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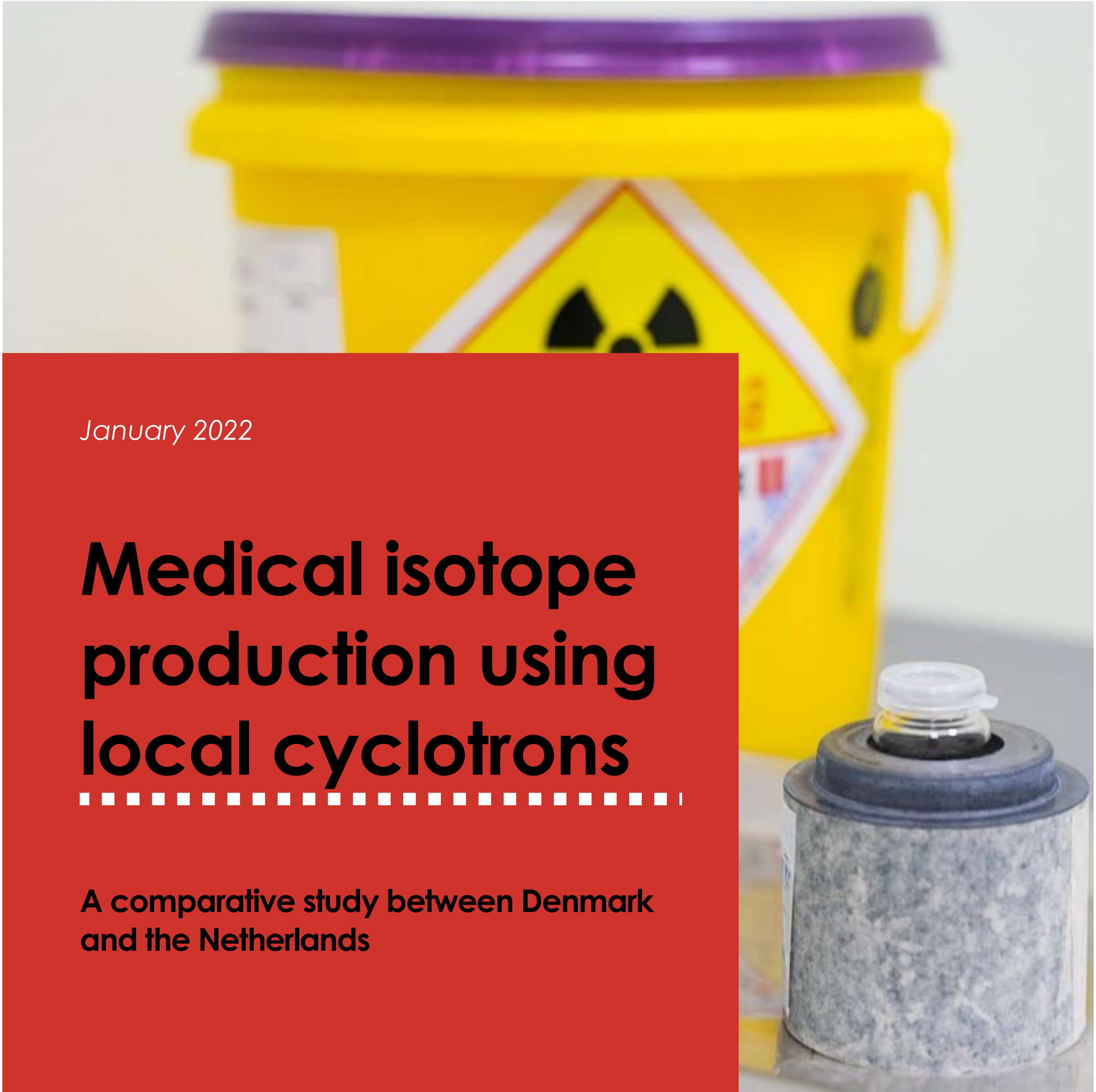

January 2022

Medical isotope production using local cyclotrons

A comparative study between Denmark and the Netherlands

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In opdracht van het Ministerie van Volksgezondheid, Welzijn en Sport heeft Technopolis Group een vergelijkend onderzoek uitgevoerd naar de productie van medische isotopen met cyclotrons in Denemarken en Nederland. De situatie in Denemarken is onderzocht, omdat Denemarken de hoogste dichtheid van cyclotrons (aantal cyclotrons per miljoen inwoners) heeft in Europa, driemaal hoger dan in Nederland. Daarnaast heeft Denemarken geen andersoortige bestralingsfaciliteiten voor de productie van medische isotopen dan cyclotrons. Op basis van deze vergelijking heeft Technopolis onderzocht in hoeverre een situatie zoals in Denemarken een interessant scenario voor Nederland kan zijn zodra de Hoge Flux Reactor (HFR) in Petten sluit, en welke implicaties en investeringen dat met zich mee zou brengen.

Uit het onderzoek blijkt dat het aantal medische cyclotrons dat in Denemarken is geïnstalleerd, gelijk is aan het aantal cyclotrons in Nederland. Deze cyclotrons zijn vooral geplaats in ziekenhuizen. De hogere dichtheid van cyclotrons volgt uit het feit dat Denemarken een lagere bevolkingsomvang heeft dan Nederland. Dat er relatief meer cyclotrons per hoofd van de bevolking zijn, komt enerzijds door een regionaal gezondheidssysteem en anderzijds doordat landen met vergelijkbare landoppervlakte evenveel cyclotrons nodig hebben om kortlevende, tijdskritische medische isotopen efficiënt te transporteren naar ziekenhuizen verspreid over het land.

De hoge dichtheid van cyclotrons in Denemarken is niet ingegeven vanuit de ambitie om zelfvoorzienend te zijn in de productie van medische isotopen, maar vanuit ambities op het gebied van verbeterde opsporing van kanker. Denemarken heeft voor verbeterde opsporing van kanker ingezet op een grotere beschikbaarheid van PET-scanners. Dat heeft geleid tot een toename van het aantal PET-scanners en cyclotrons in het afgelopen decennium – een trend die overigens ook in Nederland zichtbaar is vanwege de superieure beeldkwaliteit van PET in de meeste diagnostische onderzoeken. Cyclotrons kunnen echter maar een beperkt palet van medische isotopen produceren, voornamelijk voor diagnostische doeleinden. Hierdoor is volledig zelfvoorzienend zijn in medische isotopen in Denemarken niet mogelijk, zeker niet voor therapeutische doeleinden.

Voor medische isotopen die niet in cyclotrons geproduceerd kunnen worden, is Denemarken volledig afhankelijk van buitenlandse levering (bijvoorbeeld vanuit Nederland). De levering van deze reactor-geproduceerde medische isotopen voor diagnostiek en therapie is doorgaans betrouwbaar. Men heeft daarom ook nooit gestreefd naar substitutie, hoewel er tijdens de Molybdeen/Technetium Crises, in de eerste decennia van deze eeuw, SPECT-diagnostiek (met reactorisotopen) deels vervangen is door PET-diagnostiek.

Denemarken heeft geen nationale mitigatiestrategie voor tekorten aan medische isotopen. Eventuele tekorten worden ad-hoc opgelost tussen ziekenhuizen en gezondheidsregio's. Er is nooit serieus overwogen om technetium-99m (^{99m}Tc), de meeste gebruikte reactor-geproduceerde SPECT-isotoop[1], met cyclotrons te produceren – voornamelijk vanuit praktische, regulatoire en economische redenen. Vanwege de afhankelijkheid van het buitenland voor diverse medische isotopen en de onzekere toekomstplannen van nieuwe nucleaire onderzoeksreactoren in Europa, uitten geïnterviewde experts uit Denemarken zorgen over de toekomstige leveringszekerheid van medische isotopen.

[1] In nucleaire onderzoeksreactoren wordt molybdeen-99 (^{99}Mo) geproduceerd, wat vervalt tot ^{99m}Tc. ^{99}Mo heeft een langere halfwaardetijd (66 uur) en kan daardoor internationaal gedistribueerd worden als generator waaruit ziekenhuizen het vervalproduct ^{99m}Tc kunnen elueren ('aftappen').

Voor diagnostiek in de klinische praktijk in Nederland zal door vervanging van SPECT door PET meer gebruik gemaakt (kunnen) worden van medische isotopen die met cyclotrons geproduceerd worden. Voor de groeiende mogelijkheden van medische isotopen voor therapeutische doeleinden is het doorgaans echter niet mogelijk om meer gebruik te maken van cyclotron-geproduceerde medische isotopen.

Een situatie zoals in Denemarken, waarbij Nederland alleen een netwerk van cyclotrons heeft voor het produceren van medische isotopen (voor PET), zou Nederland meer afhankelijk maken van buitenlandse producenten van medische isotopen (voor andere doeleinden dan PET). De onzekerheid rondom vervangende bestralingscapaciteit voor de HFR in Europa, maakt het bovendien aannemelijk dat de leveringszekerheid van diverse medische isotopen niet gegarandeerd is. Het huidige cyclotronnetwerk in Nederland volstaat voor de levering van PET-isotopen in Nederland – een hogere dichtheid van cyclotrons is niet nodig.

Overheidsinvesteringen in cyclotrons liggen alleen voor de hand indien er niet geïnvesteerd wordt in een vervanger van de HFR (d.w.z. Pallas) en er een politieke keuze wordt gemaakt om enkele andere medische isotopen met cyclotrons te produceren (voornamelijk technetium-99m zoals in Canada) om zo minder afhankelijk te zijn van buitenlandse levering. Daarvoor is nog flink wat innovatie nodig. Daarnaast vereist het investeringen in enkele grotere cyclotrons in Nederland, investeringen die kunnen oplopen tot €120m. Die investeringen zullen niet door de markt worden opgepakt, omdat het produceren van dergelijke isotopen – in de huidige markt – economisch niet interessant is.

De belangrijkste conclusies die volgen uit deze studie zijn:

- **De cyclotronnetwerken in Denemarken en Nederland zijn verschillend, maar vergelijkbaar in omvang en beide toereikend voor de binnenlandse vraag naar PET-isotopen**. Zonder de ambitie om een breder palet aan medische isotopen te produceren met cyclotrons (d.w.z. innovatie) is er geen noodzaak tot investeringen in additionele cyclotrons in Nederland.
- **Een situatie zoals in Denemarken, waarbij medische isotopen alleen met cyclotrons worden geproduceerd, is geen volwaardig alternatief voor de productie van medische isotopen met een nieuwe onderzoeksreactor.** Cyclotrons zijn primair geschikt voor de productie van PET-isotopen en kunnen diverse, vanuit medisch perspectief belangrijke, (m.n. therapeutische) isotopen niet produceren. Daarvoor blijft een nucleaire reactor noodzakelijk.
- **Productie van medische isotopen met alleen cyclotrons (d.w.z. geen Nederlandse onderzoeksreactor), maakt Nederland meer afhankelijk van de buitenlandse levering van diverse medische isotopen.** Gezien de noodzaak voor nieuwe reactorcapaciteit in Europa om de levering van medische isotopen veilig te stellen, is het aannemelijk dat dit ook voor Nederland zal leiden tot verminderde leveringszekerheid van diverse medische isotopen na het volgende decennium.

Technopolis komt op basis hiervan tot de volgende drie aanbevelingen voor het Ministerie van Volksgezondheid, Welzijn en Sport:

- **Investeer alleen in cyclotron-infrastructuur indien het doel is om innovatie naar alternatieve productieroutes voor medische isotopen te stimuleren.** Dit zal waarschijnlijk niet door de markt worden opgepakt.
- **Behoud een internationaal perspectief bij het nemen van besluiten voor investeringen in bestralingsfaciliteiten voor medische isotopen.** Terugvallen op alleen een cyclotronnetwerk in Nederland vereist dat andere initiatieven voor de productie van medische isotopen in Europa het gat dat de HFR achterlaat vullen. Dat is uiterst onzeker en vormt een risico voor de leveringszekerheid van medische isotopen in Europa en Nederland.

- **Focus op het verbeteren van de toegang tot PET-diagnostiek in Nederland**. Niet alleen vanwege betere diagnostiek voor de patiënt, maar ook om de afhankelijkheid van buitenlandse levering van medische isotopen voor diagnostiek te beperken indien nodig.

Management summary

Commissioned by the Ministry of Health, Welfare and Sport, Technopolis Group conducted a comparative study into the production of medical isotopes with cyclotrons in Denmark and the Netherlands. The situation in Denmark was studied because Denmark has the highest density of cyclotrons (number of cyclotrons per million population) in Europe, three times higher than in the Netherlands. In addition, Denmark has no other types of irradiation facilities to produce medical isotopes than cyclotrons. Based on this comparison, Technopolis investigated to what extent a situation like the one in Denmark could be an interesting scenario for the Netherlands once the High Flux Reactor (HFR) in Petten closes, and what implications and investments that would entail.

The study shows that the number of medical cyclotrons installed in Denmark is equal to the number of cyclotrons in the Netherlands. These cyclotrons are mainly placed in hospitals. The higher density of cyclotrons follows from the fact that Denmark has a lower population size than the Netherlands. The fact that there are relatively more cyclotrons per capita is partly due to a regional healthcare system and partly because countries with a similar land area need the same number of cyclotrons to efficiently transport short-lived, time-critical medical isotopes to hospitals spread across the country.

The high density of cyclotrons in Denmark is not motivated by the ambition to be self-sufficient in the production of medical isotopes, but by ambitions in the field of improved cancer detection. Denmark has focused on increasing the availability of PET scanners for improved cancer detection. This has led to an increase in the number of PET scanners and cyclotrons in the past decade - a trend that is also visible in the Netherlands, due to the superior image quality of PET in most diagnostic examinations. However, cyclotrons can only produce a limited range of medical isotopes, esp. for diagnostic purposes. This means that complete self-sufficiency in medical isotopes is not possible in Denmark, certainly not for therapeutic purposes.

For medical isotopes that cannot be produced in cyclotrons, Denmark is fully dependent on foreign supply (e.g. from the Netherlands). The supply of these reactor-produced medical isotopes for diagnostics and therapy is usually reliable. Therefore, substitution has never been the ambition, although during the Molybdenum/Technetium Crises, in the first decades of this century, SPECT diagnostics (with reactor isotopes) was partly replaced by PET diagnostics.

Denmark has no national mitigation strategy for medical isotope shortages. Any shortages are solved ad hoc between hospitals and health regions. Cyclotron production of technetium-99m (^{99m}Tc), the most widely used reactor-produced SPECT isotope[2], has never been seriously considered – mainly for practical, regulatory, and economic reasons. Because of the dependence on foreign sources for various medical isotopes and the uncertain future plans for new nuclear research reactors in Europe, interviewed Danish experts expressed concerns about the future security of supply of medical isotopes.

For diagnostics in clinical practice in the Netherlands, the replacement of SPECT by PET will mean more use of medical isotopes produced with cyclotrons. However, for the growing

[2] In nuclear research reactors, molybdenum-99 (^{99}Mo) is produced, which decays to ^{99m}Tc. ^{99}Mo has a longer half-life (66 hours) and can therefore be distributed internationally in a generator from which hospitals can elute ('tap') the decay product ^{99m}Tc.

possibilities of medical isotopes for therapeutic purposes, it is in most cases not possible to make more use of cyclotron-produced medical isotopes.

A situation as in Denmark, where the Netherlands only has a network of cyclotrons to produce medical isotopes (for PET), would make the Netherlands more dependent on foreign producers of medical isotopes (for purposes other than PET). Moreover, the uncertainty surrounding replacement irradiation capacity for the HFR in Europe makes it likely that the security of supply for various medical isotopes is not guaranteed. The current cyclotron network in the Netherlands is sufficient for the supply of PET isotopes in the Netherlands – a higher density of cyclotrons is not needed.

Public investment in cyclotrons only makes sense if there is no investment in a replacement for the HFR (i.e. Pallas) and if a political choice is made to produce some non-PET medical isotopes with cyclotrons (mainly technetium-99m as in Canada) to be less dependent on foreign supply. This still requires a lot of innovation. It also requires investments in a few larger cyclotrons in the Netherlands, which would involve investments of up to €120m. These investments are not taken up by the market because producing such isotopes is – in the current market – not economically interesting.

The main conclusions that follow from this study are:

- **The cyclotron networks in Denmark and the Netherlands are different, but similar in size and both sufficient for the national supply of PET isotopes**. Without the ambition to produce a wider range of medical isotopes with cyclotrons (i.e. innovation), there is no need to invest in additional cyclotrons in the Netherlands.
- **A situation such as in Denmark, in which medical isotopes are produced in cyclotrons only, is not a full alternative for a new nuclear research reactor for medical isotope production**. Cyclotrons are primarily suitable to produce PET isotopes and cannot produce various (esp. therapeutic) isotopes that are important from a medical perspective. For this a nuclear reactor remains necessary.
- **Cyclotron-only production of medical isotopes (i.e. no Dutch research reactor) will make the Netherlands more dependent on foreign supply for various medical isotopes, as is the case in Denmark**. In view of the need for new reactor capacity in Europe to secure the supply of medical isotopes, it is likely that this will also result in reduced security of supply of various medical isotopes for the Netherlands beyond the next decade.

Based on this, Technopolis has come to the following three recommendations for the Ministry of Health, Welfare and Sport:

- **Invest only in cyclotron infrastructure if one wishes to promote innovation into alternative production routes for medical isotopes**. This is unlikely to be taken up by the market.
- **Keep an international perspective when making decisions for investments in medical isotope irradiation facilities**. Falling back on only a cyclotron network in the Netherlands would require other medical isotope production initiatives in Europe to fill the gap of the HFR. This is highly uncertain and poses a risk to the security of supply of medical isotopes in Europe and the Netherlands.
- **Focus on achieving improved access to PET diagnostics in the Netherlands based on patient needs.** Not only for better diagnostics for patients, but also to limit the dependence on foreign supply of medical isotopes for diagnostics if needed.

t

1 Introduction

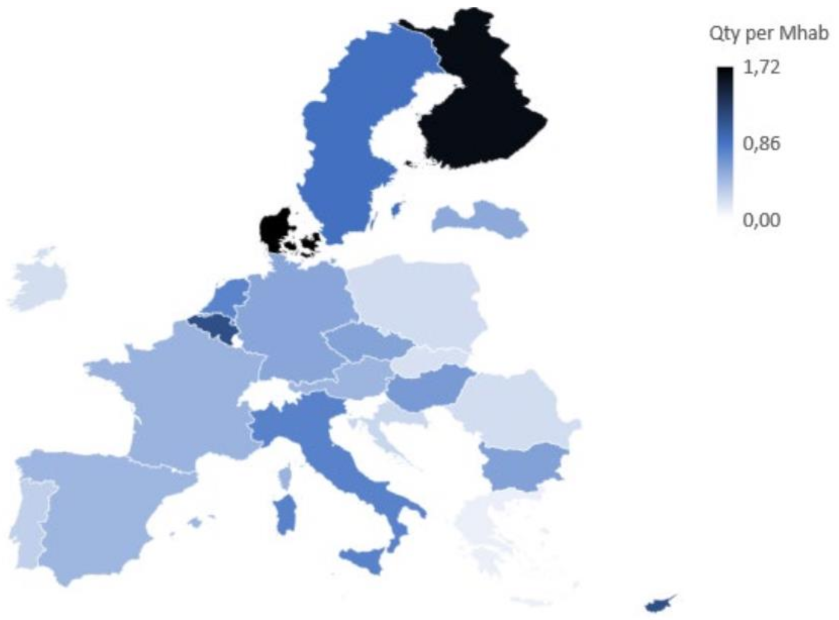
The Ministry of Health, Welfare and Sport has commissioned Technopolis Group to study medical isotope production using local cyclotrons, based on a comparison between Denmark and the Netherlands. The study was conducted between November 2021 and January 2022, using desk research (literature review) and interviews. This report presents the results of the study and Technopolis' conclusions and recommendations to the Ministry.

In this first chapter, we introduce the relevance of comparing Denmark to the Netherlands and some background information on medical isotopes and cyclotrons. In Chapter 2 we zoom in on the situation in Denmark and make some comparisons with the Netherlands. In Chapter 3 we zoom in on the Netherlands and discuss investments and implications of a scenario as in Denmark for the Netherlands. In the final chapter, we provide our conclusions and recommendations, which are followed by the appendices with some additional background information.

1.1 Relevance of the Denmark case to the Netherlands

Denmark is a country with a well-established national cyclotron network. A not very densely populated country, **Denmark has the highest density of cyclotrons per million population in the European Union (EU)** as seen in Figure 1. There are no nuclear reactors producing radioisotopes in Denmark, thus the country relies fully on the local production of isotopes in cyclotrons as well as the import of foreign-produced isotopes.

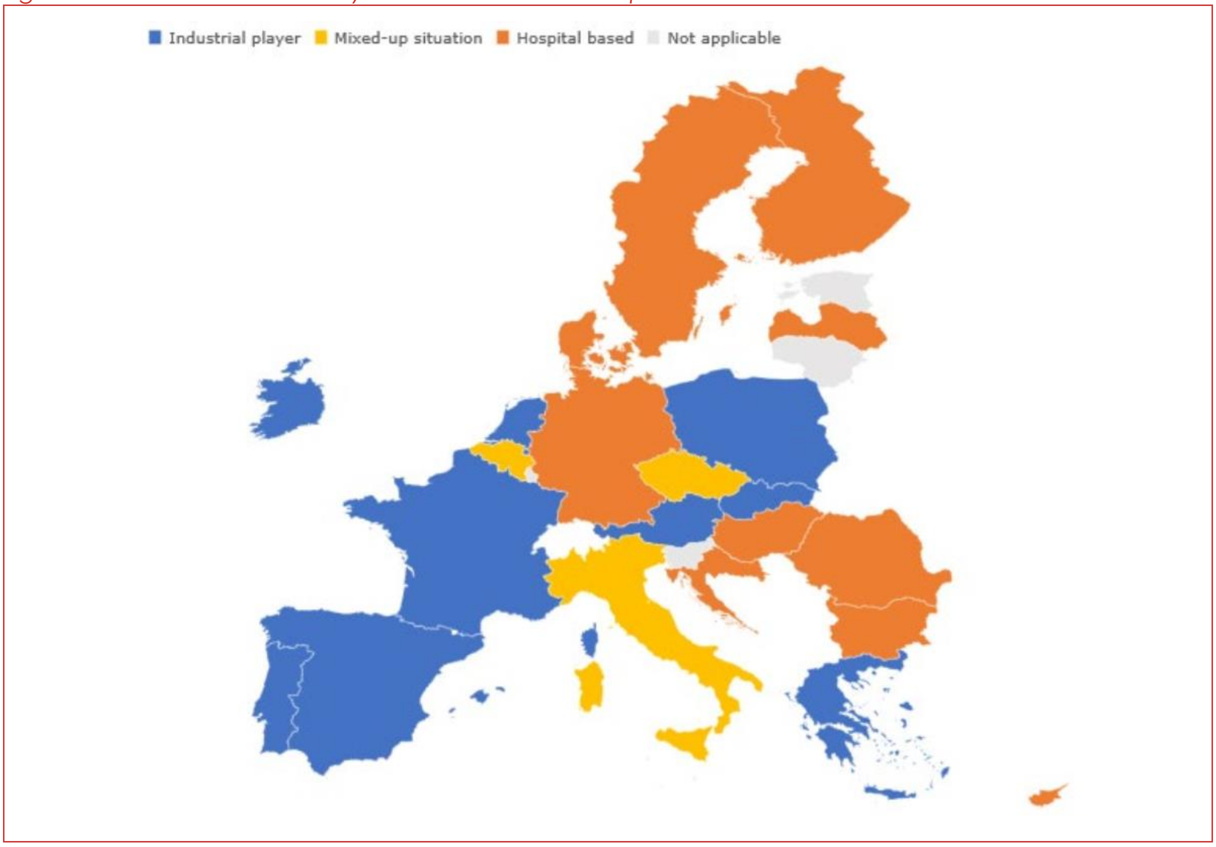
Figure 1 Distribution of cyclotrons per million inhabitants in Europe



Source: NucAdvisor (2021) based on IAEA

In Europe, various schemes for the production of radionuclides in cyclotrons exist (see Figure 2). Denmark has **a hospital-based production of isotopes in cyclotrons** (cyclotrons are decentrally installed in hospitals). The Netherlands follows an industrial player production model (isotopes are mainly produced more centrally in industrial cyclotrons owned by commercial parties and then supplied to hospitals).

Figure 2 Structure of the EU cyclotron network in Europe



Source: NucAdvisor (2021)

Although currently there is a major difference in the density of cyclotrons as well as the type of cyclotron networks between the Netherlands and Denmark, **the Danish model presents an interesting case study, which might become more relevant to the Dutch situation in case the nuclear reactor in Petten will be decommissioned without replacement**. In such a case, the Netherlands may become more reliant on the cyclotron-produced radioisotopes and may benefit from additional cyclotron capacity as in the example of Denmark.

1.2 Background: use of radioisotopes in medicine

The use of radioactive isotopes is the cornerstone of many medical procedures today. Isotopes are used in **diagnostics (imaging)** and **treatment (therapy)** of many diseases, including cardiovascular diseases, cancer, diabetes, lung and respiratory tract conditions and dementia.

The use of radioisotopes for **imaging purposes** is further divided into single-photon emission computed tomography (SPECT) and positron emission tomography (PET).[3] Both techniques use gamma radiation emitted by isotopes to produce images of the distribution of radioactivity in the body. An overview of existing isotopes used in in clinical imaging is provided in Table 1, while their production routes are illustrated in Figure 4.

[3] IAEA (2009). Cyclotron produced radionuclides. Physical characteristics and production methods. Available from: https://www-pub.iaea.org/mtcd/publications/pdf/trs468_web.pdf

Table 1 The most used radioisotopes for imaging

SPECT	PET
^{99m}Tc	^{18}F
^{123}I	^{11}C
^{201}Tl	^{82}Rb
^{67}Ga	^{13}N

Source: IAEA, 2009[3]

Technetium-99m (^{99m}Tc) is used in most SPECT scans, while PET scans primarily use fluorine-18 (^{18}F). PET scanners are generally more expensive to purchase and to operate than SPECT scanners, but the quality of diagnostic images produced in PET scans is superior to those of SPECT, although the latter technology keeps improving. The use of either scan often depends on several factors including quality and appropriateness in each given patient case, price (both costs to health systems, insurers, and the cost to patient), as well as preferences of the medical specialists.[4] Combined use of both technologies for best diagnostic results is also common.

The use of radioisotopes in **therapeutic purposes** is rather limited, however, it has become more prevalent in recent years and is predicted to become even more important as new research in the area takes place. Therapeutic use of radioisotopes is divided into radiotherapy, nuclear medicine therapy and palliative therapy. The main isotopes used for these purposes in Europe are iodine-131 (^{131}I, e.g. used for thyroid diseases and neuroblastoma), lutetium-177 (^{177}Lu, e.g. used for neuroendocrine tumours, lymphoma and prostate cancer) and yttrium-90 (^{90}Y, e.g. used for liver cancer, lymphoma and neuroendocrine tumours).[5]

1.3 Background: producing medical isotopes with cyclotrons

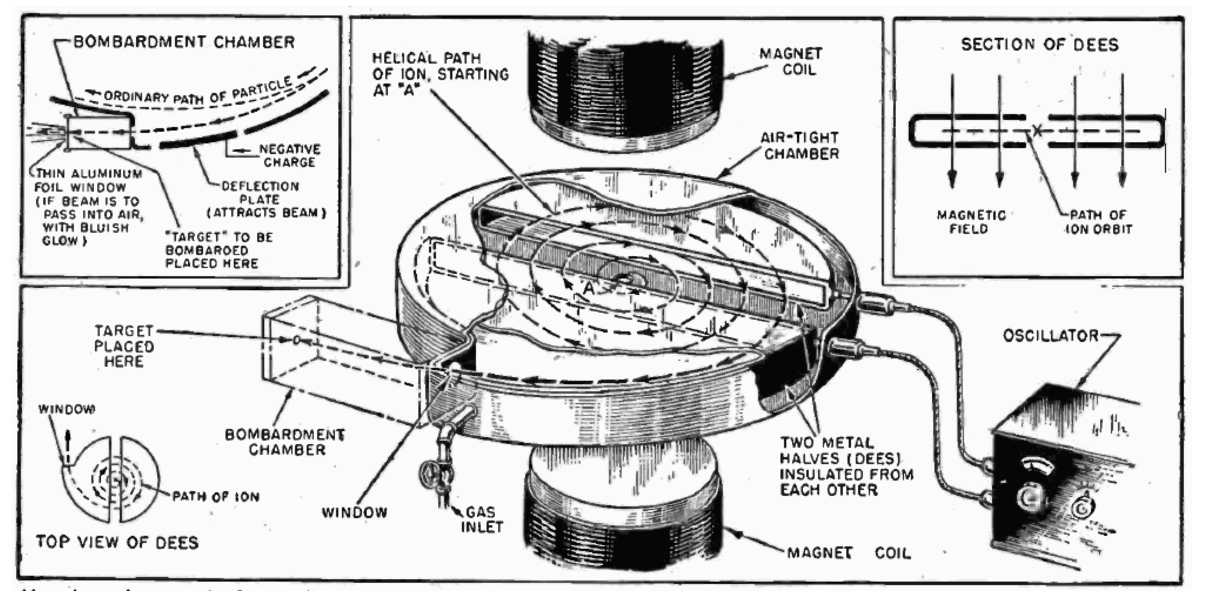
Cyclotrons are particle accelerators, machines that use electromagnetic fields to accelerate charged particles to very high velocities and energies. These machines can produce radioisotopes, elements that emit alpha (α), beta (β) and/or gamma (γ) radiation.[6] The basic principles of operation of all cyclotrons are the same. There is an ion source to produce ions charged particles, an acceleration chamber to accelerate them and a magnet to contain the particles on a circular path. Just like in a nuclear reactor, the (beam of) accelerated particles are bombarded to a target to produce a nuclear reaction within the target. The medical isotopes are the product of such a reaction and are extracted from the target. Figure 3 sketches the basic principle and elements of a classical cyclotron.

[4] Technopolis Group (2008). Het medisch gebruik van radioisotopen tot 2025.

[5] Technopolis Group (2021). Study on sustainable and resilient supply of medical radioisotopes in the EU: Therapeutic Radionuclides. JRC.

[6] Radioisotopes, International Atomic Energy Agency. Available from: https://www.iaea.org/topics/nuclear-science/isotopes/radioisotopes

Figure 3 Working principals of a (classical) cyclotron



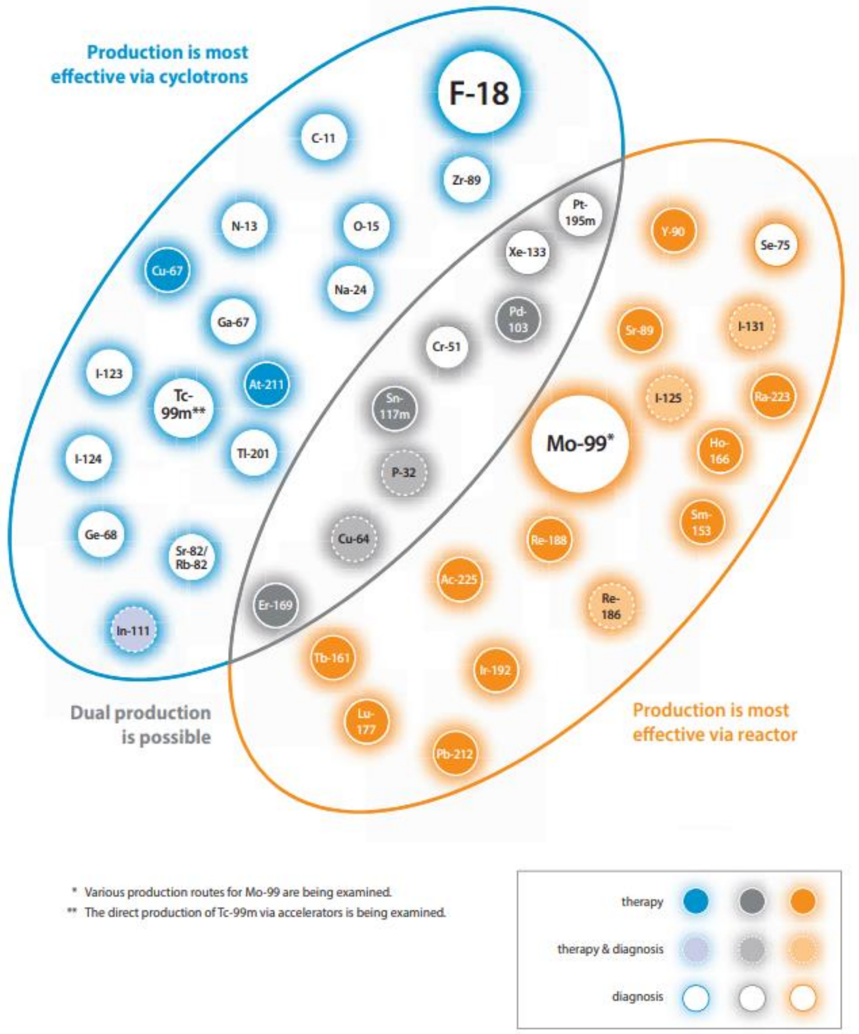
Source: Radio Craft (1947), Creative Commons

The invention of the first cyclotron in 1934 has paved the way for several critical developments in the application of radioisotopes in clinical practice. Today, cyclotrons are a crucial element in the supply of numerous radioisotopes, however not every medical isotope can be produced in a cyclotron.

Figure 4 provides an overview of various isotopes as well as their production routes. Most cyclotron-produced isotopes are used for PET diagnostic purposes. Technetium-99m (^{99m}Tc), the main isotope used in nearly all SPECT scans is produced in nuclear reactors (as ^{99}Mo for ^{99m}Tc generators), but production in cyclotrons is currently being investigated. However, the economics of producing ^{99m}Tc in a cyclotron cannot compete with the current extremely low costs of producing it in a reactor.[7] The main therapeutic isotopes, namely iodine-131 (^{131}I), lutetium-177 (^{177}Lu) and yttrium-90 (^{90}Y)), are all produced in nuclear reactors only.

[7] IAEA (2009). Cyclotron produced radionuclides. Physical characteristics and production methods. Available from: https://www-pub.iaea.org/mtcd/publications/pdf/trs468_web.pdf

Figure 4 Overview of reactor isotopes and cyclotron isotopes



Source: Nuclear Netherlands, 2017.[8] Note: Mo-99 is a molybdenum-technetium generator system used to deliver Tc-99m

Cyclotrons can be classified depending on the maximum energy of the beam available:

- small medical cyclotrons with fixed energies less than 20 MeV protons;
- intermediate energy cyclotrons with variable energy from 20 MeV to 35 MeV protons;
- high energy cyclotrons with energies more than 35 MeV.[9]

Small medical cyclotrons are mostly located in hospitals, universities, and small-scale industrial radionuclide production plants. They serve to produce radionuclides for in-house use, research, and commercial purposes. Often, they produce short-lived standard radionuclides for PET studies. [10] Intermediate energy cyclotrons tend to be located at bigger radiopharmaceutical

[8] Nuclear Netherlands (2017). Medical isotopes: Global importance and opportunities for the Netherlands in a European context.

[9] Synowiecki MA, Perk LR, Nijsen JFW. (2018). Production of novel diagnostic radionuclides in small medical cyclotrons. EJNMMI Radiopharm Chem, 3(1). Available from: https://pubmed.ncbi.nlm.nih.gov/29503860/

[10] Ibid.

commercial plants or research institutes and have the capacity of producing the standard PET radionuclides as well as standard SPECT and novel PET radionuclides. [11] High-energy cyclotrons are rare and are installed in advanced research institutes. Those cyclotrons can produce a wide range of SPECT and PET radionuclides.[12]

To further discuss the specific characteristics of the cyclotron network in Denmark, it is important to first understand some of the aspects related to the logistics and the supply chain of cyclotron-produced radioisotopes. The entire supply chain of these isotopes revolves, to a large extent, around the concept of radioactive decay, more specifically the **half-life** of produced radioisotopes. In radioactivity, half-life indicates the time required for a radioisotope to lose half of its activity (i.e. to become twice less radioactive than before). Many medical isotopes have a relatively short half-life (in the order of hours or minutes), thus their transportation from the production site to the patient must happen in a specified tight timeframe for those radioisotopes to be effective for medical use. For example, the half-life of ^{18}F, the most used isotope for PET imaging, is 110 minutes. Thus, if transport from the production site to the hospital would take exactly 110 minutes, one would need to order two times the needed activity for the procedure, as half of the activity is lost during transport.

There are differences concerning the production of radionuclides in cyclotrons as opposed to nuclear reactors. The main issues are summarised in Table 2. Both production routes have their own pros and cons. For cyclotrons, a major disadvantage is the limited number and volume of isotopes that they can produce, while comparative affordability and safety (in terms of radioactive waste production) make them attractive. For reactors, safety concerns, radioactive waste and high cost of reactor installation and upkeep are the main disadvantages, however, the broad production spectrum of radioisotopes and the longer half-life of produced isotopes are far superior to the cyclotrons.

Table 2 Comparison of radionuclide production techniques (reactors vs cyclotrons)

	Nuclear reactors	**Cyclotrons**
Principle of production	• Target material inserted in the neutron flux field undergoes fission or neutron activation transmuting into radionuclide of interest.	• Target material irradiation by charged particle beams. Inducing nuclear reactions that transmute the material into radionuclide of interest.
Advantages	• Production of neutron-rich radionuclides, mostly for therapeutic use. • High production efficiency • Centralized production: one research reactor able to supply to large regions or, in some cases, globally.	• Production of proton-rich elements used as β+ emitters for PET scans • Decentralized production allows for backup chains. • High uptime. • High specific activity in most cases. • A small investment in comparison to nuclear reactor. • Little long-lived radioactive waste.
Disadvantages	• Extremely high investment cost • High operational costs • Considerable amounts of long-lived radioactive waste	• A regional network of cyclotrons and complex logistics needed for short-lived produced radionuclides

[11] Ibid.

[12] Ibid.

	Nuclear reactors	Cyclotrons
	• Long out-of-service periods • Trouble to back-up in case of unforeseen downtime • Demanding logistics, often involving air transport • Public safety concerns • Non-proliferation treaty concerns	• Radionuclide production limited depending on installed beam energy

Source: Synowiecki et al. (2018)

2 Denmark: medical isotopes from cyclotrons and foreign supply

2.1 Current production capacity within Denmark

The production of medical isotopes in Denmark is solely done with cyclotrons. Denmark has no other irradiation facilities (e.g. nuclear research reactors) capable of producing medical isotopes.

Denmark has a long history in the use of cyclotrons to produce isotopes for biological and medical applications.[13] One of the first cyclotrons in Europe was placed in Copenhagen at the Institute of Theoretical Physics in 1938. The cyclotron was acquired by the famous Danish nuclear and quantum physicist Niels Bohr and the chemist George de Hevesy – who developed radioactive tracers – and was funded by The Rockefeller Foundation. This cyclotron was operational until 1993 and contributed to various developments in medical isotopes and nuclear medicine.

Today, **Denmark has 13 cyclotrons across the country that are used for medical purposes**. Most of these cyclotrons produce medical isotopes for PET diagnostics. One cyclotron is used for proton therapy and does not produce medical isotopes, but produces a proton beam that is directly used for radiation therapy.[14]

Table 3 provides an overview of all cyclotrons in Denmark. Most of these cyclotrons are **standard small or medium-sized medical cyclotrons that are primarily used to produce ^{18}F** – which could be considered the work horse for PET diagnostics. These cyclotrons are generally based at hospitals and form a close network to produce short-lived diagnostic isotopes.

Table 3 Current cyclotrons for medical isotope or radiation production in Denmark

#	Location	Organisation	Year commissioned	Specs	Type	Purpose/use
1	Aarhus	Aarhus University Hospital	1993	GE PETtrace, 16MeV	Medium medical cyclotron	Production of PET isotopes
2	Aarhus	Aarhus University Hospital	2010	GE PETtrace, 16MeV	Medium medical cyclotron	Production of PET isotopes
3	Aarhus	Aarhus University Hospital	2010	IBA CYCLONE 18/9, 18MeV	Medium medical cyclotron	Production of PET isotopes
4	Aarhus	Dansk Center for Partikelterapi	2019	Varian ProBeam, 230-250MeV	Extra-large medical cyclotron (single purpose)	Proton therapy
5	Copenhagen	University Hospital of Copenhagen	1993	Scanditronix MC 32NI, 32MeV (also d & a beams)	Large medical cyclotron (advanced)	Production of PET isotopes and a few other diagnostic and therapeutic isotopes
6	Copenhagen	University Hospital of Copenhagen	2005	CTI/Siemens RDS Eclipse HP, 11Mev	Medium medical cyclotron	Production of PET isotopes

[13] Niels Bohr Institute (2014). Part 4: Explosion of new knowledge. See: https://nbi.ku.dk/english/www/george_/de_hevesy/foerste_dokument/

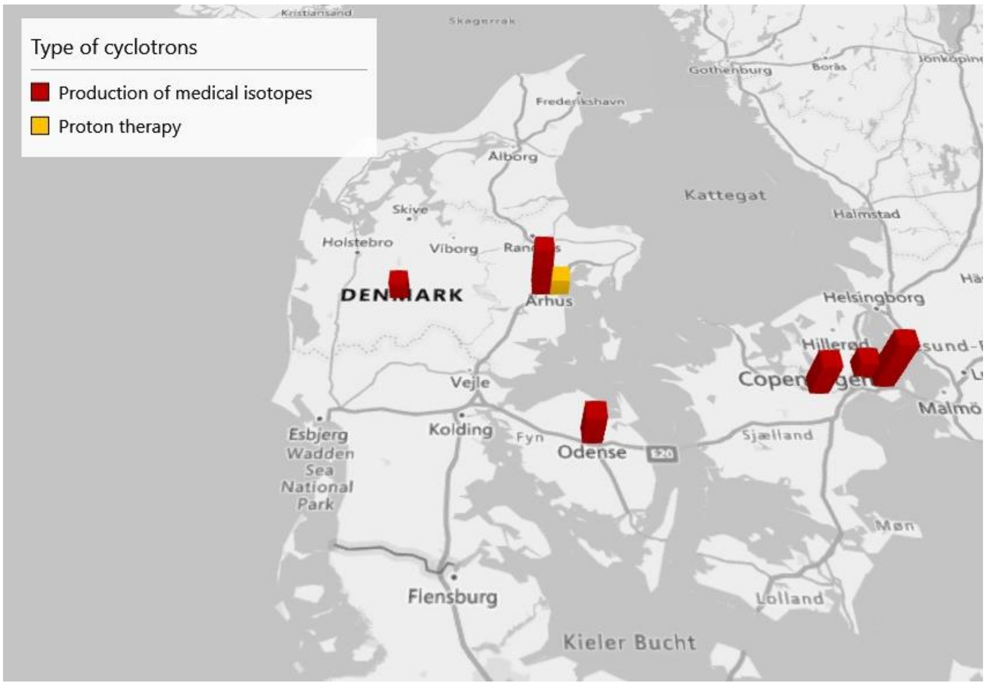
[14] See: https://www.en.auh.dk/departments/the-danish-centre-for-particle-therapy/centre-profile/

#	Location	Organisation	Year commissioned	Specs	Type	Purpose/use
7	Copenhagen	Bispebjerg Hospital	2020	GE GeNTrace, 7.8 MeV	Small medical cyclotron	Production of PET isotopes
8	Herlev	Herlev Hospital	2009	IBA CYCLONE 18/9, 18MeV	Medium medical cyclotron	Production of PET isotopes
9	Odense	Odense University Hospital	2006	GE PETtrace, 16MeV	Medium medical cyclotron	Production of PET isotopes
10	Odense	Odense University Hospital	2017	GE PETtrace, 16MeV	Medium medical cyclotron	Production of PET isotopes
11	Roskilde	Hevesy Laboratory DTU	2005	GE PETtrace, 16MeV	Medium medical cyclotron	Production of PET isotopes
12	Roskilde	Hevesy Laboratory DTU	2011	GE PETtrace-600, 7.8MeV	Small medical cyclotron	Prototype used for isotope research
13	Herning	Gødstrup Hospital	2021	GE MINItrace, 9.6Mev	Small medical cyclotron	Production of PET isotopes

Source: IAEA - Database of Cyclotrons for Radionuclide Production and H. Jensen (2009) - Cyclotrons and production of radioactive isotopes at Rigshospitalet, complemented with information from interviews and desk research

Cyclotrons are not evenly distributed across Denmark. Most cyclotrons are located in the Capital/Zealand region and in the Central Denmark region. These regions have the highest population in Denmark. A map with the types and locations of cyclotrons is provided in Figure 5.

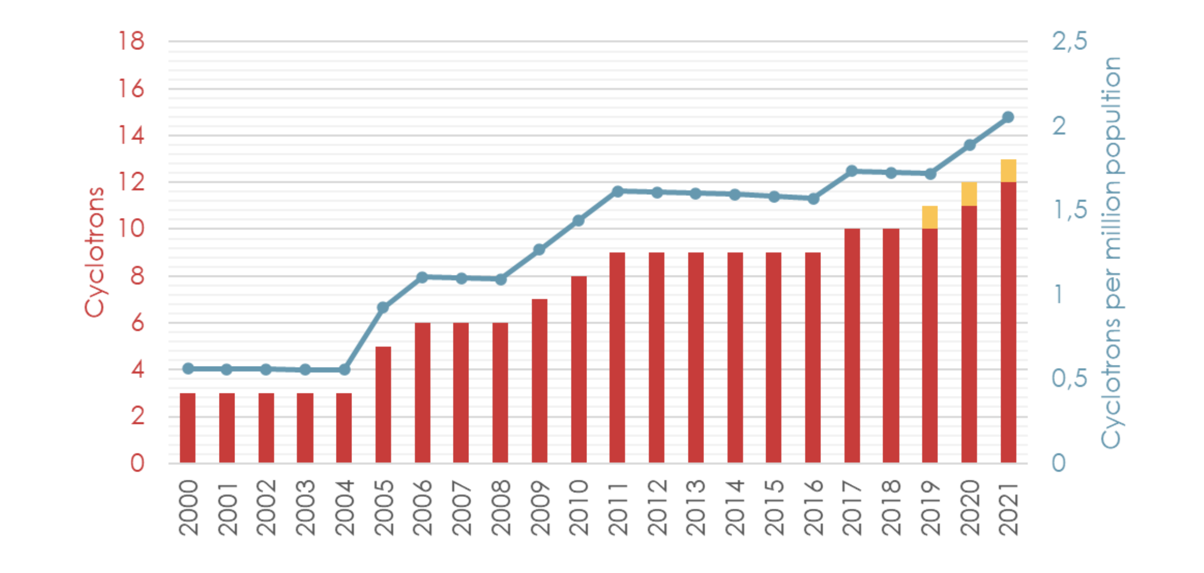
Figure 5 Map with cyclotrons in Denmark



Technopolis Group (2022), based on data from Table 3– the bar height corresponds with number of cyclotrons

Over the past 20 years, the number of cyclotrons in Denmark has tripled, resulting in a high density of cyclotrons per million inhabitants (see Figure 6). This increase also reflects the increased use of PET (see section 2.3). Denmark now has a network of cyclotrons spread over six different cities across the country. While initially the cyclotron network has been limited to university hospitals and universities, in the last decade also non-academic hospitals have installed cyclotrons to provide medical isotopes for their PET diagnostics. In some cases, this was driven by the use of very short-lived isotopes for certain PET-based diagnoses, such as $H_2[^{15}O]$ (half-life time of 2.037 minutes) in cardiology.

Figure 6 Evolution of the number and density of medical cyclotrons in Denmark



Source: Table 3 and World Bank population statistics, note: in yellow cyclotrons used for proton therapy

2.1.1 Medical isotopes produced in Denmark

The Danish cyclotrons produce a variety of medical isotopes, of which most are used for diagnostic purposes. These diagnostic isotopes are mainly used for PET tracers, of which ^{18}F and ^{11}C is most used and produced. The cyclotrons at the DTU's Hevesy Laboratory and the Copenhagen University Hospital produce a wider set of medical isotopes that are also used for research purposes. These include ^{211}At, which is studied in clinical trials as a therapeutic radionuclide, ^{64}Cu used for diagnostics and studied for therapeutics (potential theragnostic) and $^{81}Rb/^{81m}Kr$ generators used in SPECT (alternative for $^{99}Mo/^{99m}Tc$ for some specific diagnoses). Also, some less commonly used PET isotopes are produced at some centres, such as ^{15}O, which cannot be distributed easily due to a short half-life time. A (non-exhaustive) overview of the isotopes produced in Denmark is provided in Table 4.

Table 4 Non-exhaustive overview of isotopes produced in Danish cyclotrons

Medical isotope	Half-life time	Use	Notes about production
^{18}F	109.77 min	Diagnostic tracers for PET (wide variety of diagnoses)	Major isotope produced in all medical cyclotrons in Denmark
^{11}C	20.39 min	Diagnostic tracers for PET (wide variety of diagnoses)	Major isotope can be produced in all medical cyclotrons in Denmark

Medical isotope	Half-life time	Use	Notes about production
^{13}N	9.965 min	Diagnostic tracers for PET (mainly used for blood flow diagnoses)	Short half-lifetime to distribute.
^{15}O	2.037 min	Diagnostic tracers for PET (mainly blood flow/volume, and oxygen consumption diagnoses)	Only a few cyclotrons in Denmark produce ^{15}O. It has a very short lifetime and thus cannot be easily distributed.
^{68}Ga	68 min	Diagnostic tracers for PET (mainly blood-brain permeability diagnoses)	Can be produced in small cyclotrons but is only done by a few cyclotrons in Denmark.
^{64}Cu	12.700 h	Theragnostic, used for diagnostics (apoptosis/ hypoxic cells) and being studied for therapeutic use	Only at DTU (commercially)
^{82}Rb	76 sec	Diagnostic tracers for PET (mainly blood flow diagnoses)	Only at University Hospital Copenhagen.
$^{81}Rb/^{81m}Kr$ (generator)	4.57h (^{81}Rb)	Diagnostic tracer for SPECT (mainly lung ventilation diagnoses)	Only at University Hospital Copenhagen (marketing authorisation). Can replace $^{99}Mo/^{99m}Tc$ for some applications of SPECT only.
^{211}At	7.214 h	Radionuclide therapy, but not used in marketed radiopharmaceuticals	Only at University Hospital Copenhagen, one of the very few producers in Europe

Source: H. Jensen (2017) – Cyclotrons and production of radioactive isotopes at Rigs Hospitalet, R. Lecomte (2007) – Biomedical Imaging: SPECT and PET, various interviews

2.1.2 Transport of medical isotopes from cyclotron to hospital

Hospitals owning a cyclotron primarily produce isotopes for their own use, but also distribute their medical isotopes to neighbouring hospitals or sometimes even abroad. As the healthcare system in Denmark is organised in regions, distribution is focussed on the own region, covering small distances and transport times. Smaller transport distances require also lower local production volumes, as less activity is lost during transport. Due to the regional healthcare system, with regional reimbursements, and limited cooperation or alignment between regions, distribution of medical isotopes across regions occurs but is limited according to interviewed experts. It is also highlighted by the interviewees, **that the structure of the healthcare system, preferring regional self-sustainability, likely contributed to the high density of cyclotrons in Denmark**. The cyclotrons at the DTU's Hevesy Laboratory and the Copenhagen University Hospital do however produce medical isotopes for a wide group of customers (incl. abroad), and for research purposes.

The network of cyclotrons in Denmark creates resilience in the supply of PET isotopes: if one cyclotron is experiencing unforeseen downtime, transport from another cyclotron is for several PET isotopes possible. **Supply issues of isotopes produced within Denmark are not often reported** by experts. The transport radius from the cyclotron to the hospital is in Denmark usually limited to the distance that can be covered within one half-life time (rule of thumb). This distance is still considered efficient given the loss of activity during transport. From the interview, we know that transport radii for ^{18}F may vary from 20km (preferred) to 100 km. Cyclotrons may however serve as back-up to hospitals that are located further away (up to 250km have been mentioned), although this is not considered efficient transport: one needs to accept more loss of product during transport and higher costs per unit of activity at the time of administration.

2.2 Foreign dependency and security of supply

The national supply within Denmark is theoretically limited to medical isotopes that can be produced by cyclotrons with proton energy below 32MeV. In practice, only a limited number of the possible medical isotopes are produced in Denmark. Significant amounts are limited to often used tracers in PET diagnostics, mainly ^{18}F and ^{11}C. **There are no therapeutic medical isotopes produced in Denmark that are used in clinical practice** – ^{64}Cu and ^{211}At are produced in small amounts only, for research on their therapeutic application.

Denmark needs to import most non-PET isotopes from abroad. These concern diagnostic isotopes with longer half-life times that cannot be efficiently produced in cyclotrons, such as the commonly used ^{99m}Tc for SPECT imaging, and therapeutic isotopes that are virtually all produced in nuclear reactors.

In theory, cyclotrons can produce more commonly used isotopes than now produced in Denmark, which might seem attractive from a security of supply perspective. However, **such ambitions have not been documented or indicated by any of the interviewed experts**. It would in some cases require a more powerful cyclotron and different licensing for longer-lived medical isotopes, while for many therapeutic isotopes the amounts that can be produced with cyclotrons are not sufficient for patient treatment and the current prices of reactor-produced isotopes do not incentivise such investments. For instance, the cyclotron production of ^{99m}Tc from ^{100}Mo in small medical cyclotrons would result in long-lived isotopes for which the hospital cyclotrons in Denmark are not equipped nor licensed. Furthermore, the focus in Denmark has been much more on PET than SPECT and in-hospital production of medical isotopes (not on industrial sites).

The current supply of foreign medical isotopes has been stable. Denmark has experienced some supply issues in the past, most notably the supply of ^{99}Mo/^{99m}Tc during the Molybdenum/Technetium Crises in the late 2000s and more recently a few disruptions in the supply of ^{131}I. These shortages have been mitigated among hospitals, by using generators a bit more efficient/longer, sharing between hospitals and using Na[^{18}F] in PET as an alternative to ^{99m}Tc. During the Molybdenum/Technetium Crises cyclotron-produced Na[^{18}F] has been used compassionately in Denmark, using PET as an alternative to several SPECT diagnostic procedures (mainly bone scanning), but this has been a temporary shift. After the crisis, ^{99m}Tc was cheaper and pushed Na[^{18}F] again to a smaller market share.

Supply issues are not managed nationally but are dealt with by the regions and the hospitals. Due to a lack of experienced supply issues currently, no particular mitigation strategies employed in Denmark have been identified. Disruption in the supply of diagnostic medical isotopes can likely be mitigated to some extent by moving to PET alternatives. **Disruptions in the supply of therapeutic medical isotopes cannot be easily mitigated with Danish supply**, although generally alternative, less preferred treatments can be provided to mitigate such shortages. The general expectation is that the market will solve supply issues.

Several interviewed Danish experts were concerned about the uncertainty of future (research) reactor capacity in Europe to produce medical isotopes. Insufficient supply capacity for reactor-based medical isotopes will affect Denmark as much as many other countries in Europe (or even beyond).

2.3 Use of medical isotopes in nuclear medicine

The use of medical isotopes in nuclear medicine in Denmark is not much different than in other countries. **The fact that Denmark relies on foreign supply for various medical isotopes, has not led to a search for cyclotron-based alternatives**. Only during the Molybdenum/Technetium

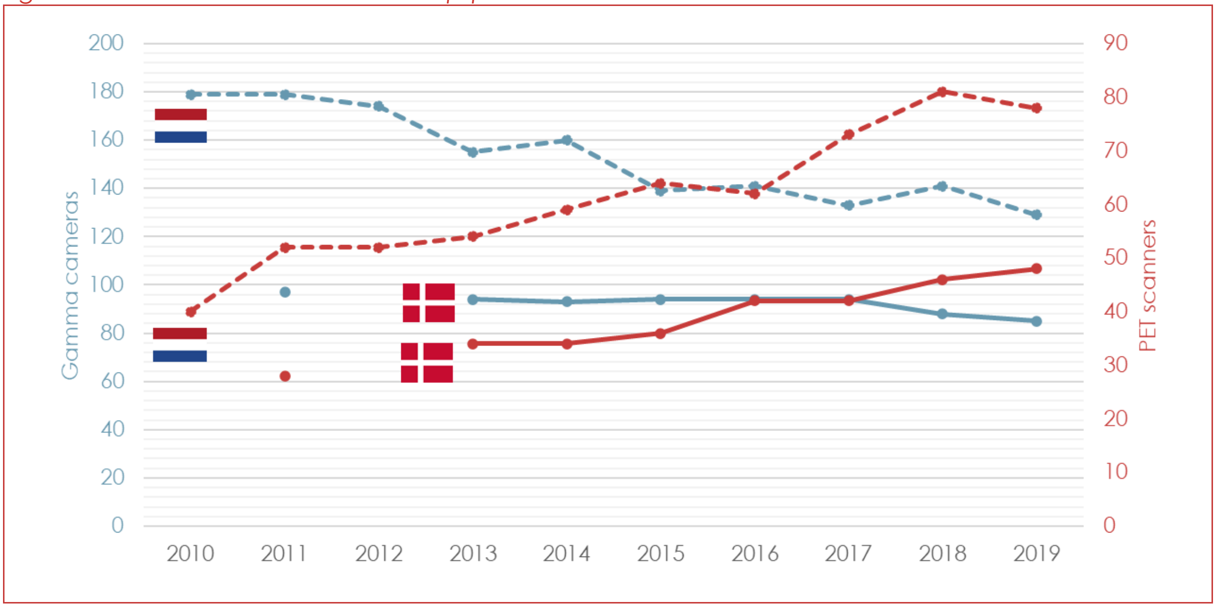
Crises, hospitals temporarily moved to alternative, more expensive, diagnostic procedures requiring cyclotron-produced isotopes. **For therapeutic purposes, no alternative cyclotron-produced isotopes are available** (only for some treatments, but just in small quantities).

The use of medical isotopes is related to the best-available and cost-effective treatment of patients and based on the decisions of doctors. In recent years, the use of PET scans has become more common. This trend is explained by several factors, including the following:

- There is a level of **perceived diagnostic superiority of PET scans as compared to SPECT scans**. PET scans often provide better quality images thus allowing for improved tumour identification, earlier diagnosis, and overall better patient outcomes. Other advantages of PET scans include higher spatial resolution and the capability to perform quantitative measurements at the peak of stress and speed.
- The shorter duration of the PET scan makes it also more attractive for the physicians because it overall leads to a more pleasant patients' experience.

Over time, Denmark has increased the use of PET (see Figure 7). Overall, **the number of PET scanners installed in Denmark has increased by 71% over the last 10 years**. At the same time, the number of SPECT scanners (gamma cameras) has decreased by 12% over that same period, signalling **at least some shift from SPECT to PET**. This also indicates a somewhat decreased reliance on foreign reactor-based medical isotopes for diagnostic procedures, although the decrease has been limited. The European market for SPECT isotopes is documented to be mature and is expected to remain fairly stable.[15]

Figure 7 Number of SPECT and PET equipment in Denmark and the Netherlands



Source: OECD Health Statistics, most recent statistics, extracted 30 November 2021

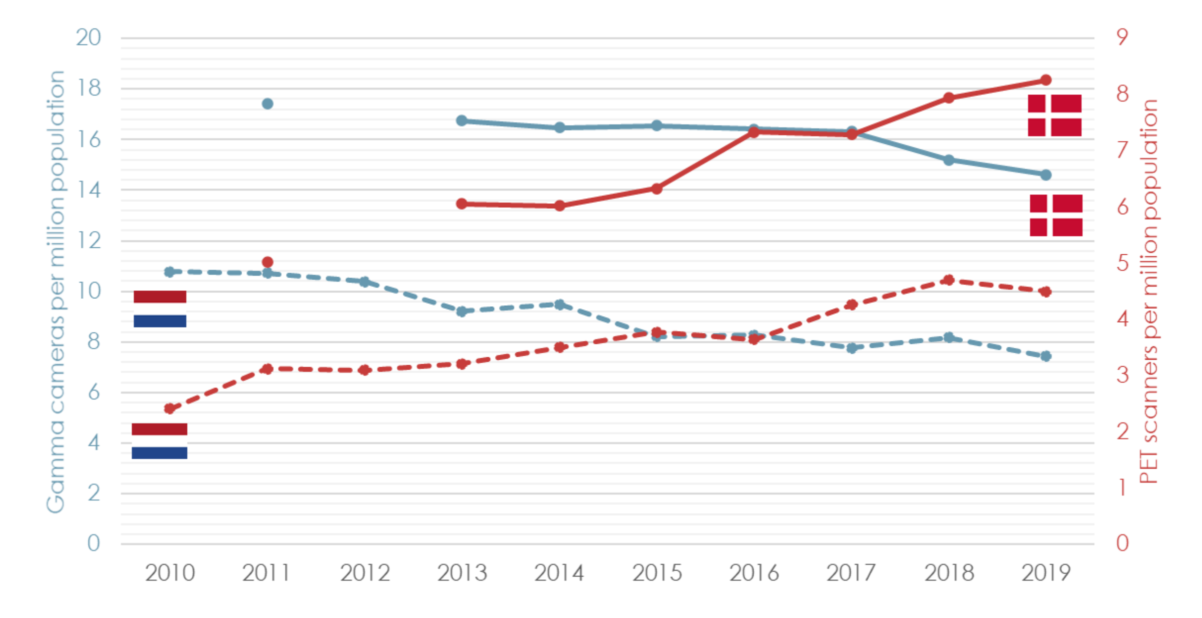
A similar trend observed in Denmark is also observed in the Netherlands (see Figure 7). **In the past decade, the number of PET scanners has strongly increased in the Netherlands as well – with 95%** even stronger than in Denmark. Equally, a stronger drop of 28% in the number of SPECT scanners (gamma cameras) has been observed in the same period in the Netherlands as

15 NucAdvisor (2021). Co-ordinated Approach to the Development and Supply of Radionuclides in the EU. European Commission.

compared to Denmark. Also here, **some shift from SPECT to PET has taken place**. Interviewees and literature[16] expect that the trend of increasing use of PET will continue in the coming years.

In relative terms, **Denmark has a higher density of PET and SPECT equipment per million population than the Netherlands**. This suggests that access to these kinds of diagnostic procedures is potentially better in Denmark than in the Netherlands.[17] A likely explanation for this difference is in the way healthcare is organised in Denmark: **the regional healthcare systems promote a relatively higher density of equipment**.

Figure 8 Number of SPECT and PET equipment per million population in Denmark and the Netherlands



Source: OECD Health Statistics, most recent statistics, extracted 30 November 2021

2.3.1 *Innovation and the use of novel medical isotopes*

Denmark has a long history in cyclotron research and has been at the forefront of the use of PET and required cyclotrons in Scandinavia according to interviewees. Despite the fairly large number of cyclotrons in Denmark, **only a few cyclotrons are used for research purposes**.

Research and innovation on medical isotope production are primarily conducted at the Hevesy Laboratory of the DTU[18], the Copenhagen University Hospital[19], and Aarhus University Hospital [20]. The investigated isotopes include among others, ^{211}At, ^{89}Rb, ^{64}Cu, ^{11}C, ^{13}N. It is worth noting, that although those isotopes are investigated, their use in clinical settings is not common

[16] Ibid.

[17] This will of course depend on various factors, including on how efficient the equipment is used on the prevalence of diseases that require SPECT and PET among the population.

[18] Selected research outputs of DTU are described at https://www.healthtech.dtu.dk/english/research/research-sections/section-biotherapeutic-engineering-and-drug-targeting/group-targeted-radionuclides/publikationsliste

[19] Annual reports on research performed in Copenhagen University Hospital available at Annual reports on research performed in Aarhus University Hospital available at https://www.en.auh.dk/departments/department-of-nuclear-medicine--pet-centre/publications/

[20] Annual reports on research performed in Aarhus University Hospital available at https://www.en.auh.dk/departments/department-of-nuclear-medicine--pet-centre/publications/

in Denmark. ^{11}C has received approval for compassionate use in Denmark – but **compassionate use is rare in Denmark**. For more experimental therapies under compassionate use structures, patients are often sent to Germany where such treatments are far more common.

Experts also report that **the ability of, hospitals, even the smaller ones, to have cyclotrons has led to increased use of certain novel procedures which require on-site isotope production**. For example, interviewed experts report that many hospitals in Denmark administrate radioactive water ($H_2[^{15}O]$) for diagnostic purposes to patients with cardiovascular issues.

2.4 Policy: strategy and responses

2.4.1 Policy background

To understand the development of the cyclotron network in Denmark, it is important to look at the potential policy developments and decision that might have led to the creation of the network. Since the early 2000s, the cancer policy in Denmark has been guided by the national cancer care plans, developed jointly by relevant national organisations such as patient associations, the Ministry of Health, health professionals' societies, etc. The National Board of Health has to date produced four national cancer care plans: [21]

- Cancer Care Plan I, adopted in 2000, provided 10 general recommendations for improving cancer treatment. It led to **a marked increase in the capacity for diagnostics and radiotherapy** and the education of health care personnel
- Cancer Care Plan II, adopted in 2005 (further updated in 2007), focused on tobacco prevention, improved organisation of care and a strengthening of the surgical cancer treatments. The plan also centred around integrated care and **improving coordination between departments, hospitals, and the primary and secondary sectors**. National integrated cancer pathways were defined as a key concept
- Cancer Care Plan III, adopted in 2010, focused on early diagnostics, screening, rehabilitation, and palliation. A special **diagnostic fast track pathway for patients with unspecific symptoms of the serious disease** was introduced to develop binding integrated cancer pathways as organisational and clinical standards for the diagnosis and treatment for most types of cancer.
- Cancer Care Plan IV, adopted in 2016, builds on the provisions of previous plans and prioritises further **focus on prevention, improved diagnostics, and treatment**. The plan sets out an ambition to increase cancer survival rates to reach the highest level among all Nordic countries by 2030 by adopting 16 new initiatives, including those in early screening and development of new and targeted treatments.

In 2006 the Danish Health Authority (DHA) set up a special Working Group that produced an important report on the recommendations for expanding PET and FDG production in Denmark. The Working Group **recommended that PET scanners should be rolled out for broad use across the country**, concentrated primarily in university hospitals as main oncology research and treatment centres. The report foresaw an increased need for PET scanners in the years to come and **called for extended local production of radioisotopes**, primarily Fludeoxyglucose F18 (FDG) used in most diagnostic PET procedures. At that point (2006) the radioisotope was produced in only two centres in Denmark (Aarhus Hospital and Copenhagen University Hospital). The

[21] Olejaz M, Annegrete, Nielsen J, Rudkjøbing A, Hans, Birk O, et al. (2012). Denmark Health system review. Health Systems in Transition.

recommendations of the working group were **incorporated in the second national Cancer Care Plan II** in 2007. [22]

2.4.2 *Practical implementation of cyclotron network*

Although on the national level, the DHA called for an extended local production capacity of radioisotopes for PET diagnostics, the introduction of new cyclotron facilities, as well as the rollout of the regional cyclotron networks, was **not centrally coordinated**. According to the interviewed experts, this is largely due to the nature of the Danish healthcare system which relies on a highly decentralised approach.

As briefly mentioned earlier in this report, the provision of primary and secondary care lies with the regions and municipalities in Denmark. The country is divided into 5 regions, each with its own budgets, hospitals administrations, and reimbursement rules. All hospitals, which have access to or have a cyclotron, are owned by their respective regions. The regions run and fund the hospitals and provide reimbursement for pharmaceutical care.[23]

The roll-out of cyclotrons has therefore been implemented largely on the regional level, often to ensure sufficient coverage and self-reliance in each given region, but ultimately **leading to an establishment of a well-connected national network**.

Given that the cost of acquiring and installing cyclotrons are high, experts highlight that regions rarely make such investments on their own. Instead, hospitals rely on donation programmes, particularly from private sector foundations (such as the Novo Nordisk Foundation, Lundbeck Foundation, the VELUX Foundations, etc), which often procure costly equipment for Danish hospitals free of charge.[24] In Denmark private foundations' donations into medical equipment for public hospitals as well as public medical research and development programmes are common. [25,26] According to the interviewed experts, once the equipment is installed, regions continue financing through the provision of professional staff. Thus, **the Danish cyclotrons as such are not financed through public sources**, however nuclear physicists, chemists, and other staff involved in the production process are.

[22] Udgivet af Sundhedsstyrelsen (2006). PET: Anbefalinger for udbygning af PET og FDG (flourodeoxyglukose) production. Available from: https://www.sst.dk/Udgivelser/2006/~/media/7F59BB99E34A414CBC65C3B462AD92BA.ashx

[23] Olejaz M, Annegrete, Nielsen J, Rudkjøbing A, Hans, Birk O, et al. (2012). Denmark Health system review. Health Systems in Transition.

[24] Ibid.

[25] Deloitte (2018). Trend report on Danish foundations 2018 Zooming in on their philanthropic activities.

[26] DEA Think Tank (2012). Private foundations-a unique player in Danish research funding.

3 Netherlands: implications of a Denmark scenario

Based on the previous chapter we could describe the **Denmark scenario** as a situation in which the Netherlands would only have an installed cyclotron base to produce medical isotopes. This would entail a high density of cyclotrons per million population and reliance on foreign supply for various medical isotopes that cannot be produced in cyclotrons.

In this scenario, there would be no replacement of the current High Flux Reactor (HFR) in Petten that produces a wide variety of medical isotopes that are supplied to the Netherlands and beyond. Recent studies[27] show that such reactor capacity would be needed for a sustainable supply of medical isotopes in Europe next to an installed cyclotron base. **This scenario would thus require new reactor-based production capacity outside the Netherlands to fill the gap of the HFR**.

3.1 Current production capacity within the Netherlands

The Netherlands is an important producer of medical isotopes in Europe. The current HFR is one of the five major producers of medical isotopes worldwide.[28] Unlike Denmark, the Netherlands has a production capacity that is more diversified with both cyclotrons and a nuclear research reactor, producing diagnostic and therapeutic radionuclides within the national borders.

The Netherlands has 12 cyclotrons that are used to produce medical isotopes. The cyclotrons in Amsterdam, Petten, Groningen and Eindhoven distribute medical isotopes nation-wide, while the cyclotrons in Alkmaar, Rotterdam and Nijmegen only produce for local use.[29] Most of these cyclotrons are used to produce isotopes for PET diagnostics.

There are three more cyclotrons in the Netherlands that are used for different purposes. The AGOR cyclotron in Groningen is used for scientific purposes only. Three other cyclotrons, in Delft, Maastricht and Groningen, are solely used to produce proton beams for external beam radiation in proton therapy (like in Aarhus).

Table 2 provides an overview of all cyclotrons in the Netherlands. Most of these cyclotrons are standard small or medium-sized medical cyclotrons that are primarily used to produce PET isotopes. These cyclotrons for medical isotope production are generally based at or near hospitals, except for the cyclotrons in Eindhoven and Petten.

Table 5 Current cyclotrons for medical isotope or radiation production in the Netherlands

#	Location	Organisation	Year commissioned	Specs	Type	Purpose/use
1	Alkmaar	Cyclotron Noordwest BV	2013	IBA CYCLONE 18/9, 18MeV	Medium medical cyclotron	Local production of PET isotopes
2	Amsterdam	BV Cyclotron VU	1997	IBA CYCLONE 18/9, 18MeV	Medium medical cyclotron	National production of PET isotopes

[27] Technopolis Group (2021). Study on sustainable and resilient supply of medical radioisotopes in the EU: Therapeutic Radionuclides. JRC; NucAdvisor (2021). Co-ordinated Approach to the Development and Supply of Radionuclides in the EU. European Commission.

[28] The other nuclear reactors that are main producers of medical isotopes are the BR2 in Belgium, the Maria reactor in Poland, the

[29] Letter to Parliament from 10 February 2021: IENW/BSK-2021/20084

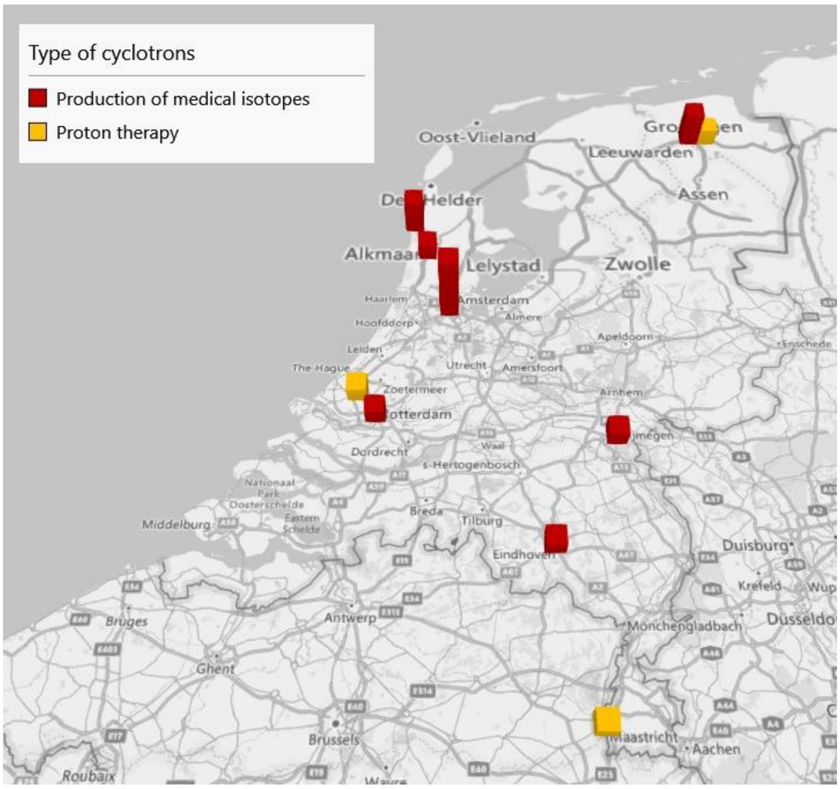
#	Location	Organisation	Year commissioned	Specs	Type	Purpose/use
3	Amsterdam	BV Cyclotron VU	2004	IBA Cyclone KIUBE-180, 18MeV	Medium medical cyclotron	National production of PET isotopes
4	Amsterdam	BV Cyclotron VU	2009	IBA Cyclone KIUBE-300, 18 MeV	Medium medical cyclotron	National production of PET isotopes
5	Amsterdam	Stichting VUmc	Est. 2010-2015	IBA Cyclone 3D, 3.6MeV	Small medical cyclotron	
6	Nijmegen	Radboud Translational Medicine	2015	Siemens Eclipse HP, 11MeV	Medium medical cyclotron	Local production of PET isotopes
7	Eindhoven	AccTec BV / GE Healthcare	2003	IBA Cyclone 30, 15-30MeV	Large medical cyclotron	National
8	Groningen	Groningen University Hospital	1991	Scanditronix MC 17F, 8.5-17MeV (p, d beams)	Medium medical cyclotron	National production of PET isotopes
9	Groningen	Groningen University Hospital	2018	IBA Proteus PLUS 230, 230MeV	Extra-large medical cyclotron (single purpose)	Proton therapy
10	Groningen	Groningen University Hospital	Est. 2005-2010	IBA Cyclone 18, 18 MeV	Medium medical cyclotron	National production of PET isotopes
11	Rotterdam	Cyclotron Rotterdam B.V.	Ext. 2010-2015	GE PETtrace 880, 8,4-16,5MeV (p. d beams)	Medium medical cyclotron	Local production of PET isotopes
12	Maastricht	Maastro Clinic	2019	MEVION S250i PTS, 250MeV	Extra-large medical cyclotron (single purpose)	Proton therapy
13	Petten	Curium	Ext. <2000	IBA Cyclone 30, 30MeV	Large medical cyclotron	Production of various medical isotopes
14	Petten	Curium	1968	Philips AVF, 30MeV	Large medical cyclotron	Production of various medical isotopes
15	Delft	HollandPTC	2018	Varian ProBeam, 240MeV	Extra-large medical cyclotron (single purpose)	Proton therapy
16	Groningen	KIVI	1996	AGOR Cyclotron, 190MeV	Scientific/research cyclotron	Scientific research

Source: IAEA - Database of Cyclotrons for Radionuclide Production and KEW licenses of organisations, complemented with information from interviews and desk research

The medical cyclotrons in the Netherlands mainly supply ^{18}F products. Radboud Translational Medicine (Nijmegen), Cyclotron Noordwest (Alkmaar) and BV Cyclotron VU (Amsterdam) have a larger portfolio of products: ^{13}N is produced in Nijmegen and Alkmaar, ^{11}C is produced in Nijmegen, and ^{89}Zr and $^{81}Rb/^{81m}Kr$ generators are produced in Amsterdam. The latter two are produced exclusively for Perkin Elmer and Curium respectively[30] and are also exported. UMCG in Groningen produces mainly products for internal use and for clinical studies. Almost all products produced/supplied are used for PET tracers, all known products from these cyclotrons are used in diagnostics.

Cyclotrons are distributed across the country with most cyclotrons in the Randstad. This is also the highest populated part of the country. A map with the types and locations of cyclotrons is provided in Figure 9.

Figure 9 Map with cyclotrons in the Netherlands

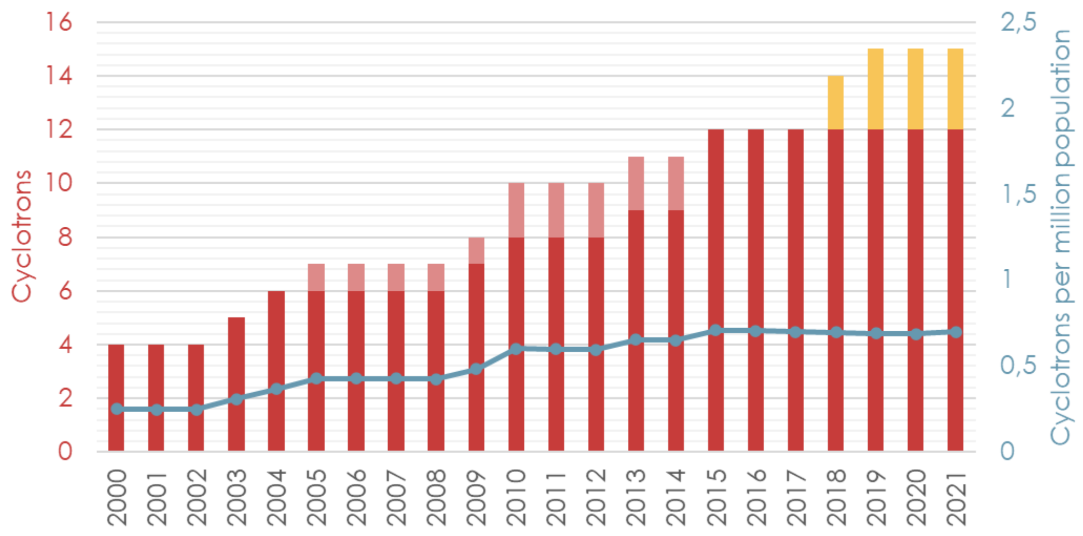


Technopolis Group (2022), based on data from Table 5 – the bar height corresponds with number of cyclotrons

Over the past 20 years, the number of cyclotrons producing medical isotopes in the Netherlands has tripled (see Figure 10). This increasing trend is similar in size to the trend we observed in Denmark. This increase is in line with the increased use of PET in the Netherlands (see discussion in section 2.3).

30 BV Cyclotron VU (2022). Website: https://www.cyclotron.nl/.

Figure 10 Evolution of the number and density of medical cyclotrons in the Netherlands



Source: Table 5 and World Bank population statistics, note: in yellow cyclotrons used for proton therapy; the AGOR cyclotron (used for scientific research only) is not included in this data

The Netherlands and Denmark currently have both 12 cyclotrons installed that are used for the production of medical isotopes. The Netherlands has more (3) cyclotrons for proton therapy as compared to Denmark (1). Denmark has however a three times higher density of medical cyclotrons per million population than the Netherlands (2.2/mhab versus 0.7/mhab). This difference can be explained by the fact that the total land area of Denmark and the Netherlands is roughly equal[31], while the population size of the Netherlands is three times higher than in Denmark[32]. To cover the whole country with an efficient supply of cyclotron-produced medical isotopes (i.e. not too long transport distances), Denmark thus needs a similar number of cyclotrons as the Netherlands to ensure patient access to these kinds of treatments. Given the differences in population size, the Netherlands likely needs to produce larger volumes (more activity) of medical isotopes than Denmark – suggesting a more intensive use of the installed production capacity.

3.2 Needed investments in cyclotron capacity in the Denmark scenario

In the Denmark scenario, the current installed cyclotron capacity would remain. The main difference with the Denmark situation would then be the cyclotron density per million population. The cyclotron density per million population in is Denmark three times higher than in the Netherlands. This **higher density of cyclotrons does not necessarily lead to better access to cyclotron-produced isotopes and should thus not be an aim per se**.

The current density and number of cyclotrons in the Netherlands is according to interviewees sufficient to supply the 50+ Dutch hospitals that have PET scanners with the isotopes/tracers they need. The main products that are supplied are ^{18}F tracers which are distributed in the Netherlands across a 2h transport radius from the cyclotron site. With 2h driving time from

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[31] The land area of Denmark is 42,933 km^2, while the land area of the Netherlands is 41,543 km^2.

[32] The population size of Denmark is 5.84 million, while the population size of the Netherlands is 17,18 million in 2021 according to the national statistical bureaus.

Amsterdam, Eindhoven, Petten and Groningen (those who supply nationally) the Netherlands can be fully covered. Only with increasing demand, additional cyclotrons may be needed.

Given the commercial nature of the medical isotope market, **one may expect that with sustained increased demand, additional supply capacity will be installed to meet demand**. The investments for installing an additional cyclotron within an existing production environment are commercially viable according to interviewees. Table 6 provides an overview of the estimated costs for such investments.

Table 6 Estimated costs for cyclotrons and full production environment

Type of cyclotron	**Estimated cost of a cyclotron**	**Typical CAPEX range for full production environment**
Cyclotrons with energies <20 MeV: small/medium medical cyclotrons	€1m-€2m	~€10m
Cyclotron with energies >20 MeV: medium/large medical cyclotrons	€5m-€10m	€20m-€30m

Source: NucAdvisor (2021), RIVM (2009) and figures provided in interviews

The cyclotrons currently installed in the Netherlands have received limited public funding. Most are commercially funded, funded by universities, or received some public funding according to interviewees. BV Cyclotron VU, AccTec BV and Curium are fully commercial suppliers of diagnostic radiopharmaceuticals, most of the other suppliers are part of a hospital and produce primarily for in-hospital or regional use.

The medical isotopes produced in cyclotrons in Denmark and the Netherlands does not differ much. Only a few additional isotopes are produced in small quantities in Denmark (for example ^{211}At). Certainly, no reactor-produced medical isotopes are routinely replaced in healthcare by cyclotron-produced medical isotopes due to the high density of cyclotrons in Denmark. The fairly small difference in isotopes produced does not signal a need for additional investments in cyclotrons in the Netherlands.

We foresee only two situations in which additional investments in medical cyclotrons could be relevant in a Denmark scenario and would result in an increased density of cyclotrons per million population:

- **A significant increase in PET use, increasing the demand for cyclotron-produced PET isotopes (situation B)**: the expectation is that the use of PET will increase in coming years[33], resulting in a higher demand for cyclotron-produced PET isotopes. NucAdvisor (2021) reports an increase of 20%-50% for ^{18}F, the most used PET isotope, in 2040. Such a high increase would require an increase in the number of cyclotrons in the Netherlands.
- **A political drive to invest in producing a wider variety of medical isotopes in cyclotrons (situation C)**: this could be a political response to a foreseen unstable reactor-based supply chain in the future, but insufficient to provide the wide variety of medical isotopes that can be produced by nuclear reactors.[34] This especially provides no solution to neutron activated medical isotopes (esp. for therapeutic purposes), such as ^{177}Lu. Canada has ventured this

[33] Pallas (2021). Beating Cancer with Isotopes. Presentation.; RIVM (2017). Productie en gebruik van medische radio-isotopen in Nederland.; various interviews; increased demand of 20%-50% for ^{18}F expected in in 2040 by NucAdvisor (2021).

[34] RIVM (2019). Marktontwikkeling en leveringszekerheid voor medische radionucliden; NucAdvisor (2021). Co-ordinated Approach to the Development and Supply of Radionuclides in the EU. European Commission.

path to invest in projects to produce ^{99m}Tc with cyclotrons. Also, some other medical isotopes, potentially interesting but still under research or not yet industrialised, such as ^{225}Ac, ^{67}Cu, ^{186}Re, ^{223}Ra and ^{211}At could in principle be produced in cyclotrons.[35] This will require innovation and is not yet considered interesting by any of the current cyclotron operators in the Netherlands and Denmark according to our interviewees. So far, such initiatives have been based on political or innovation drivers only.

In Table 7 we provide estimates for investment costs for three situations that would require an increased installed base of cyclotrons in the Netherlands and thus a higher density[36]. We consider **aiming for a similar high density of cyclotrons as in Denmark (situation A) not a realistic situation**: this would result in overcapacity even with projected increases in demand for PET isotopes. The other situations are linked to the two situations described above. In situation B this would not require any public investments as **likely the market will accommodate increased demand**. Situation C would require public investments as this is based on a political drive and not considered economically interesting so far.

Table 7 Rough estimates of investment costs for additional cyclotrons in the Netherlands

Situations	**A. Investments needed to obtain a similar cyclotron density as Denmark**	**B. Investments needed to sustain increased demand for PET isotopes**	**C. Investments needed to produce a wider variety of medical isotopes in cyclotrons, esp. ^{99m}Tc**
Additional cyclotrons	25-26 (most <20 MeV)	2-6 (<20 MeV)	3-6 (dedicated, ~20 MeV)[37]
Estimated additional investments (range)	€250m-€350m	€10m-€60m	€60m-€120m
Assessment	This is not realistic nor needed (overcapacity); independent on installed reactor base	Likely to be covered by the market; independent on installed reactor base	Economically not yet interesting; politically driven when sufficient installed reactor base is lacking

Assessment by Technopolis Group

3.3 Implications for nuclear medicine and security of supply

A Denmark scenario would not necessarily have implications for nuclear medicine and the security of supply in the Netherlands, provided that other foreign suppliers will fill the gap of the HFR. In that situation, hospitals will still be supplied with the necessary medical isotopes for diagnostics and therapy. However, recent European studies[38] have shown that **there is a need for additional reactor capacity to secure the European supply of medical isotopes, especially therapeutic medical isotopes**. The supply chain for reactor-produced medical isotopes is fragile with most European research reactors reaching the end of their lifetime in less than 20 years. There is uncertainty about planned new-build production capacity, both in terms of

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[35] NucAdvisor (2021). Co-ordinated Approach to the Development and Supply of Radionuclides in the EU. European Commission; Technopolis Group (2021). Study on sustainable and resilient supply of medical radioisotopes in the EU: Therapeutic Radionuclides. JRC.

[36] Given that the Dutch population growth until 2040 is expected to be about 12% according to CBS: https://www.cbs.nl/en-gb/news/2021/50/forecast-population-growth-picks-up-again.

[37] H. Van der Keur (2014). Pallasreactor of deeltjesversnellers? De toekomst van medische isotopenproductie in Nederland. LAKA; NRG en Pallas (2014). De ontwikkelingen bij NRG, de markt voor medische isotopen en het vooruitzicht op Pallas; this range fits 1/28 of the number of cyclotrons that NucAdvisor (2021) estimates for Europe.

[38] NucAdvisor (2021). Co-ordinated Approach to the Development and Supply of Radionuclides in the EU. European Commission; Technopolis Group (2021). Study on sustainable and resilient supply of medical radioisotopes in the EU: Therapeutic Radionuclides. JRC.

timing as well as the variety and quantity of medical isotopes produced. It is therefore not obvious that a foreign supplier will fill the gap of the HFR within a suitable timeframe.

In case the current supply of the HFR will not be compensated by foreign supply, **effects on nuclear medicine and the security of supply will likely emerge beyond the next decade** This would hold not only for the Netherlands but also for other European countries, including Denmark. Following NucAdvisor (2021), in the best case, most diagnostic medical isotopes can be supplied by Dutch cyclotrons, new initiatives such as SHINE[39] and other foreign suppliers. For therapeutic medical isotopes, the Netherlands may be dependent on non-EU supply, although for several therapeutic medical isotopes such as ^{177}Lu this will likely be an issue[40]. In the worst case the Netherlands (and other countries globally), will experience shortages of ^{99m}Tc and several therapeutic medical isotopes. This will directly influence the availability of various treatments (mainly for cancer) to patients and likely (assuming normal market mechanisms) increased prices for medical isotopes.

In terms of innovation, the Netherlands currently has a nuclear knowledge infrastructure in which almost all parts of the nuclear supply chain are covered, although with only a limited number of players.[41] Innovation in nuclear medicine occurs at the hospital level (e.g. development and testing of new pharmaceuticals, therapies, and diagnostic procedures often through clinical trials) as well as at the level of irradiation facilities. The FIELD-LAB in Petten[42], and the research and production organisations surrounding the HFR, contribute to the development of new reactor-produced medical isotopes. **Without a research reactor, many innovations at the level of irradiation are hard to achieve** and will likely be limited to the smaller spectrum of medical isotopes that can be produced in cyclotrons. Collaborations between nuclear medicine professionals and such high flux irradiators (i.e. research reactors), for instance within the FIELD-LAB, will be hard to continue. To a much smaller extent, this may also affect research and innovation more downstream among nuclear medicine professions – although this is often very much international, less dependent on medical isotope suppliers and at the level of pharmaceuticals. At the same time, innovation and **R&D in the production of medical isotopes with cyclotrons <u>may</u> see an increase, although this field is likely more competitive** due to the higher number of institutions worldwide having access to cyclotrons. Innovations in this field in Denmark serve as an example.

One of the main risks of a Denmark scenario for innovation is the loss of expertise, businesses, and jobs. This will also affect the position of the Netherlands in this R&D domain. Without a nuclear research reactor, **the perspective of organisations and people with expertise in developing reactor-produced medical isotopes will significantly reduce**. Perhaps some of this nuclear expertise will move abroad or to the energy sector – given the ambitions of the newly installed Cabinet to build new nuclear power plants[43]. Some of the expertise may venture into medical isotope production with cyclotrons, although it is unclear how much could be absorbed by this industry segment.

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[39] SHINE (2022). [Wat is SHINE? Hoe Werkt SHINE? | SHINE Nederland (shinefusion.com)](shinefusion.com).

[40] Technopolis Group (2021). Study on sustainable and resilient supply of medical radioisotopes in the EU: Therapeutic Radionuclides. JRC.

[41] Technopolis Group (2016). Nucleaire kennisinfrastructuur in Nederland. Inventarisatie en relatie met publieke belangen.

[42] See: https://www.advancingnuclearmedicine.com/field-lab

[43] Coalitieakkoord (2021). 'Omzien naar elkaar, vooruitkijken naar de toekomst'

3.3.1 *Overview of pros and cons*

Based on the issues discussed above, Table 8 presents an overview of the main pros and cons of the application of the Danish cyclotron network scenario in the Netherlands.

Table 8 Pros and cons of application of Danish cyclotron network scenario in the Netherlands

Pros	Notes
1. Increased production capacity of PET diagnostic isotopes in the Netherlands. 2. Higher PET screening capacity in the country. 3. Improved PET diagnostic capacity may lead to improved (early) diagnosis and overall improved patient outcomes. 4. Decreased radioactive waste production (as compared to reactor-produced waste). Less long-lived waste production. 5. Improved capacity for research and development of novel cyclotron-based radioisotope production. 6. Less investments would be needed than for a new nuclear research reactor.	(1)-(3): The gains are dependent on the availability of PET scanners in hospitals. To realise the full potential of the gains, the number of PET scanners in the country should increase proportionately to the increase in PET isotope production in (new) cyclotrons or vice versa. (5): For improved research and development outcomes, higher energy beam cyclotrons would need to be installed.
Cons	**Notes**
1. No change in the reliance on reactor-based isotopes for SPECT diagnostics and (esp.) therapeutic purposes. 2. Increased need for trained personnel needed to operate the (new) cyclotrons and associated facilities. 3. Potentially weakened supply chain of SPECT and therapeutic isotopes in the Netherlands. 4. Potential disruption in the supply chain of SPECT and therapeutic isotopes in Europe/globally. 5. Negative implications for personnel of the HFR and businesses that rely on it. 6. Threat to the sustainability of groups working in research and innovation of reactor-based technologies In the Netherlands.	(3)-(6): This would be the case shall the HFR be decommissioned without replacement in favour of a cyclotron-only production in the Netherlands.

Technopolis Group (2022)

4 Conclusions and Recommendations

4.1 Main conclusions

Based on a comparative study between medical isotope production with cyclotrons in Denmark and the Netherland, our main conclusions are:

- **The cyclotron networks in Denmark and the Netherlands are different, but similar in size and both sufficient for the national supply of PET isotopes**. There is no need for investments in additional cyclotrons in the Netherlands, unless one would wish to produce a wider variety of medical isotopes with cyclotrons.
- **A situation such as in Denmark, in which medical isotopes are produced in cyclotrons only, is not a full alternative for a new nuclear research reactor for medical isotope production**. Cyclotrons can primarily produce PET isotopes (although some other isotopes are possible) and will require other production technologies for various other medically important isotopes, primarily those for SPECT and radionuclide therapy. A nuclear research reactor could produce a wider variety of medical isotopes, but still requires a cyclotron network to produce short-lived isotopes as is currently the case in the Netherlands.
- **Cyclotron-only production of medical isotopes (i.e. no Dutch research reactor) will make the Netherlands more dependent on foreign supply for various medical isotopes, as is the case in Denmark**. Given the need for additional reactor capacity to secure European supply of medical isotopes, this will likely result in unstable security of supply of various medical isotopes in the Netherlands as well beyond the next decade. It will also affect the position and industry of the Netherlands in medical isotope production. New national initiatives such as SHINE could provide some national supply of primarily technetium-99m/molybdenum-99 (for SPECT) in absence of Pallas and next to a cyclotron-network.

4.2 Specific conclusions

Our specific conclusions directly relate to the research questions (RQ) of this study as listed in Appendix C.

4.2.1 Specific conclusions related to the situation in Denmark

- The number of medical cyclotrons installed in the Netherlands is equal to Denmark (both 12 medical cyclotrons) and equally sufficient to supply the installed base of PET scanners in the country. [RQA]
- The high density of cyclotrons in Denmark is a result of its regional healthcare system and geography. Although a lower population size, Denmark needs a similar number of cyclotrons as the Netherlands to ensure an efficient supply of short-lived PET isotopes across the country. [RQB]
- Denmark has never aimed for self-sufficiency in medical isotope production with its cyclotron capacity, as cyclotrons cannot produce all used medical isotopes. Policy has only aimed for improved cancer care, resulting in more PET scanners and thus more cyclotrons to provide the required short-lived PET isotopes. [RQC1]
- For non-cyclotron-produced isotopes, Denmark fully relies on foreign supply. Especially for therapeutic purposes, isotopes are imported from abroad. [RQC2]
- There has been little substitution of reactor-produced medical isotopes with cyclotron-produced medical isotopes. Only during the Molybdenum/Technetium Crises to a small extent substitution for ^{99m}Tc has occurred for some diagnoses under temporal approval, although this did not sustain beyond the crises due to costs and regulation. [RQC3]

- Denmark has until now not experienced significant disruptions in the foreign supply of medical isotopes. However, several Danish interviewees have expressed concern about the unclarity regarding Pallas, as this may affect the sustainability of supply in the future. [RQD2]
- There is no (national) mitigation strategy for shortages in medical isotopes in Denmark. Shortages are solved ad-hoc, between hospitals and/or by healthcare regions. For cyclotron-produced medical isotopes, this means transportation from one hospital/cyclotron centre to the other. For reactor-produced medical isotopes solutions are less obvious, but for diagnostics this may include replacing SPECT with PET where possible. [RQD2]
- Denmark has never considered producing technetium-99m (^{99m}Tc) with cyclotrons (like in Canada), due to practical, regulatory, and economic reasons. [RQD2]

4.2.2 Specific conclusions related to the Netherlands

- For the Netherlands, it would only to some extent be possible to change the current clinical use of medical isotopes towards more use/dependency on cyclotron-produced medical isotopes. This is possible for diagnostics by replacing SPECT with PET for various diagnostic procedures (where possible), which is already an ongoing trend for many years now. [RQE1]
- For radionuclide therapy, no alternatives to reactor-produced medical isotopes are currently available in sufficient amounts. Only very few therapeutic medical isotopes can be produced in cyclotrons at all and much of that is still in the research phase (far from being marketed). [RQE1]
- A Denmark scenario, in which the Netherlands would have only cyclotrons to produce medical isotopes, would not require much change. Currently, the Netherlands has sufficient cyclotron capacity to meet the current demand for cyclotron-produced isotopes. [RQE2]
- Additional public investments would be needed should the Netherlands, unlike Denmark, would wish to produce a wider variety of medical isotopes with cyclotrons. It would require additional, medium-large sized cyclotrons and investments of up to €120m and still quite some innovation. [RQE2]
- Such cyclotrons could potentially replace a few of the reactor-produced medical isotopes but would still require foreign supply or other solutions for many other medical isotopes (incl. most therapeutic medical isotopes). [RQE2]
- The advantages (+) and disadvantages (-) of having only (a high density of) cyclotrons to produce medical isotopes are related to costs (+), security of supply (-), waste (+), innovation (+/-), nuclear industry (-) and human capital (-). A summary of pros and cons is provided in Table 8. [RQE3]
- An up-to-date geographical overview of the Dutch nuclear knowledge infrastructure is provided in Appendix A. [RQF]

4.3 Key recommendations

Based on the findings in this study, we have three recommendations to the Ministry of Health, Welfare and Sport:

- **Invest only in cyclotron infrastructure if one wishes to promote innovation into alternative production routes for medical isotopes**. There seems to be no need for increasing the current installed cyclotron capacity (higher density) for the current demand for cyclotron-produced isotopes. Only if the aim is to foster innovation in novel cyclotron-produced medical isotopes or to produce a wider variety of medical isotopes, additional investments are needed. This will likely not be picked up by the market.

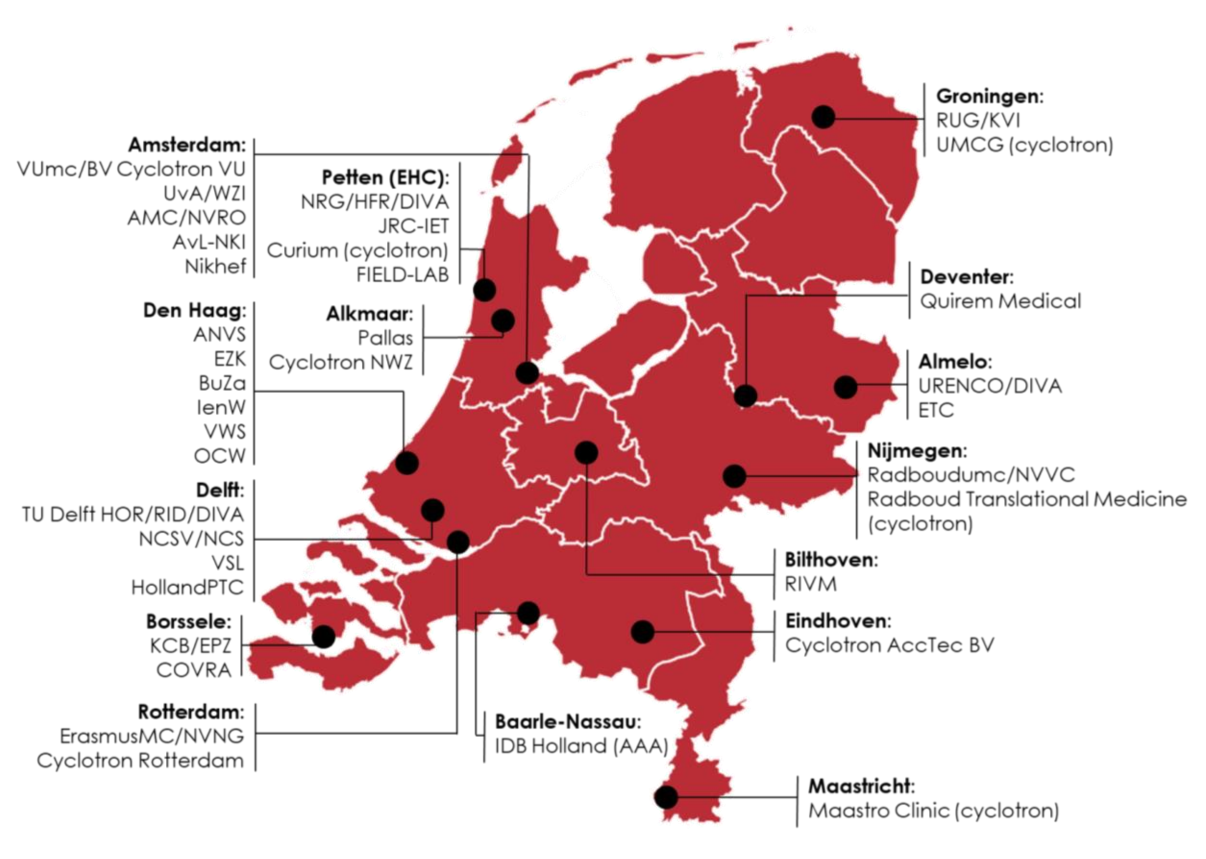
- **Keep an international perspective when making decisions for investments in medical isotope irradiation facilities**. Decisions in the Netherlands will affect the European (and international) supply of medical isotopes (esp. beyond 2030), and thus the supply in the Netherlands and Denmark. Falling back to only a cyclotron network in the Netherlands requires other initiatives in Europe to fill the gap of the HFR for various medical isotopes. Initiatives such as SHINE could possibly fill that gap partially.[44] Recent studies for the EC and JRC have highlighted the fragility of the current installed reactor capacity in Europe and the future uncertainties in new reactor capacity, creating risks for the sustainability of supply beyond the next decade.[45]
- **Focus on achieving improved access to PET diagnostics in the Netherlands based on patient needs.** PET scans are superior to SPECT because they allow for improved (early) diagnosis and ultimately lead to better patient outcomes**.** Denmark has promoted the use of PET as part of their Cancer Plans for these reasons. In addition, it will also reduce dependency on reactor-produced medical isotopes for diagnosis, which could be interesting when relying more on foreign supply.

[44] RIVM (2019). Marktontwikkeling en leveringszekerheid voor medische radionucliden.; SHINE (2021): What Is Molybdenum-99 (Mo-99)? - SHINE Technologies (shinefusion.com)

[45] Technopolis and NucAdvisor (2019); Technopolis Group (2021). Study on sustainable and resilient supply of medical radioisotopes in the EU: Therapeutic Radionuclides. JRC; NucAdvisor (2021). Co-ordinated Approach to the Development and Supply of Radionuclides in the EU. European Commission.

Appendix A Map of the Dutch nuclear knowledge infrastructure

Figure 11 Map of the Dutch nuclear knowledge infrastructure



Technopolis Group (2021), update from Technopolis Group (2016)[46]

Comments regarding cyclotrons in the Netherlands:

- Delft, Groningen, and Maastricht have a dedicated cyclotron for proton therapy. These cyclotrons are not used to produce medical isotopes, but to generate a proton beam for direct use in radiotherapy.

[46] Technopolis Group (2016). Nucleaire kennisinfrastructuur in Nederland. Inventarisatie en relatie met publieke belangen. Den Haag: Ministerie van Economische Zaken. Available from: https://www.tweedekamer.nl/kamerstukken/brieven_regering/detail?id=2016Z18757&did=2016D38573

Appendix B Overview of stakeholders and experts interviewed

Name	Organisation
Dr. Søren Baarsgaard Hansen	Aarhus University Hospital (DK)
Dr. Søren Hess	Danish Society for Clinical Physiology and Nuclear Medicine (DK)
Dr. Holger Jensen	Copenhagen University Hospital (DK)
Dr. Lars Thorbjørn Jensen	Herlev Hospital (DK)
Prof. Mikael Jensen	DTU Health Tech (DK)
Dr. Maria Vosjan	BV Cyclotron VU (NL)
Dr. Hanne Waltenburg	Danish Health Authority (DK)

Appendix C Research questions: relation to methods and report sections

#	Research question	Methods	Report section(s)
A	What is the cyclotron capacity in Denmark and the Netherlands?	• Desk study	• 2.1 • 3.1
B	What is a possible explanation for the difference in cyclotron capacity between Denmark and the Netherlands?	• Desk study • Interviews • Our expertise	• 2.4
C1	Has Denmark made a conscious choice to strengthen its self-sufficiency in medical isotopes with its cyclotron capacity?	• Desk study • Interviews	• 2.4
C2	To what extent does Denmark rely on foreign reactor-produced medical isotopes?	• Desk study • Interviews	• 2.2
C3	To what extent are reactor-produced medical isotopes being replaced by alternative cyclotron-produced medical isotopes in treatment and diagnostics in Denmark?	• Desk study • Interviews	• 2.3
D1	To what extent does Denmark experience shortages in the supply of (reactor-produced) medical isotopes?	• Desk study • Interviews	• 2.2
D2	How are these shortages mitigated in Denmark?	• Interviews	• 2.2 • 2.3
E1	To what extent is it feasible to change the current clinical use of medical isotopes in the Netherlands towards more use/dependency on cyclotron-produced medical isotopes, as is presumably the case in Denmark?	• Desk study • Interviews	• 3.2 • 3.3 • 4.1
E2	What would be needed to realise the change in E1 (including financially)?	• Desk study • Interviews • Our expertise	• 3.2
E3	What are the advantages and disadvantages of the change in E1 for current nuclear medicine practice in the Netherlands?	• Desk study • Interviews • Our expertise	• 3.3 • 3.4
F	What does the Dutch nuclear knowledge infrastructure look like geographically?	• Desk study	• 3.1 • Appendix A