in alternative means of producing Mo-99/Tc-99m. However, the latter two options could be costly.

Key findings

Technetium-99m (Tc-99m) is the most commonly used radioisotope in nuclear medicine (NM) diagnostic scans. It is essential for accurate diagnoses of diseases and effective patient care in health systems of OECD countries. For example, Tc-99m is used for diagnoses of cancer, heart disease and neurological disorders including dementia and movement disorders.

This report presents findings of joint work between the OECD Health Committee and the OECD Nuclear Energy Agency (NEA) on the supply of Tc-99m. The geographic focus is on Australia, Canada, Japan and the United States, the four non-European countries that are the largest end-users of Tc-99m, as well as countries of the European Union and Switzerland. Collectively, these countries account for most of global demand.

Some health systems rely heavily on Tc-99m and substitution would be costly

Nuclear medicine (NM) diagnostic scans can image and demonstrate the physiology and function of many body parts, including the heart, the skeleton, the thyroid and salivary glands, and the brain, supporting a broad range of medical specialities. NM scans involve the administration of trace amounts of radioactive pharmaceuticals, referred to as radiopharmaceuticals, into a patient's body. Preparation of a patient dose involves the "labelling" of a non-radioactive biomolecule, which is specific to the organ system or anatomical area scanned, with a radioactive medical isotope. Technetium-99m (Tc-99m) is used as the medical isotope in 85% of NM diagnostic scans performed worldwide, or around 30 million scans, every year. Once internalised by a patient, radiopharmaceuticals are physiologically distributed within the body. As they undergo radioactive decay, they emit gamma photons, which are captured by gamma cameras. Each detected photon is registered as a point. Hundreds of thousands of points are collected during a scan to form an image. NM is called a *functional* imaging modality as it visualises normal and abnormal organ and tissue physiology, based on the bio-distribution of the radiopharmaceutical used. It thus allows assessing the function or physiology of various tissues, organs or organ systems. This is in contrast to other common imaging modalities, such as x-ray, computed tomography (CT) and magnetic resonance imaging (MRI), which characterise the body anatomy and structure but not necessarily its functions, and are therefore referred to as *anatomical* imaging.

No comparable substitutes to Tc-99m 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 particular for paediatric bone and renal scans. There are also some areas in which Tc-99m-based scans are the preferred standard of care, such as whole-body bone scans to screen for skeletal metastases.

Although substitution of Tc-99m is possible, notably for cardiac and bone scans, which are a large share of all Tc-99m-based diagnostic scans, effective substitution of these scans would require significant long-term investments in alternative scanning equipment and human resources. There is currently insufficient equipment and a lack of trained personnel to increase substantially the use of alternative imaging modalities, including positron emission tomography (PET), computed tomography (CT) and magnetic resonance imaging (MRI). PET scans in particular also tend to be more expensive than Tc-99m-based

scans, so that substitution would imply increases in current health expenditures. CT can produce cross-sectional images of tissue density by transmitting x-rays through a patient and registering the “shadows”. In MRI, patients are put into a strong pulsing magnetic field, which causes hydrogen atoms to line up and relax in an orderly fashion with each pulse, changes that are recorded and converted into detailed images. PET, on the other hand, is another form of NM diagnostic imaging, using radioisotopes other than Tc-99m that emit two photons that move in opposite directions and are captured by positron emission tomography – computed tomography (PET/CT) cameras for imaging.

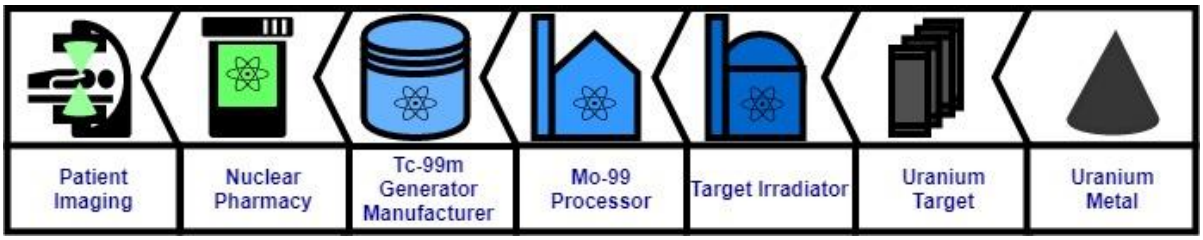
As in other domains of medicine, NM practice patterns and the use of Tc-99m-based diagnostic scans vary markedly between countries. This is true in terms of the numbers of Tc-99m scans performed relative to the population and in terms of the share of each organ system in the total number of scans. While the reasons for this variation are multiple and sometimes unclear, it means that the potential impacts of future shortages of Tc-99m and the scope for substitution are not the same across countries. Scan rates vary from nearly 50 scans per 1 000 people in Canada and between 30 and 40 scans in Belgium and the United States to as few as 2-3 scans per 1 000 population in Estonia and Poland. Among five of six countries for which data are available, bone and cardiac scans are the most common types of scan, collectively accounting for between 60% and 76% of all scans. Bone scans are more common than cardiac scans in all countries for which data are available, except in the United States, where cardiac scans are 55% of the total and bone scans only 14%. Germany is another notable exception, where endocrine scans are more than 40% of the total while this share is less than 10% in all other countries.

Technetium-99m supply is a complex and just-in-time activity, and supply remains unstable

The supply of Technetium-99m (Tc-99m) requires continuous production in a complicated and aging supply chain that combines a mix of governmental and commercial entities. Governments essentially control both ends of the supply chain, i.e. uranium supply and policy on health care provider payment, as well as the regulatory framework. The central steps of the supply chain are mainly commercial. Tc-99m is obtained from radioactive decay of its parent isotope, Molybdenum-99 (Mo-99). While Mo-99 has a half-life of 66 hours, the half-life of Tc-99m is only six hours. Therefore, these products cannot be stored and supply is a just-in-time activity that requires sufficient capacity for ongoing production plus a reserve in case of unplanned outages.

To prepare doses for patient scans, specialised pharmacies, called nuclear pharmacies, elute Tc-99m daily from Mo-99 containers. These containers are called *Tc-99m generators* and their manufacturers require marketing authorisation by the pharmaceutical regulatory authority responsible for each jurisdiction to sell them. Pharmaceutical companies, which include firms specialised in nuclear medicine as well as large and diversified firms, manufacture and sell Tc-99m generators commercially. They buy Mo-99 in bulk from processing entities that transform irradiated uranium into a Mo-99 liquid used to fill Tc-99m generators. Processors procure uranium as a raw material and contract with nuclear research reactors (NRRs) that perform irradiation services. Figure 1 shows the main steps in the supply chain. NRRs, also referred to as irradiators, have a range of purposes aside from medical isotope production and were not originally designed for the commercial supply of medical isotopes. Their activities include nuclear technology testing, fundamental scientific research and industrial isotope production. Some of these activities are undertaken on a commercial basis; however most commonly they are funded by governments, in part or in full.

Figure 1. Simplified structure of the Mo-99/Tc-99m supply chain



Note: Technetium-99m (Tc-99m) generators are specialised containers of Molybdenum-99 (Mo-99) from which nuclear pharmacies elute Tc- 99m to prepare patient doses.
Source: Authors

Supply of Tc-99m to health care providers has been unreliable over the past decade due to unexpected shutdowns and extended maintenance periods at several of the facilities in the supply chain. Many of these facilities, including NRRs and processors, are relatively old. In response to the severe supply crisis in 2009-10, the OECD Nuclear Energy Agency (NEA) established the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) to help secure stable and economically sustainable supply of these products in the short- and long-term. In a 2010 economic study of the supply chain, the NEA concluded that supply was unreliable because prices of Mo-99 were too low to allow NRRs to cover their full costs of production and to invest in sufficient production and reserve capacity. Government funding of NRRs allowed Mo-99 production to continue despite unsustainably low prices but also distorted price signals in the supply chain. The HLG-MR has since made efforts to encourage price increases in the supply chain, a policy principle referred to as full-cost recovery (FCR) in the framework for supply security developed by the HLG-MR.

While progress has been made since past supply crises, the inability of NRRs to increase prices sufficiently and the resulting lack of reserve capacity at various steps of the supply chain leave supply vulnerable and the market economically unsustainable. Supply frailty was demonstrated between late 2017 and early 2019, with chronic shortages occurring regularly due to unplanned outages.

The main barrier to price increases is found in the supply chain

The main barrier to full-cost recovery (FCR) is found in the current structure of the supply chain, the cost structure and funding of NRRs and in the resulting behaviours of supply chain participants. NRRs are capital-intensive enterprises that have high fixed costs while irradiation services for Mo-99 production have low marginal costs. Due to transport constraints and radioactive decay, NRRs are captive to local processors and have little choice but to continue supplying irradiation services even at prices that are too low to cover fixed and marginal costs, while continued government funding allows their operations to be sustained. Downstream, competition creates a disincentive for each supply chain participant to increase prices unilaterally as this might result in losing business to a competitor. Processors compete globally for business from Tc-99m generator manufacturers, which are commercial organisations that in turn compete for business from nuclear pharmacies and health care providers.

Health care provider payment must not be neglected, but provider incentives to contain the cost of Tc-99m are likely to be weak in most cases and are not the main barrier to price increases

Although the responsiveness of payment mechanisms and financial incentives to health care providers must not be neglected in further efforts to increase prices, health care provider payment is not the main barrier. Tc-99m represents a small item in the overall cost structure of nuclear medicine (NM) providers. The price increase necessary to achieve FCR is currently estimated to be less than USD 1 per patient dose on average, a 4% increase of the average price of Tc-99m at the point of dispensing. Health care providers could absorb such a price increase in most cases.

Providers of NM diagnostic scans are usually paid prospectively fixed amounts for their services, rather than being reimbursed for costs actually incurred. They therefore bear the financial risk related to differences between payments and their input costs. This means that they have an incentive to control input costs, including the cost of Tc-99m. Such incentives are stronger where payments are low relative to input costs and where providers have little scope to substitute activities towards more profitable ones, which can allow them to cross-subsidise activities that incur losses.

Three types of health care providers deliver Tc-99m-based scans to patients: office-based physicians, other types of outpatient providers (such as diagnostic centres and radiological clinics) and hospitals (to in- and out-patients). Outpatient scans represent the majority of all scans. While payment amounts for all provider types are set prospectively, payments cover service bundles of varying breadths. Outpatient providers are typically paid fee-for-service (FFS), i.e. a fixed fee that applies to the entire diagnostic service and covers all provider costs related to that service. The breadth of bundling tends to increase with the provider size and scope of activities. Hospitals are often paid for broad service bundles, such as all services related to a diagnosis-related group (DRG) for inpatient care or through global budgets. Providers are required to cover their costs for procuring Tc-99m from these payments in all countries, except some providers in four countries. All providers in Belgium and Japan, outpatient providers paid FFS in Germany, and specialists paid FFS by Medicare in the United States receive separate payments for radiopharmaceuticals used. Increases in Tc-99m prices may be more difficult to absorb for small providers, such as office-based NM specialists, who rely exclusively on NM scans for revenue and whose FFS payments are not responsive to input costs. Hospitals that generate revenue from a wide range of activities may be able to absorb cost increases more easily.

While a detailed analysis of the strength of financial incentives for providers to contain costs of Tc-99m is not possible with the data available, such incentives are probably relatively weak. The average cost of an individual patient dose at the point of dispensing of Tc-99m is estimated to be around 21 USD, which is small relative to the broader provider payments for the diagnostic service, the DRG or the global budget. Where providers receive unbundled payments that specifically cover the cost of Tc-99m, providers have a weak incentive to contain costs when such payments are sufficient to cover actual costs of purchasing Tc-99m, but may resist cost increases where such payments are insufficient. In most countries, outpatient provider fees are revised annually, allowing providers to negotiate payment increases if costs increase. There are however, exceptions, for instance in Australia and France, where fees have not been increased for several years. At the same time, data on the actual cost of purchasing Tc-99m is often not taken into account when determining provider payments. Provider payment can therefore also be relatively unresponsive to increases in the cost of Tc-99m.

Policies could catalyse price increases in the supply chain

This Report presents five main policy options that could help increase the prices of Molybdenum-99 (Mo-99) in the supply chain to achieve full-cost recovery (FCR) and improve the reliability of Mo-99/Tc-99m supply (see Options 1 to 5 in Figure 2).

A phased and co-ordinated discontinuation of funding of the commercial production of Mo-99 and other medical isotopes by governments of producing countries would likely be necessary to catalyse price increases (Option 1). This would compel nuclear research reactors (NRRs) to increase prices of irradiation services, while not requiring direct government intervention in the supply chain and leaving the adjustment of supply contracts and prices along the supply chain to market forces.

Because a policy of withdrawing government funding of the production of medical isotopes could further destabilise supply in the short-term, it would need to be accompanied, at least temporarily, by one or several other measures that would help ensure that price increases are passed on through the supply chain. One option to achieve this would be to increase price transparency (Option 2), to provide a mechanism of peer-pressure among supply chain participants to comply with commitments to increase prices. Price regulation for irradiation services (Option 3) would be another option and the most direct means of ensuring that prices increase. A price floor could be imposed temporarily along with the withdrawal of government funding to ensure that NRRs are able to make up for the reduction of government funding through additional revenue. The establishment of a commodities trading platform for bulk Mo-99 (Option 4) could be another option, to make prices more responsive to supply and demand and thereby help ensure that the appropriate level of production capacity is made available.

As an alternative to market-based approaches, governments could maintain funding of irradiation services but have end-user countries bear the costs in proportion to the share of total supply they consume, based on an new inter-governmental agreement between producing and end-user countries (Option 5).

The Report also presents two options for governments to reduce the reliance on the current supply chain, through substituting Tc-99m with alternative isotopes or diagnostic modalities, or by investing in alternative means of producing Mo-99/Tc-99m (Options 6 to 7). However, these last two options could be costly.

Figure 2. Overview of policy options

Policies to move towards full-cost recovery within the current Mo-99/Tc-99m supply chain

Policy to catalyse price increases of irradiation and downstream supply chain activities

1. Phased and co-ordinated discontinuation of funding of NRR costs attributable to Mo-99 production by governments of producing countries

Policy options that could accompany withdrawal of government funding for Mo-99 production by NRRs

2. Increasing price transparency in the supply chain
3. Setting a temporary price floor for irradiation
4. Introducing a commodities trading platform for bulk Mo-99

Possible alternative to a market-based approach

5. Direct funding of Mo-99 production by end-user countries

Policies to reduce the reliance on the current Mo-99/Tc-99m supply chain

6. Increasing use of substitute diagnostic imaging modalities or substitute isotopes
7. Move towards alternative methods to produce Mo-99/Tc-99m

Based on the analyses presented in this report, no single option can be recommended as the preferred solution to current issues with the reliability of supply. Each option has a number of strengths and weaknesses. The main contribution of this report is to explore the issue of the reliability of Mo-99/Tc-99m supply from a health system perspective and it concludes that the main barrier to price increases is not in health care provider payment but rather *within the supply chain*. However, data on the structure of the supply chain, such as ownership, revenue and cost structures of players, their respective market shares and prices of intermediary Mo-99 products, are limited. The discussion of policy options is therefore inevitably superficial and may not exhaustively identify all strengths and weaknesses across all countries.

While governments of producer and end-user countries need to co-ordinate their efforts, they should also evaluate each option locally in more depth and in co-operation with all stakeholders, to identify the most acceptable solutions in their respective jurisdictions. In particular, the choice and implementation of policies that could help achieve FCR should be informed by a more detailed study of NRR- and processor specific production costs, the extent and purpose of current government funding, and the magnitude of price increases that would be necessary to achieve FCR at each facility.

Notes

[1] Available at https://www.oecd-nea.org/med-radio/supply-series.html

[2] Respondents of 13 of 23 countries that are members of the European Union and the OECD responded to the OECD Health Division Survey on Health Care Provider Payment for Nuclear Medicine Diagnostic Services: Belgium, the Czech Republic, Denmark, France, Germany, Latvia, Lithuania, Luxembourg, the Netherlands, Poland, Slovenia, Sweden, United Kingdom (England only).

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.

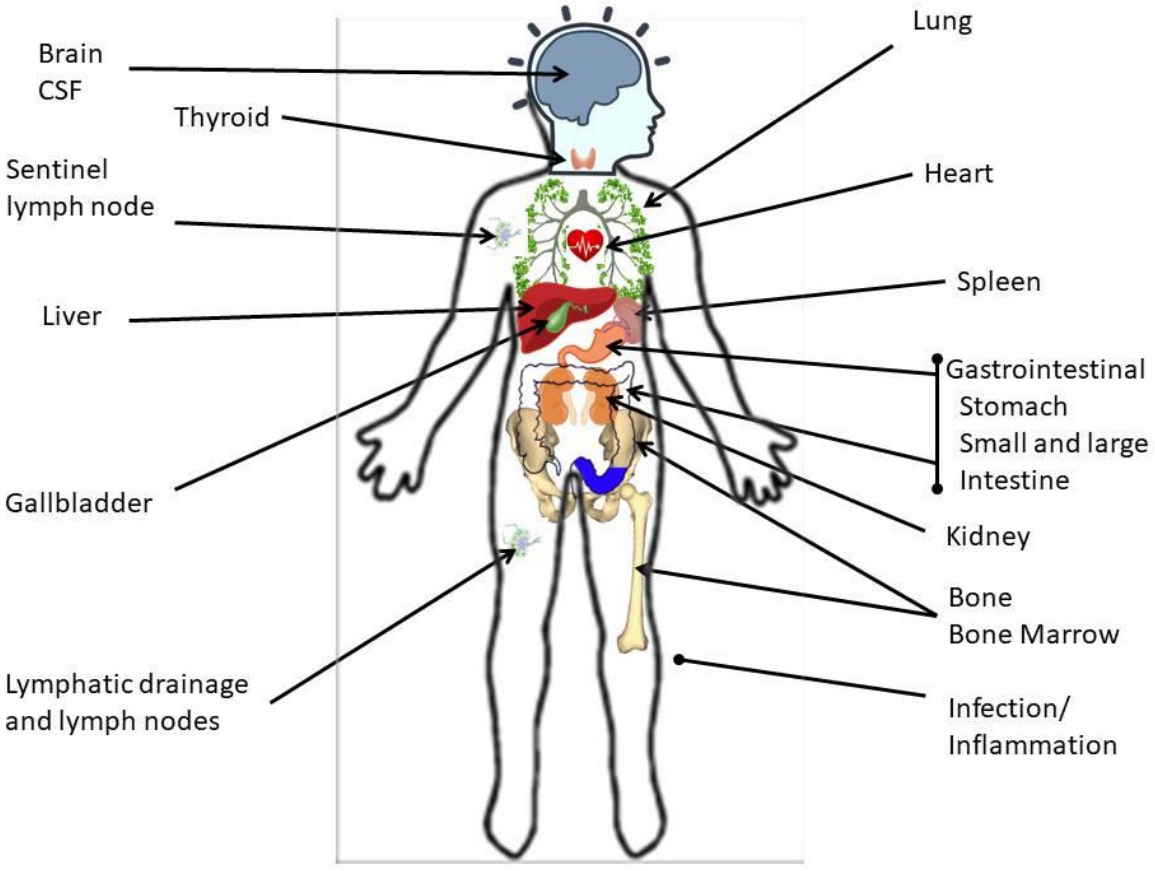
1.2.1. NM diagnostics are used for a wide range of indications

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.

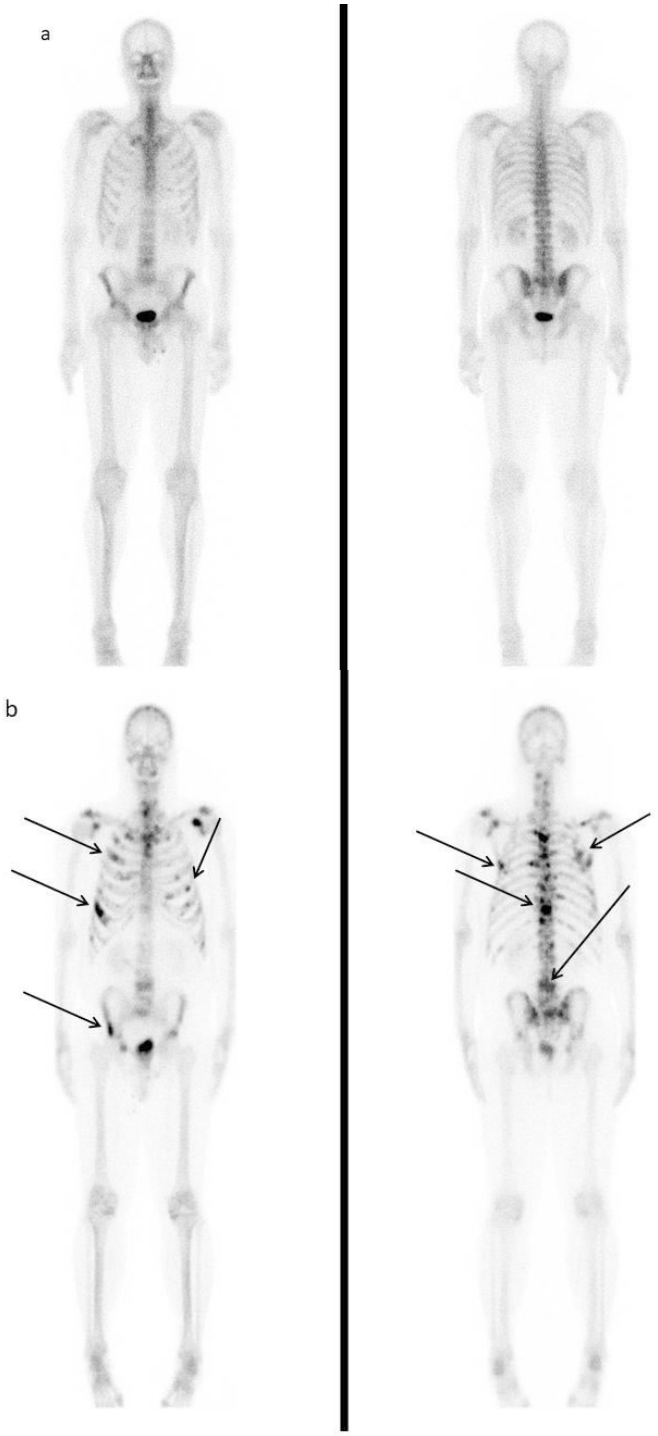
In NM diagnostic imaging, diagnostic radiopharmaceuticals undergo radioactive decay and emit gamma photons which are registered on detectors in gamma cameras. Each detected photon is registered as a “point” and, during scanning, hundreds of thousands of points are collected to form a final image. This 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).

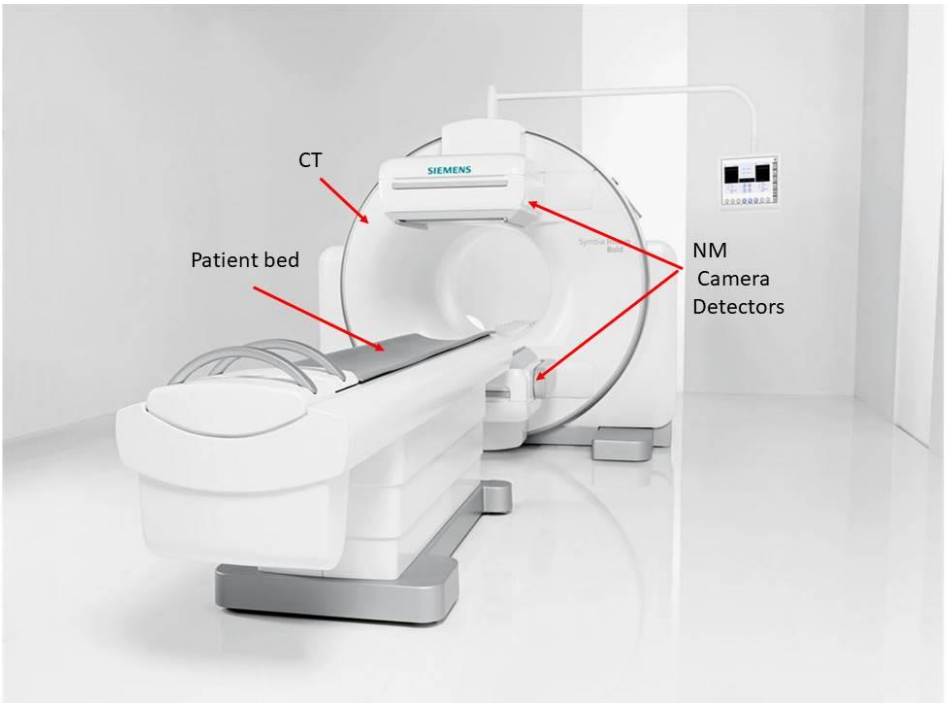
1.2.3. The evidence base for traditional Tc-99m-based NM diagnostics is relatively weak

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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2 The use of nuclear medicine diagnostics and Tc-99m varies significantly across countries

Diagnostic imaging modalities using Technetium-99m account for around 30 million examinations worldwide every year and approximately 85% of all nuclear medicine diagnostic scans. Following a decrease with the 2009/10 supply crisis, demand for Tc-99m has been flat in recent years and little growth is forecast for OECD countries through 2023. Imaging rates vary significantly between countries, from 2-3 Tc-99m-based scans per 1 000 population per year in some Eastern European countries to 30-50 in Belgium and North America. The ten most populous countries and countries with high scan rates account for more than 90% of the aggregate volume of Tc-99m-based scans across the countries in scope of this Report. There are also significant differences between countries in the utilisation patterns by organ system and anatomical areas scanned. The potential impacts of future shortages and the scope for substitution are therefore not the same across countries.

2.1. Introduction

This Chapter provides a brief overview of the global demand for radioisotopes, and for Technetium-99 (Tc-99m) in particular. The Chapter compares NM diagnostic imaging activity across the countries in scope. It shows that NM diagnostic imaging rates vary significantly between countries and that ten countries represent more than 90% of all the aggregate volume of Tc-99m-based scans across the countries in scope. There are also significant differences between countries in the utilisation patterns by organ systems and anatomical areas scanned. The potential impacts of future shortages and the scope for substitution are therefore not the same across countries.

2.2. Global demand for Mo-99/Tc-99m has been flat since 2012

Medical diagnostic imaging modalities using Tc-99m account for approximately 85% of all nuclear medicine procedures, representing around 30 million examinations worldwide every year (NEA, 2018[1]). NEA estimates that mature markets account for 84% of global demand for Mo-99/Tc-99m, and developing markets for 16%. Estimated market growth rates are 0.5% annually for mature markets and 5% for developing markets through 2023 (ibid.).

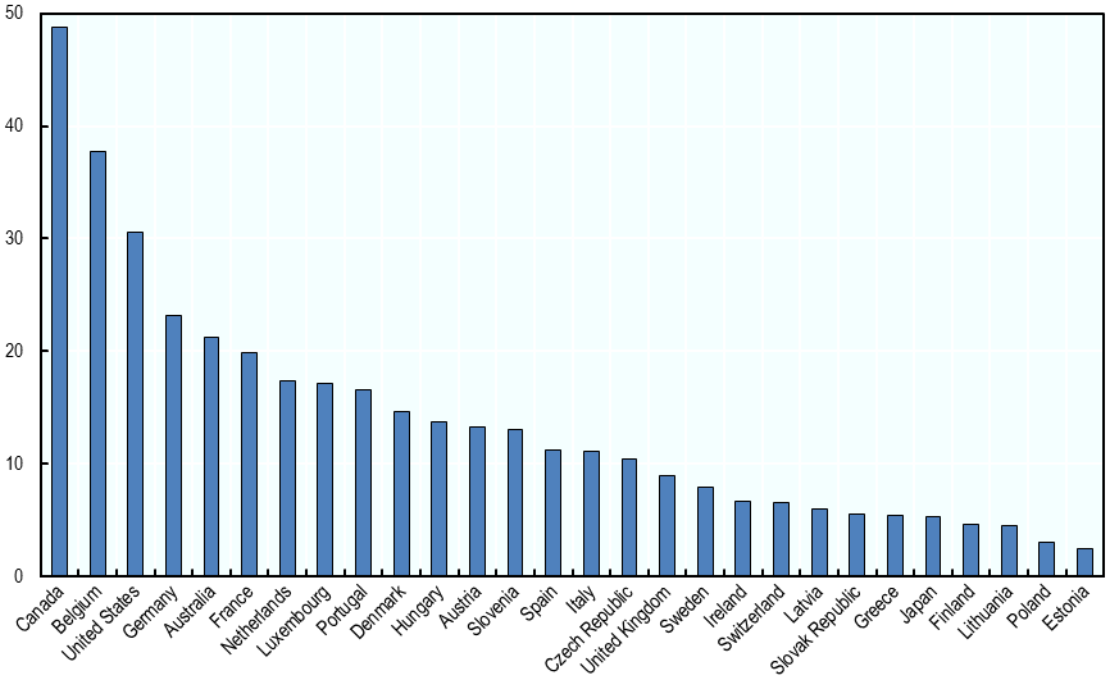
Successive NEA demand forecasts have assessed market demand since 2011. Following the 2009/2010 supply crisis, demand decreased by around 20% driven by better use of available Mo-99/Tc-99m, more efficient elution of Tc-99m generators, adjustments to patient scheduling, some reductions in average injected dose due to technical improvements in gamma cameras and some retention of substitute diagnostic tests/isotopes (NEA, 2018[1]). Greater efficiency in the use of Tc-99m generator activity may also be a result of increased generator prices due to gradual implementation of full-cost recovery (FCR) (ibid.).

Since 2012, the demand has been relatively flat. There have been some increases in production required at the irradiator and processor level of the supply chain in the period since 2016 to overcome the decay loss in transport to the large North American market, following the end of routine production in Canada. Data for 2017 reconfirm that recent global demand for Mo-99 is close to 9 400 six-day curies per week end-of-processing,[1] with some demand fluctuations seen at a quarterly level (NEA, 2018, p. 8[1]).

2.3. A small number of populous countries and countries with high scan rates account for a large share of utilisation

The use of NM diagnostic imaging varies widely across countries in scope of this report. Similar to other diagnostic imaging modalities (OECD, 2018[2]), there are large differences in utilisation rates of NM diagnostic imaging relative to the population between countries. For example, estimates collated by the OECD Health Division research indicate that only about 2-3 Tc-99m-based scans are performed per ‘000 population per year in Estonia and Poland, while 31 and 38 scans are performed per ‘000 population per year in the United States and Belgium respectively, and this number may be close to 50 in Canada. Figure 2.1 shows estimates of the rate of Tc-99m-based NM diagnostic scan per ‘000 population.

Figure 2.1. Number of Tc-99m-based NM diagnostic scans per ’000 population per year

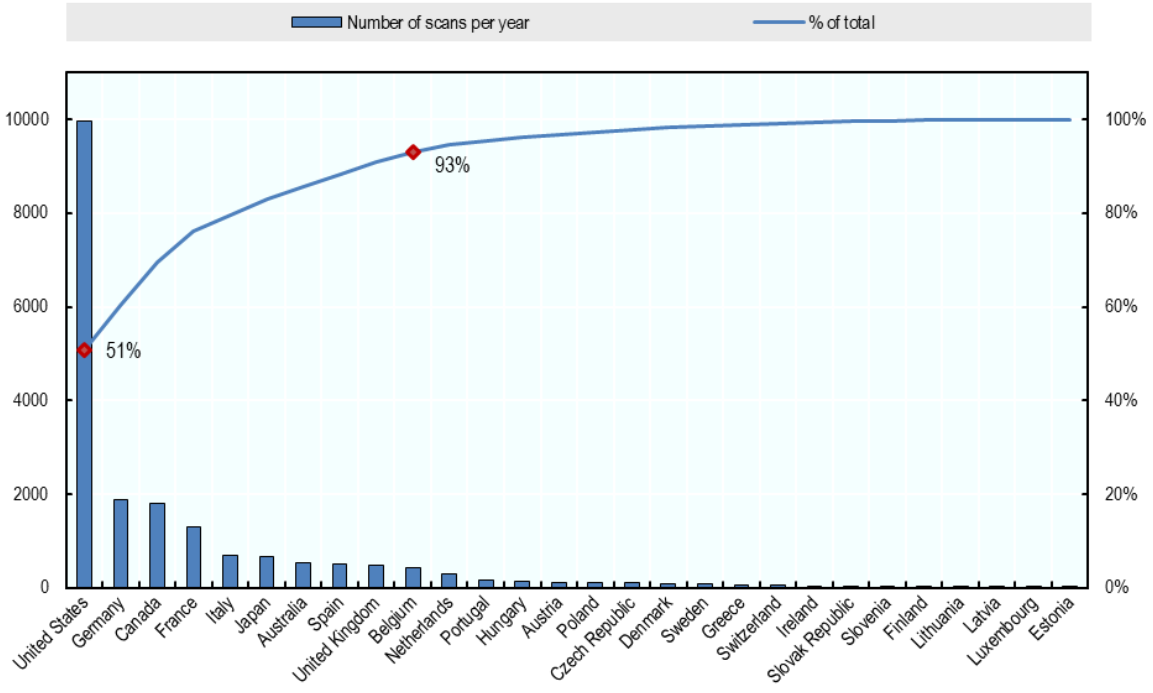


Note: Data was collated from various sources and may not be fully accurate or comparable. Refer to Annex B for data accuracy and comparability issues.
Source: Author based on Health Division survey and various public sources. Refer to Annex B for details.

A large proportion of total NM diagnostic activity is found in countries that have large populations and/or relatively high NM diagnostic imaging rates. According to estimates collated by the OECD Health Division, around 10 million Tc-99m-based diagnostic scans are performed in the United States per year, which alone represents more than 50% of the total number of scans across countries in scope. Scans performed in Canada, Germany, France, Japan, Italy, Spain, Belgium and the United Kingdom collectively represent another 40% of total activity so that these 10 countries together account for more than 90% of scans across countries in scope. Figure 2.2 shows the number of Tc-99m-based NM diagnostic scans per year.

Figure 2.2.Absolute number of Tc-99m-based NM diagnostic scans per year by country

Number of scans in '000s.

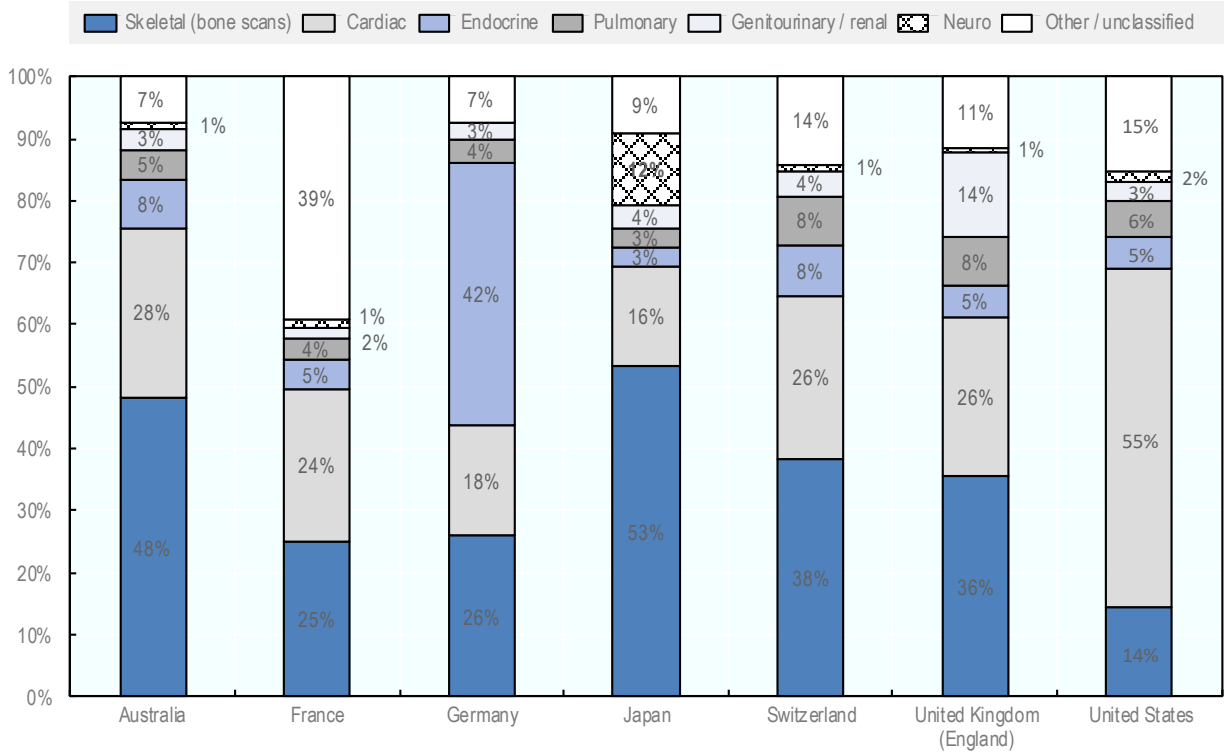


Note: Data was collated from various sources and may not be fully accurate or comparable. Refer to Annex B for data accuracy and comparability issues.
Source: Author based on Health Division survey various public sources. Refer to Annex B for details.

Patterns in utilisation of Tc-99m-based NM diagnostic scans also vary between countries when broken down by organ system or anatomical region scanned. Figure 2.3 breaks down the total number of scans in Australia, France, Germany, Japan, Switzerland, the United Kingdom (England) and the United States into seven main organ systems. Except in Germany, bone and cardiac scans are the most common types of scan, collectively representing between 60% and 76% of all activity. While bone scans are more common than cardiac scans in six of the seven countries, the opposite is true in the United States, where cardiac scans represent 55% of the total and bone scans only 14%. In Germany, endocrine scans are the most common type, representing 42% of the total. In Japan, bone scans represent 53% of the total and neurological scans of the brain or spinal cord are also a relatively large category, representing 12%, while neurological scans represent 2% or less of the total in the six other countries. It should be noted that, as described in the notes to Figure 2.3 and in Annex B, these data should be interpreted with some caution and viewed only as an illustration of variation between countries because they are not fully comparable between countries.

Figure 2.3. Proportion of scans by organ system

Data available for Australia, France, Germany, Japan, Switzerland, the United Kingdom (England) and the United States.



Note: Data were collated from various sources and may not be fully accurate or comparable. For example, data from Japan include Tc-99m-based scans only, which represent 61% of all NM diagnostic scans; when including all NM isotopes use, the proportion of cardiac scans (using Tl-201 more commonly than Tc-99m) increases to 28%, the proportion of neurological scans (using I-123 more commonly than Tc-99m) to 24%, and the proportion of bone scans (using Tc-99m only) decreases to 32%. Billing data from Australia, France, Germany and England do not allow for a precise isolation of Tc-99m-based scans from other isotopes used. The French nomenclature includes several generic billing codes that cannot be allocated to a single anatomical area (e.g. tomo-scintigraphy complementing a planar image), explaining the large proportion of unclassified scans. Estimates for the United States include all NM diagnostic scans except PET scans. Refer to Annex B for further information on data sources, accuracy and comparability.
Source: Authors based on various sources. Refer to Annex B for details.

References

(n.a.) (n.d.), *X*. [3]

NEA (2018), *The Supply of Medical Radioisotopes. 2018 Medical Isotope Demand and Capacity Projection for the 2018-2023 Period*, OECD Nuclear Energy Agency, Paris, https://www.oecd-nea.org/cen/docs/2018/sen-hlgmr2018-3.pdf. [1]

OECD (2018), *OECD Health Statistics 2018*, http://www.oecd.org/els/health-systems/health-data.htm (accessed on 11 September 2018). [2]

Notes

[1] A 6-day curie is the measurement of the remaining radioactivity of Mo-99 six days after it leaves the processing facility (i.e. at the end of processing – EOP). In International System Units, 1 Ci is equal to 37 GBq.

3 Health care providers have varying incentives to contain the cost of Tc-99m

Nuclear medicine (NM) providers receive prospectively set payments for their services, which cover service bundles of varying breadths. Outpatient providers are typically paid fee-for-service (FFS). The breadth of bundling increases with the provider size and hospitals are often paid for broad service bundles, such as diagnosis-related groups, or through global budgets. The cost of Tc-99m is included in these payments in all countries, with some exceptions in Belgium, Germany, Japan, and in the United States. Because payments are set prospectively and providers bear financial risk related to differences between payments and their costs, providers have an incentive to control input costs, including the cost of Tc-99m. Such incentives are stronger where payments are low and where providers have little scope to substitute activities. Thus, increases in Tc-99m prices may be difficult to absorb for small providers who rely exclusively on NM scans for revenue and whose FFS payments are not responsive to input costs. Hospitals with a wide range of activities may be able absorb increases more easily. But provider payments are revised regularly in most countries, allowing providers to negotiate increases if costs increase. Australia and France are exceptions, where fees have not been updated for several years.

3.1. Introduction

This Chapter identifies the types of health care providers that deliver nuclear medicine (NM) diagnostic services (Section 3.2); describes the mechanisms through which the main third-party payers of health care or insurance schemes pay providers for such services and how providers fund the purchase of Tc-99m-based radiopharmaceuticals (Section 3.3); and outlines the financial incentives for providers that arise from payment mechanisms (Section 3.4).

Section 3.3 on provider payment mechanisms first provides an overview across all countries in Sub-Sections 3.3.1 and 0. This is followed by a more detailed description in Sub-Section 3.3.3 of provider payment in a sub-set of countries with the highest volume of NM diagnostic services: the United States, Germany, Canada, France, Japan, the United Kingdom (England only), Australia and Belgium (refer to Chapter 2 for the volume of NM diagnostic service by country).

The main data source for this Chapter is the survey on "Health Care Provider Payment for Nuclear Medicine Diagnostic Services" conducted by the OECD Health Division between April and August 2018 and it covers 17 countries that responded to the survey (see Annex C for details on the survey). Unless other sources are cited, all country-specific information presented in this Chapter is based on survey responses. For the ten countries with a high volume of NM diagnostic activity listed above, data from survey responses were complemented by data retrieved from publicly available sources, including peer-reviewed and grey literature, identified in desk research by the OECD Health Division.

Although no survey response was submitted by the United States, the United States is also covered because it represents more than 50% of the total volume of Tc-99m-based scans across all countries in scope; all information on the United States is based on public sources. For Canada, information is presented by province or territory because health care provision is decentralised and mainly a responsibility of provinces and territories (see Section 3.3.3); only the provinces and territories that submitted a survey response are covered. Despite being in the top 10 of countries in terms of NM diagnostic activity (see Chapter 2), Italy and Spain are not covered because they did not submit a survey response. The level of detail in the information presented depends on survey responses and public availability of data.

3.2. Three main health care provider types deliver nuclear medicine diagnostic services

Nuclear medicine (NM) diagnostic services that use Tc-99m are provided by three main types of health care providers:

1. Office-based physicians, including physicians practicing solo or in group practices who are specialised in nuclear medicine or physicians of other specialities who are authorised to conduct NM diagnostic procedures;
2. Other types of out-patient providers, in particular larger diagnostic centres or radiological clinics that provide a range of diagnostic services including nuclear medicine and other imaging modalities but also specialised clinics, such as cancer treatment centres; and,
3. Hospitals that provide NM diagnostic services to inpatients and outpatients.

Physician offices and other outpatient providers deliver NM diagnostic services in 7 and 11 of 18 countries respectively. Hospitals, on the other hand, provide NM diagnostics in all 18 countries for which data were available. Table 3.2 summarises the provider types by country.

Table 3.1. Types of health care providers delivering NM diagnostics by country

In countries that responded to the OECD Health Division survey and the United States.

Country	Specialist offices	Other outpatient providers	Hospitals
Australia	1	1	1
Belgium	0	0	1
Canada[1]	1	1	1
Alberta	1	1	1
Br Columbia	0	0	1
Manitoba	0	1	1
Newfoundland	0	0	1
Nova Scotia	0	0	1
Czech Republic	0	1	1
Denmark	0	0	1
Germany	1	0	1
France	1	1	1
Japan	1	1	1
Latvia	0	1	1
Lithuania	0	1	1
Luxembourg	0	0	1
Netherlands	0	1	1
Poland	0	1	1
Slovenia	0	0	1
Sweden	0	0	1
Switzerland	1	1	1
United Kingdom (England)	0	0	1
United States	1	1	1
Total number of countries	**7**	**11**	**18**

Notes: Covers all countries that responded to the OECD Health Division survey.
1. In Canada, information is broken down by province or territory because the delivery of health care is an autonomous responsibility of provincial and territorial governments.
Source: Author based on OECD Health Division survey.

While the mode of operation varies between providers in the same country and between countries, the general range of activities and the way they are performed follow similar patterns. As an example, a local outpatient provider and a major university hospital would likely perform the same types of scans in similar ways but the range of different scans performed, and their respective proportions of total activity, may significantly differ.

In countries from which such data are available, the share of services provided in an outpatient setting exceeds the inpatient share. For example, based on data sources described in Annex B, Tc-99m-based NM diagnostic scans performed on an outpatient-basis represent approximately 80% of all scans in Germany and 90% in England.

3.3. Provider payment mechanisms and attendant financial incentives vary by provider type

Through generating financial incentives, mechanisms to pay health care providers are a key policy lever for countries to drive health system performance and they generally vary by provider type. Over time,

payment has generally moved from retrospective "reimbursement" of provider costs towards prospective payment mechanisms that have shifted some financial risk to providers. This Section provides a brief summary of the main types of provider payment mechanisms for NM diagnostics services and attendant financial incentives for providers. For further information on provider payment mechanisms in general and a more detailed discussion of national policies in OECD countries, readers can refer to prior OECD publications (OECD, 2016[1]; OECD, 2016[2]; Paris, Devaux and Wei, 2010[3]).

3.3.1. There are three main payment mechanisms for NM diagnostic services

In many OECD countries a large proportion of health care is funded through pre-paid insurance contributions or from tax revenue and patients therefore do not bear the full cost of care at point of service. This can create incentives for patients to consume and for providers to deliver services in excess of what may be necessary because patients do not face the full marginal cost of their service consumption. This is referred to as *moral hazard* in the literature on insurance markets. Funds that flow from the population to providers are pooled by intermediaries, such as governments, social insurance funds or private health insurers, also referred to as *third-party payers* or *payers*. Payers are responsible for allocating funds to providers and aim to create financial incentives that are conducive to achieving health system goals, in particular service provision that is appropriate for patient needs.

To contain costs and improve the quality of care, payers generally attempt to taper financial incentives for providers to increase the volume of services provided. While there is little doubt that providers act in the best interest of their patients, it has been shown that they also respond to financial incentives (OECD, 2016[2]). Financial incentives for providers can be modulated by two mechanisms, both of which can shift some financial risk between payers and providers:

1. The prospective setting and changing of payment rates, or prices, for predefined sets of services rather than reimbursing providers retrospectively for all costs incurred; and,
2. Changing the breadth of the bundle of services covered by a single prospectively set payment.

Nowadays, the vast majority of payment mechanisms used in health systems of OECD countries is based on prospective prices or budgets. The breadth of these service bundles covered by prospective payments varies and various payment mechanisms can be meaningfully analysed in terms of the degree of bundling, and thus the level of risk borne by providers - the broader the bundle of services covered by a payment, the greater the risk to the provider (OECD, 2016[2]). Payers therefore adapt payment mechanisms not only to modulate incentives but also according to the size of provider organisations and their ability to bear risk.

For example, a predetermined price can be paid for a specified NM diagnostic scan such as a myocardial perfusion study, covering a bundle of all associated cost items including the physician time, use of premises, the gamma camera, and other overheads as well as the Tc-99m-based product used. In this case, the provider only bears risk related to the cost of inputs required for the scan because any additional service rendered by the provider will attract an additional payment. However if, for example, a myocardial perfusion study is performed as part of an inpatient stay at a hospital, a predetermined price based on the diagnosis and expected treatment protocol may apply to the entire patient stay, covering all cost items associated with the stay, including not only the diagnostic scan but also patient accommodation and all treatments and services received by the patient during the stay. This presents a greater financial risk to the provider because additional services provided, or a length of patient stay that exceeded expectations, would not attract additional payment.

The following three broad types of provider payment mechanisms are used for NM diagnostic services (in ascending order according to the degree of bundling):

1. Fee-for-service (FFS): activity-based payment of a price for each unit of service delivered. Service units and corresponding prices are defined prospectively in fee schedules. Fee schedules may directly associate a monetary amount with each service or take the form of resource-based relative

value scales (RBRVS) that are then converted to a monetary amount based on conversion factors that may vary between geographic areas (see Box 3.1). Service units are usually defined narrowly, for example a single physician/patient consultation or the scan of a specific organ using a specific imaging modality.

2. Case-based payments (also referred to as Diagnosis-related Groups or DRGs): activity-based payment for an entire patient case, usually for hospitals only and most commonly used for inpatients. Patient cases are classified into groups based on diagnoses and resource use (DRGs), which cover entire episodes of diagnoses and treatments with relatively homogenous levels of resource use. DRGs and their prices are defined prospectively, often based on historical data on patient cases and related resource use (see Box 3.1).
3. Global budgets: Prospective lump-sum payment covering a range of services and time period independent of the actual volume of services provided, usually for hospitals only.

Box 3.1. Resource-based Relative Value Scales (RBRVS) and DRG cost weights

The monetary amounts paid to providers under FFS or DRG mechanisms are often determined by multiplying a base rate by a factor that reflects the relative prices of all services or DRGs. This is based on the principle that services that are more expensive to produce should attract higher payments.

In DRG systems, the multiplication factor is often referred to as *cost weight.* It is equal to one for the average inpatient case treated by hospitals, referred to as the *base case*. All DRGs are associated with a cost weight that is higher or lower than 1, representing their prices relative to the base case. Cost weights are usually computed based on historical cost data submitted by a sample of hospitals or all hospitals in a jurisdiction, for example using the mean cost by DRG or some other parameter in the cost distribution across hospitals. Base rates may be set based on a variety of factors, such as overall resource constraints or overall policy goals related to provider funding, and can be uniform across a jurisdiction or vary locally to reflect differences in the prices of production factors, such as labour and buildings. Such mechanisms can create a form of cost-based competition among hospitals, also referred to as *yardstick competition*, because hospitals retain any surplus between DRG payments and their *actual* costs associated with each DRG and therefore have an incentive to reduce costs. As hospitals reduce costs of a given DRG and their cost data is used as the basis of subsequent iterations of cost weights, the respective DRG cost weight decreases over time.

RBRVS that underlie FFS payments work in a similar way except that the process to set relative prices is not always data-driven. Relative prices and base rates can be the results of a negotiation process between health care providers and payers.

Retrospective reimbursement by payers of actual costs incurred by providers may only be used in some cases, for instance for some services paid by Medicaid in the United States (see Section 3.3.3) or where payers reimburse providers for the cost of medicines or other material, including radiopharmaceuticals.

A more general discussion of provider payment and price-setting mechanisms can be found in Barber, Lorenzoni and Ong (2019[4]).

Office-based physicians and other non-hospital outpatient providers are always paid FFS, while hospitals are paid through a mixture of FFS, DRGs and global budgets. Table 3.2 shows which payment mechanism is used for each of provider type that delivers NM diagnostic services in each country.

Table 3.2. Payment mechanisms for NM diagnostics by provider type and country

In countries that responded to the OECD Health Division survey and the United States.

Country	Specialist offices	Other Outpatient Providers	Hospital outpatients / day cases	Hospital inpatients
Australia[1]	FFS	FFS	Global budgets (FFS)	Global budgets (FFS)
Belgium			FFS	FFS
Canada[2]				
Alberta[3]	*FFS*	*FFS*	*FFS* *Global budgets*	*FFS* *Global budgets*
Br Columbia			*FFS*	*Global budgets*
Manitoba		*FFS*	*Global budgets*	*Global budgets*
Newfoundland			*Global budgets*	*Global budgets*
Nova Scotia			*Global budgets*	*Global budgets*
Czech Republic		FFS	FFS	FFS
Denmark			DRGs	DRGs
France	FFS		FFS	DRGs
Germany	FFS		FFS DRGs	DRGs
Japan	FFS	FFS	FFS	FFS
Latvia		FFS	FFS	DRGs
Lithuania		FFS	FFS	DRGs
Luxembourg			FFS *Global budgets*	FFS *Global budgets*
Netherlands		DRGs	DRGs	DRGs
Poland		n/d	FFS	DRGs
Slovenia			FFS	*Global budgets*
Sweden			*Global budgets*	*Global budgets*
Switzerland	FFS	FFS	FFS	DRGs
United Kingdom (England)			FFS	DRGs
United States	See Table 3.4			

Notes: Payment for hospital services may vary between inpatients and patients treated as day cases or outpatient departments and are therefore presented in separate columns.
1. Public hospitals in Australia are generally funded by states and territories for all activity except "private" physician practice on hospital premises. Physicians engaging in private practice in hospitals are paid FFS or on a per-session basis and their services can be eligible for Medicare subsidies (see Section 3.3.3).
2. In Canada, information is broken down by province or territory because the delivery of health care is an autonomous responsibility of provincial and territorial governments.
3. Physicians are paid FFS for NM diagnostic services but hospital cover all costs from global budgets.
Source: Author based on OECD Health Division survey.

3.3.2. Most countries do not compensate providers directly for the actual cost of Tc-99m

In most countries, providers fund the cost of Tc-99m from broader provider payments described in Section 3.3.1, such as FFS payments for the diagnostic procedure, payments for DRGs or global hospital budgets. Among the 16 countries that responded to the OECD Health Division survey, only payers in Belgium, Germany and Japan make payments to providers that are unbundled from the service and to cover specifically the cost of Tc-99m used in each procedure. In these three countries, unbundled payments are only made in addition to FFS payments; no unbundled payments for Tc-99m are made in

addition to DRG-based payments to hospitals in Germany. In the United States, office-based specialists receive additional payments for Tc-99m for procedures paid FFS by Medicare based on the Resource-based Relative Value Scale (RBRVS) (see Section 3.3.3). In Luxembourg, the cost of Tc-99m is funded from hospital pharmacy budgets; while this is unbundled from payments for services, but budgets are not specific to Tc-99m.

In Belgium, hospitals currently receive an unbundled payment of EUR 18.59 per procedure in which Tc-99m is used in addition to EUR 18.59 for each cold kit used. This amount is the same regardless of the type of scan performed, the amount of activity in the dose and the specific Tc-99m-based cold kit product used (INAMI, 2018[5]).

In Germany, outpatient providers that are paid FFS based on the national uniform value scale (EBM) receive unbundled payments for the cost of Tc-99m. Prices are defined by type of scan and type of Tc-99m-based product used. In the current version of the EBM, payments range from EUR 1.50 when using Tc-99m pertechnetate in a thyroid scan to EUR 382 when using Tc-99m-labeled antibodies in a scan of bone marrow or to localise inflammations (KBV, 2018[6]). A full list of unbundled Tc-99m payments in the current version of the EBM is provided in Annex D.

In Japan, all providers receive FFS payments and additional unbundled payments specific to each Tc-99m product and manufacturer. Prices are either defined by patient dose or by the amount of radioactivity. A full list of unbundled Tc-99m payments in the current version of the national fee schedule is provided in Annex D.

Table 3.3 shows the provider types to which unbundled payments are made as well as the types of unbundled payment in the Belgium, Germany, Japan, the United States as well as Luxembourg. Further details on provider payment mechanisms and on setting unbundled payments for Tc-99m in these three countries are provided in Section 3.3.3.

Table 3.3. Unbundled payments specific to Tc-99m by provider type and country

Country	Specialist offices	Other Outpatient Providers	Hospital inpatients	Hospital outpatients / day cases
Belgium	n/a	n/a	Isotope-specific	Isotope-specific
Germany	Procedure- and isotope-specific	n/a	None	None
Japan	Product-specific	Product-specific	Product-specific	Product-specific
Luxembourg			Global pharmacy budget	Global pharmacy budget
United States	Medicare reimbursement of invoice price	None	None	None

Source: Author based on OECD Health Division survey and public information for the United States.

3.3.3. Country Details

This Section provides more detailed descriptions of provider payment in each of the 17 countries in the final scope of this report. Collectively, the eight countries with the highest volume of Tc-99m-based diagnostic scans (the United States, Germany, Canada, France, Japan, Australia, the United Kingdom (England only) and Belgium) are estimated to account for 88% of the volume of Tc-99m-based scans performed across the countries included in the initial scope of this study (see Chapter 2). There is a country-specific Section below for each of these eight countries, in descending order based on the estimated annual volume of Tc-99m-based scans. A final Section summarises information on provider payment for NM diagnostic services in the remaining nine countries in the final scope.

United States

Compared to most other OECD countries, health insurance coverage in the United States is fragmented. The majority of nuclear medicine (NM) diagnostic services are delivered in outpatient settings (SNMMI, personal communication). Provider payment mechanisms cannot be summarised easily – they depend not only on the type of service and the type of provider but also on the payer and the insurance coverage scheme operated by the payer. Table 3.4 summarises the main provider payment mechanisms employed by the main groups of payers. The Sections below provide a general overview of health insurance in the United States and short descriptions of how providers are paid under Medicare and Medicaid, the two main publicly funded coverage schemes.

Despite a large private insurance market, a large portion of health care the United States is funded publicly: in 2015, approximately 50% of total health expenditure was funded publicly (OECD, 2017[7]). Private health insurance accounted for another 35% of health expenditure and out-of-pocket payments for 11% (ibid.). In the same year, 61% of the population was covered by private insurance, while Medicare and Medicaid covered about 17% and 22% of the population respectively; 9% of the population were uninsured (Cuckler et al., 2018[8]).[1] Uninsured persons pay providers directly or may receive care at no cost from charity (Rice et al., 2013[9]). While prices for uninsured persons vary on a case-to-case basis, they are often based on provider price lists and can far exceed the prices paid by public or private payers (ibid.).

Medicare and Medicaid are the two main public health coverage schemes, collectively accounting for about 40% of health expenditure (Cuckler et al., 2018[8]). Medicare covers the disabled and elderly (those aged 65 years and older), and Medicaid covers people with incomes below a state-specific poverty threshold, defined as a percentage of the federal poverty guidelines issued by the United States Department of Health and Human Services (HHS).[2] Other publicly funded coverage schemes include, for example, the Children's Health Insurance Program, or coverage for the armed forces by the Department of Defence and for war veterans by the Department of Veterans Affairs (Cuckler et al., 2018[8]). Federal funds available to public coverage schemes are based on annual budgets, proposed by the United States President and Congressional budget resolutions that can amend and ultimately approve the budget (Rice et al., 2013[9]). While Medicare is mainly funded by the federal budget, including premiums paid by beneficiaries, state governments co-finance Medicaid (ibid.).

Table 3.4. Provider payment mechanisms in the United States by payer

	Office-based specialists and other outpatient providers	Hospital outpatient services	Hospital inpatient services
Medicare	FFS, capitation	OPPS: FFS, APC	IPPS: DRGs
Medicaid	FFS, capitation	FFS, cost reimbursement, variations of Medicare OPPS	DRGs, per-diems, capitation, cost reimbursement
Private insurers	FFS, capitation, salaries	No data	DRGs, FFS, per diems
Uninsured persons	Transaction-specific	Transaction-specific	Transaction-specific

Note: Procedural groups in the Medicare hospital Outpatient Prospective Payment System (OPPS) are referred to as Ambulatory Payment Classification (APC) and can apply to broader DRG-like service bundles or more narrowly defined services or procedures. IPPS stands for Medicare hospital Inpatient Prospective Payment System

Source: Adapted by the Author from Rice et al. (2013[9]).

Medicare and Medicaid

Medicare coverage has three main parts: Part A covers inpatient hospital stays, care in skilled nursing facilities, hospice care, and some home health care; Part B covers certain doctors' services, outpatient care, medical supplies and preventive services; and Part D adds prescription medicine coverage.[3] Part C is offered by private payers approved by Medicare as a combined alternative to Parts A and B and usually also Part D. Medicaid coverage and provider payment mechanisms are specific to each state. Provider payments by Medicare and Medicaid are either direct through claims processing contractors (under Medicare Parts A and B and Medicaid FFS – as described below) or indirect through other payers and health coverage schemes that may provide managed care.

Medicare Part B pays physicians on a fee-for-service (FFS) basis, based on the Resource-based Relative Value Scale (RBRVS). Fees are updated annually by the Centres for Medicare & Medicaid Services (CMS) (Rice et al., 2013[9]). Fees are calculated by multiplying the relative value units associated with each service, reflecting reported costs of physician work, office expenses and professional insurance, with a "geographic practice cost index" for each cost component reflecting geographical differences in costs and a monetary "conversion factor", both determined by CMS. The conversion factor takes into account inflation for non-physician services and a number of different variables for physician services, with the overall goal of keeping spending within budget (ibid.). There is an annual notice and comment period when new fees are proposed (CMS, 2018[10]). Specialists can opt to either receive direct payment from Medicare (for all or selected services only) or receive payment from patients who claim reimbursement from Medicare (Rice et al., 2013[9]). In the former case, physicians accept RBRVS-based fees as full payment and Medicare generally pays 80% of the fee defined in the schedule with patients making a 20% co-payment. Only in the latter case can specialists bill more than the fee specified in the Medicare schedule (Rice et al., 2013[9]). Table 3.5 provides examples of NM diagnostic procedures and applicable services fees in the 2018 Medicare RBRVS.

The fees applicable for NM diagnostic services according to the RBRVS do not include costs of the radiopharmaceuticals used in the procedures. A separate payment is made through Medicare contractors to cover the cost of radiopharmaceuticals. Payment mechanisms are specific to Medicare contractors however payments are commonly based on actual prices invoiced by Mo-99/Tc-99m vendors to health care providers, or the reported wholesale acquisition cost. This is different from many other medicines covered under Medicare Part B, for which providers commonly receive payment based on the average sales prices calculated by CMS from submissions by manufacturers plus a statutorily mandated add-on of 6%. Payment rates based on average sales prices are updated quarterly (CMS, 2018[11]).

Medicare Part A payments for hospital services are based on a combination of DRGs and FFS (Rice et al., 2013[9]), although there are exceptions in some states to the national Medicare payment systems. Separate payment systems apply to inpatient stays and outpatient hospital services.

Inpatient services are paid through the Inpatient Prospective Payment System (IPPS) using DRGs (CMS and MLN, 2018[12]). No additional payments are made for radiopharmaceuticals (Lantheus, 2018[13]), although, in addition to various adjustments to DRG payments described below, "add-on" payments can be made temporarily for new and costly technology where DRG amounts are shown to be inadequate to cover costs (CMS, 2018[14]). DRG prices are determined by multiplying base rates for labour-related and non-labour shares of the service associated with a DRG by the cost weight of the DRG and adjusting the labour-related share for the wage index of the area where the hospital is located and the non-labour share for a cost of living factor (CMS and MLN, 2018[12]). Additional payments are made to hospitals with a high proportion of low-income patients in the population they treat, for providing medical education if the hospital is an approved teaching hospital, and for patient cases that are unusually costly. CMS update annually the cost weights for Medicare DRGs based on detailed billing data from all hospitals that claim Medicare payments and base rates (CMS and MLN, 2018[12]). Hospital accounting rules allow for significant top-down cost allocation (Raulinajtys-Grzybek, 2014[15]) and billing data does not provide micro-cost data. Base rates reflect operating and capital costs that efficient facilities are expected to incur in furnishing covered inpatient services (CMS and MLN, 2018[12]). Overall, CMS is required to maintain 'budget neutrality' in updating IPPS, meaning that updates to the payment system can change the relative prices of DRGs but must also ensure that hospital funding remains within an overall budget constraint.

Outpatient services by health care providers that are licensed as hospitals are paid by Medicare through the Hospital Outpatient Prospective Payment System (OPPS), which uses a combination of broader DRG-like service bundles and FFS payments for more narrowly defined services or procedures. There is a quarterly update process for OPPS by CMS, but the most significant changes, including prices, are made once a year (Guidi, 2010[16]). Prices are set at the level of Ambulatory Payment Classification (APC) groups, which may bundle several types of services. Similar to DRGs, each APC code is assigned a relative cost weight, based on CMS estimates of the costs associated with the services assigned to APCs using data from hospital claims (Guidi, 2010[16]). Payments for services are adjusted for geographic wage variations (Guidi, 2010[16]). CMS must also respect 'budget neutrality' in updating the OPPS. The cost of medicines can either be included in broader service bundles or attract a separate payment. Medicines whose costs exceed a threshold (USD 110 per day in 2017) have separate APC codes (MedPac, 2017[17]). In general, the cost of radiopharmaceuticals used in diagnostic NM services, including Tc-99m-based radiopharmaceuticals, is included in the APC payment rate while therapeutic radiopharmaceuticals attract a separate payment (SNMMI, 2017[18]; Lantheus, 2018[13]). However, each procedure using Tc-99m from non-high enriched uranium (HEU) attracts an additional payment of USD 10 to cover additional cost of producing Tc-99m from such sources and to incentivise the use of these materials (SNMMI, 2017[18]; Lantheus, 2018[13]). Table 3.5 provides examples of NM diagnostic procedures and applicable payment rates to hospitals in the 2018 Medicare OPPS.

Medicare Part C, also referred to as Medicare Advantage, covers the same services as Parts A and B, and optionally also Part D, but provider payments are made by private payers and health coverage schemes that receive risk-adjusted capitated funding from Medicare (Rice et al., 2013[9]). Enrolment is voluntary and replaces 'traditional' parts A and B (Rice et al., 2013[9]). Payers that receive Medicare Part C funding have some discretion as to how they pay providers on behalf of Medicare, and beneficiaries are often enrolled in managed care but payment mechanisms can also include FFS.

Medicaid may pay specialists directly FFS or make capitated payments to private managed care organisations, which in turn pay specialists either FFS or also through capitation (Rice et al., 2013[9]). The majority of Medicaid beneficiaries are enrolled in managed care. Payment mechanisms for specialist physicians vary by state but also include direct FFS payments for beneficiaries who are not enrolled in managed care (Rice et al., 2013[9]). Medicaid fees tend to be lower than those paid by Medicare (Rice et al., 2013[9]). Medicaid FFS payments are based on state-specific fee schedules, which usually also use a relative-value approach, i.e. with services requiring more inputs attracting higher fees (Rice et al., 2013[9]). Medicaid payments for hospital services vary by state and comprise DRGs, per-diem payments

and cost reimbursement (Rice et al., 2013[9]). Medicaid managed care programmes operate a similar model as Medicare Part C, whereby Medicaid state agencies pay a capitated amount per insured person to insurers that provide a specified benefit package, which includes inpatient services (Rice et al., 2013[9]).

Table 3.5. Selected NM diagnostic services and Medicare payment rates 2018

All prices in USD.

CPT Code	Description	RBRVS fee for non-hospital providers	OPPS payment for hospitals
78700	Kidney imaging morphology	181.80	349.42
78305	Bone and/or joint imaging; multiple areas	297.00	349.42
78306	Bone and/or joint imaging; whole body	320.40	349.42
78453	Myocardial perfusion imaging, planar (including qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); single study, at rest or stress (exercise or pharmacologic)	320.76	1 202.60
78606	Brain imaging, minimum 4 static views; with vascular flow	347.76	453.05
78451	Myocardial perfusion imaging, tomographic (SPECT) (including attenuation correction, qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); single study, at rest or stress (exercise or pharmacologic)	359.28	1 202.60
Q9969	Non-HEU Tc-99m add-on per study dose Tc-99m from non-high enriched uranium source, full cost recovery add-on, per study dose	n/a	10.00

Note: RBRVS payment rates do not reflect adjustments for the geographic practice cost index. OPPS payments include cost of radiopharmaceuticals, except the USD 10 add-on for Tc-99m from non-HEU sources, RBRVS fees do not include cost of radiopharmaceuticals.
Source: Author based on United States Society of Nuclear Medicine and Molecular Imaging (SNMMI, 2017[18]; SNMMI, 2017[19]).

Private insurers

The private insurance market is fragmented, and coverage and provider payment mechanisms vary significantly between states and among individual payers (Rice et al., 2013[9]). Private payers pay specialists FFS, salaries or capitated rates. Hospital services are paid through FFS, DRGs or per-diems. Insurers may negotiate discounts on prices set by hospitals or employ Medicare DRGs but may assign different prices by DRG. Similarly, private insurers may use the Medicare RBRVS fee schedule as a basis for payment for physician services but assign different prices based on negotiations (ibid.). The contents of the contractual arrangements between providers and private insurers are not in the public domain. However, there is evidence that the prices private payers pay providers vary widely between individual payers (Clemens, Gottlieb and Molnár, 2017[20]; IFHP, 2016[21]; Reinhardt, 2011[22]). Prior studies of provider payment in general also found that prices paid by private payers significantly exceed provider costs and Medicare payment rates (Cooper et al., 2015[23]; Selden et al., 2015[24]).

Canada

Funding and delivery of health care in Canada are highly decentralised and mainly a responsibility of provinces and territories. The federal government only has responsibility in specific aspects of health care, such as regulation and safety of medicines and funding and delivery of health services for eligible First Nations people and Inuit, members of the Canadian armed forces, veterans, inmates in federal penitentiaries and eligible refugee claimants (Marchildon, 2013[25]). In addition, the federal government also funds a portion of government health expenditures in provinces and territories through the Canada Health Transfer (ibid.). Publicly funded coverage of services, however, is similar across provinces and broadly defined by the Canada Health Act, which states that residents are entitled to medically necessary hospital, diagnostic and physician services (Allin and Rudoler, 2017[26]; Marchildon, 2013[25]).

While it is not possible to summarise provider payment for all of Canada, fee-for-service (FFS) payment for physician services is common across all provinces, including for specialists working in hospitals, and hospitals often receive global budgets directly from the provincial government or regional health authorities (RHAs) (ibid.). Specialists are mainly self-employed and commonly work in hospitals (Allin and Rudoler, 2017[26]). Hospitals are either integrated into RHAs that are funded by provinces and hold a budget for their operations or contract with RHAs, in which case they may also have global budgets or receive activity-based funding (Allin and Rudoler, 2017[26]; Marchildon, 2013[25]). Global budgets are often based on historical spending and high level adjustments irrespective of the number of patients treated or projected demand for services (Sutherland et al., 2013[27]). Initiatives to shift hospital payment mechanisms towards activity-based funding, such as payment by DRG, have been underway for some time in Alberta, British Columbia and Ontario (ibid.).

The types of providers that deliver nuclear medicine (NM) diagnostic services and corresponding provider payment mechanisms are therefore specific to provinces and territories.

Alberta

Office-based specialists, diagnostic centres and radiological clinics as well as hospitals provide NM diagnostic services in Alberta and all physician services are paid fee-for-service (FFS) by Alberta Health Services, the single health authority of the province responsible for delivery of health care on behalf of the provincial ministry of health. Hospitals have an operational budget for diagnostic imaging, which covers all costs of NM diagnostic services, physician fees and radiopharmaceuticals but also overhead, costs of other staff and equipment.

Physician fees are regulated in the Alberta Schedule of Medical Benefits and physicians can only bill the exact fees determined in the schedule. There is no defined interval for updates to the schedule and it is updated as required. The current schedule is applicable since 1 April 2017 (Alberta Health, 2017[28]).

British Columbia

Hospitals provide nuclear medicine (NM) diagnostic services in British Columbia and services are paid on a fee-for-service (FFS) basis for outpatients while global hospital budgets cover services for inpatients. FFS payments and hospital budgets cover the entire cost of NM diagnostic services, including the cost of radiopharmaceuticals and other service components, such as physician time. Only hospitals are permitted to bill the Medical Services Plan (MSP), the main health insurance scheme funded by the government of British Columbia for its residents, and physicians are paid by hospitals.

Fees for outpatient services are regulated in the Payment Schedule revised and published annually by the British Columbia Medical Services Commission (MSC) under the master agreement between the government of British Columbia and the MSC and the British Columbia Medical Association. The MSC Payment Schedule is also the binding catalogue of services for which providers can bill the MSP. Providers can only bill the exact amount determined in the schedule. Annual revisions take into account the cost of overhead and staff and an allocation of capital equipment costs.

The current MSC Payment Schedule is valid for the calendar year of 2018. Although it lists a number of separate items for administration of radiopharmaceuticals (e.g. item no. 09896 for lumbar administration of radionuclide, attracting a fee of CAD 32.61), no separate payments are made to cover the costs of radiopharmaceuticals. The service-related fee specified in the schedule also covers the cost of the radiopharmaceuticals used. Service fees range from CAD 73.80 for a thyroid scan using Tc-99m pertechnetate (item no. 09825) to CAD 1 387.10 for tumour imaging with a metabolic or biological imaging agent (item no. 09826).

Manitoba

Diagnostic centres and radiological clinics as well as hospitals provide NM diagnostics services in Manitoba. Diagnostic centres and radiological clinics are paid fee-for-service (FFS) while all hospital activity is covered by global budgets.

Service fees are regulated in contracts that are valid for up to 5 years and providers can only bill the exact amount determined in the regulation. The current fee schedule applies since 2014. Data on actual costs are generally not considered when setting fees.

Neither diagnostic centres and radiological clinics nor hospitals receive additional payments to cover the cost of radiopharmaceuticals. The service fees and global budgets also cover the cost of Tc-99m.

Newfoundland and Labrador and Nova Scotia

Hospitals provide nuclear medicine (NM) diagnostic services in Newfoundland and Labrador and all hospital activity (in- and outpatient) is covered by global budgets. Hospitals receive no additional payments to cover the cost of radiopharmaceuticals. Budgets also cover the cost of Tc-99m. In Newfoundland and Labrador budgets are allocated by RHAs while there is a single health authority in Nova Scotia.

Japan

Office-based specialists, diagnostic centres and radiological clinics as well as hospitals provide NM diagnostics services in Japan and all providers are paid fee-for-service (FFS). Providers receive separate payments for radiopharmaceuticals. Service fees and payments for radiopharmaceuticals are regulated by a national fee schedule, which serves as a binding catalogue of goods and services for which providers can bill social health insurance (SHI) and also defines strict billing conditions that must be met for a listed service to be paid by SHI (Ikegami, 2014[29]). Adherence to billing conditions is routinely audited in processing provider payment (ibid.). Providers are not permitted to charge prices in excess of the fees set in the national schedule.

The national fee schedule, which sets prices and billing conditions for medical services, medicines and devices for all providers, is revised every other year in a two-step process (Ikegami, 2014[29]):

1. The Minister of Finance and the Minister of Health, Labour and Welfare set an overall price increase or decrease for all goods and services in the fee schedule based on the macro-economic and budgetary context and the effect of non-price factors (such as increases in demand for services due to demographic changes or shifts towards the use of more expensive goods and services). This effectively determines an overall budget. The overall budget decision also takes into account separately the market prices of medicines and devices that are listed in the schedule and determines an overall price increase or decrease for services. The Ministry of Health, Labour and Welfare (MHLW) elicits market prices of medicines and devices in a survey, which are often below the corresponding payments made to providers per the fee schedule because of competition among vendors of medicines and devices, and estimates overall savings that can be achieved by aligning payments to providers in the schedule with prevailing market prices. Savings from price reductions of medicines can be reallocated to services to determine the overall price change for services.
2. A micro-level review of each item listed in the fee schedule, including prices and billing conditions. The Minister of HLW is ultimately responsible for setting fees in consultation with the Central Social Insurance Medical Council, an advisory panel to the MHLW, but the process includes negotiations between provider representations and the MHLW. While for medicines and devices, payments to providers are mainly aligned with market prices, updates to services fee aim to achieve expenditure control by reducing fees for items whose volumes have increased rapidly and/or can be delivered

at lower costs; to maintain appropriate and equitable margins across providers; and to incentivise providers for provision of certain services by listing new items or raising applicable fees.

The MHLW actively uses the national fee schedule as a policy lever – prices are increased or reduced to incentivise providers and improve quality of care (OECD, 2015[30]). While FFS payment is generally associated with incentives for providers to increase activities, low fee levels and billing conditions are actively used by the Japanese Government as mechanisms to constrain activity and health care expenditure (Ikegami, 2014[29]; OECD, 2015[30]). Price adjustments for medicines in the overall step 1 of the bi-annual fee revision have been negative between 1990 and 2012 while for medical services, price adjustments were negative in the 2002 and 2006 revisions, with increases below 2% since 2008 (ibid).

Fees for procedures using new technology are set based on fees for existing procedures that are similar to the new one. When there is evidence that the new technology is more effective than any of the existing procedures, the new procedure will attract a higher fee and vice versa. When no comparable procedure exists, the fee for the procedure using new technology can be set based on cost-related factors.

In addition to price adjustments, billing conditions play a key role in constraining activity and expenditure and are used to ensure use that is considered appropriate. For example, when Positron Emission Tomography (PET) was first listed in the national schedule, billing conditions restricted use to patients who had a confirmed diagnosis of cancer, precluding its use for screening (Ikegami, 2014[29]).

For NM diagnostics, fee negotiations can take into account overhead and fixed costs, staff costs and the cost of capital equipment. The current fee schedule is effective since 1 April 2018 and contains four NM diagnostic services. Fees are uniform for all provider types and range from JPY 13 000 for a series of static scintigrams of a body part to JPY 22 000 for a series of scintigrams of the whole body. A SPECT scan attracts a fee of JPY 18 000. Providers receive separate payment for radiopharmaceuticals listed in the national fee schedule. The national schedule lists all reimbursable radiopharmaceutical products and their manufactures as well as prices that are payable to providers, depending on the product either by patient dose or by the amount of radioactivity of the generator.

Germany

Office-based specialists and hospitals provide nuclear medicine (NM) diagnostic services in Germany are paid through separate mechanisms by social health insurance (SHI). Services that are not paid by SHI are not covered in this Section. SHI and government transfers fund approximately 80% of all health expenditure in Germany (OECD, 2018[31]). A minority of the population is covered by private insurance instead of SHI.

Specialist Offices

Office-based specialists are paid fee-for-service (FFS) by regional associations of health insurance-affiliated (SHI) physicians according to a national uniform value scale (EBM) and regional adjustments that ultimately determine service fees in absolute monetary terms. The EBM serves as the binding catalogue of services physicians can bill to SHI and sets the relative prices of most services in terms of points or, for some services, nationally uniform prices in terms of EUR. The EBM also defines national reference prices in EUR for all services based on a national reference valuation of each point. However, in negotiating annual remuneration contracts and regional fee schedules, state-level associations of sickness funds and physicians have some leeway to digress from national reference prices, in particular to reflect regional specificities in cost and supply structures (Kriedel, 2012[32]). Regional physician associations and regional associations of sickness funds negotiate the total aggregate budget for the vast majority of physician services taking into account, among other factors, trends in morbidity in the insured population (KBV, 2018[33]; Busse and Blümel, 2014[34]).

Physicians are paid quarterly by regional physician associations. Every quarter, regional physician associations first split their aggregate funding received from sickness funds between primary care and

specialists. The portion allocated to specialists is then allocated to each physician practice based on the total number of points associated with the services provided, as specified in the EBM, and prices defined in the regional fee schedule. In order not to exceed the quarterly funding available and taper incentives for physicians to increase activity, regional associations also define a physician practice-specific volume cap beyond which services that are not explicitly exempted from the cap are either paid at a reduced price or not paid at all (Busse and Blümel, 2014[34]).

For NM diagnostic services, fee negotiations can take into account overhead and fixed costs, costs for staff, costs of capital equipment and costs of procuring Tc-99m. The cost of Tc-99m is covered by a payment also determined in the EBM but that is separate from the service fee.

According to the 2018 version of the fee schedule for NM specialists (KBV, 2018[35]), physicians receive a fee per consultation plus additional fees for the diagnostic procedure depending on the organ system or anatomical area scanned, a modality-specific additional fee if the imaging modality is not a single-phase scintigraphy (e.g. SPECT, sequential scintigraphy) and a fee for the cost of the radiopharmaceutical used (also see Section 0). Based on the national reference value of a point in the EBM, the consultation fee is EUR 9.38 and fees for the diagnostic procedure range from EUR 43.15 for an examination of the thyroid gland to EUR 102.49 for a myocardial scintigraphy. Payments for the Tc-99m and related material (cold kits) are described in Section 0 and Annex D.

For an entire diagnostic service, for example, a simple thyroid scan can attract a total fee of EUR 54: sum of EUR 9.38 for the consultation, EUR 43.15 for the scan and EUR 1.50 for the Tc-99m-based radiopharmaceutical used. A cardiac stress test using dual- or multi-headed SPECT can attract a total fee of EUR 279: sum of EUR 9.38 for the consultation, EUR 98.77 for the scan, EUR 111.34 for the use of dual- or multi-headed SPECT and EUR 60 for the Tc-99m-based radiopharmaceutical used.

Hospitals

For inpatient care and selected day care procedures hospitals receive payments based on DRGs that cover an entire patient stay or treatment episode and no separate payments are made for nuclear medicine diagnostic procedures or radiopharmaceuticals. These case-based payments are determined by multiplying a DRG-specific ‘cost weight’ with a ‘base rate’ that is uniform for each federal state. Cost weights are determined using historic cost averages reported by hospitals, which are based on micro-cost data and some top-down cost allocations (Geissler et al., 2011[36]; InEK, 2016[37]). Both factors are updated annually but are determined in two separate processes:

1. The regional base rate is negotiated between regional hospital associations and insurers but must lie within +2.5% and -1.25% of a federal reference base rate and year-on-year increases cannot exceed the increase of the federal base rate. The federal base rate is agreed upon between the National Association of Statutory Health Insurance Funds (GKV-SV), private insurers and the National Association of Hospitals (DKG). Both negotiations broadly take into account factors such overall cost projections, including costs for salaries and equipment, and changes in the number and severity of cases. For further details, see (Busse and Blümel, 2014[34]; de Lagasnerie et al., 2015[38]).
2. The DRG catalogue and corresponding cost weights are agreed upon between the DKG, GKV-SV and private insurers, based on calculations by the Institute for the Payment System in Hospitals (InEK). To determine cost weights, InEK calculates average costs per DRG using data from a sample of hospitals that participate in a voluntary data-sharing programme (InEK, 2016[37]). Hospitals submit data according to standardised cost accounting guidelines, which require the reporting of micro-level cost data for some items but also allow for using allocation algorithms where detailed reporting is not feasible (ibid.). Given the data collection and calculation process, cost weights in any given year are based on data pertaining to two years earlier (Busse and Blümel, 2014[34]). For medicines, hospitals are only required to submit micro-level cost data, i.e. actual unit

purchase prices, for products whose prices exceed EUR 300 per patient case (InEK, 2016[37]). The cost of radioisotopes and radiopharmaceuticals per patient case may be below this threshold.

DRG payments are tapered in two main ways to attenuate the incentive for hospitals to increase volume but also to limit the financial risk for hospitals. First, each DRG includes a minimum and maximum length of patient stay, and payments are reduced for patient stays below the minimum and increased for stays longer than the maximum. Second, all hospitals negotiate annual revenue budgets with insurers, which determine a target volume in terms of the sum of cost weights associated with DRGs. Significantly reduced rates apply to services provided in excess of the volume provided in the prior year and volume provided in excess of the negotiated targets. Conversely, if volume remains below the targets, hospitals receive a partial payment for the difference between actual volume and the target (de Lagasnerie et al., 2015[38]).

Hospitals may receive additional payments on top of DRG-based payments for new technology if (1) a hospital wishing to employ and receive such payments for a new technology applies to InEK; (2) if the application is accepted, the hospital successfully negotiates such payments with the sickness funds; and (3) the technology can ultimately be included in regular DRGs (Geissler et al., 2011[36]). Other exceptional and additional payments can be agreed upon for services that incur high costs and cannot be integrated into a DRG.

The cost of a nuclear medicine diagnostic procedure, and the associated cost of the radiopharmaceutical, likely represent only a small portion of hospital payment based on a DRG. For example, according to annual national statistics on the volume of hospital procedures performed, the most common type of nuclear medicine procedure performed on hospital inpatients in 2015 was scintigraphy of the musculoskeletal system (Hellwig et al., 2017[39]). This procedure can be associated with various diagnoses and treatments and therefore various DRGs. The three most common DRGs associated with this procedure in 2015 attracted hospital payments (in 2018) of EUR 3 700 to 5 200; details are shown in Table 3.6.

Table 3.6. Top 3 DRGs associated with scintigraphy of the musculoskeletal system on inpatients in German hospitals

Based on the 2018 DRG catalogue.

DRG code and title	Mean length of stay (days)	Cost weight relative to base case	Federal reference base rate (EUR)	Hospital payment (EUR)
J07B – Minor interventions on the breast with lymph node excision or extremely severe or severe complications or co-morbidities with malignant neoplasm, without bilateral surgery, without intervention on the ovary	4.5	1.326	3 467.30	4 597.64
J23Z – Major interventions on the breast for malignant neoplasm without complex intervention, without specific intervention on the female genitalia for malignant neoplasm	6.0	1.496	3 467.30	5 187.08
E02C – Other procedures on the respiratory system, patient age >9 years, without specific intervention on the larynx or trachea, without moderate intervention, without extremely severe complications or comorbidities	5.8	1.067	3 467.30	3 699.61

Note: Hospital payments in this table are based on the federal reference base rate and assume a length of stay within the minimum and maximum.
Source: Author based on Reimbursement Institut (2018[40])

France

Office-based specialists, diagnostic centres and radiological clinics, specialised cancer centres and hospitals provide nuclear medicine (NM) diagnostic services in France and are paid through separate mechanisms by social health insurance (SHI). Services that are not paid by SHI are not covered in this Section. SHI and government transfers fund more than 80% of all health expenditure in France (OECD,

2018[31]), with private insurance mainly covering patient co-payments; SHI can therefore be assumed to cover nearly all NM activity in France.

NM diagnostic services paid fee-for-service (FFS) represent approximately 90% of all NM diagnostic services, including all services delivered by office-based specialists, diagnostic centres / radiological clinics and specialised cancer centres and some services delivered by hospitals (see below). NM diagnostic services that are part of hospital inpatient stays are generally paid through DRGs.

Specialist Offices and Other Outpatient Providers

Office-based specialists and all other NM diagnostic services delivered on an outpatient-bases are paid FFS and fees are negotiated between the National Association of Social Health Insurance Funds (UNCAM) and associations of relevant health professionals.

A new national medical service catalogue (CCAM) and applicable fees were established in 2005. In this complete overhaul of the service catalogue, fees were aligned with historic cost data as far as possible but where differences between new cost-based fees and prior fees were large, gradual convergence was negotiated. Since then, fees are partially updated as planned in the *medical conventions* signed between the national association of physicians and UNCAM for 5-year terms. However, both parties can request amendments to the convention during the 5-year interval if specific issues need to be addressed. In addition, where legislation allows, the head of UNCAM may trigger to renegotiation of fees with professionals who use large capital equipment and suggest revisions of fees for technical aspects of the service.

Physicians paid on a FFS-basis can either accept CCAM fees paid by SHI as full payment for their services (referred to as Sector 1), in return for paying reduced SHI contributions themselves, or set higher fees freely (Sector 2), with patients covering the difference between the CCAM fee paid by SHI and the physician fee. Most people have private complementary insurance that covers these differences. It is generally more common among specialists to opt for Sector 2 than among general practitioners. However, Sector 2 remuneration is uncommon among nuclear medicine specialists (l'Assurance Maladie, 2017[41]).

Table 3.7. Examples of outpatient NM diagnostic procedures and applicable fees in France

Based on CCAM fee schedule applicable since 14 July 2018.

CCAM Billing Code	Description	Fee (EUR)
FEQL006	Radio-isotopic search of blood in stool	53.06
KCQL003	Thyroid scintigraphy	109.70
PAQL002	Whole-body bone scintigraphy, multi-phase	251.39
DAQL009	Myocardial perfusion tomoscintigraphy (rest test), with myocardial perfusion tomoscintigraphy after exercise test or pharmacological test with electrocardiogram synchronisation	472.72
GFQL002	Pulmonary ventilation and perfusion exam	534.15
F	Additional fee for a scan performed on a Sunday or public holiday	19.06
G	Additional fee for a scan of a patient under 3 years of age	+25%
A	Additional fee for general or local anaesthesia in a patient under 4 years or over 80 years of age	23.00
S	Additional fee for emergency scan performed general practitioners or midwives or emergency therapeutic procedure performed under general or local anaesthesia by doctors of other specialties, between midnight and 08.00am	40.00

Source: Author based on l'Assurance Maladie (2018[42]).

Since the establishment of CCAM, fees for NM diagnostic services have generally been revised downwards. The latest version of the CCAM contains 109 procedure codes related to NM diagnostics, including five codes related to "complementary services" (such as image production without reinjection,

complementary to a standard procedure). For the same patient, no more than two procedures performed on the same day and in one session are paid, at 100% of the specified fee; additional procedures are not paid.

An additional fee per unit of service can be payable for procedures performed as part of emergencies out-of-hours or based on patient age (i.e. for young children and patients aged 80 and above receiving the scan under anaesthesia), per the conditions stated in the fee schedule.

The current fee schedule is applicable since 14 July 2018. Fees range from EUR 53 for a radio-isotopic search of blood in stool to EUR 534 for a pulmonary ventilation and perfusion exam (excluding possible additional fees for emergency procedures and procedures for children and the elderly). Table 3.7 shows examples of NM diagnostic procedures and applicable fees since 2018.

Hospitals

Hospitals receive FFS payments for outpatients and DRG-based payments for inpatient stays (referred to in France as GHS – *Groupe homogène de séjours*). Fees for outpatients are the same as those for office-based specialists described above, governed by the CCAM. For inpatient stays, no separate payments are made for nuclear medicine diagnostic procedures or radiopharmaceuticals in addition to payment for the DRG.

GHS prices public and private non-profit hospitals cover all costs associated with a patient stay while GHS for private for-profit hospitals exclude remuneration of doctors (Or and Bellanger, 2011[43]) (who are paid FFS based on the CCAM). Subject to a number of conditions, doctors are also allowed to engage in private practice on public hospital premises. In the latter case, doctors also receive FFS payments based on the CCAM but cede a portion of the fee to the hospital for use of hospital premises and equipment.

GHS prices are determined by allocating an overall annual budget for GHS payments according to cost weights of GHS based on historic cost data (Or and Bellanger, 2011[43]). A hospital-specific coefficient, based on each hospital's own historic cost data, is applied to smooth year-on-year fluctuations and a regional adjustment factor is also applied to hospitals in the metropolitan area of Paris and in French overseas territories to account for higher labour costs. The annual budget defines a target volume of hospital activity and is set by the Ministry of Health.

GHS payments are tapered according to minimum and maximum lengths of patient stay, and payments are reduced for patient stays below the minimum and increased for stays longer than the maximum (Or and Bellanger, 2011[43]). GHS prices are also reduced for all hospitals once the annual target volume of hospital services is reached (de Lagasnerie et al., 2015[38]).

Cost weights are updated annually by the National Agency for Hospital Information (ATIH) on the basis of cost data submitted by a sample of hospitals participating in a voluntary data sharing scheme, which account for approximately 13% of total hospital stays in France (Or and Bellanger, 2011[43]). Cost weights for a given year were calculated in the prior year based on data pertaining to two years earlier (Or and Bellanger, 2011[43]). Cost data are analysed separately for private for-profit hospitals from public and private non-profit hospitals and resulting GHS prices differ because they cover different cost categories.

Hospitals submitting cost data to ATIH follow common accounting rules defined by government decree, using mainly top-down cost allocation but also some bottom-up micro-costing. Participating hospitals must provide patient-level information on all procedures performed, and detailed cost data for certain medicines and medical devices, and blood and external laboratory tests as well as private physicians fees (Or and Bellanger, 2011[43]).

Hospitals receive additional payments on top of DRG-based payments for innovative and costly medicines and medical devices included in a national list (ATIH, 2018[44]). Prices of products in this list are regulated at the national level by the Economic Committee for Health Products (CEPS), which also regulates prices

of prescription medicines dispensed in the outpatient sector. No Tc-99m-based radiopharmaceuticals are currently included in the list (ibid.).

United Kingdom (England)

National Health Service (NHS) hospitals provide nearly all NM diagnostic services in England. Hospitals are generally paid by DRG, referred to as Health Care Resource Groups (HRGs) in England. The national HRG catalogue also includes service-specific HRG codes (locally referred to as "unbundled services"), which effectively represent a service-specific FFS payment. NHS England defines the HRG catalogue at a national level. Prices are set nationally by NHS Improvement or locally by NHS commissioners (referred to as Clinical Commissioning Groups), in cases where either no national prices apply or price variations are permitted by NHS England and NHS Improvement (NHS England and NHS Improvment, 2018[45]).

According to data provided by NHS England, 90% of NM diagnostic services are delivered to outpatients or day cases in NHS hospitals.[4] These services attract FFS payments based on service-specific HRGs and nationally set prices. Costs of the remaining 10% of procedures performed as part of inpatient stays is covered by the broader HRG associated with the inpatient stay.

The amounts hospitals receive for a given HRG with a national price are determined by multiplying the national price (locally referred to as "tariff") by a hospital-specific market forces factor (MFF) to reflect local prices of labour, land and buildings (NHS England and NHS Improvment, 2018[45]). Table 3.8 shows examples of HRGs for NM diagnostic services and corresponding prices for the financial years 2017 to 2019.

National prices are published annually or bi-annually by NHS Improvement. NHS Improvement periodically re-calculates national prices based on estimates of historic average costs by HRG or adjusts prices that applied in a prior year for inflation and expected efficiency gains (ibid.). Cost data are submitted by all NHS hospitals according to a national NHS Costing Manual; costs reflect a mixture of micro-cost data and allocations to each service from the general ledgers of hospitals. For example, prices applicable in the financial years 2017/18 to and 2018/19 are based on cost data pertaining to 2014/15 and various adjustments made to reflect the lag in cost data (ibid.).[5]

Table 3.8. Examples of NM diagnostic HRGs in England

Applicable for FYs 2017/18 and 2018/19; all prices in GBP, including the cost of reporting of results.

HRG code	HRG name	Tariff incl. cost of reporting	Cost of reporting	Min after MFF adj	Max after MFF adj
RN08A	Single Photon Emission Computed Tomography (SPECT), 19 years and over	133	26	133	173
RN13Z	Nuclear Medicine Infection Scan or White Cell Scan	380	53	380	493
RN15A	Multi-phased Nuclear Bone Scan, 19 years and over	181	19	181	235
RN18A	Lung Ventilation or Perfusion Scan, 19 years and over	214	19	214	278
RN20Z	Myocardial Perfusion Scan	133	26	133	173
RN21Z	Myocardial Perfusion Scan, Stress Only	190	26	190	247
RN25A	Renogram, 19 years and over	209	19	209	271
RN32A	Thyroid Scan, 19 years and over	143	19	143	186

Note: The market forces factor adjustment ranges from 1.0 for a hospital in Cornwall to 1.2976 for a hospital in central London.
Source: Author based on NHS England and NHS Improvement (2018[46])

Hospitals receive payments in addition to HRGs for high-cost drugs and devices. These apply to all drugs and devices catalogued in a list published by NHS England and NHS Improvement together with the HRG catalogue and national prices ((NHS England and NHS Improvement, 2018[46]). Radiopharmaceuticals are currently not part of this list.

Belgium

Hospitals provide nuclear medicine (NM) diagnostic services in Belgium and service are paid on a fee-for-service (FFS) basis. In general, hospitals receive funding through two separate mechanisms depending on the type of service they provide: while medical and "medico-technical" services (including diagnostic imaging procedures) are mainly paid FFS, patient accommodation, emergency services and nursing activities in day hospitalisations are covered by budgets (Gerkens and Merkur, 2010[47]). For inpatient services FFS payments are always made to hospitals (central invoicing by hospitals is mandatory by law for inpatients) while for outpatients central invoicing is not mandatory. In general, however, FFS payments for outpatient services are also made to hospitals and not to physicians. Physicians have individual contracts with hospitals that determine financial arrangements between both parties.

A uniform national fee schedule negotiated between sickness funds of the National Institute for Health- and Disability Insurance (RIZIV-INAMI) and the professional representations of physicians represents the binding catalogue of goods and services payable by compulsory health insurance and regulates the fees for medical services delivered by physicians to patients with compulsory health insurance, including by hospital-based specialists (ibid.). Physicians have some freedom to charge fees in excess of the what is specified in the national fee schedule, for example when treating inpatients who have requested accommodation in a single room or when the physician delivering the service is not bound by the collective agreement with RIVIZ-INAMI and the patient has been informed upfront (ibid.). Fees can cover all service costs or only the portion pertaining to the physician service; in the former case hospitals retain a part of the fee to cover costs of equipment and other staff while in the former case all non-physician costs are funded by the hospital from its budget (ibid.). While hospitals also have a pharmaceutical budget for inpatients, this budget excludes radiopharmaceuticals and other specified types of medicines (ibid.).

For NM diagnostic services, FFS payments to providers are broken down into two main components: (1) a payment for the medical procedure, the amount of which is dependent on the type of scan performed and (2) payments for the isotope used and, if applicable, the cold kit. The national fee schedule also lists all isotopes and radiopharmaceuticals covered by compulsory health insurance and the corresponding fees.

The fee schedule is updated on an ad-hoc basis, whenever deemed necessary. The current fee schedule is in force since June 2015. For all Tc-99m based radiopharmaceuticals, until May 2015, hospitals received a fixed fee of EUR 37.18 per procedure to cover the cost of Tc-99m and the cold kit in addition to the fee for the medical procedure; this amount had been unchanged for several years. With the June 2015 update of the fee schedule, this fee was split and hospitals now receive EUR 18.59 per procedure for the Tc-99m used and EUR 18.59 per cold kit used (INAMI, 2018[5]). For hospital outpatients, a part of the fee for diagnostic radiopharmaceuticals, including for Tc-99m, is funded from a patient co-payment, which is also defined by law (KCE, 2008[48]). The co-payment is defined as a percentage of the fee, currently either 15% (EUR 2.78) for preferential beneficiaries or 25% (EUR 4.64) for all other patients, and is subject to an overall cap.

Australia

Office-based specialists, diagnostic centres and radiological clinics and hospitals provide NM diagnostic services in Australia. Within public hospitals, some physicians engage in dual practice – i.e. on salaried basis (referred to as "seeing public patients") and on a private fee-for-service-basis (referred to as "seeing private patients"). Public hospitals are funded by state and territory governments, as well as by the

Australian Government. Hospitals generally have global budgets that cover all non-private practice; no detailed information on funding of NM diagnostic services is available for this part of hospital activity.

All providers other than public hospitals can determine their fees freely and their services can attract subsidies from Medicare, the main health coverage scheme funded by the Australian Government. Providers cover the entire cost of services, including the cost of Tc-99m, from MBS fees (see below) and patient out of pocket payments.

Medicare subsidises all medical services which have been assessed as safe, effective and cost effective and which are provided by eligible providers. A specified Medicare fee applies to each service item listed in a national service catalogue and fee schedule (MBS). The MBS fee "is that which is regarded as being reasonable on average for that service having regard to usual and reasonable variations in the time involved in performing the service on different occasions and to reasonable ranges of complexity and technical difficulty encountered" (Australian Government Department of Health, 2018, p. 28[49]). Services can be eligible for a subsidy of 75%, 85% or 100% of the fee and, where patients pay the full fee charged by the provider upfront and claim reimbursement of the subsidy from Medicare, patients are liable for the gap between the subsidy and the provider fee.[6] Providers can also opt to bill Medicare directly for eligible services (referred to as "bulk-billing"), in which case providers accept the applicable Medicare subsidy as full payment for the service and cannot charge higher fees (Australian Government Department of Health, 2018[49]).

Private health insurance is available to cover the 25% difference between the 75% Medicare subsidy and the total MBS fee (Australian Government Department of Health, 2018[49]). Some private health insurers may choose to cover above this amount, but this depends on the insurance cover and the type of gap arrangement in place with the provider. Medicare provides safety nets payments for the difference between subsidy and the 100% MBS fees once an annual threshold for such payments is reached ("Original Safety Net") and an "Extended Safety Net" for all out-of-pocket payments beyond an annual threshold (ibid.)

The 100% benefit only applies to primary care services while NM diagnostic services attract subsidies of 75% or 85% if patients pay upfront and claim reimbursement, depending on the setting in which the service is provided (ibid.):

- 75% for professional services provided as part of an episode of hospital treatment in private practice (i.e. not for "public patients"), and for professional services rendered as part of an episode of hospital-substitute treatment, or,
- 85% or the MBS fee less AUD 81.70 (amount indexed annually in November), whichever is the greater, for all other professional services; also for hospital services provided on the day of admission or discharge but before admission or after discharge (instead of 75% for services on any other day of the episode of hospital treatment).

A 95% subsidy applies when providers charge Medicare directly. Lower fees apply for scans conducted with capital equipment aged 10 years or more, except in remote areas. Lower fees also apply if there are multiple scans of the same patient on the same day.

Fees are revised when deemed necessary and are usually subject to an annual inflation adjustment. However, fees for diagnostic imaging, including NM, have been frozen for more than 10 years. The current MBS, valid since May 2018, includes 158 item codes related to NM diagnostic services (using Tc-99m and other isotopes) (Australian Government Department of Health, 2018[49]). Fees (100%) range from approximately AUD 60 for a dynamic blood flow study conducted with aged equipment to AUD 880 for an adrenal study; further examples of listed services and applicable fees are shown in Table 3.9.

Table 3.9. Examples of NM diagnostic services in the MBS

Applicable since 1 May 2018, all prices in AUD.

MBS Item	Description	Schedule Fee	75% Benefit	85% Benefit
61689	Dynamic blood flow study or regional blood volume quantitative study… (R) (NK)	59.45	44.60	50.55
61674	Oesophageal clearance study (R) (NK)	71.70	53.80	60.95
61473	Thyroid study including uptake measurement when undertaken (R)	175.40	131.55	149.10
61446	Localised bone or joint study, including when undertaken, blood flow, blood pool and repeat imaging on a separate occasion (R)	333.55	250.20	283.55
61302	Single stress or rest myocardial perfusion study – planar imaging(R)	448.85	336.65	381.55
61306	Combined stress and rest, stress and re-injection or rest and redistribution myocardial perfusion study, including delayed imaging or re-injection protocol on a … (R)	709.70	532.30	628.00
61484	Adrenal study (R)	880.85	660.65	799.15

Note: Suffix (R) denotes a "request requirement" (referral): Medicare benefits are payable for R-type services only if, prior to commencing the relevant service, the provider receives a signed and dated request from a requesting provider with a valid Medicare Provider number who determined the service was necessary. Suffix (NK) denotes services delivered with capital equipment aged 10 years or more, except in remote areas.
Source: Author based on Australian Government Department of Health (2018[49])

Other countries

Czech Republic: a FFS schedule determines payments for all provider types (radiological clinics, hospital in- and out-patient activity) and providers can only bill the exact amount determined in the fee schedule. Fees are updated annually, with the latest version applicable to 2018, but actual costs are not considered in setting fees. Service fees also cover the cost of Tc-99m and providers receive no unbundled payments for Tc-99m.

Denmark: hospitals the only providers, which receive DRG-based payments for in- and out-patient activity. Micro-cost data are considered in updating DRG prices. DRG payments also cover the cost of Tc-99m and hospitals receive no unbundled payments for Tc-99m.

Latvia: radiological clinic and hospital out-patient activity paid FFS. Fees updated annually taking into account actual cost of Tc-99m as well as overhead and fixed costs, staff costs and capital equipment costs. Providers have some freedom to bill above or below the regulated fee. Hospital inpatient activity paid by DRGs. Micro-cost data are not considered when updating DRG prices. Service fees and DRG payments also cover the cost of Tc-99m and providers receive no unbundled payments for Tc-99m.

Lithuania: All outpatient activity, including services delivered by diagnostic centres / radiological clinics and by hospitals to outpatients, are paid FFS. Fees are regulated in a fee schedule and providers can only bill the exact amount determined in the schedule. Fees are updated on an ad-hoc basis every 2-4 years and updates take into account actual costs of overhead, staff and Tc-99m. Hospital inpatient activity is paid through DRGs. DRG payment rates are based on cost allocations and micro-cost data is not considered when updating DRG-based payment rates. Service fees and DRG payments also cover the cost of Tc-99m and providers receive no unbundled payments for Tc-99m.

Luxembourg: Only hospitals provide NM diagnostic services. The hospital activity is paid by global budget and the medical activity on FFS-basis. However, fees only cover costs of provision of professional services and of the use of capital equipment. The cost of Tc-99m is covered by broader hospital pharmacy budgets, which are not set based on actual cost of Tc-99m.

Netherlands: all NM diagnostic services, including inpatient and outpatient scans provided by hospitals and scans provided by other types of outpatient providers, are paid through DRGs. DRG payment rates

are updated annually, based on negotiations between payers and providers. DRG payments also cover the cost of Tc-99m and providers receive no unbundled payments for Tc-99m.

Poland: radiological clinic and hospital out-patient activity is paid FFS. Fees updated on an ad-hoc and individual basis, taking into account actual costs of supply of Tc-99m and costs of all other items that are part of the service. Hospital in-patient activity paid by DRG. Service fees and DRG payments also cover the cost of Tc-99m and providers receive no unbundled payments for Tc-99m.

Slovenia: Only hospitals provide NM diagnostic services. Hospital in-patient activity is covered by global budgets. Hospital out-patient activity is paid FFS. Fees are regulated and hospitals can only bill the exact amount determined in the fee schedule. Fees are updated annually but actual cost data is not considered in updating fees. Service fees and hospital budgets also cover the cost of Tc-99m and hospitals receive no unbundled payments for Tc-99m.

Sweden: Only hospitals provide NM diagnostic services and all hospital activity is covered by global budgets. Hospital budgets also cover the cost of Tc-99m and no unbundled payments are made for Tc-99m.

Switzerland: All outpatient activity, including services provided by office-based specialists, diagnostic centres / radiological clinics and hospitals are paid FFS. Fees are regulated but providers have some freedom to bill above or below the regulated fee. Fees are updated on an ad-hoc basis and data on actual cost of overhead, staff, capital equipment and Tc-99m are considered in fee updates. Current fees cover the cost of Tc-99m based on a price assumption of CHF 1.70 per MBq. The cost of Tc-99m therefore only represents a minor part of the overall service costs, approximately CHF 9 for a bone scan or CHF 30 for a cardiac scan. Hospital inpatient activity is paid through DRGs, which are updated annually. DRG cost weights are based on data submitted by all Swiss hospitals. Hospitals are required to report micro-cost data for all medicines, implants and other material whose costs exceed CHF 1 000 (Holzer, 2012[50]). Service fees and DRG payments also cover the cost of Tc-99m and providers receive no unbundled payments for Tc-99m.

3.4. What financial incentives arise from these payment mechanisms?

In the countries described above, providers generally have a financial incentive to contain the cost of Tc-99m. This is because provider payments are almost exclusively based on prospectively set payment amounts or budgets from which providers have to fund their activity. The exception is where providers receive reimbursement of the *actual cost* of Tc-99m purchased, which is only the case in a subset of the NM diagnostic scans paid by Medicare and Medicaid in the United States.

However, the strength of incentives to contain or reduce costs may vary significantly between different types of providers and payers and payment mechanisms that determine financial flows between them. The strength of incentives depends on various factors. These include the level of financial risk borne by providers, the extent to which payments to providers cover or exceed the costs of service provision actually incurred, and the ability of providers to substitute distinct activities and the supplies required to perform them. A greater ability to substitute gives providers more scope to cross-subsidise activities from various sources of income and adjust their cost structures. Where providers bear financial risk and payments for NM diagnostic services are lower than costs, providers either need to reduce their costs per unit of service or, where they can, substitute away from costly towards cheaper services or cross-subsidise NM activities from other sources of income.

All providers in Belgium and Japan as well as office-based specialists paid FFS in Germany and the United States (Medicare only) receive unbundled payments for Tc-99m (see Section 0). To the extent that these payments are sufficient to cover costs of purchasing Tc-99m, providers have a weak incentive to reduce costs.

Where providers receive no unbundled payment that specifically funds their purchases of Tc-99m, which is the case in most countries and provider settings (see Section 0), providers may have stronger incentives to reduce to cost of Tc-99m or substitute Tc-99m with less costly alternatives. The three payment mechanisms for NM diagnostic services are listed in Section 3.3.1 in ascending order according to the degree of bundling. The broader the service bundles for which providers are paid, the greater their financial risk and their incentives to substitute towards less costly activities and supplies. Providers bear the least risk when paid FFS, more risk when paid by case or DRG and the highest level of risk when receiving global budgets. More specifically:

1. FFS: Providers bear financial risk related to the use of resources, such as costs of physician time, capital or consumables, for each unit of service; providers bear no risk related to the number of patients or the severity of patient cases because each additional unit of service delivered attracts additional payment.
2. Case-based payments (DRGs): Providers bear greater financial risk related to resource use per case, because the payment covers a much broader bundle of services, including all diagnostic procedures, consultations, treatments and patient accommodation that are part of the case, and payment is based on expected resource use. Providers bear no risk related to the number of patients because each additional case will attract an additional payment. Providers bear some risk related to severity of patient case, to the extent that more severe cases with the same diagnoses that require more resources are not classified in a separate and more resource-intensive DRG.
3. Global budgets: Providers bear the highest level of risk, including risk related to the number of patients treated in the time period covered by the budget, the severity of patient cases and resource use for each patient case. Payment is independent of the actual volume and types of services provided, so additional service volume will not attract additional payment. This may lead to under-provision of services if budgets are insufficient.

In general, hospitals receiving global budgets have the strongest incentives to contain cost through constraining the number of services provided and their unit cost, while hospitals paid per DRG have a weaker cost containment incentive through controlling the unit cost of each DRG and providers paid FFS only have a weak incentive to contain the unit cost of each service (Geissler et al., 2011[51]).

However, even when providers are paid FFS, they can have strong incentives to contain unit costs of services if the fee is below the cost they incur. It is therefore not possible to fully understand provider incentives without comparing costs they incur with payments they receive. More generally, the frequency with which prospectively set prices are updated to align them with actual costs is another factor that determines financial incentives. Table 3.10 summarises the frequency of updates to service fees and DRG prices by country and provider type.

While it is not possible to evaluate financial incentives for providers to contain or reduce cost of Tc-99m in greater detail with the data available for this report, such incentives can be assumed to remain relatively weak. This is because data on provider payment presented in this Section and Tc-99m price data presented in Chapter 4 suggest that the cost of Tc-99m likely represents a relatively small portion of the broader provider payment for the diagnostic service, the DRG or the global budget. Where providers receive unbundled payments that specifically fund the cost of Tc-99m, providers have a weak incentive to reduce costs when such payments are sufficient to cover *actual* costs of purchasing Tc-99m, but may resist cost increases where such payments are insufficient. At the same time, data on the actual cost of purchasing Tc-99m is often not taken into account when setting prices of services. Provider payment is therefore also relatively unresponsive to increases in the cost of Tc-99m.

Table 3.10. Frequency of updates to provider payment (and latest update)

Information refers to the payment mechanism that covers the cost of Tc-99m (unbundled, FFS or DRG).

Country	Specialist offices	Other outpatient providers	Hospital inpatients	Hospital outpatients / day cases
Australia	Ad-hoc (2018[1])	Ad-hoc (2018[1])	n/a	n/a
Belgium	n/a	n/a	Ad-hoc (2015)	Ad-hoc (2015)
Canada				
Alberta	*Ad-hoc (2017)*	*Ad-hoc (2017)*	*Ad-hoc (2017)*	*Ad-hoc (2017)*
Br Columbia	*n/a*	*n/a*	*n/a*	*Annual (2017)*
Manitoba	*n/a*	*<5 years (2014)*	*n/a*	*n/a*
Newfoundland / Labrador	*n/a*	*n/a*	*n/a*	*n/a*
Nova Scotia	*n/a*	*n/a*	*n/a*	*n/a*
Czech Republic	n/a	Annual (2018)	Annual (2018)	Annual (2018)
Denmark	n/a	n/a	Annual (n/d)	Annual (n/d)
France	5 years, or Ad-hoc (2018)	5 years, or Ad-hoc (2018)	Annual (2018)	5 years, or Ad-hoc (2018)
Germany	Annual (2018)	n/d	Annual (2018)	Annual (2018)
Japan	Bi-annual (2018)	Bi-annual (2018)	Bi-annual (2018)	Bi-annual (2018)
Latvia	n/a	Annual (n/d)	n/d	Annual (n/d)
Lithuania	n/a	Ad-hoc (2017)	n/d	Ad-hoc (2017)
Luxembourg	n/a	n/a	Bi-annual (n/d)	Bi-annual (n/d)
Netherlands	n/a	Annual (2018)	Annual (2018)	Annual (2018)
Poland	n/a	Ad-hoc (n/d)	n/d	Ad-hoc (n/d)
Slovenia	n/a	n/a	n/a	Annual (2018)
Sweden	n/a	n/a	n/a	n/a
Switzerland	Ad-hoc (n/d)	Ad-hoc (n/d)	Annual (2018)	Ad-hoc (n/d)
United Kingdom (England)	n/a	n/a	Bi-annual (2017)	Bi-annual (2017)
United States[2]	Annual (2018)	Annual (2018)	Annual (2018)	Annual (2018)

Notes: 1. Refers to the latest update of the Australian MBS. Fees for NM diagnostic services have been frozen for more than 10 years.
2. Only refers to Medicare FFS, OPPS and IPPS, to which updates are made at least annually. Contracts between private health insurers and providers are not in the public domain.
n/a… not applicable because the provider type does not provide NM diagnostic scans in the country, n/d…no data available.
Source: Author based on OECD Health Division survey and public sources (Stephani et al., 2018[52]).

3.5. Conclusion

Office-based physicians, other types of outpatient providers (such as diagnostic centres and radiological clinics) and hospitals provide nuclear medicine (NM) diagnostic scans. In countries where data are available, outpatient scans represent the majority of all scans. All of these provider types receive prospectively set payments for such services, which cover service bundles of varying breadths. Outpatient providers are typically paid fee-for-service (FFS), i.e. a fixed fee that applies to the entire diagnostic service and covers all provider costs related to that service, including costs of physician time, capital equipment used and consumables, including Tc-99m. The breadth of bundling tends to increase with the provider size and hospitals are often paid for broad service bundles, such as all services related to a diagnosis-related group (DRG) or through global budgets. The cost of Tc-99m is included in these provider payments in all countries, except in Belgium, in Germany for outpatient providers paid FFS, in Japan and in the United States for specialists paid FFS by Medicare, the main publicly funded coverage scheme.

Because providers are paid prospectively set amounts and bear financial risk related to differences between payments and their costs, rather than being reimbursed for costs actually incurred, providers generally have an incentive to control input costs, including the cost of Tc-99m. Such incentives are stronger where payments are low relative to input costs and where providers have little scope to substitute activities towards more profitable ones, which can allow them to cross-subsidise activities that incur losses. Thus, increases in Tc-99m prices may be difficult to absorb for small providers, such as office-based NM specialists, who rely exclusively on NM scans for revenue and whose FFS payments are not responsive to input costs. Hospitals that generate revenue from a wide range of activities may be able absorb cost increases more easily. In most countries, outpatient provider fees are revised annually, allowing providers to negotiate payment increases if costs increase. However, there are exceptions, such as Australia and France, where fees have not been updated in several years.

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Notes

[1] Persons can be covered by more than one coverage scheme at the time. Therefore, the sum of these percentages do not add up to 100%.

[2] In some states, single men are not covered by Medicare irrespective of their income relative to the federal poverty guidelines. In 2018, for example, the federal poverty guideline for a 1-person household was USD 12 140 in all states except Alaska and Hawaii (15 180 and 13 960 respectively) (HHS, 2018[53]).

[3] See https://www.medicare.gov/what-medicare-covers/your-medicare-coverage-choices/whats-medicare and https://www.hhs.gov/answers/medicare-and-medicaid/what-is-medicare-part-c/index.html

[4] NHS England response to OECD Health Division survey, based on national Diagnostic Imaging Dataset.

[5] In England, financial years run from 1 April to 31 March and do not coincide with calendar years.

[6] The extent of the gap is dependent on the service provider (i.e. public or private) because provider fees are set freely.

4 The Tc-99m supply chain is technically complex and characterised by market imperfections

Supply of Technetium-99m (Tc-99m) is a just-in-time activity requiring continuous production in a complicated and aging supply chain that combines a mix of governmental and commercial entities. Governments control the availability of enriched uranium required for medical isotope production and also largely control the regulatory framework and the legislation around health care provider payment for nuclear medicine diagnostic scans. The central steps of the supply chain, including processing and generator manufacturing are mainly commercial. Processors and generator manufacturers wield market power and market concentration has increased in these parts of the supply chain, while supply continues to be supported by some government funding of nuclear research reactors that perform irradiation and of some processors. The resulting inability by reactors to increase prices sufficiently for full cost recovery and insufficient outage reserve capacity at various steps of the supply chain leave security of supply vulnerable and the market economically unsustainable.

4.1. Introduction

This Chapter describes the global supply chain for Mo-99/Tc-99m. It breaks the supply chain down into the main steps, between irradiation of uranium targets in nuclear research reactors (NRRs) and Tc-99m administered to patients, and describes the structure of the industry and product market at each step. It then explores historical factors that contributed to market imperfections and an economically unviable supply chain. The Chapter concludes with an assessment of the viability of the supply chain based on current estimates.

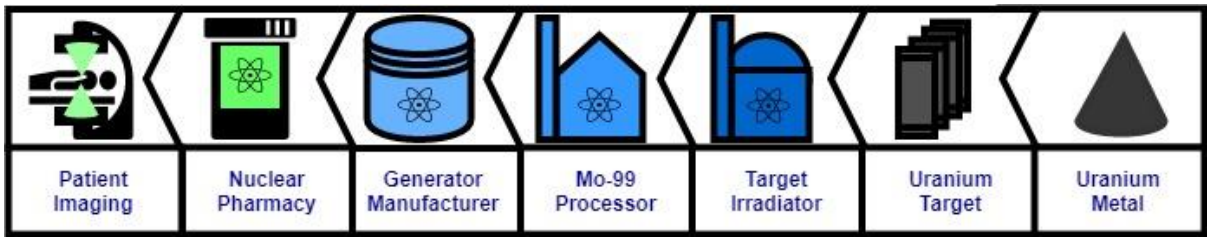
4.2. Overview of the supply chain

Patients are the ultimate beneficiary of the medical isotope supply chain. As described in Chapter 1, there is substantial value to health care from successful diagnosis of medical conditions, the assessment of patients for future therapeutic interventions and the monitoring of their treatment in real-time.

The short half-life of Mo-99 requires continuous production and just-in-time delivery. Overall, the Mo-99/Tc-99m supply chain is complex and faces a number of significant challenges, both in the short- and long-terms. An ever-present factor in the supply chain is the need to get the product to patients quickly to minimise decay and the related loss of its value. Given the short half-lives of Mo-99 (66 hours) and Tc-99m (6 hours), Mo-99 cannot be efficiently stored and Tc-99m must be prepared at least daily. In all practical terms, the economics and medical utility of Mo-99/Tc-99m imaging depends upon near continuous production of Mo-99, logistical efficiency and just-in-time delivery throughout the global supply chain.

Each radiopharmaceutical dose for a nuclear medicine imaging procedure is prepared locally on the day of use by independent nuclear pharmacies or by in-hospital radiopharmacy departments. They elute Tc-99m at least once per working day from Tc-99m generators and use it to label “cold kits.” Tc-99m can also be used in a more limited way directly as pertechnetate. Cold kits are non-radioactive chemicals and bio-molecules that are specific to the organ system or anatomical area targeted in individual imaging procedures. The generators, which last for up to two weeks, are delivered on a number of prescribed days per week from specialist generator manufacturers, who produce and distribute them at a local or regional level, using bulk Mo-99 purchased from processor organisations that operate globally. Processors procure special uranium targets and arrange their irradiation in nuclear research reactors (NRRs) with suitable characteristics. Processors thus play the main co-ordinating role in the supply chain and have the primary responsibility for ensuring sufficient supply is always available. Figure 4.1 is a simplified illustration of the mains steps in the Mo-99 supply chain, from the uranium raw material to the patient scan.

Figure 4.1. Simplified structure of the Mo-99 supply chain



Source: Authors

4.3. There are five main steps in the current supply chain

This Section describes in some detail the structure and economics of the global Mo-99 supply chain. A sub-section is dedicated to each of the five main types of participants in the supply chain: patients and health care providers; nuclear pharmacies; generator manufacturers; processors and nuclear research reactors (NRRs). Each sub-section describes the structural characteristics of the industry and the main implications for the economics of the supply chain.

4.3.1. Patients and health care providers

Specialised health care providers perform NM diagnostic scans and require a continuous supply of medical isotopes. Details on the types of providers that perform scans in each country are provided in Chapter 3.

Individual patient doses are prepared against individual prescriptions on the day of use and administered shortly before the patient is scanned. Imaging facilities require a range of highly skilled medical staff, suites of imaging cameras and high power computing capability to collect, analyse and store the data created by the procedures. All the equipment is dedicated to the purpose of nuclear medicine imaging, with some even dedicated to a specific sub-set of procedures (e.g. cardiology) and the facilities must be built and equipped with specialist infrastructure to receive, store and use radioactive materials while also being subject to pharmaceutical regulatory controls.

The cost to set up, operate and regulate nuclear medicine imaging facilities is high, the equipment is expensive and cannot be repurposed, and the staff is specialised. Some providers operate independently, while others operate within larger departments that offer other types of medical imaging services.

Without a secure daily supply of medical isotopes, an imaging facility must immediately change, limit, or cease operations. During isotope shortages, staff must continuously work to manage the difficult balance between the continuing demand for patient examinations while making the best use of the limited and decaying stock of isotopes available. Staff often will go to extreme lengths and personal inconvenience to maintain as many services as possible. Chapter 1 of this report discusses the options and challenges associated with substituting Tc-99m – based scans with alternative diagnostic services during times of supply shortage.

4.3.2. Nuclear pharmacies

The role of the nuclear pharmacies varies significantly between countries

Doses, either as an individually named patient dose, or as multi-dose vial for further sub-dispensing within an imaging facility, are normally prepared in a specialist nuclear pharmacy, also referred to in some countries as “radiopharmacy.” The primary type of nuclear pharmacy model in a country has a strong influence on the way patient dose provision is arranged. This may also influence the cost of the NM imaging services.

Nuclear pharmacies may be an integrated part of a hospital or clinic providing only local services or may be independent organisations that provide commercial services to multiple imaging providers. Nuclear pharmacies may compete fiercely where imaging providers can source patient doses from a number of commercial nuclear pharmacies. This is in stark contrast to the dynamics of an in-house local radiopharmacy model, where pharmacies do not compete. There are many shades between competitive models and where such competition is completely absent. In France, for example, independent nuclear pharmacies do not exist. In the United States, competing commercial nuclear pharmacies are the predominant suppliers. Some countries, such as the United Kingdom, have the full range and publicly owned nuclear pharmacies that serve their local hospital may also compete with independent commercial services.

Nuclear pharmacies can have market power in some countries

Nuclear Pharmacies may operate in large chains and these chains can have significant market power. Generator manufacturers who supply commercial nuclear pharmacies with significant market shares are faced with customers that have market power. For example, the largest nuclear pharmacy chain in the United States, supplies around 50% of all demand in the United States and consumes more than 20% of all Mo-99 produced worldwide.

In some large markets, the number of Tc-99m-based imaging examinations has declined since 2010. For example, in the United States the nuclear medicine scan rates per 1 000 enrolled Medicare beneficiaries declined by 25% in the period from 2010 to 2014 (Levin et al., 2017[1]). Worldwide revenue of the two manufacturers that dominate the United States market declined by 11.3% between 2012 and 2013[1] and the number of commercial nuclear pharmacies operating in the United States also declined in that period. A declining market with strong competition among nuclear pharmacies created further price pressure upstream in the supply chain.

Nuclear pharmacies drive the efficiency of Tc-99m use through patterns of delivery and elution

To provide patient dose services, nuclear pharmacies purchase generators from specialist pharmaceutical companies. Generators are sold in a wide range of activity sizes, based upon their Mo-99 content at a specified time point. That time point, referred to as *pre-calibration*, is often a fixed number of days after the generator's delivery to the nuclear pharmacy. Pre-calibration was originally developed when Mo-99 supply was both plentiful and cheap and has since become entrenched in the industry. It was often a feature used in product marketing but the practice also serves to conceal the true amount of material required by the market to provide the necessary imaging services. Pre-calibration thus understates the actual Mo-99 content of the generator at the time of delivery and understates the amount of material that must be produced every week by the supply chain to maintain imaging services.

To nuclear pharmacies, product value depends on the total Tc-99m that can be eluted during the usable lifetime of the generator, which directly determines the economics of generator use. The timing of the delivery of the generator to a facility, the length of time elapsed since it was produced by the generator manufacturer and the timing of the first usable elution are all factors that play a role in determining the maximum usable activity of Tc-99m. The activity from the first usable elution can be used to calculate the maximum theoretical activity of Tc-99m that can be obtained from that generator and is therefore the single most important metric to nuclear pharmacies.

The total cost of a generator compared to its theoretical maximum usable activity of Tc-99m can be used to compare input costs between different nuclear pharmacies. The actual use of that theoretical maximum activity in terms of patient doses eluted can be used as a metric of generator use efficiency. These factors were investigated in the in Study on Sustainable and Resilient Supply of Medical Radioisotopes in the European Union (SMER) funded by the European Commission (EC).

However, it is the actual operational practice within an individual nuclear pharmacy (factors like – single or multiple elution per day, single week use, or elution during the second week and the total number of generators per week used in the facility) that will determine the actual efficiency of use of the generator. Efficiency of use is important in determining the cost of an average patient dose made by an individual nuclear pharmacy. The wide range of nuclear pharmacy practices leads to a wide range of effective efficiency of use and, combined with different generator selling prices in different markets, leads to a wide range in average cost per patient dose.

4.3.3. Generator manufacturers

Technetium Generators are delivered at least weekly

Generator manufacturers were mostly established through the development of nuclear medicine in a specific country and are, as a result, well distributed around the world. Many are now purely commercial organisations but may have governmental origins and some remain linked to semi-governmental organisations. Some are vertically integrated with processors. Partly due to their origins, generator manufacturers today fall into two main categories, those that primarily supply a country or a local area and produce a relatively small number of generators and those supplying large numbers of generators internationally. Market concentration has increased in recent years, with the consolidation of two of the larger suppliers into one commercial organisation (Curium) that maintains three production facilities in France, the Netherlands and the United States. The manufacturer historically based in the United Kingdom (GE Healthcare) has ceased production recently and entered a supply agreement with Curium. This has further concentrated the market, with the largest supplier now holding dominant market positions in many large countries and representing around 50% of all global generator production.

Generators are highly regulated products; they must be produced according to the conditions of their medical licence as well as under strict regulated controls for handling radioactive material. Generator manufacturers typically source bulk Mo-99 from a number of processor organisations to provide operational flexibility and to have back-up options in the event of supply problems. Not all processors can produce and supply material every week of the year. The problems experienced in the 2009-2010 period of Mo-99 supply crisis led to increased multi-sourcing by generator manufacturers and multi-sourcing subsequently became more common throughout the supply chain.

Multi-sourcing is important for security of supply, but brings additional costs; medical licences must be maintained for each separate supplier, even if that supplier is only used infrequently. The addition of a new processor to a medical licence can be a time consuming and expensive process for both the generator manufacturer and the prospective supplier. Likewise, the adjustment of medical licences can be necessary as a result of upstream changes in the supply chain, such as an adjustment to the manufacturing process, and these can also be burdensome. The complexities of medical licencing in the Mo-99/Tc-99m supply chain have been clearly demonstrated during the process of conversion from high enriched uranium (HEU) to low enriched uranium (LEU) targets in recent years.

Generator manufacturers typically have production runs on a number of different days of the week. The production days have a regular pattern based upon the preferred delivery days of their primary markets. The timing of the receipt of bulk Mo-99 is synchronised as much as possible with the regular generator production days to minimise delays and waste through product decay. The cost of decay loss of the bulk Mo-99 during distribution and during any waiting period (approximately 1% per hour) is borne by either the generator manufacturer or by the processor providing the bulk product. With the global distribution of bulk Mo-99 often taking place by a combination of surface and air transport, the level of the decay loss incurred between the end of processing and the time that a completed generator is shipped can be significant and can represent a substantial cost.

“Package deals” determine market prices and generators are often loss leaders

Generator manufacturers typically provide other products to the nuclear pharmacies such as the “cold kits” needed for preparing the final Tc-99m imaging dose, as well as supplying other short-lived medical isotopes. These are often offered as a *package deal* for the combination of the generator and the other products and can have economic advantages as the other products typically “travel for free” when they are delivered with the generator. Supply contracts typically have a term of at least one year, and often of multi-year periods.

In some markets the practice of package deals led to the use of the generator as a *loss leader* product, with the objective of establishing the regular supply of the generator (often at a low profit margin or loss) in order to earn profits from the supply of the other products with higher profit margins. The practice of using generators as loss leaders has tended to keep downward pressure on generator prices, and this has continued in some markets despite increasing costs of production. In many respects, the loss leader model has collapsed in recent years with most cold kits becoming generic, implying sharp decreases of prices and profit margins. The loss of income to some companies from generic competition for cold kits has been profound and has reduced the ability of those companies to counterbalance the low margins historically associated with generators.

4.3.4. Processors

Processors are the main co-ordinators of Mo-99 production

Generator manufacturers purchase bulk Mo-99 from processors based on long-term, often multi-year, contracts that determine many important aspects of supply, including who pays for the decay loss during the delivery process. While contracts will typically contain general agreements about the overall average quantities and planned schedules of bulk Mo-99 delivery, actual daily/weekly demand fluctuates.

The processor industry is relatively concentrated. Among a total of eight processor organisations worldwide, the four largest ones collectively account for nearly 90% of global capacity and the largest one for 32% alone. While the largest one is a commercial organisation, the other three main processors are governmental or semi-governmental. Table 4.1 shows the main characteristics of processors to provide a structural overview of the industry.

Table 4.1. Overview of the processor industry

Processor Name	Country	Average no of Mo-99 production weeks/year	Maximum capacity per week (6-day Ci ^{99}Mo)	Share of annual total world capacity	Type of Organisation[1]	Importance of Mo-99 processing to the organisation[2]
ANM	Australia	43	3 500	18%	Governmental	Very High
CNEA	Argentina	46	400	2%	Governmental	High
Curium	Netherlands	52	5 000	32%	Commercial	High
IRE	Belgium	52	3 500	22%	Semi-governmental/ commercial	High
NorthStar	United States	52	750	5%	Commercial	High
NTP	South Africa	44	3 000	16%	Semi-governmental	Very High
Rosatom (RIAR and KARPOV)	Russian Federation	50	890	5%	Semi-governmental	Low

Notes: 1. Types of organisation in increasing level of commercialisation: governmental, semi-governmental, semi-governmental/commercial and commercial.
2. Level of importance of the Mo-99 processing as an activity in terms of relative importance to the organisation as a whole, from: low, moderate, high and very high.
Sources: NEA reports and analysis; Table reviewed by the named organisations.

Some generator manufacturers may have a primary processor of choice that will supply the majority of the material they need and they will only take occasional limited quantities of material from secondary suppliers. Other generator manufacturers will spread their demand more evenly between a number of processors. Some may rely upon a single processor to supply them on the basis that this processor is also

responsible for sourcing extra material in the event that they have insufficient processing capacity of their own. Extensive cross-supply and co-operation arrangements exist between different processors, either as part of commercial supply agreements, or as formal or informal reserve capacity arrangements.

Bulk Mo-99 is shipped in special transport containers either by surface transport or by air. The timing of the shipments is critical as any delay is costly and could lead to a supply shortage, as the quantity of material shipped reduces by approximately 1% per hour.

Each processor carefully plans production levels to match the variable demands made on them by their generator manufacturer customers and it is the responsibility of the processors to manage the production level needed to achieve this. Each processor arranges the availability of their own enriched uranium targets and determines the schedule of irradiations that are performed under contract by nuclear research reactors (NRRs). After the scheduled irradiation, targets are delivered by surface transport to the processors in special transport containers carried in customised vehicles by specially licenced transport companies. Air transport of irradiated targets is not practicable, so the transport of irradiated targets is a loco-regional activity conducted by surface transport only. The scheduled end of each irradiation, the associated specialist transport logistics to the processor site and the processing of the targets are all led and co-ordinated by the processor organisations.

Processors contract with nuclear fuel fabricators in a highly regulated environment

Un-irradiated enriched uranium is a strategic material and must be purchased from a limited number of government repositories, making it a highly regulated market with only a small number of players. Nuclear fuel fabricators are contracted to produce special enriched uranium targets for Mo-99 production in bulk quantities. The purchase and delivery of enriched uranium and the production of enriched uranium targets is very specialised and covered by many nuclear safeguards; much of the market is supplied by a single fabricator located in France. Prior to irradiation, the fabricated targets are shipped in special transport containers and stored securely for the processor at contracted NRRs that have the technical and operational capabilities including licences to hold, store and to irradiate those targets.

4.3.5. Nuclear Research Reactors

Irradiation and processing are geographically close or integrated except in Europe

Nuclear research reactors (NRRs) perform the primary irradiation services. Most irradiations are performed by NRRs located close to processor facilities. In some cases (Argentina, Australia and South Africa), the NRR and the processor are co-located within the same organisational structure and the single local NRR is the sole irradiator for the processing facility. Thus, if the NRR is out of operation for a period, the processor cannot operate and if the processor is out of operation, the output from the NRR cannot be processed. The transport of irradiated targets to the processing facility is less difficult when both facilities are on the same site. In Russia two processing locations in different parts of the country each work with their respective NRRs, but co-operate formally to provide a continuous supply of bulk Mo-99 through a single commercial outlet.

The main exception is in Europe, where presently an informal network of four NRRs (located in Belgium, the Czech Republic, the Netherlands and Poland) supply two processors (located in Belgium and the Netherlands). In this informal “network” model, even when a NRR is located in the same country as a processor, the NRR and the processor do not operate within the same organisational structure and, in the case of Belgium, are not located on the same site.

Table 4.2 shows the main characteristics of irradiators to provide a structural overview of the industry.

Table 4.2. Overview of Nuclear Research Reactor irradiators

Reactor Name	Country	Average no of Mo-99 production weeks/year	Maximum capacity per week (6-day Ci ^{99}Mo)	Share of annual total world capacity	Type of Organisation[1]	Importance of Mo-99 irradiation to organisation[2]
ANSTO (OPAL)	Australia	43	3 500	16%	Governmental	High
CNEA (RA-3)	Argentina	46	400	2%	Governmental	High
NCBJ (MARIA)	Poland	36	2 200	9%	Semi-governmental	Moderate
NECSA (SAFARI-1)	South Africa	44	3 000	14%	Semi-governmental	Very High
NRG (HFR)	Netherlands	39	6 200	26%	Semi-governmental/ commercial	High
RC Rez (LVR-15)	Czech Republic	30	3 000	10%	Semi-governmental/ commercial	High
Rosatom (RIAR and KARPOV)	Russian Federation	50	890	5%	Semi-governmental	Low
SCK-CEN (BR-2)	Belgium	21	6 500	15%	Semi-governmental	Moderate
University of Missouri (MURR)	United States	52	750	4%	Independent non-profit	Moderate

Notes: 1. Types of organisation in increasing level of commercialisation: governmental and independent non-profit, semi governmental, semi-governmental/commercial and commercial.
2. Level of importance of the Mo-99 processing as an activity in terms of relative importance to the organisation as a whole, from: Low, Moderate, High and Very high.
Sources: NEA reports and analysis; Table reviewed by the named organisations.

There is a range of different commercial arrangements between processors and NRRs, with the relationship between a processor directly linked within the same organisational structure generally being different to that between a processor and NRRs acting in an informal network of supply (i.e. in the informal 'European model'). In linked facilities, the processor has a direct obligation to sufficiently fund the activities of the NRR, whereas with a network, the processor can choose between different irradiators and holds market power. In principle, the commercial arrangement between a processor and a NRR should make provision for the supply and payment for outage reserve capacity (ORC) services, but this is not yet universally the case (NEA, 2017[2]). Holding sufficient paid ORC services ensures the flexibility to manage periods of supply problem and payment for the provision of ORC services is essential for the NNRs to achieve full cost recovery (FCR) for the whole range of services they provide.

Two main operating patterns dictate the flexibility and efficiency of irradiations

NRRs do not run continuously and normally operate following two main patterns. The first pattern is relatively long operating cycles of around one month or more, where targets can be loaded and unloaded at any time during the cycle. The second pattern is relatively short cycles (usually of less than a week); where the targets can only be loaded and unloaded during stop periods. NRRs that follow the first pattern provide more flexibility to processors as they can unload targets more than once per week and can adjust the irradiation period, or if needed, add extra targets, at short notice. This added flexibility allows for the most efficient use of freshly irradiated targets on multiple processing days per week.

NRRs that follow the second pattern of short cycles can only efficiently provide irradiation services for material needed shortly after the end of the fixed cycle plan. This either restricts the availability of freshly irradiated material to a processor to certain days of the week, or demands that the NRR operator arranges the cycles specifically to align with the needs of the processor. An advantage of operating shorter cycles is that the NRR may have a greater number of operational weeks per year.

All NRRs require maintenance periods. Some maintenance can be performed in the periods between operating cycles, but most take extended planned stops for more extensive preventive maintenance work. NRRs normally operate predetermined cycle programmes with major preventive maintenance plans being established some years in advance. Many NRRs have a range of purposes aside from medical isotope production, which include nuclear technology testing, fundamental scientific research and industrial isotope production. Some of these activities are undertaken on a commercial basis; however they are most commonly funded by governments, in part or in full. The long-term planning of NRR operations is needed with regard to efficient operation of the NRR for all of its purposes and not solely for medical isotope production. Generally, when a NRR has a large number of purposes not related to medical isotope production, it has less flexibility to adjust operating plans.

4.4. Irradiation capacity is co-ordinated globally

In the period around the 2009-2010 supply crisis, only five reactors produced around 90% of global Mo-99 supply and, at that time, they were all over 40 years old. Following the supply crisis, additional NRRs became involved in the supply chain (in the Czech Republic, Poland, and Russia), however these were also relatively old. Only one newer NRR, the OPAL in Australia has joined the international supply network and further investments in new processing facilities in Australia have recently increased the overall level of supply available from that NRR. Since the supply crisis, important NRRs in Canada and France have ceased operation. Their planned closures took place in 2017 and 2015 respectively, with a commensurate reduction in the total irradiation capacity available.

The overall planning of NRR operating cycles and the extended maintenance periods is critical and has to be co-ordinated between all NRRs providing irradiation services to avoid periods of supply shortage. The global co-ordination is today managed through the Nuclear Medicine Europe (NMeu)[2] Security of Supply Working Group (SoS). NMeu is an independent European Economic Interest Group funded by the medical imaging industry and includes all NRRs involved in Mo-99 production around the world as associate members. NMeu-SoS meets regularly to discuss long-term reactor scheduling. During this process, potential weaknesses in global supply are identified and requests are made to individual NRRs to investigate the possibility of cycle adjustments. It is this extensive and *not-for-profit* co-ordination activity of NMEu that allows the industry to ensure sufficient NRR capacity is continuously scheduled.

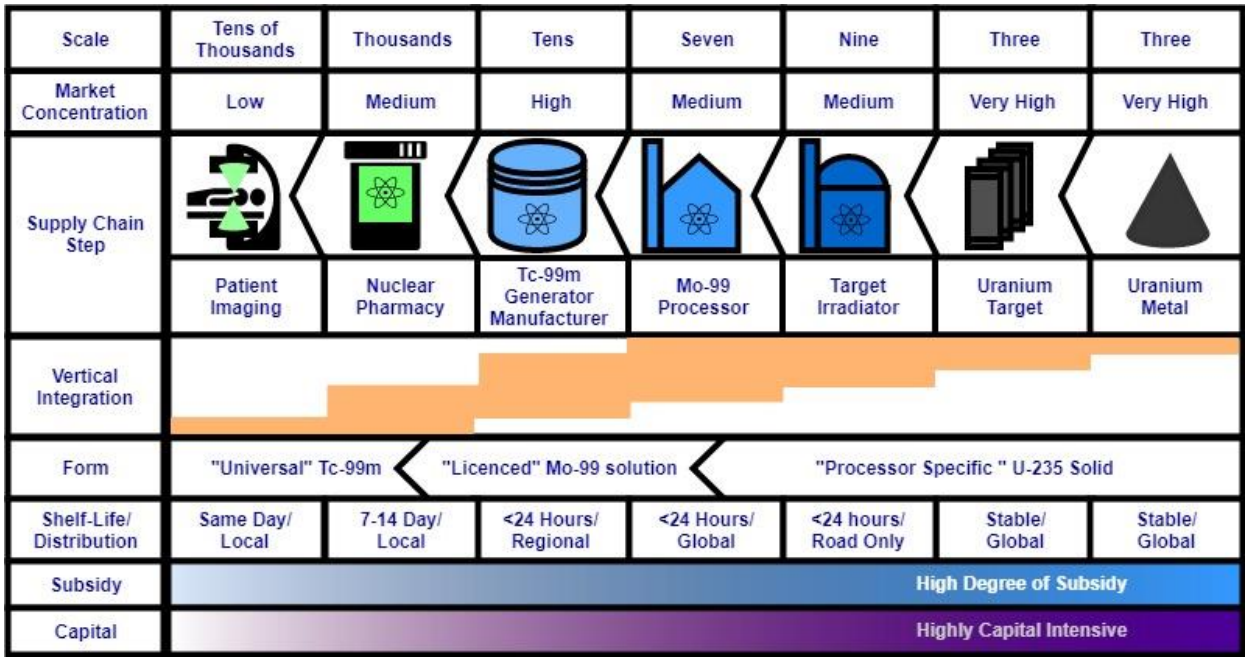
If an unplanned event occurs that could lead to supply disruptions, NMeu-SoS calls together at short notice a so-called Emergency Response Team (ERT) that represents NRRs, processors and generator manufacturers globally. It is primarily the responsibility of the processor organisations to identify potential supply weaknesses and for the ERT group to discuss the risks and propose potential planning adjustments that could alleviate the problem. The ERT group also takes a prime responsibility in communicating the risk of any potential supply problem to governments and to stakeholders. ERT communication is co-ordinated through the NMEu directorate to the Euratom EU Observatory co-ordinator and through the secretariat of the NEA HLG-MR. ERT communication activity has proven invaluable during recent supply problem periods. For example, starting from November 2017 the ERT convened and communicated to stakeholders on more than 45 occasions during the approximate one-year period that NTP (South Africa) experienced operational problems.

4.5. Despite progress, the supply chain remains unviable

Although progress has been made to overcome some of the issues described in Section 4.5.1, product markets along the main steps of the Mo-99/Tc-99m supply chain depart significantly from the idealised model of perfectly competitive markets. The main structural characteristics of the Mo-99/Tc-99m supply chain are shown in Figure 4.2. Supply progresses from right to left starting with bulk enriched uranium supply, through target supply, NRR irradiators and processors to generator manufacturers, then on to nuclear pharmacies, providers of imaging services and finally patients.

Market concentration is high, in particular upstream. Steps on the right side of Figure 4.2, where the product is in the form of a uranium metal target, all have very limited numbers of players and very high market concentrations. There is a somewhat higher number of players in the central steps of the chain, from irradiators through processors and generator manufacturers, but market concentration is still medium and high. From nuclear pharmacies onwards the numbers of market players increase substantially and market concentration is lower. However, as noted above, in some countries such as the United States, commercial nuclear pharmacies can also hold large market shares and wield market power.

Figure 4.2. Structural characteristics of the Mo-99/Tc-99m supply chain



Source: Authors

High capital intensity creates barriers to entry, in particular upstream on the right hand side of the Figure. These organisation rely more significantly on government subsidies.

Logistical requirements also constrain the ability for market players at various steps to exploit competition among suppliers. While solid uranium is stable, un-irradiated enriched uranium is a strategic material, the supply of which is completely controlled by governments. As the product is transformed into bulk Mo-99 and finally Tc-99m, decay becomes an issue so that geographic proximity between NRRs, processors, generator manufacturers and nuclear pharmacies is a relevant factor that constrains competition.

There are many instances of vertical integration within the supply chain, with for example the steps from irradiation through to bulk Mo-99 processing and generator manufacturing all being performed within a

single organisation and even on the same site. There are also examples of vertical integration of fewer steps in the chain, with examples of vertical integration at every level of the supply chain up to the imaging provider. In general, vertical integration protects subsequent steps in the chain from competition and often implies reduced transport distances and reduced decay loss with the associated economic benefits.

4.5.1. Some historical barriers to full-cost recovery remain

Historical irradiation prices were too low to cover costs and support investments

The NEA (2010[3]) Economic Study concluded that the *"overall impact of the historical market development on the current situation is that there is currently not enough reliable reactor capacity and there are constraints on processing capacity"* (p.11). This was *"caused by a market structure that developed around an unsustainable economic model that did not remunerate reactor operators and processors sufficiently well enough to provide incentives to invest in new infrastructure to meet growing demand or to maintain reserve capacity"* (pp.11-12). It concluded that *"lack of investment resulted in a system reliant on older reactors that have had reliability concerns over the last decade. The shortage seen in 2009 and 2010 is a symptom of this economic problem"* (p.12).

The report also warned that, *"once the shutdown reactors return to operation and the short-term supply becomes stable again, it is important to stress that although the symptom has been addressed, the underlying problem – the unsustainable economic structure – has not."* (p.12)

The observations in the NEA 2010 Economic Study were well founded and subsequently many stakeholders reported that the market did *"return to historical market behaviour"* in the period after supply had stabilised and information in a number of publically available annual reports for generator manufacturers identified that major new contracts were won on the basis of price reductions.

Irradiation prices were also too low to cover costs and support infrastructure investments

Prior to the 2009-2010 supply crisis period, irradiation services were seen as a by-product, with historical NRR capital costs already paid off or fully justified. Most processors originally contracted target irradiations in multipurpose NRRs constructed and operated with 100% government funding. As a result, the historical pricing of irradiation services reportedly included only limited direct marginal costs and did not account for replacement costs and full direct and indirect marginal costs. The historical non-inclusion of those costs resulted in the prices charged for target irradiation being too low to sustainably support the portion of NRR operations that could be attributed to Mo-99 production. They also did not contribute sufficiently to covering the costs of replacing or refurbishing ageing reactors. Also, with historical pricing set too low at the irradiation step, all further steps in the supply chain were likely to be priced too low to support full-cost recovery (FCR) pricing at the irradiator step of the supply chain.

A further historical factor complicating the achievement of FCR was the existence of excess irradiation capacity while the economic value of outage reserve capacity (ORC) was not recognised. Although a certain level of excess capacity is essential for reliable supply, it is difficult to determine the difference between essential reserve capacity and overcapacity when ORC services are not properly valued or paid for. The NEA established a minimum guideline of market demand +35% ORC to establish a safe minimum level of paid ORC that should be held at all levels in the supply chain. This was identified as a level that should be sufficient for the supply chain to manage the single unplanned outage of a major reactor or a processor.

Waste management is an important issue for processors; it is generally agreed that a full economic model that incorporates the final treatment and disposal costs of the radioactive waste from LEU or HEU target irradiations is still not available and that final waste disposal costs are still not fully included in bulk Mo-99 pricing. The enforced conversion to LEU targets since the 2009-2010 supply crisis period has reinforced

this concern; with increased waste volumes resulting from the LEU processes, the related costs are likely to increase, but those costs are not fully accounted for.

Some governments continue to subsidise irradiators

Most processors originally contracted target irradiations in multipurpose NRRs constructed and operated with 100% government funding. A question raised in the NEA (2010[3]) Economic Study economic survey was, *"If the supply chain pricing structure was such that the irradiation services were unable to be offered on an economically sustainable basis, why did reactors continue to irradiate targets?"* (p.52). The answer at that time identified the relationship that governments had established with NRRs and the medical community in the historical social contract. That is, governments subsidised the development of NRRs, the related infrastructure and its operation, including waste management, and NRR operators used part of this funding to produce Mo-99. In return for this use of taxpayer funds, citizens would receive a reliable supply of medical isotopes.

However, governments were not always aware of the extent to which Mo-99 production relied on subsidies. Although NRR operators were aware that government financial support was increasingly used for Mo-99 and other isotope production, this development may not have been transparent for some governments. In some cases, the magnitude did not become evident until there were requests to subsidise the refurbishment or the construction of a new NRR. Some governments were essentially subsidising the production of Mo-99 that was exported to other countries, thus subsidising imaging services in importing countries.

Governments have questioned the historical social contract and while they have encouraged the supply chain to achieve FCR, there has not been universal agreement on what a new social contract should be. As a result, some governments have faced a choice between providing continued support to some irradiators and processors in order to keep them financially viable or otherwise closing a loss making activity. Closing the activity could potentially result in a substantial shortage; this has been seen as unacceptable by some. In this regard, the social conscience of some governments has led to decisions to continue subsidies rather than taking the risk of triggering shortages.

Other countries have decided to allow older facilities that were operating below FCR to cease operations and have not subsidised extensions of their working lifetime. While this increased the risk of insufficient supply or challenged reserve capacity, decisions to end the operation of facilities unable to achieve FCR have been helpful in achieving the six NEA policy principles (see Foreword) by removing subsidised services from the market. These actions also reduced the level of subsidised reserve capacity and reduced perceived overcapacity within the market.

Some countries have decided to provide support in a number of ways to the development of domestic alternative technologies. These technologies are well described in a 2016 publication by the US National Academy of Sciences (Committee on State of Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium et al., 2016[4]). New technologies fall into areas including accelerator-driven systems, alternative uranium fission processes and new chemical separation technologies. Some alternative technology projects use more than one new technology. However, with the exception of the licencing in 2018 of the RadioGenix® generator system, those initiatives have yet to provide new capacity. Also, it has not yet been demonstrated that the new technologies are economically viable at present market prices.

Processors have market power

Processors were initially also funded by governments as part of their efforts to develop the use of medical isotopes, having recognised their utility in health care. In some markets in the 1980s and 1990s, the processors were separated from NRR operators and commercialised. Although that commercialisation

process was originally thought to benefit all parties, NRR operators were disadvantaged in the process. In the NEA 2010 Economic Study, interviewees indicated *"that governments created the commercial contracts based on historical perceptions of cost and pricing structures, this resulted in long-term contracts with favourable terms for the commercial processors"* (NEA, 2010, p. 9[3]). The separation of activities often did not lead to a change to commercial prices charged for the irradiation step in the supply chain and once these long-term contracts had been established, they set the standard for potential new entrants.

The partial commercialisation process helped establish market power of some processors. There were examples of contracts that provided for an exclusive relationship between the processor and the NRR, creating a situation of monopsony whereby NRRs had only very limited avenues for selling Mo-99-related irradiation services to other buyers. The restriction to surface transport of irradiated targets also creates a geographic constraint, severely limiting the processors that an irradiator can supply. This market power has historically contributed to maintaining low prices for irradiation services.

Conversion to low enriched uranium increased costs

The NEA (2010[3]) Economic Study report identified that conversion to LEU targets for the production of Mo-99 had been agreed by most governments for security and non-proliferation reasons, but that while LEU conversion was agreed to be necessary, it was not financially supported by the market. This was identified as one of a number of issues within the industry that could increase the impact of the economically unsustainable supply chain, stating that, *"Industry stakeholders are being faced with possible additional economic pressures as a result of the conversion to LEU targets and changing levels of government financial support for overall and reserve capacity"* (p.14). It also identified the risk following LEU conversion, of an *"increase in costs per curie of product produced"*, as there would be *"a need for some degree of additional irradiation and processing capacity to continue to produce the same quantity of Mo-99 globally, depending on the uranium density that can be achieved in the target"* (p.15) and that *"there may also be an increase in waste management costs (capital and operational) since more total uranium waste and liquid wastes will need to be managed"* (p.15).

These observations have held true. Efficiency losses, increased waste and increased costs have been reported as a direct result of LEU conversion and these additional costs remain largely unrecognised downstream in the supply chain. Special uranium targets were previously made using HEU with enrichment levels often above 95% U-235. LEU, on the other hand, has enrichment of <20% U-235. This implies lower overall efficiency of Mo-99 production and more waste from LEU targets, leading to higher waste management costs. LEU targets are more difficult to make than HEU targets as they contain a higher total load of uranium (approximately 4.5 times higher) that must be securely embedded in metal plates using the minimum possible plate material. In January 2018, the Curium processing facility in the Netherlands announced a 100% change to the use of LEU targets. With that change, more than 70% of all of the world supply of Mo-99 was produced using LEU targets.

Some financial support has been provided from governments to individual processors to support the costs associated with the research, development, licencing and implementation of conversion projects that required capital investments. However, this has not covered the full costs associated with LEU conversion, with the remainder to be absorbed by processors and the market for bulk Mo-99. Since LEU conversion, a number of NRRs have reported irradiation efficiency losses of around 20% in terms of the activity of Mo-99 produced per target.

Irradiation price increases were not absorbed in the downstream supply chain

The historical undervaluation of the Mo-99 cost component in generator pricing and *loss leader* strategies described in Section 4.3.4 had a feedback effect on upstream prices. Manufacturers continue to compete on price and were not willing or able to absorb the upstream price increases needed to achieve FCR and paid ORC within their generator prices.

The cost of the Tc-99m component in the costs of final patient doses and imaging procedures is also one factor among many that determine the setting of health care provider payment rates for Tc-99m-based imaging procedures. An unsustainably low price of the Tc-99m component may have historically led to low prices of Tc-99m-based procedures. In turn, procedure prices may have had feedback effects that have helped maintain low prices in the upstream supply chain.

The NEA Third Self-Assessment showed that in many countries there had been little or no increase in provider payment rates for Tc-99m-based diagnostic procedures for a number of years (2012-2016). In some countries, this represented a price reduction in real-terms as even inflation was not accounted for. Health care provider payment is discussed in detail in Chapter 3.

4.5.2. Progress has been made but FCR is not yet achieved

A further 40% price increase by irradiators is necessary to achieve FCR

Following the supply crisis and the work of the NEA HLG-MR, governments gained a better understanding of the historical levels of subsidies and agreement was reached through the adoption of the NEA HLG-MR six policy principles. The subsequent Joint Declaration (see Annex A) stated that the subsidy of the production of medical isotopes should end. Although countries have taken a number of different actions to help achieve that goal, it has not been fully achieved so far.

All of the players throughout the supply chain have been strongly encouraged to achieve FCR. The NRRs that responded to the NEA Third Self-Assessment indicated that they had substantially increased charges for irradiation services to processors in recent years. However, as of late 2016, reactors representing around 70% of the global irradiation capacity were yet to fully implement FCR pricing for irradiation services.

From the data available in 2016, the NEA estimated that the total global charge for irradiation services to processors needed to increase by at least a further 40% to achieve FCR at the irradiator level. While prices are assumed to have increased since 2016 and the gap to breakeven has likely narrowed, FCR is still not achieved at the irradiator level, especially within the informal European network.

Analysis for the NEA Third Self-Assessment identified that many market players have experienced cost increases beyond the ones described above as a result of the implementation of tighter security regulations (due to terrorist concerns) and emergency preparedness (in response to the Fukushima accident).

Outage reserve capacity is still undervalued

The processors that responded to the NEA Third Self-Assessment indicated that they had increased the contracting of ORC, but information received from NRRs in the European informal network indicated that ORC did not reach the minimum target. In some cases no payments were made for an irradiator holding ORC although those services were available and were actively used during periods of supply stress.

The insufficiency of ORC manifested itself during the extended unplanned outage of the NTP facility (South Africa) between late 2017 and early 2019. The outage led to extended periods of shortage, whereas the level of theoretical reserve capacity in the system should have been sufficient to cover the loss of the NTP capacity.

Market entry remains difficult and unattractive for new players

In the NEA 2010 Economic Study, interviewees indicated that incumbent market players created barriers to keep new entrants from entering the market and competing profitably. Such barriers included aggressive pricing strategies and exclusive contracts. These add to significant entry barriers already present in a highly regulated industry that is knowledge and capital intensive (see Section 4.5.1).

Since the supply crisis period, it has primarily been existing market players who have successfully added production capacity to the supply chain. It is reasonable to speculate that this has only been possible by existing players being able to leverage privileged positions, or by a reliance on further support by some governments during a transition period.

Market entry by new players has been hampered by a combination of technical delays and the time it takes to gain the licences needed to build and operate prospective new facilities and to gain medical licence approvals. One of the most significant impediments to entry, however, has been economic: new commercial investment has been difficult to justify. The historical economic and structural characteristics of the supply chain continue to determine the current market structure, its economics and the (in)ability of the market to adjust.

Latest estimates confirm that the industry is unsustainable

The 2010 NEA economic study presented a costing model for the period prior to the supply crisis based on information received during interviews with market participants at all stages of the supply chain. The model yielded a median estimate of about EUR 11 for the Tc-99m element of a patient dose (or USD 13 at 2018 exchange rates[3]). Although, the model was not universally accepted by all market participants, however, all participants agreed that the cost of the medical isotope was small compared to the overall cost of associated imaging procedures.

A review of publically available data and preliminary findings of the recent EC SMER study indicate that the average cost of a Tc-99m dose has increased in the last decade. This is likely in part a response to the supply shortage experienced in 2009-2010 and in part due to subsequent efforts to achieve FCR in the supply chain. The EC SMER study identified a wide range of generator prices in Europe and of activity eluted by nuclear pharmacies to prepare doses. These factors collectively result in a wide range of costs of an individual patient dose. Mean estimates are therefore only indicative illustrations of cost structures; no individual supply chain participant should expect to recognise their own cost in mean estimates.

Based on preliminary findings of the EC SMER study and publically available data, the average cost of an individual patient dose at the point of dispensing of Tc-99m from generators (i.e. at selling prices of generators to nuclear pharmacies, with no costs added for nuclear pharmacy staff, facilities or cold kits) is around USD 21 (EUR 18[3]). This suggests an overall world market value of technetium generators of around USD 630M per year.

Assuming a world market demand of around 9 000 six-day Ci Mo-99 at “End of Processing” (EOP) per week, recent disclosures by publicly listed generator manufacturers[4] indicate a global Mo-99 market value of around USD 230M per year at the selling point of bulk Mo-99 from processors to generator manufacturers. Assuming that around 30 million patient doses are dispensed per year, the overall average cost of a Tc-99m patient dose at the selling point of bulk Mo-99 from processors is around USD 8. This suggests an overall value added of around 170% between bulk Mo-99 supply and technetium generator delivery.

No data are publicly available to estimate the current cost per patient dose at the supply chain step between irradiators and processors. It is believed that this step in the supply chain does not fully meet FCR in all cases. However, processors have three main variable cost components: the cost of the target including the enriched uranium content, the cost of irradiation (performed by the NRRs) and the cost of their own processing activities including long-term management and waste disposal. Processors additionally have to cover fixed costs associated with developing processes, buildings, maintaining and licencing of facilities and staff needed to manage target processing, including all regulatory costs associated with maintaining both nuclear and medical licences. It appears unlikely that irradiation itself would represent more than 25% of the total cost of processed bulk Mo-99.This would imply that the average cost of a Tc-99m patient dose at the selling point of irradiation services to processors is unlikely to be above USD 2. This estimate is substantially higher than the cost of irradiation per patient dose suggested in the NEA (2010[3]) Economic

Study of USD 0.37, confirming that prices have increased and suggesting a present world market for irradiation services of around USD 58M per year.

It should be recalled that the cost structure of generator manufacturing typically includes fixed cost items for every generator for the recyclable and once-only use parts of the generator, the manpower involved in production, and the costs of distribution and, where done by generator manufacturers, costs of recovery for disposal and recycling. These items represent the full costs of producing, shipping and recycling generators, except the cost of the bulk Mo-99 loaded onto generators. The cost of the bulk Mo-99 depends on the quantity loaded onto the generator. The 170% value added by generator manufacturing estimated above includes all of these fixed cost items for every generator, as well as the variable cost of the quantity of bulk Mo-99 and a significant allowance for the cost of Mo-99 decay loss between bulk Mo-99 receipt by the generator manufacturer and the final activity of the generator delivered.

There are some specificities within the global estimates above. Japan, for instance, is an anomaly at the selling point bulk Mo-99 from processors to generator manufacturers. The majority of material in Japan is used in highly centralised Tc-99m production followed by national distribution, rather than in decentralised generator elution and dose distribution. National distribution of Tc-99m, which has a shorter half-life than Mo-99, increases the decay loss experienced in that supply model with greater supply distances for Tc-99m, so a greater quantity of bulk Mo-99 is required to service the number of individual patient doses. The resulting cost of each Tc-99m dose at the bulk Mo-99 delivery step is substantially higher in Japan. Conversely, the cost of the final Tc-99m dose does not include the costs for generator manufacture and recycling which are largely excluded in the Japanese model.

In other countries, the size and number of generators utilised by a conventional nuclear pharmacy are important factors. The EC SMER study confirmed that in Europe many nuclear pharmacies (around 75% of respondents) receive only a single generator per week and often only elute that generator once per day. European generators typically also have a relatively low Mo-99 activity content. In countries like the United States, where commercial nuclear pharmacies are predominant, higher Mo-99 activity generators are typical, with multiple generator deliveries per week to each pharmacy and multiple elutions per day. The EC SMER analysis also showed that the use of multiple generators per week and the multiple elutions of generators in a day make use of Mo-99 more efficient, further improving the financial economies of use when the generator activities are relatively large (e.g. in a centralised nuclear pharmacy). Market data indicate that the relative cost per individual patient Tc-99m dose at the point of dispensing from the generator is lower in countries with centralised nuclear pharmacies.

Generator distribution costs are also important. Within much of Europe, for example, where there are multiple and geographically spread generator manufacturing facilities, many generators are delivered close to their production point and only surface transport required. While larger generators lead to higher efficiency in Tc-99m use, in North America, on the other hand, generator distribution distances are typically much longer, except where imaging facilities are close to one of the two generator manufacturing sites. Delivery to more distant medical facilities is a combination of road and air. Some more remote locations in Europe (e.g. Scandinavia) have distribution challenges similar to North America.

4.6. Conclusion

Mo-99/Tc-99m supply is a just-in-time activity requiring continuous production in a complicated and aging supply chain that combines a mix of governmental and commercial entities. Governments essentially control both ends of the supply chain. They completely control the availability of enriched uranium required to make targets for medical isotope production and to fuel nuclear research reactors. Governments also largely control the regulatory framework, including medical licencing requirements, regulation of the use of nuclear materials and the legislation around health care provider payment for nuclear medicine imaging

studies. The central steps of the supply chain are mainly commercial, in particular generator manufacturing and, in some countries, also nuclear pharmacies.

The current structure of the supply chain, with governmental or semi-governmental irradiators and semi-commercialisation of processors, was established by governments and bestowed market power on processors. Generator manufacturers also wield market power. The market was recognised as being economically unsustainable in the NEA (2010[3]) Economic Study. While progress has been made in all areas, the inability of achieving full cost recovery (FCR) by irradiators and insufficient outage reserve capacity (ORC) at various steps of the supply chain leave security of supply vulnerable and the market economically unsustainable. Continued market frailty was demonstrated from late 2017 to early 2019, with chronic shortages occurring regularly due to unplanned outages at the NTP facility. As of the end of 2018, only one alternative technology has been brought to market and then only in the United States.

Supply continues to be supported by some subsidies to irradiators and processors. Processors and generator manufacturers continue to wield market power, and market concentration has actually increased in these parts of the supply chain.

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Notes

[1] See annual 10-K filings by Mallinckrodt and Lantheus with the U.S. Securities and Exchange Commission (SEC), available at http://www.mallinckrodt.com/investors/sec-filings/ and http://investor.lantheus.com/sec-filings.

[2] Formerly the *Association of Isotope Producers and Equipment Suppliers*.

[3] EUR 0.847 per USD 1 on average in 2018 (http://dotstat.oecd.org).

[4] See, for example, Lantheus 2018. Form 10-Q. http://investor.lantheus.com/sec-filings/sec-filing/10-q/0001628280-18-005734

5 Barriers to Full-Cost Recovery and Policy Options

The structure of the supply chain, the cost structure and funding of nuclear research reactors (NRRs) and the resulting behaviours of supply chain participants are the main barriers to full-cost recovery. NRRs have high fixed costs while marginal costs of irradiation are low. NRRs are captive to local processors and have little choice but to continue supply even at prices that are too low, while government funding sustains their operations. Downstream, price competition creates a disincentive for processors and generator manufacturers to increase prices unilaterally. Although health care provider payment must not be neglected, it is not the main barrier because Technetium-99m (Tc-99m) is a small item in the overall cost structure of nuclear medicine providers who could absorb necessary price increases in most cases. A number of policies could help achieve full-cost recovery and improve the reliability of Tc-99m supply. A phased and co-ordinated discontinuation of government funding of irradiation-related costs for NRRs could catalyse price increases. This could be accompanied by policies ranging from increased price transparency to price regulation. Funding of irradiation by end-user countries could be an alternative option. However, no single policy can be recommended as the preferred solution and each option has strengths and weaknesses. Governments need to co-ordinate their efforts and evaluate options in more depth in co-operation with all stakeholders to identify the most acceptable solutions in their respective jurisdictions.

5.1. Introduction

This Chapter complements prior analyses by the OECD Nuclear Energy Agency (NEA) and lays out the implications of analyses presented in the preceding Chapters 3 and 4. It identifies the main barriers to implementation of full-cost recovery (FCR), Policy Principle 1 of the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR), and proposes a number of policy options for countries to encourage more reliable supply of Tc-99m.

5.2. Competitive pressures in the supply chain constitutes the main barrier to FCR

Despite efforts at various levels, results of the latest OECD Nuclear Energy Agency (NEA) self-assessments indicate that full-cost recovery has not yet been fully achieved at the irradiation and processing steps of the supply chain. Governments of some producing countries continue to subsidise Mo-99 production and the supply chain struggles to make available sufficient capacity to reliably meet the global demand for Mo-99/Tc-99m. With the exception of the NorthStar RadioGenix® system, which represents a new production technology whose entry into operation was partly funded by the United States Government (see below), no new entrants have added capacity to the supply chain.

This report focuses on end users, in particular on current clinical practices in the use of Tc-99m and mechanisms to pay health care providers for nuclear medicine (NM) diagnostic scans, to establish whether the main barriers to FCR are found within health care systems that pay for NM diagnostic scans or rather in the Mo-99/Tc-99m supply chain. Analyses in this report thus complement and complete prior analyses by the OECD NEA that focused exclusively on the supply chain.

5.2.1. Health care provider payment plays a role but does not constitute the main barrier to FCR

The main barriers to achieving FCR are not found in health care provider payment, although the responsiveness of payment mechanisms and financial incentives to health care providers must not be neglected in further efforts to achieve FCR. Analyses confirm prior findings, for instance in the NEA (2010) Economic Study, that Tc-99m represents a small item in the overall cost structure of nuclear medicine (NM) providers and price increases necessary to achieve FCR in the medical isotope supply chain would be small compared to the procedure cost. Health care providers could therefore likely absorb such price increases. In addition, this report shows that, albeit with some delay, health care provider payment mechanisms are responsive to changes in the costs of service provision, provided that these changes apply equally to all providers and are material to the cost structure of providers.

Available data do not allow for estimating the average cost of a Tc-99m patient dose with precision. Also, even a precise mean estimate would mask a wide range. Costs vary between countries, health care providers and individual scans due to varying patient characteristics and different types of scanning techniques as well as varying levels of decay cost caused by differences between countries and providers in Mo-99 distribution and generator eluting practices. Nevertheless, data analysed in Chapter 4 suggest that the cost of an average patient dose, at the point of sale of Tc-99m generators to nuclear pharmacies, is around USD 21. However, only some USD 2 of the cost of the average patient dose (<10% of the cost of the dose at generator delivery) are associated with the irradiation step in the supply chain. The NEA also estimated that nuclear research reactors (NRRs) that provide irradiation services would need to increase prices by a further 40% to achieve FCR, which would imply that an increase of 4% in the price of the average patient dose at the point of generator sale (equivalent to USD 0.8) would be sufficient to achieve FCR at irradiation.

The order of magnitude of the current cost of Tc-99m doses can be compared to prices paid for NM diagnostic services by health care payers. Data presented in Chapter 3 show that, where payers make fee-for-service (FFS) payments to NM providers, these range from approximately USD 45-65 for the simplest scans, such as a thyroid scan using Tc-99m pertechnetate or a dynamic blood flow study, to more than USD 600 for the most complex studies, such as pulmonary ventilation scans.[1] Scans performed in hospitals are often included in broad service bundles, such as diagnosis-related groups (DRGs) that cover entire episodes of inpatient stays and attract payments of several thousands of dollars, or are funded from hospital budgets.

Price increases to achieve FCR of the magnitude estimated above could therefore likely be absorbed by many health care providers without changes to current payment systems or significant increases to provider payment rates. Absorbing price increases may be more difficult for small and very specialised providers, in particular office-based nuclear medicine specialists, who already operate in a resource constrained environment and where fee-for-service payments, or payments specific to Tc-99m, are insufficient to cover costs. Responses to the OECD Health Division survey indicate that, for example, in Australia, Medicare fees for outpatient nuclear medicine services have not been increased for 10 years and that, in France, fees have generally decreased over time. In Belgium, the fixed amount paid to hospitals for each diagnostic scan is based on historical provider fees and has not been adjusted to trends in Tc-99m prices. Since provider payments for NM services are generally made for the entire service, or a bundle of services (see Chapter 3), it is not possible with data available for this report to assess whether current payment rates are sufficient to cover provider costs.

However, the specific exceptions above notwithstanding, health care provider payment mechanisms generally consider actual provider costs. Where hospitals are paid by diagnosis-related groups (DRGs), cost weights associated with each DRG are based on hospital accounting data so that, with a lag, successive iterations of cost weights mechanically take into account changes in input costs, if these are material enough to be reflected in accounting data. For other providers, payments are often based on negotiations between provider associations and payers so that providers also have a chance to negotiate increases in payments if costs increase.

Changes to health care provider payment are thus generally made in reaction to a change in provider costs. Therefore, an increase in the price of Tc-99m has to be driven by suppliers, i.e. generator manufacturers or nuclear pharmacies. Health care payers will not increase provider payment unless there is a substantial increase in costs of inputs for all health care providers that deliver NM imaging services to patients.

5.2.2. The structure of the supply chain, the cost structure and funding of NRRs and the resulting behaviours of supply chain participants are barriers to full-cost recovery

Analyses in this report suggest that the main barriers to full-cost recovery (FCR) are found in the current structure of the supply chain, the cost structure and funding of nuclear research reactors (NRRs) and in the resulting behaviours of supply chain participants. NRRs are capital-intensive enterprises that have high fixed costs and low marginal costs of irradiation services for Mo-99 production. Due to transport constraints and radioactive decay, NRRs are captive to processors that are geographically close and have little choice but to continue supplying irradiation services even at prices that are too low to cover fixed and marginal costs. Existing supply arrangements may be enshrined in long-term contracts.

At the same time, irradiation services by NRRs for production of Mo-99 continue to be funded, at least partially, by governments of their host countries. The relative importance of irradiation services in their overall operations varies between individual NRRs. Some NRRs rely heavily on the sale of irradiation services to generate revenue, while this represents only a marginal activity to others and operations are funded mainly from activities other than irradiation for medical isotope production.

Post-processing, transportation of bulk Mo-99 is less of a constraint and participants in the supply chain are subject to competitive pressures. Processors, generator manufacturers and, in some countries, such as the United States, also nuclear pharmacies are commercial organisations that compete for business from downstream supply chain participants. While processors are in a position of market power vis-à-vis NRRs (in particular since their organisational separation from NRRs described in Chapter 4), they are mainly commercial organisations and compete globally for business from generator manufacturers. In contrast to NRRs, they rely substantially on the sale of bulk Mo-99 to fund their operations. Most generator manufacturers are diversified commercial organisations and some have market power. The three largest generator manufacturers supply most of Europe and North America. In North America, the three largest chains of nuclear pharmacies also have market power.

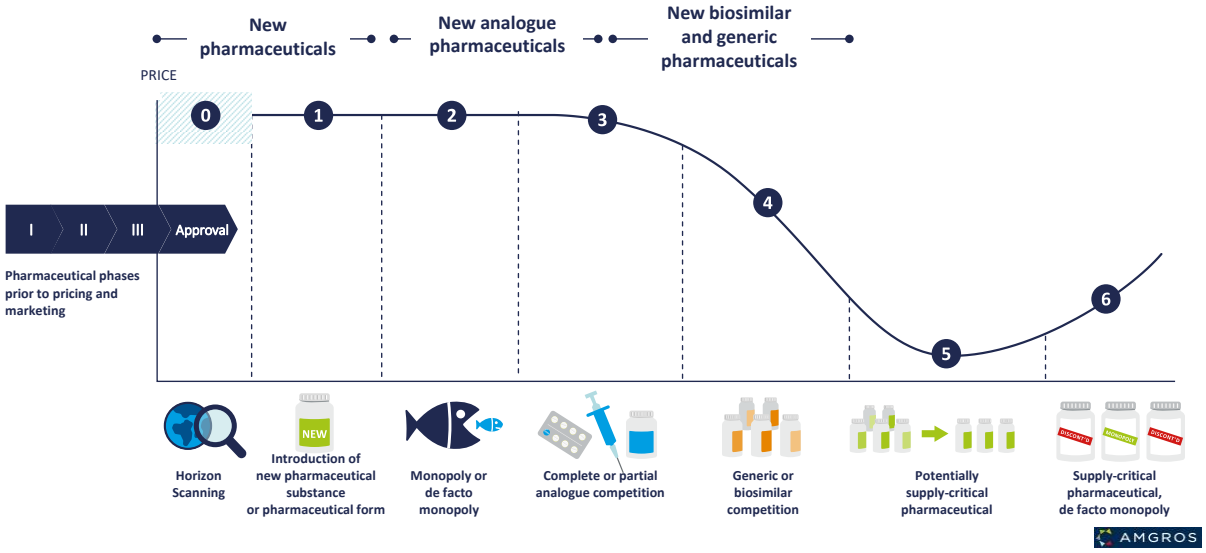
None of the commercial supply chain participants, between NRRs and health care providers, have an incentive to increase prices unilaterally, as this may entail loss of business to competitors if it is not certain that all other competitors also increase prices. At the same time, government funding of NRRs allows for continued provision of irradiation services at prices below FCR, so that downstream supply chain participants do not receive sufficiently strong signals that price increases are necessary.

5.2.3. The Mo-99/Tc-99m supply chain is unique

Analysis of the Mo-99/Tc-99m supply chain in Chapter 4 and comparison to supply chains of other medical products show that the Mo-99/Tc-99m supply chain is unique in health care. Production and distribution relies on a complex combination of entities, some that receive government funding and commercial entities that deliver a product that cannot be stored. Production and distribution costs represent a large proportion of the total cost of the final product.

In contrast, other technically complex medical supplies, such as medicines and medical devices, are durable and relatively cheap to produce. Prices often decline over time as competition intensifies. In the life cycle of a new medicine, for example, prices may initially be significantly above marginal production costs during the period of patent protection and market exclusivity to allow manufacturers to recoup earlier R&D costs and earn profits. Prices then typically decline as the medicine faces competition from alternative treatments and, in particular, as generic versions of the same medicine enter the market following the end of market exclusivity. Coverage schemes by health care payers often take into account price declines to reduce attendant reimbursement amounts or health care provider payments. In some cases generic competition may lead to suppliers exiting from the market, increasing market concentration and market power of incumbents, which may in some cases lead to less reliable supply and price increases in the long run. Figure 5.1 shows a typical trend in the prices of a medicine during its life cycle.

Figure 5.1. Price during the typical life cycle of medicines



Source: © Amgros, Denmark

There is therefore no perfect analogy in other markets of medical supplies that could serve as a blueprint for overcoming the barriers to FCR. There are, however, some instructive similarities with a number of products.

The supply chain of **outpatient medicines**, for instance, also relies on a multi-level supply chain with the ultimate goal of ensuring stable supply of medicines to patients. One of the goals of price regulation is to stabilise revenue of supply chain participants that are downstream of manufacturers, in particular community pharmacies, which make medicines readily available to patients. However, in contrast to Mo-99/Tc-99m, medicines are typically relatively straightforward to manufacture and manufacturing and distribution costs most often represent a smaller share of final product costs. The primary goal of price regulation is often to countervail the market power of manufacturers, who may be monopolists or oligopolists during periods of market exclusivity. Where prices are regulated at one step of the supply chain, fixed mark-ups may apply to other steps in the chain, effectively regulating prices at several levels.

Similar to Mo-99/Tc-99m, shortages have also occurred in the supply of medicines, in particular in the context of **generics**. These have occurred in many countries especially for products with low prices, either because markets are very competitive, such as in the United States, or because of resource constraints in health care systems (Barlas, 2018[1]; Dave et al., 2018[2]; EAHP, 2014[3]; Casassus, 2015[4]). Low prices have often been identified as a root cause of shortages, because they can lead manufacturers to exit the market or underinvest in production capacity while prioritising more profitable products (Dave et al., 2018[2]; Gottlieb and Woodcook, 2018[5]). This can then result in the reliance on a few or a single supplier, and shortages may occur when remaining suppliers are unable to provide sufficient product volumes. Shortages in generic medicines have sometimes led to sharp price increases by the remaining manufacturers who find themselves in *de-facto* monopoly positions. A number of policies have been suggested to prevent and manage shortages, including improved monitoring of supply and reporting of anticipated shortages, stakeholder co-operation, quicker regulatory approval of new market entrants, and adopting procurement systems that ensure that prices are not pushed below sustainable levels (EAHP, 2014[3]; Gottlieb and Woodcook, 2018[5]; WHO, 2016[6]). In contrast to Mo-99/Tc-99m, however, medicines can be stored and the production of generics is less capital intensive, thus allowing quicker market entry when prices increase.

Hospital **inpatient medicines and other supplies**, including relatively complex products such as surgical equipment or implantable devices, resemble Mo-99/Tc-99m-based products in that their cost is typically included in bundled payments, such as payments for diagnosis-related groups (DRGs), or hospital budgets. Also, prices are often unregulated and determined in negotiations or tendering between hospitals, hospital purchasing groups or regional health authorities that operate hospitals. However, supply chains are usually simpler, with manufacturers selling to hospitals directly or through wholesalers and distributors, and products are durable and can be stored. Similar to outpatient medicines, prices can be high when innovative products are introduced but then often decline over time as competition increases and hospitals face incentives to contain costs.

The supply of **energy**, and in particular electricity and district heating, also bears some resemblance to Mo-99/Tc-99m because these products cannot be easily stored and both demand and supply can be volatile, requiring reserve capacity. Production is capital intensive but can have relatively low marginal costs. Subsidised production of electricity from certain sources, such as renewables, can lead to low market prices which in turn make investments in new production capacity less viable (IEA, 2016[7]). Some countries with liberalised electricity markets have implemented capacity markets as a mechanism to ensure the availability of sufficient capacity to meet supply reliability goals. These markets may operate separately from the core market for electricity and are generally the result of regulatory intervention rather than an unregulated market (ibid.). There are however a number of differences that limit this comparison. For example, electricity and heat are not transformed between production and consumption. Respective markets also differ in terms of concentration and market power of individual suppliers and buyers. While electricity distribution grids are very costly to establish and maintain, once a grid is in place, electricity can be transported relatively easily, providing distances between producers and consumers are not too great. Also, many producers supply a grid that potentially links them with a large number of consumers. In district heating markets, supply often relies on a local heating plant that has some degree of natural monopoly and that sells the product to a large number of consumers (IEA, 2004[8]). Regulation often aims to constrain market power of a monopolist producer, or to encourage entry of new producers that may bring additional benefits to the market, such lower environmental impacts.

5.3. Policies to increase the reliability of Tc-99m need to tackle barriers in the supply chain

This section proposes seven policy options that could help improve the reliability of Mo-99/Tc-99m supply and thereby ensure the sustained availability of NM diagnostic scans to patients. The Section first presents options that could help increase prices and achieve full-cost recovery (FCR) within the current supply chain. It then presents an alternative to market-based approaches to FCR in the current supply chain. Two final options are presented that may be pursued in parallel to or instead of FCR within the current structure of the supply chain to encourage more reliable supply. Figure 5.2 shows an overview of the seven options.

Based on the analyses presented in this report, no single policy option can be recommended as the preferred solution to current issues with the reliability of supply. Each option has a number of strengths and weaknesses.

Also, the preceding Chapters 1 to 3 deliberately explore the issue of the reliability of Mo-99/Tc-99m supply from a health system perspective but, together with the review of the supply chain in Chapter 4., find that the main barrier to FCR lies within the supply chain itself. Data on the structure of the supply chain, such as ownership, revenue and cost structures of players, their respective market shares and prices of intermediary Mo-99 products, are limited. At the same time, the supply chain is complex and its structure varies between different countries and regions. The discussion of policy options is therefore inevitably superficial and may not exhaustively identify all strength and weaknesses across all countries and markets.

While governments of producer and end-user countries need to co-ordinate their efforts, they should also evaluate each option in more depth locally and in co-operation with all stakeholders, and identify the most acceptable solutions in their respective jurisdictions. In particular, the choice and implementation of policies that could help achieve FCR should be informed by a more detailed study of NRR- and processor-specific production costs, the extent and purpose of current government funding of producers, and the magnitude of price increases that would be necessary to achieve FCR. Such information would be essential, for example, for anticipating the effects on the supply chain of withdrawing government funding of NRRs (Option 1) or to determine appropriate price floors (Option 3).

Figure 5.2. Overview of policy options

Policies to move towards full-cost recovery within the current Mo-99/Tc-99m supply chain

Policy to catalyse price increases of irradiation and downstream supply chain activities

1. Phased and co-ordinated discontinuation of funding of NRR costs attributable to Mo-99 production by governments of producing countries

Policy options that could accompany withdrawal of government funding for Mo-99 production by NRRs

2. Increasing price transparency in the supply chain
3. Setting a temporary price floor for irradiation
4. Introducing a commodities trading platform for bulk Mo-99

Possible alternative to a market-based approach

5. Direct funding of Mo-99 production by end-user countries

Policies to reduce the reliance on the current Mo-99/Tc-99m supply chain

6. Increasing use of substitute diagnostic imaging modalities or substitute isotopes
7. Move towards alternative methods to produce Mo-99/Tc-99m

Source: Author

5.3.1. Options to continue moving towards full cost recovery within the current Mo-99/Tc-99m supply chain

This Section proposes four policy options to encourage a move to FCR at the point of irradiation in the Mo-99 supply chain. A phased and co-ordinated discontinuation of funding of the commercial production of Mo-99 and other medical isotopes by governments of producing countries (Option 1) is the main policy that could catalyse price increases in the supply chain. This would compel nuclear research reactors

(NRRs) to increase prices of irradiation services. Because a policy of withdrawing government funding of the production of medical isotopes could further destabilise supply in the short-term, it would need to be accompanied, at least temporarily, by one or several other measures that would help ensure that price increases are passed on through the supply chain (Options 2 to 4).

The goal of all options presented below would be to increase the price of irradiation services. Price increases could also entail changes in the units for which prices are set, such as setting prices for capacity separately from prices for the product volume sold. Whichever option(s) producer countries may choose to adopt, the policies and their anticipated effect on Mo-99/Tc-99m prices throughout the supply chain and, ultimately, to health care providers must be communicated clearly. That would allow supply chain participants to plan and respond appropriately. In particular, health care payers and providers would need to evaluate whether providers could absorb price increases with existing payments or whether payment would need to increase. Changes to health care provider payment may be necessary in particular in countries where payment has not been adjusted for a long time and/or service provision relies on small provider entities, such as office-based specialists, who have a limited capacity to bear financial risk.

Option 1: Phased and co-ordinated discontinuation of funding of NRR costs attributable to Mo-99 production by governments of producing countries

One way of catalysing price increases in the supply chain to achieve FCR by NRRs would be to cease government funding of NRRs for the commercial production of Mo-99 and other medical isotopes. An inter-governmental agreement among producer countries might be necessary to achieve this. Such an agreement could foresee a co-ordinated withdrawal of such funding that is phased over several years. Certainty gradual withdrawal of funding from irradiation services for the production of medical isotopes would allow renegotiation of supply contracts among supply chain participants and price increases to be passed on to downstream participants, and ultimately health care payers. Co-ordination among producing countries in the schedule to withdraw funding could minimise market distortions, for instance to avoid putting a single NRR at a disadvantage because its funding is withdrawn before those of other producers. An unco-ordinated and distortionary withdrawal could lead to a further deterioration of supply reliability if efficient suppliers that lose government funding first were forced to exit the market while some countries continue to fund irradiation services for the production of medical isotopes to other suppliers. To increase confidence that the process is non-distortionary, the inter-governmental agreement could include a mechanism for verification and certification of the withdrawal of funding according to schedule by an independent party.

The main strength of this option is that it would compel NRRs to increase prices of irradiation services while not requiring direct government intervention in the supply chain and leaving the adjustment of supply contracts and prices along the supply chain to market forces.

However, a number of difficulties may be associated with this option. First, governments of producing countries may not reach consensus on a co-ordinated and phased withdrawal of NRR funding of or may, even if an agreement is reached, fail to honour their commitments. Some governments currently continue funding NRRs directly despite earlier commitments to FCR (see Annex A). In particular, countries that are producers and end-users at the same time may want to continue funding irradiation in order to supply their domestic markets. Second, all of the NRRs that currently supply commercial irradiation services also engage in other activities that may warrant government funding. It might therefore not be straightforward to isolate irradiation in Mo-99 production within their cost structures and then only withdraw funding for this activity while maintaining funding of other activities. Increased cost transparency might be necessary to support an effective withdrawal of government funding. Third, the withdrawal of funding and a move towards FCR may reveal large differences in production costs between NRRs, leading to shifts in market shares and potentially to some NRRs and processors going out of business if their FCR prices are not

competitive. This may cause temporary supply instability until a reduction in capacity resulting from market exit of some players is compensated by investments in additional capacity elsewhere.

Finally, it is difficult to predict whether prices would self-adjust quickly along the entire supply chain to a withdrawal of government funding. As discussed in Chapter 4, product markets along the Mo-99 supply chain depart significantly from an ideal model of perfect competition and a number of supply chain participants have market power. Existing supply arrangements between supply chain participants can be enshrined in long-term contracts. While health care provider payment is responsive to changes in input costs in most countries (see Chapter 3), changes to provider payment are usually made with some lag after costs increase. There are also some countries in which health care provider payment has not been responsive at all in the recent past, forcing providers or patients to absorb cost increases (see, for example, see Australia in Chapter 3). If it turns out that supply chain participants cannot pass on price increases quickly enough, Mo-99 production may become even less economically viable, at least temporarily, leading to a further deterioration of reliability of supply.

Given the risk that this option may pose to reliability of supply, such a policy should not be adopted on its own. A phased and co-ordinated discontinuation of funding of NRR irradiation services for the production of medical isotopes by governments of producing countries would therefore likely need to be combined with other policies described below, such as increased price transparency or price regulation.

Option 2: Increasing price transparency in the supply chain

Nuclear research reactors (NRRs) and processors could agree to establish a process to report average prices for irradiation services. To ensure that prices of individual supply chain participants are not disclosed, this process would need to be implemented under the auspices of an independent party, such as the OECD Nuclear Energy Agency (NEA) or the EU Observatory. Supply chain participants would confidentially report their revenue and an appropriate measure of product / service volume of past financial reporting periods to the independent party, which would allow the independent party to aggregate revenue and volume, and compute and publish an average price. Similar processes exist, for instance, in the medical device industry where manufacturers co-operate voluntarily through an independent party to estimate market sizes and average device prices and to benchmark their own performances against the market.

Increased price transparency could provide a mechanism of peer-pressure among supply chain participants to comply with commitments to achieve FCR.

The main strength of this option is that it could be implemented relatively easily within the existing supply chain structure and by parties that already play a co-ordinating role. It would not require any additional regulatory intervention in the supply chain.

Its main weakness is that it would not directly address the underlying barrier in the supply chain that currently keeps participants from raising prices. Like the previous self-assessment process performed by the NEA, it would rely on self-reported information and unilateral initiatives by existing supply chain participants to raise prices. However, compared to the previous self-assessment, periodic reporting of actual prices might provide stronger peer-pressure among supply chain participants.

While the publication of a market price could help identify anti-competitive behaviour, such as predatory pricing, the exchange of data on revenue and volume, and thereby average prices, may also lead to risk of infringement of anti-trust and competition law. The option would require a thorough legal assessment to ensure that the process could not be abused for unlawful collusion between supply chain participants and that legal risks are mitigated appropriately.

Option 3: Direct price regulation in the supply chain

The most direct means of achieving FCR by NRR would be to impose price regulation and set a mandatory minimum price, or price floor, for irradiation services provided by NRRs. A price floor could be imposed temporarily, along with the withdrawal of subsidies, to ensure that NRRs are able to make up for the loss of government funding through additional revenue. To reintroduce competition and responsiveness to supply and demand signals, the price floor could be removed after full withdrawal of production subsidies and a transition period and once prices that are sufficient for FCR have been established in contracts between supply chain participants.

The main strength of this option is that it would no longer allow individual processors to gain an advantage in price competition by contracting irradiation services at prices below FCR. Basic microeconomic theory predicts that a price floor set above the unregulated equilibrium of supply and demand increases supply above equilibrium, by making additional supply economically viable, while also decreasing demand below equilibrium, by raising the price above the willingness-to-pay of some buyers, causing a surplus of the product to be supplied. To a certain extent, such an effect would be desirable in the current Mo-99/Tc-99m supply chain, given the current lack of outage reserve capacity (ORC). It could be achieved by setting a price floor above current prices to incentivise the entry of new supply chain participants or making investments in additional capacity viable.

Despite their appeal, price floors have a number of significant drawbacks and are not straightforward to implement effectively.

First, it might be difficult to determine the appropriate level at which a price floor should be set. To achieve intended effects, a price floor has to be sufficiently above the unregulated equilibrium price to change the behaviour of producers. At the same time, it must not be too high, so as to avoid the supply of an excessive production surplus at unnecessarily high prices, which would entail producer rents and welfare losses to end users. A price floor for irradiation services would have to be set high enough to increase the supply of irradiation capacity to world market demand plus the desired margin of ORC. Demand for Mo-99 can be assumed to be relatively inelastic, because substitution of Tc-99m in health care would be costly (see Chapter 1) and Tc-99m generally represents a small cost item for health care providers, whose payments are responsive to significant changes in provider costs (see Chapter 3). A price floor may thus not reduce the quantity of Mo-99 demanded significantly and would not make NM procedures less accessible for patients. Also, price increases necessary to achieve FCR are currently estimated to be relatively modest. Nevertheless, it is not straightforward for a price regulator to determine the price floor appropriate for achieving capacity targets because the underlying analysis requires information on the production and demand functions.

Second, fixed price floors reduce the responsiveness of negotiated prices to demand and supply signals in the market. Because price floors prevent prices from dropping below the regulated minimum, they insulate producers from signals of overcapacity and overproduction and do not incentivise producers to remove capacity or lower production if supply exceeds demand. They also attenuate or remove incentives for producers to improve their technical efficiency and to produce at the lowest possible cost. Conversely, price floors can act as an anchor in contract negotiations and may impede price increases above the floor even if demand would justify such an increase, especially if buyers have market power and can exercise such power in price negotiations.

To a certain extent, the drawbacks of fixed price floors discussed above can be mitigated by modulating price floors according to demand and capacity targets. Similar to price regulation in electricity markets (IEA, 2016[7]), scarcity prices could be defined upfront and higher price floors could become applicable when demand increases or production capacity is considered too low relative to current demand and ORC. Setting several price floors at the appropriate levels, however, might be technically even more challenging than finding a single price floor.

Third, beyond the technical difficulty of setting a price floor at the appropriate level, it might be practically difficult to get all producer countries to agree on a price floor. Input factor costs and cost structures of individual NRRs vary so that FCR is likely achieved at different price levels across NRRs. However, a uniform price floor across countries and NRRs would be necessary to minimise distortions to competition between processors. For such a floor to be effective, it would need to be high enough to allow for FCR by the NRR that produces the most costly irradiation services, which might be very high for NRRs that can produce such services at lower cost and result in significant economic rents for NRRs with lower production costs. Such a floor would have to be agreed upon internationally and then transposed into national regulations of producer countries.

Finally, there is little experience with the use of price floors for medical products. Regulation of prices of medicines and other medical products usually takes the form of price ceilings, or a maximum price covered by a health care coverage scheme. Also, existing price regulations are national policies, reflecting national processes and health care priorities, and prices usually vary between countries.

Option 4: Introducing a commodities trading platform for bulk Mo-99

To make prices in the supply chain more responsive to changes in supply, a commodities trading platform could be established for bulk Mo-99. This platform would set a world market price at which all processors could sell and generator manufacturers could buy bulk Mo-99.

Commodity exchanges are organised markets that provide a place where market participants buy and sell specified and homogeneous products, or contracts for future delivery of the product under pre-defined terms referred to as futures contracts. They register and publish prices as well as all information related to the commodity traded that is relevant to the market, helping market participants estimate and forecast price trends and changes in demand and supply. They also ensure that transactions occur according to an agreed code of rules, thus providing controlled platforms for the interaction of demand and supply to determine prices. These functions of commodities exchanges increase certainty for buyers and sellers. Traders are integral parts of commodities exchanges and speculative trading ensures that market prices reflect supply and demand. Metals and other raw materials are products commonly traded on commodity exchanges. The London Metal Exchange and New York Mercantile Exchange, for instance, are global market places that specialise in trading of industrial metals.

The main strength of a commodities trading platform for bulk Mo-99 would be that it could make prices more responsive to supply and demand and thereby help ensure that the appropriate level of production capacity is made available. A decrease in supply or increase in demand, for example, would cause an increase in the world market price, making additional production economically viable and thereby incentivising processors to increase supply by making available more irradiation and processing capacity. Conversely, overcapacity would lead to price decreases and incentivise producers to reduce capacity. A code of rules for the functioning of the trading platform could be laid down based on a consensus of all market participants to reflect the specificities of the bulk Mo-99 market. Such rules could avoid the current kinds of long-term supply contracts between individual supply chain participants that prevent price changes from being passed on through the supply chain. Participants could trade derivatives, such as futures contracts, which could serve as market signals in the supply chain and help align supply with demand.

This option has a number of limitations. In contrast to other commodities, production of bulk Mo-99 relies on a small number of processors, some of which have market power. Thus, suppliers in the Mo-99 market are not pure price takers and they could continue exercising their market power in a commodity market. The bulk Mo-99 market is also much smaller in value than markets for industrial metals or other commodities. Aggregate trading volumes in the smallest commodity markets for industrial metals, for instance, are in the several billions of USD per year.[2] Mo-99 trading volumes might therefore not be sufficient for establishment of a trading platform and to ensure a functioning market. In contrast to other commodity markets, Mo-99 is not a durable product so that market participants may be more reluctant to

agree to futures contracts. In addition, a functioning trading platform would require that generator manufacturers could accept delivery of Mo-99 from any processor, which would imply additional costs to generator manufacturers for licensing of all possible suppliers.

Crucially, however, this option might not provide a direct solution to the problem of irradiation prices below FCR. If NRRs remain bound to a single processor, processors could continue to exert their market power. Large generator manufacturers could also continue to exert market power. Even if prices of bulk Mo-99 were to increase, these increases may not be passed on from processors to NRRs, especially if processors continue to contract with NRRs on a long-term basis.

5.3.2. Possible alternative to a market-based approach

Rather than intervening in the complex supply chain made up of various types of semi-governmental and private entities, governments could more directly ensure that sufficient funding is available for the desired level of Mo-99 production capacity. As described in Chapter 4, the Mo-99/Tc-99m supply chain departs quite significantly from the idealised model of a perfectly competitive market and government funding of production might be an effective solution.

Option 5: Direct funding of Mo-99 production by end-user countries

Rather than aiming to recoup the full costs of producing Mo-99 through FCR pricing in the supply chain, governments in producing countries could continue direct funding of NRRs but agree with end-user countries that the cost of funding irradiation for Mo-99 production be borne by end-user countries. Producing countries and end-user countries could, for instance, estimate capacity needs and budgets jointly. The budget could be funded by end-user countries, who could contribute in proportion to the share of total production output that they consume. This could replace the historical *social contract* of domestic tax-based funding of Mo-99 production to provide a reliable supply of Tc-99m to citizens, while ensuring that countries that benefit also bear the cost. The highest number of Tc-99m-based scans are performed in the United States, followed by Germany, Canada and France (see Chapter 2), while more than 70% of irradiation and processing capacities are held in Australia, Belgium, the Netherlands and South Africa (see Chapter 4.).

Funding by end-user countries could be contingent on supply guarantees by producer countries, so that funding would only be made available if an agreed volume of Mo-99 is actually delivered to a given end-user country by a given producer. This would provide an incentive for producer countries to invest in sufficient production capacity to meet delivery commitments and avoid that end user countries pay for product volume they do not receive.

The main strength of this option is that, instead of intervening in the complex supply chain made up of various types of semi-governmental and private entities and relying on individual participants to increase prices, governments could more directly ensure that sufficient funding is available to achieve the desired level of Mo-99 production capacity, including ORC. As described in Chapter 4., the Mo-99/Tc-99m supply chain departs quite significantly from the idealised model of a perfectly competitive market, for instance as a result of entry barriers and market concentration, so that it is uncertain whether a largely unregulated and non-subsidised market self-adjusts to optimal levels of capacity and production. Compared to other capital intensive health care technologies, such as medicines or medical devices, for which global market values are in the billions of USD annually, the market for Mo-99/Tc-99m is small (USD 230M at the point of sale of bulk Mo-99 from processors to generator manufacturers per the estimates presented in Chapter 4.). Therefore, even price increases in the order of magnitude necessary to achieve FCR would provide weak incentives for commercial entrants to invest in the required production capacity. Direct government funding may be a more straightforward solution.

Market-based solutions and government funding could also be combined. End-user countries could, for example, fund only ORC directly to supplement NRR revenue from the provision of irradiation services. Such a solution could be implemented in a similar manner as in electricity markets. Some OECD countries use various funding mechanisms separate from the core market for electricity to ensure that power plants keep sufficient capacity to achieve supply reliability targets (IEA, 2016[7]).

It may, however, be difficult to gain consensus among producing and end-user countries on capacity planning and the related funding, and in particular on how to determine the contributions of each end-user country. Budgets for operating and capital cost would have to be set at the level of each individual NRR, while it may be difficult to track accurately the product flow between individual NRRs, intermediary supply chains steps and end-users, which could serve as a basis for setting budget contributions. In addition, a new inter-governmental agreement would have to be established to enshrine a funding mechanism between producing and end-user countries.

Although general taxation is a source of health care funding in all OECD countries, another difficulty may arise from the fact that other financing sources, such as social health insurance, private insurance and out-of-pocket spending by patients, also play a significant role in funding health care. Not all end-user countries may therefore agree to funding of Mo-99 production from tax revenue. The share of tax funding of health care varies significantly between OECD countries. In the United Kingdom, for example, tax-funded government transfers finance more than 80% of health expenditure, while this share is less than 40% in countries such as Switzerland and the United States, which rely more heavily on compulsory and voluntary health insurance schemes. In Germany, social health insurance finances more than 60% of total health expenditure, while government transfers represent less than 15%.

5.3.3. Options to reduce the reliance on the current Mo-99/Tc-99m supply chain

Beyond continued efforts to achieve full-cost recovery (FCR) in the current supply chain of Mo-99/Tc-99m or ensuring government funding of production capacity, countries could also aim to stabilise the availability of diagnostic services by reducing their reliance on Mo-99/Tc-99m produced by NRRs. This could be possible through increased use of alternative diagnostic imaging modalities, and NM procedures that rely on other isotopes, and through developing alternative sources of Mo-99.

Option 6: Increasing use of substitute diagnostic imaging modalities or substitute isotopes

One option to reduce the reliance on the current infrastructure of NRRs would be to substitute Tc-99m-based NM diagnostic scans with alternatives that provide comparable diagnostic results. As outlined in more detail in Chapter 1, PET/CT and CT are equal or superior alternatives for some of the most common types of Tc-99m scans, including bone scans and cardiac perfusion imaging.

Substituting a significant share of current procedural volume could allow for Tc-99m supply to be reprioritised for the types of Tc-99m scans that provide superior diagnostic results or for which no alternatives are available (e.g. sentinel node studies in breast, melanoma and head and neck cancer, and renal studies – also see Chapter 1).

Such substitution would have a number of significant drawbacks. First, it would require significant investment over a long period of time by health care systems and would likely entail aggregate cost increases. Health systems would have to make capital investments to ensure that sufficient PET and CT scanners are available to absorb the additional volume. Investment in additional human resources would also be necessary, to ensure that current NM staff capacity is redeployed and sufficient specialists are available to carry out alternative scans. Especially training and/or retraining professionals would require time. Second, 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 the aggregate cost of diagnostic imaging to health care systems. Third, a reduction in the number of Tc-99m

scans would further shrink product markets in the Mo-99/Tc-99m supply chain, making production even less attractive to commercial supply chain participants. Although substitution would allow for reprioritising the existing Mo-99 production capacity, a reduction of market sizes in the supply chain, in combination with the current challenge to achieve FCR, would likely jeopardise supply in the longer run. To ensure that Tc-99m remains available for scans that cannot be substituted, increased substitution would therefore also require parallel efforts to ensure the long-term reliability of a reduced Tc-99m supply.

Option 7: Move towards alternative methods to produce Mo-99/Tc-99m

Another option to reduce the reliance on aging NRRs for irradiation is to move towards alternative means of Mo-99 production. Alternative technologies are currently being developed in particular in North America. The Canadian Non-reactor-based Isotope Supply Contribution Program and Isotope Technology Acceleration Program supports the research, development and demonstration of cyclotron and linear accelerator technologies for the production of both Mo-99 and direct Tc-99m. The National Nuclear Security Administration of the United States Department of Energy has made efforts to establish a domestic and non-reactor-based manufacturing capacity to minimise the use of high enriched uranium (HEU) (Committee on State of Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium et al., 2016[9]).

However, these alternative production methods may be more costly than irradiation by NRRs and require substantial investment in capital and time to be brought to market. Development of these technologies is partly funded by the governments to meet strategic objectives of establishing domestic production capacity and of non-proliferation of HEU (ibid.). Production capacity will not be readily available soon for commercial supply of the world market. At the time of writing of this report, only one production facility (NorthStar RadioGenix®) was operational and it presently can only contribute less than 5% of global processing capacity (see Chapter 4).

5.4. Conclusion

The main barriers to full-cost recovery (FCR) are found in the structure of the supply chain, the cost structure and funding of nuclear research reactors (NRRs), and the resulting behaviours of supply chain participants. NRRs have high fixed costs while marginal costs of irradiation are low. Being captive to local processors because of transport constraints and radioactive decay, NRRs have little choice but to continue supply even at prices that are too low, while government funding sustains their operations. Downstream, price competition creates a disincentive for processors and generator manufacturers to increase prices unilaterally. Processors compete globally for business from generator manufacturers, which are commercial organisations that in turn compete for business from nuclear pharmacies and health care providers. Although the responsiveness of payment mechanisms and financial incentives to health care providers must not be neglected in further efforts to achieve FCR, health care provider payment is not the main barrier to FCR. As Tc-99m represents a small item in the overall cost structure of nuclear medicine (NM) providers and price increases necessary to achieve FCR are small, such price increases could likely be absorbed by health care providers in most cases.

There are a number of policies that could help achieve FCR pricing of Mo-99 in the supply chain and improve the reliability of Mo-99/Tc-99m supply. A phased and co-ordinated discontinuation of government funding of irradiation-related costs of NRRs could catalyse price increases. This could be accompanied by policies ranging from increasing price transparency in the supply chain to price regulation. Direct funding of irradiation for Mo-99 production by end-user countries could be an alternative option.

However, no single option can be recommended as the preferred solution to current issues with the reliability of supply and each option has a number of strengths and weaknesses. This report deliberately focuses on the study of the reliability of Mo-99/Tc-99m supply from a health care system perspective, and

one of the key findings is that the main barriers to FCR, as well as the policy solutions, lie within the supply chain itself. Given the complexity of the Mo-99/Tc-99m supply chain and the lack of data, the discussion of policy options is inevitably superficial and may not exhaustively identify all strengths and weaknesses across all countries. Governments of producer and end-user countries need to co-ordinate their efforts and should evaluate options in more depth in co-operation with all stakeholders, to identify the most acceptable solutions in their respective jurisdictions.

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Notes

[1] At the low end of the range, a thyroid scan attracted, for example, a fee of EUR 54 in Germany and a dynamic blood flow study using aged equipment AUD 60 in Australia; at the high end of the range, a pulmonary ventilation scan attracted EUR 534 in France and a scan of the adrenal gland AUD 880 in Australia. See Chapter 3 for details. Amounts were converted to USD at the average exchange rate in 2018 published at http://dotstat.oecd.org.

[2] See for instance http://www.mining.com/web/oil-market-bigger-metal-markets-combined/. Annual trading volume in the smallest commodity markets, such as those for lithium and uranium, total USD 3-4 billion while trading volume of crude oil exceeds USD 1.7 trillion.

Annex A. Broader responses to the 2009/10 Mo-99/Tc-99m shortage

Canada

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 as:[1]

1. "Ensure efficient and effective communication with the medical community and the public.
2. In decision-making, ensure a balance between the health and safety of the public and the health outcomes of individual patients.
3. Assure appropriate physician participation and input into the decision-making process.
4. Minimise the potential for future interruptions in the supply of medically necessary materials and equipment.
5. Mitigate the consequences of unpredicted disruptions.
6. Enhance the capability of suppliers and end users to respond to interruptions in supply.
7. Establish a clear and appropriate alignment of authority and accountability for the management of medical radioisotopes."

The following is a summary of the strategies presented at the Federal/Provincial/Territorial workshop hosted by Health Canada.

Communications

- A list of key personal were identified- e.g. NM Physicians, Senior NM Technologist, and Radiopharmacy, middle and senior health care sector mangers and key government contacts.
- E-mail communications trees were established.
- Ad hoc teleconferences were held as the crisis evolved.

Efficient Rationing

- Use of more than one Mo-99 generator vendor (there were two major vendors at the time) increased the probability of getting some activity in a given week.
- Maximise use of available activity (i.e. reduce waste due to decay) via:
    - Enhancing volumes when "fresh" generators arrived.
    - Extended weekday shifts (i.e. work into the evening).
    - Weekend shifts.
- Enhanced physician protocolling of requisitions to ensure that patients were prioritised by clinical need titrated against Tc-99m availability taking into account the utility of alternate diagnostic imaging options. Studies which had immediate impact on medical management, and for which NM was the ideal choice, were preferentially selected. An example would be pre-surgery sentinel lymph

node studies for breast cancer patients or gated cardiac studies (MUGA) prior to cancer chemotherapy.

- Sharing available activity between sites allowed for priority to be given to higher risk acute patients versus elective studies.
- Stratify response to the local, regional or provincial levels depending on the level of shortages.
- Prioritising NM studies to be done at tertiary care sites reduced loss of activity due to multisite distribution and decay during transportation.
- Co-ordination with other imaging modalities (e.g. US, CT and MRI) to ensure enhanced capacity to accommodate increased demand (e.g. CT pulmonary angiograms versus NM VQ scan to rule out pulmonary embolism).

Thinking outside the box

- Manitoba (MB) was the only Canadian Province to seek alternate Mo-99 generator sources outside of the normal commercial supply chain. Mo-99 generators were sourced from Argentina and, from a regulatory point of view, this was made possible due to the ability of the Winnipeg central radiopharmacy to conduct all required quality assurance testing and prove the product met the United States Pharmacopeia standards for Mo-99 / Tc-99m. This strategy considerably ameliorated the impact of isotope shortages in MB.

Regulatory

- Health Canada streamlined emergency access and approval for products not yet licensed in Canada (e.g. ^{18}F as NaF, for bone scans).
- Health Canada also made the drug Special Access Program (SAP) more efficient for “orphaned” radiopharmaceuticals. These radiopharmaceuticals, such as mebrofenin (used for liver imaging) and DMSA (used for kidney imaging) have relatively small markets in Canada and supply chains are not as stable as other NM radiopharmaceutical kits. At the time an SAP application was required for each patient which did not allow for efficient scheduling and batching of product/activity. A request was made for a generic “future use” SAP and this was generally well received by the regulator.
- The Government of Canada ensured co-operation that would allow the planning of preventive maintenance closures of major ^{99}Mo sources/reactors to prevent avoidable shortages in global supply.

Key challenges

- Short shelf life depending on the produced radiopharmaceutical.
- Transportation challenges (e.g. ground, air and ferry transport), especially during inclement weather.
- Uncertainty regarding the length of the NRU outage.
- Complicated, and at times limited, timely communication between various jurisdictions during the medical isotope shortage crisis.

Europe

European NM providers were faced with a 20% – 40% reduction in the delivery of NM studies. This was due to the simultaneous unexpected shutdown of the NRU combined with a planned shutdown of the HFR

in Petten.[2] One of the lessons learnt from this medical isotope crisis was to globally co-ordinate planned preventive maintenance time to minimise the effects on supply.

As an outcome the European Commission and stakeholders established on 29 June 2012 a **European Observatory on the Supply of Medical Radioisotopes**, aimed at bringing together all relevant information to the decision makers in the EU institutions and national governments in order to assist them in defining strategies and policies for their implementation.[3]

The European Observatory general strategic objectives are:[3]

- "to support secure Mo-99/Tc-99m supply for the medium and long term, across the EU taking into account the worldwide need and supply,
- to ensure that the Mo-99/Tc-99m supply issue is given high political visibility in international and national institutions, organisations and bodies,
- to encourage the creation of a sustainable economic structure of the Mo-99/Tc-99m supply chain through supporting the implementation of the full-cost recovery methodology developed by OECD/NEA High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR),
- to establish periodic reviews of the Mo-99/Tc-99m supply chain and capacities, with all stakeholders across the EU, taking into account the worldwide needs and supply capacities, and to forecast future needs."

Nuclear Medicine Europe (NMEu) through their Security of Supply Working Group have partnered with the European Commission and regularly monitor the planning and availability of irradiation and processing capacity and work to mitigate risks such as the recent temporary supply interruptions at the NTP Radioisotopes (South Africa) production facility.

Global

In 2009, the OECD Nuclear Energy Agency (NEA) established the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR). The OECD/NEA Steering Committee for Nuclear Energy subsequently confirmed its support for the policy approach suggested by the HLG-MR, which is based on the following six principles: [4]

Principle 1: All 99mTc supply chain participants should implement full-cost recovery, including costs related to capital replacement.

Principle 2: Reserve capacity should be sourced and paid for by the supply chain. A common approach should be used to determine the amount of reserve capacity required and the price of reserve capacity options.

Principle 3: Recognising and encouraging the role of the market, governments should:

- Establish the proper environment for infrastructure investment;
- Set the rules and establish the regulatory environment for safe and efficient market operation;
- Ensure that all market-ready technologies implement full-cost recovery methodology; and
- Refrain from direct intervention in day-to-day market operations as such intervention may hinder long-term security of supply.

These changes should occur expeditiously, recognising however that time will be required to allow for the market to adjust to the new pricing paradigm.

Principle 4: Given their political commitments to non-proliferation and nuclear security, governments should provide support, as appropriate, to reactors and processors to facilitate the conversion of their facilities to

low enriched uranium or to transition away from the use of highly enriched uranium, wherever technically and economically feasible.

Principle 5: International collaboration should be continued through a policy and information sharing forum, recognising the importance of a globally consistent approach to addressing security of supply of 99Mo/99mTc and the value of international consensus in encouraging domestic action.

Principle 6: There is a need for periodic review of the supply chain to verify whether 99Mo/99mTc producers are implementing full-cost recovery and whether essential players are implementing the other approaches agreed by the HLG-MR, and that the co-ordination of operating schedules or other operational activities have no negative effects on market operations.

The OECD/NEA Steering Committee for Nuclear Energy called on governments and industry to work together to implement these principles in a timely and effective manner, recognising the need for an internationally consistent approach to ensure the long-term secure supply of medical radioisotopes.

Eleven countries (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) signed a Joint Declaration on the Security of Supply of Medical Radioisotopes "which seeks to ensure the security of supply of the most widely used medical radioisotope, molybdenum-99 (^{99}Mo)."[5]

"WE COMMIT, with the aim of jointly promoting an internationally consistent approach to ensuring the long-term secure supply of medical radioisotopes, to implement the HLG-MR principles in a timely and effective manner, and to:

- Take co-ordinated steps, within our countries' powers, to ensure that ^{99}Mo or ^{99m}Tc producers and, where applicable, generator manufacturers in our countries implement a verifiable process for introducing full-cost recovery at all facilities that are part of the global supply chain for ^{99m}Tc;
- Encourage the necessary actions undertaken by ^{99}Mo processing facilities or ^{99m}Tc producers in our countries to ensure availability of reserve capacity capable of replacing the largest supplier of irradiated targets in their respective supply chain;
- Take the necessary actions to facilitate the availability of ^{99m}Tc, produced on an economically sustainable basis, as outlined in the HLG-MR principles;
- Encourage all countries involved in any aspect of the ^{99m}Tc supply chain, and that are not party to the present Joint Declaration, to take the same approach in a co-ordinated manner;
- Take the necessary actions described above by the end of December 2014 or as soon as technically and contractually feasible thereafter, aware of the need for early action to avoid potential shortages of medical radioisotopes that could arise from 2016;"

To report on an annual basis to the OECD Nuclear Energy Agency (NEA) on the progress made at the national level and support an annual review of the progress made at the international level, both in light of this Joint Declaration."[5]

The NEA has formed the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) which is referenced in the third bullet above. The HLG-MR has the main objective "…to strengthen the reliability of ^{99}Mo and ^{99m}Tc supply in the short, medium and long term…" and has broad representation from producing and end-user countries and agencies such as the European Commission (Euratom Supply Agency) and the International Atomic Energy Agency (IAEA).[5]

Annex B. NM Diagnostic activity by country – Data sources and comparability

Estimates of the number of procedures in Chapter 2 are collated from various sources described in the table below. Some estimates include all NM diagnostic procedures for which the use of Tc-99m is possible (single- and multi-phase planar scintigraphies, SPECT and SPECT/CT), irrespective of the radioisotope actually used, while some estimates only include procedures using Tc-99m. All estimates exclude NM diagnostic procedures for which the use of Tc-99m can be ruled out (e.g. PET).

Estimates in of the proportion of procedures by organ system in Chapter 2 are based on the same data sources and described below. For Australia, only Medicare statistics are used to estimate the proportion of scans by organ systems; no data are available on activity in public hospitals and other providers that are not subsidised by Medicare.

Table A B.1. Data on the number of NM diagnostic scans by country

Data sources and comparability

Country	Year	Source	Notes
Australia	2017	Medicare Statistics 2018; ANSTO press releases	Includes all NM diagnostic procedures subsidised by Medicare, based on MBS items in "Group:I4 Nuclear Medicine Imaging." MBS billing codes are not always specific to the isotope used; excludes MBS items for which use of Tc-99m can be ruled out. Medicare assumed to represent 70% of total (excluding scans in public hospitals), based on ANSTO estimates of Australian Tc-99m market size.
Austria	2007-10	European Commission RP Report 180	Tc-99m only
Belgium	2015-17	OECD HD survey, estimated based on several national surveys	Excludes services where radioisotope can be identified as non-Tc-99m.
Canada	2015-17	CADTH The Canadian Medical Imaging Inventory 2017; OECD HD survey	CADTH reports number of SPECT and SPECT-CT scans by province and for all of Canada; sum of SPECT and SPECT-CT assumed to represent 65% of total based on SPECT and SPECT-CT reported by CADTH and total number of NM scans in BC and Manitoba reported in OECD Health Division Survey. Tc-99m assumed to represent 85% of total.
Czech Republic	2007-10	OECD HD survey	Tc-99m only
Denmark	2007-10	EC RP180	Tc-99m only
Estonia	2007-10	EC RP180	Tc-99m only
Finland	2007-10	EC RP180	Tc-99m only
France	2017	L'Assurance Maladie	Includes all NM diagnostic scans per the national nomenclature of medical procedures CCAM in in- and out-patient settings of private and public providers, except PET. Tc-99m assumed to

Country	Year	Source	Notes
			represent 85% of total.
Germany	2015	Hellwig et al. 2017 based on national KBV and G-DRG statistics	All outpatient NM diagnostic procedures paid by SHI except PET, and inpatient scintigraphy, SPECT and SPECT/CT procedures coded to G-DRGs. Outpatient activity broken down by isotope; data on inpatient activity does not isolate Tc-99m. Outpatient SHI sector assumed to represent 90% of total SHI and private insurance activity.
Greece	2007-10	EC RP180	Tc-99m only
Hungary	2007-10	EC RP180	Tc-99m only
Ireland	2007-10	EC RP180	Tc-99m only
Italy	2007-10	EC RP180	Tc-99m only
Japan	2017	Subcommittee on Survey of Nuclear Medicine Practice in Japan, Report of the 8th Nationwide Survey in 2017	Tc-99m only, representing 61% of all NM diagnostic scans excl. PET.
Latvia	2017	OECD HD survey	Tc-99m only
Lithuania	not specified	OECD HD survey	Tc-99m only; midpoint of range provided in response to OECD Health Division survey (5 800 to 6 400 Tc-99m scans / per year).
Luxembourg	2016	OECD HD survey	All NM diagnostic procedures excl. PET. Tc-99m assumed to represent 85% of total.
Netherlands	2015	OECD HD survey	Tc-99m only; all NM diagnostic procedures excl. PET based on results of a national provider survey provided by respondents to the OECD HD survey. Tc-99m assumed to represent 85% of total.
Poland	2007-10	EC RP180	Tc-99m only
Portugal	2007-10	EC RP180	Tc-99m only
Slovak Republic	2007-10	EC RP180	Tc-99m only
Slovenia	not specified	OECD HD survey	Tc-99m only
Spain	2007-10	EC RP180	Tc-99m only
Sweden	2017	OECD HD survey	Tc-99m only
United Kingdom (England)	FY 2016/17	NHS England Diagnostic Imaging Dataset	All Tc-99m scans in NHS hospitals (in- and outpatient). England assumed to represent 85% of UK total based on population.
United States	2014	IMV 2015 Nuclear Medicine Benchmark Report	Based on IMV Medical Information Division 2015 survey of U.S. hospitals and non-hospitals that perform NM procedures using fixed SPECT/CT, SPECT, and planar only cameras. A total of 407 respondents, 283 from hospitals and 124 from non-hospital locations, extrapolated to a provider population of 7 091 sites (4 040 hospitals and 3 051 non-hospital locations). Tc-99m assumed to represent 85% of total.

Annex C. OECD Health Division Survey on Health Care Provider Payment for Nuclear Medicine Diagnostic Services

The initial geographic scope of this study was defined as the 23 countries that are members of the European Union and the OECD as well as Australia, Canada, Japan and the United States. An invitation to nominate respondents to the OECD Health Division Survey on Health Care Provider Payment for Nuclear Medicine Diagnostic Services was sent in January 2018 all country delegates in the OECD Health Committee. Respondents were nominated in 26 countries, including 22 countries in the initial scope and Iceland, Israel, Norway and Switzerland. All nominated respondents were contacted between April and June 2018. By September 2018, responses were submitted by respondents from 16 countries, including 15 countries that were in the initial geographic scope of the study and Switzerland. Details are presented in the table below.

Table A C.1. Responses to OECD Health Division Survey

	Country	Respondent identified	Response received
In initial scope	Australia	**Yes**	**Yes**
	Austria	**Yes**	No
	Belgium	**Yes**	**Yes**
	Canada	**Yes**	**Yes**
	Czech Republic	**Yes**	**Yes**
	Denmark	**Yes**	**Yes**
	Estonia	**Yes**	No
	Finland	No	No
	France	**Yes**	**Yes**
	Germany	**Yes**	**Yes**
	Greece	No	No
	Hungary	No	No
	Ireland	**Yes**	No
	Italy	**Yes**	No
	Japan	**Yes**	**Yes**
	Latvia	**Yes**	**Yes**
	Lithuania	**Yes**	**Yes**
	Luxembourg	**Yes**	**Yes**
	Netherlands	**Yes**	**Yes**
	Poland	**Yes**	**Yes**
	Portugal	No	No
	Slovakia	No	No
	Slovenia	**Yes**	**Yes**
	Spain	**Yes**	No
	Sweden	**Yes**	**Yes**

	Country	Respondent identified	Response received
	United Kingdom (England)	**Yes**	**Yes**
	United States	**Yes**	No
	N of "Yes" of countries in initial scope	***22***	***16***
	% of countries in initial scope	*81%*	*59%*
Not in initial scope	*Chile*	*No*	*No*
	Iceland	***Yes***	*No*
	Israel	***Yes***	*No*
	Korea	*No*	*No*
	Mexico	*No*	*No*
	New Zealand	*No*	*No*
	Norway	***Yes***	*No*
	Switzerland	***Yes***	***Yes***
	Turkey	*No*	*No*
	Total N of "Yes"	***26***	***17***
	% of all OECD countries	*72%*	*47%*

Source: OECD Health Division survey.

Annex D. Current unbundled Tc-99m payments in Germany and Japan

Germany

Table A D.1. Unbundled Tc-99m billing codes and prices for office-based specialists paid FFS according to the German national uniform value scale (EBM)

EBM Version 3rd quarter 2018

EBM Billing Code	Description	Price (EUR)
40500	Material costs related to the provision of services in accordance with EBM billing codes 17310 or 17320 when using 99mTc pertechnetate (thyroid)	1.50
40502	Material costs related to the provision of services in accordance with EBM billing codes 17310 or 17311 when using 99mTc phosphonates (bone / skeleton)	19.00
40504	Material costs related to the provision of the service according to the EBM billing code 17310 using 99mTc macroaggregates (lung)	29.00
40506	Material costs related to the provision of the service according to EBM billing code 17310 using 99mTc aerosol (lung)	133.00
40508	Material costs related to the provision of the service according to the EBM billing code 17310 using 99mTc-HMPAO, 99mTc-ECD (brain)	205.00
40510	Material costs related to the provision of services according to the EBM billing codes 17310 or 17340 when using 99mTc-DMSA, 99mTc-DTPA (kidney)	40.00
40512	Material costs related to the provision of the service according to according to the EBM billing code 17310 using 99mTc-DTPA (brain)	40.00
40514	Material costs related to the provision of the service according to the EBM billing code 17340 when using 99mTc-MAG3 (kidney)	92.00
40516	Material costs related to the provision of services according EBM billing codes 17310 or 17351 using 99mTc colloid (liver)	42.00
40518	Material costs related to the provision of the service according to EBM billing code 17351 using 99mTc IDA compounds (bile)	42.00
40520	Material costs related the provision of services according to EBM billing codes 17330, 17331 and 17310 using 99mTc-labeled perfusion markers (heart, thyroid)	76.00
40522	Material costs related to the provision of services according to EBM billing codes 17332, 17333 and 17350 using of 99mTc-labeled auto-erythrocytes (heart, liver, abdominal bleed search)	60.00
40524	Material costs related to the provision of services according to EBM billing codes 17310 or 17311 when using 99mTc-labeled ligands (tumor localization)	375.00
40526	Material costs related to the provision of services according to EBM billing codes 17310, 17311 or 17350 using 99mTc-labeled antibodies (bone marrow, inflammation localization)	382.00
40528	Material costs related to the provision of services according to EBM billing codes 17310 or 17311 using 99mTc-labeled micro- / nanocolloids (lymph node diagnostics)	70.00
40530	Material costs related to the provision of the service according EBM billing code 17351 using a 99mTc-labeled test meal (gastrointestinal motility)	40.00

Note: Prices reflect national reference values and may vary by federal state.
Source: Translated by the Authors from the German national uniform value scale (EBM) (KBV, 2018, pp. 220-21[1])

Japan

Table A D.2. Radiopharmaceutical products and reimbursement prices in the national fee schedule

Pharmaceutical name	Company name	Standard unit	2018 price (JPY)
Asialoscinti Injectable	Nihon Medi-Physics Co., Ltd	10MBq	826
Ultra-Techne Kow	FUJIFILM Toyama Chemical Co., Ltd.	10MBq	261
Cardiolite Daiichi	FUJIFILM Toyama Chemical Co., Ltd.	One dose	29 764
Cardiolite injection Daiichi	FUJIFILM Toyama Chemical Co., Ltd.	370MBq/syringe	25 333
		600MBq/syringe	48 683
		740MBq/syringe	50 115
Sodium Pertechnetate (99mTc) Injection		10MBq	280
Technescinti Injectable - 20M	Nihon Medi-Physics Co., Ltd	10MBq	280
Technesol	FUJIFILM Toyama Chemical Co., Ltd.	10MBq	280
Technescinti Injectable - 10M	Nihon Medi-Physics Co., Ltd	10MBq	284
Kidneyscinti Kit	Nihon Medi-Physics Co., Ltd	One dose	3 127
Kidneyscinti Tc-99m Injectable	Nihon Medi-Physics Co., Ltd	10MBq	660
Clearbone Kit	Nihon Medi-Physics Co., Ltd	One dose	3 304
Clearbone Injectable	Nihon Medi-Physics Co., Ltd	10MBq	397
Tin Colloid Tc-99m Injectable	Nihon Medi-Physics Co., Ltd	10MBq	N/A
Tin Colloid Tc-99m Kit	Nihon Medi-Physics Co., Ltd	One dose	2 643
Cerebrotec Kit	Nihon Medi-Physics Co., Ltd	One dose	20 939
Techne Albumin Kit	FUJIFILM Toyama Chemical Co., Ltd.	One dose	4 251
Techne MAA Kit	FUJIFILM Toyama Chemical Co., Ltd.	One dose	4 237
Techne MAG3 Kit	FUJIFILM Toyama Chemical Co., Ltd.	One dose	25 443
Techne MAG3 Injection	FUJIFILM Toyama Chemical Co., Ltd.	200MBq/syringe	23 564
		300MBq/syringe	34 652
		400MBq/syringe	45 674
Techne MDP Kit	FUJIFILM Toyama Chemical Co., Ltd.	One dose	3 086
Techne MDP Injection	FUJIFILM Toyama Chemical Co., Ltd.	370MBq/syringe	21 566
		555MBq/syringe	21 566
		740MBq/syringe	28 495
		925MBq/syringe	36 762
Techne DMSA Kit	FUJIFILM Toyama Chemical Co., Ltd.	One dose	3 116
Techne DTPA Kit	FUJIFILM Toyama Chemical Co., Ltd.	One dose	3 110
Techne Pyrophosphate Kit	FUJIFILM Toyama Chemical Co., Ltd.	One dose	3 110
Techne Phytate Kit	FUJIFILM Toyama Chemical Co., Ltd.	One dose	2 545
Neurolite Daiichi	FUJIFILM Toyama Chemical Co., Ltd.	One dose	18 389
Neurolite Injection Daiichi	FUJIFILM Toyama Chemical Co., Ltd.	400MBq/syringe	28 697
		600MBq/syringe	43 506
Poolscinti Injectable	Nihon Medi-Physics Co., Ltd	10MBq	570
Hepatimage Injectable	Nihon Medi-Physics Co., Ltd	10MBq	796
Myoview for Injection	Nihon Medi-Physics Co., Ltd	One dose	29 556
Myoview Injectable Syringe	Nihon Medi-Physics Co., Ltd	296MBq/syringe	23 795
		592MBq/syringe	43 401
		740MBq/syringe	48 247
MAGscinti Injectable	Nihon Medi-Physics Co., Ltd	222MBq/syringe	23 514
		333MBq/syringe	34 534
		555MBq/syringe	56 655
Meditec	Nihon Medi-Physics Co., Ltd	10MBq	272
Lungscinti Tc-99m Injectable	Nihon Medi-Physics Co., Ltd	10MBq	531

Note: Status per March 5, 2018 (Notification No. 46 of Ministry of Health, Labour and Welfare), Implementation April 1, 2018.
Source: OECD Health Division survey, translated by the Authors from Japanese. The national fee schedule is available at https://www.mhlw.go.jp/topics/2018/04/tp20180401-01.html

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The Supply of Medical Isotopes

AN ECONOMIC DIAGNOSIS AND POSSIBLE SOLUTIONS

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