EUROPEAN NUCLEAR SOCIETY

Unlocking the Potential of Radiopharmaceuticals in Europe

Part 1: Setting the Scene

ENS High Scientific Council Briefing Paper

March 2026

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Setting the scene

ENS High Scientific Council Position Paper

Executive summary

This ENS High Scientific Council Paper is **the Part 1 of a series presenting the status and challenges of nuclear medicine**. In this part, status, importance and advancements of radiopharmaceuticals are presented. The key findings contained in this chapter, include:

1

Nuclear medicine is a life-saving technology
Every year, more than **10 million European patients** benefit from nuclear medicine for diagnosis and treatment. Radiopharmaceuticals enable early disease detection and targeted therapies that improve clinical outcomes and support **personalized patient care**, ultimately saving lives across a range of medical fields including oncology, cardiology, neurology, and endocrinology.

2

Radiopharmaceuticals Enable Precise Diagnosis and Treatment
Radiopharmaceuticals are used for **non-invasive imaging** (PET, SPECT, hybrid imaging) and for **targeted therapy**, allowing clinicians to visualize, characterize, and manage diseases at the **molecular level**. This dual diagnostic-therapeutic role supports accurate staging, monitoring, and individualized treatment plans.

3

Theranostic approach allows precision treatment of cancers
The **combination of diagnostic and therapeutic radiopharmaceuticals** (theranostics) allows clinicians to detect and treat the same disease targets, adjusting therapies in real time. This personalized approach is already **showing success in conditions such as prostate cancer and neuroendocrine tumors**.

4

Innovations progress in Radiopharmaceutical Chemistry and Production
Advancements in **radiolabeling techniques**, including **click chemistry and bioorthogonal reactions**, as well as improved **production methods**, chelators, and stabilizing agents, are enhancing the quality, safety, and efficacy of radiopharmaceuticals. These innovations support the development of new agents with **greater specificity and reduced toxicity**.

5

AI and Future Directions that shape Nuclear Medicine
Artificial intelligence is being integrated into radiopharmaceutical development, imaging analysis, and treatment planning. Future trends include **predictive models** for treatment response, **patient stratification**, and **multimodal imaging integration**, paving the way for **fully personalized nuclear medicine**.

As is summarized in this paper, radiopharmaceuticals have provided large benefits in the past, and have great potentials to increasingly improve the human health in future, with EU being the forefront of nuclear medicine services and research activities. However, radiopharmaceuticals present multiple challenges, from technological, production and distribution issues, to radiation safety and regulatory framework challenges. The progress in these fields is necessary for meeting the growing demand for live-saving nuclear medicine procedures and to realize the tremendous potential of innovation for the benefit of patients. Therefore, **Part 2 of this paper series will treat the challenges of the radiopharmaceuticals supply in the EU and related expert recommendations**.

Introduction

Nuclear medicine stands at the forefront of modern healthcare, with both diagnostics and treatment evolving through the use of radiopharmaceuticals. The integration of advanced science with clinical applications is enhancing patient outcomes and shaping the future of personalized medicine. In this paper we present the role of radiopharmaceuticals and their innovations emerging in nuclear medicine, to set the stage for understanding the challenges that this field is facing.

Radiopharmaceuticals enable clinicians to visualize, localize, characterize and treat diseases at a molecular level. They can be tracked by imaging systems, highlighting physiological and biochemical processes within the body. In treatment, they deliver radiation directly to affected tissues, targeting the disease while minimizing harm to the surrounding healthy areas. This approach helps detect diseases early, improve treatment plans, and support personalized patient care.

Radiopharmaceuticals are drugs that contain radioactive isotopes, used for diagnostic or treatment purposes. Unlike radiography and radiotherapy, that is administered externally, radiopharmaceuticals are used internally, allowing to diagnose and treat diseases with great precision

Every year, **more than 10 million European patients** [1] **benefit from nuclear medicine** for diagnosis and treatment of various pathologies. In general, the number of nuclear medicine procedures worldwide has significantly increased over the past few decades, driven by advancements in imaging technology, development of new radiopharmaceuticals, expanded clinical applications and a growing demand for early and precise disease diagnosis and treatment.

Many radioisotopes can be used for nuclear medicine purposes, varying in their emission patterns and energies, allowing to select appropriate approach from a wide range of nuclides for a variety of applications. The production methods differ depending on the radioisotope: as shown in Figure 1, all technologies, including the reactor-based and accelerator-based (predominantly cyclotron-based) technologies are essential for producing a range of radioisotopes needed to ensure the effective functioning of nuclear medicine services, ultimately benefiting patients.

[1] EANM Position Paper – Nuclear Medicine: What it is. Where it goes. What it needs (EANM, Vienna, 2024) (access link)

Production of Isotopes in Medicine

Legend	Research Reactors	Dual Production	Cyclotrons
Therapy	90 Y Yttrium	103 Pd Palladium	67 Cu Copper
Therapy & Diagnosis	131 I Iodine	32 P Phosphorus	111 In Indium
Diagnosis	99 Mo Molybdenum	133 Xe Xenon	99m Tc Technetium

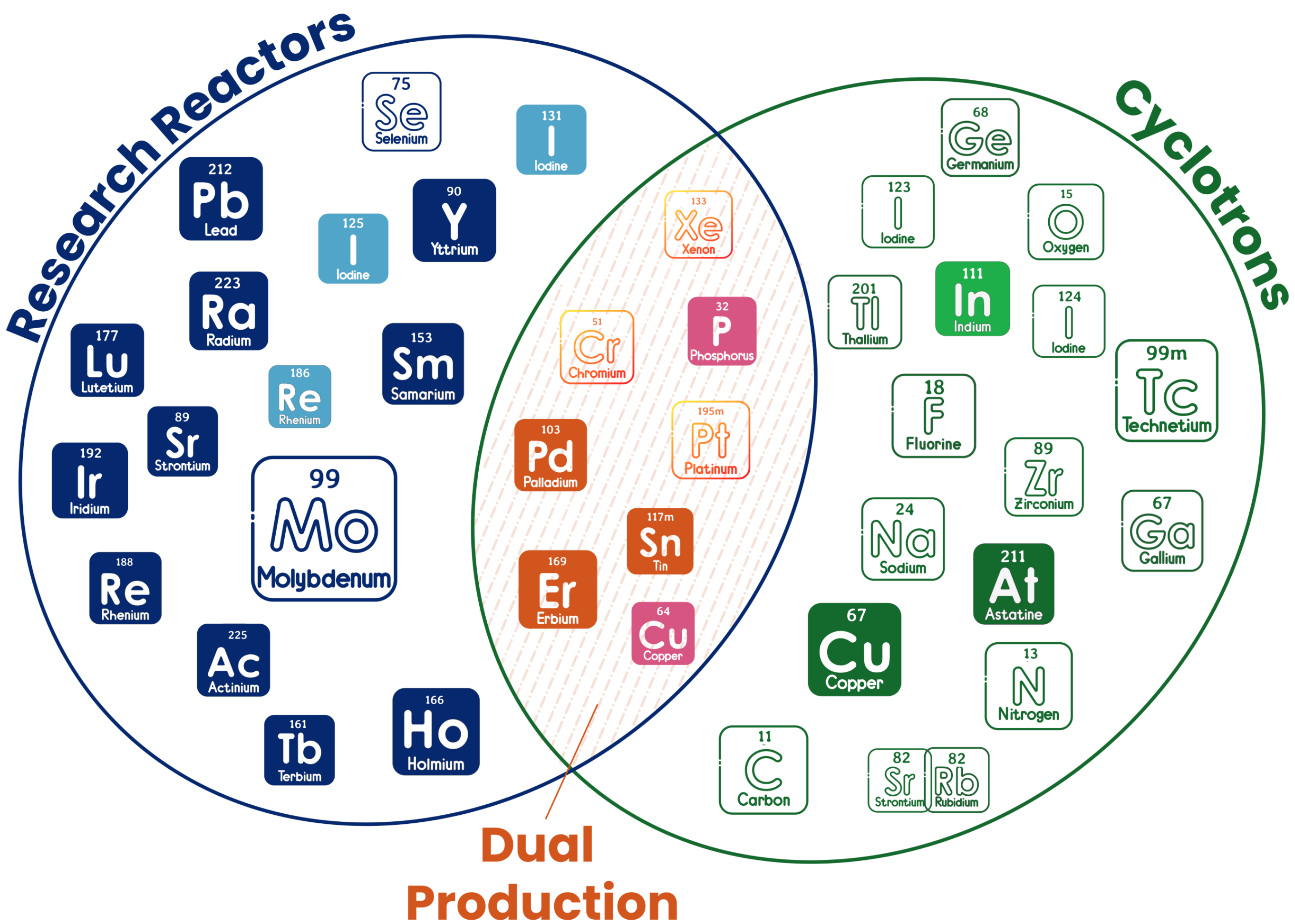

Figure 1: Production of most important radioisotopes in medicine
– both accelerators (predominantly cyclotrons) and nuclear reactors are necessary [2]

[2] Medical Isotopes – Global Importance and Opportunities for the Netherlands in a European Context (Nucleair Nederland, 2023) (access link)

Radiopharmaceuticals in nuclear medicine

The unique composition of radiopharmaceuticals, which combines radioisotopes with biological targeting mechanisms, enables high specificity in detecting and treating conditions, while also facilitating personalized treatment.

1. Unique properties and mechanism of action

Radiopharmaceuticals are molecules, often complex, designed to deliver radiation to specific tissues or cells for diagnostic or therapeutic purposes. Their structure typically includes three essential components:

1. Radioisotope: The radioactive element that emits radiation for imaging or therapeutic effects.
2. Chelator: A chemical compound that securely binds the radioisotope to the ligand/vector, ensuring stability and preventing the release of free radioisotopes in the body
3. Ligand/Vector: A molecule that targets specific tissues, organs, or cells by binding to their specific receptors or molecular markers.

"This cohesive structure makes radiopharmaceuticals well-suited for personalized medicine, enabling precise diagnosis, treatment monitoring, and targeted therapy with minimized side effects."

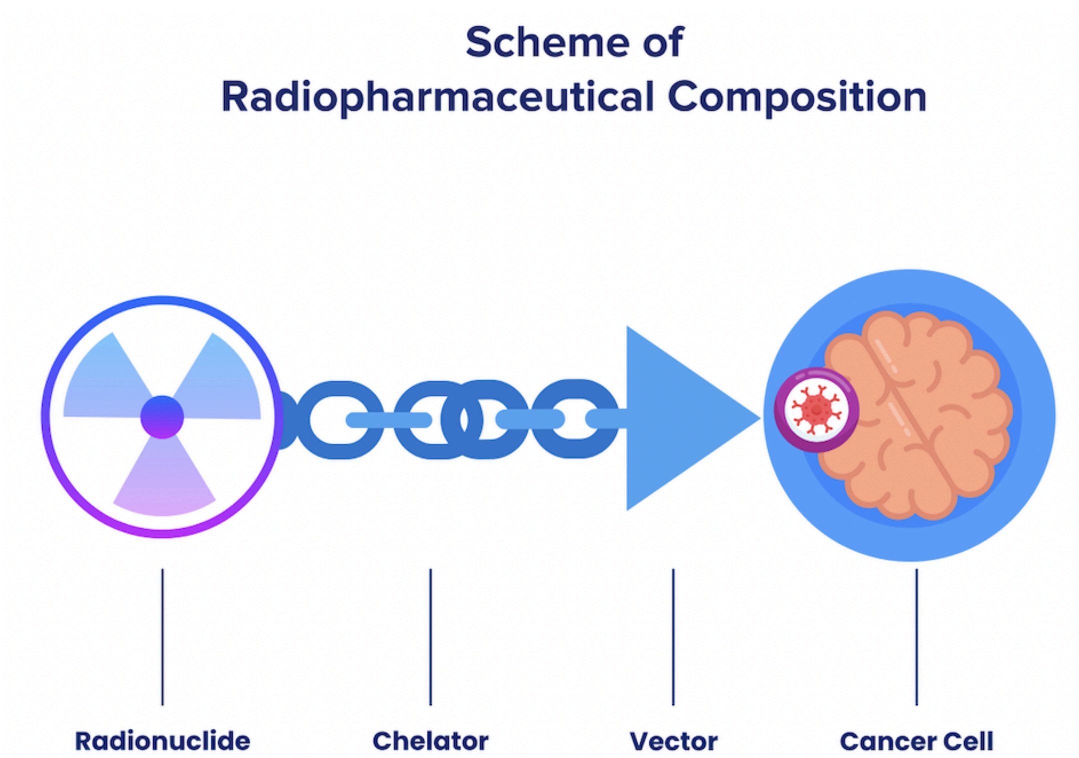

Figure 2: Scheme of radiopharmaceutical composition

Ligand/Vector component

The ligand or vector is crucial for directing the radiopharmaceutical to the desired biological target, offering high specificity and minimal off-target effects. Different types of vectors are tailored to target various biological processes or disease markers:

- **Small molecules**: Ideal for rapidly targeting tissues with high permeability, often used in oncology, e.g. **Prostate-Specific Membrane Antigen** (or **PSMA**) **ligands** for prostate cancer).
- **Peptides**: Designed to bind to specific cell receptors, such as **somatostatin receptors** in neuroendocrine tumors (used in **PRRT** with ^{177}**Lu**).
- **Antibodies**: Offer high specificity for certain antigens, as seen in **radioimmunotherapy** for lymphoma (^{131}**I** or ^{90}**Y** labeled antibodies).
- **Nanoparticles**: Emerging vectors with potential for multifunctional targeting and drug delivery.

Chelator component

The chelator plays a crucial role for the stability of the radiopharmaceutical by securely binding the radioisotope to the ligand/vector. This minimizes side effects or non-specific radiation exposure. Key features of chelators include:

- **Stability**: Ensuring the radioisotope remains attached under physiological conditions.
- **Biocompatibility**: Minimizing toxicity and unwanted interactions with healthy tissues.
- **Specificity**: Designed for particular radioisotopes, optimizing binding strength and minimizing degradation.

Common chelators are:

- **DOTA**: Widely used for binding isotopes like ^{177}**Lu** and ^{68}**Ga**.
- **NOTA**: Preferred for ^{68}**Ga** due to its smaller size.
- **DFO** : Effective for binding ^{89}**Zr** in immuno-PET imaging.

Synergy of components

The interplay between the ligand/vector, chelator, and radioisotope defines the effectiveness of a radiopharmaceutical. Optimal design ensures:

- **High specificity** for the target tissue.
- **Minimal off-target radiation** to healthy tissues.
- **Stability in vivo**, reducing toxicity.
- **Effective removal** from non-target tissues to enhance imaging quality.

This cohesive structure makes radiopharmaceuticals particularly well-suited for **personalized medicine**, enabling precise diagnosis, treatment monitoring, and targeted therapy with minimized side effects.

2. Diagnostic and therapeutic applications of radiopharmaceuticals

Nuclear medicine plays a crucial role in both diagnostics and therapy across a variety of medical specialties. Currently, 67 radiopharmaceuticals are approved for use worldwide, and Figure 3 illustrates some of the key diagnostics and therapeutic applications.

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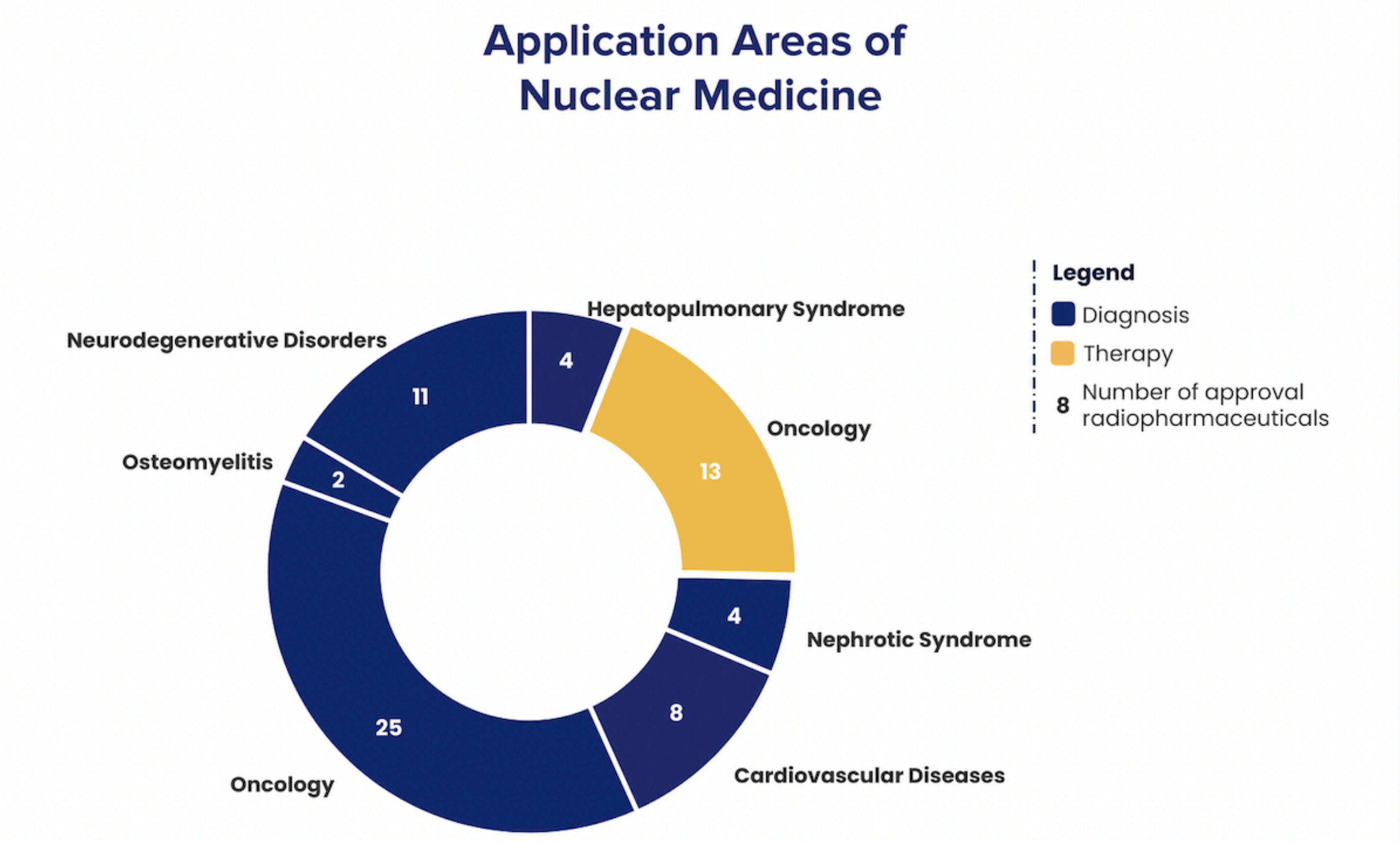

Figure 3: Application Areas of Nuclear Medicine [3]**: Number of approved radiopharmaceuticals used in diagnosis and therapy for different diseases**

2.1. Diagnostic applications of radiopharmaceuticals

The use of radiopharmaceuticals for diagnostics provides several ways of performing imaging:

- **Single-Photon Emission Computed Tomography (SPECT)**, which provides in-depth images of blood flow and organ function, particularly useful in cardiology for evaluating myocardial perfusion. SPECT operates by administering a radiotracer [4] that emits gamma rays, allowing detection by a gamma camera to create detailed images of the distribution of the substance within the body. The data collected from multiple angles can be reconstructed using computational algorithms to produce cross-sectional images that represent the functional and physiological activity of tissues and organs.

[3] Zhang, S., Wang, X., Gao, X. *et al.* Radiopharmaceuticals and Their Applications in Medicine (Signal Transduction and Targeted Therapy, 10:1, 2025) (access link)

[4] Radiotracer – General term for any chemical compound in which one or more atoms have been replaced by a radioisotope (for use in medicine, industry, etc.)

- A technique resulting in higher resolution images, **Positron Emission Tomography (PET)** is particularly valuable in oncology, as it allows for the observation of metabolic processes, such as the heightened glucose uptake in cancer cells, helping to localize tumors and assess their metabolic behavior. PET involves the injection of a radiotracer, typically a glucose analog, which emits positrons as it decays. When these positrons interact with electrons in the body, they produce gamma rays, which are detected by the PET scanner to create detailed images that reveal metabolic activity and cellular function.

- Modern medicine uses also **Hybrid Imaging Techniques**, which combine PET or SPECT with computed tomography (CT) or magnetic resonance imaging (MRI), and offer even greater precision. This integration provides a comprehensive view, enhancing diagnostic accuracy by precisely localizing functional abnormalities within the context of detailed anatomical structures.

Radiopharmaceuticals are crucial in diagnosing a range of conditions, e.g.:

- In **Oncology**, PET scans with the use of ingested Fluorodeoxyglucose (FDG) identify cancerous tissues and help track metastasis and guide choices between surgical versus non-surgical interventions.
- In **Cardiology**, SPECT imaging is used to evaluate heart function, and in particular, to assess coronary artery disease.
- In **Neurology**, PET and SPECT help in diagnosing neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.
- In the **Inflammation Imaging**, radiopharmaceuticals can localize infection sites and inflammatory processes, aiding in treatment decisions.

The radiopharmaceutical imaging is essential in various medical specialties for determining the stage of a disease, assessing the extent of its spread, and guiding treatment decisions. In addition, this type of imaging can help in monitoring how well a patient is responding, allowing for timely adjustments to treatment plans

2.2. Therapeutic applications of radiopharmaceuticals

Radiopharmaceuticals used therapeutically mainly in oncology, deliver targeted radiation to diseased cells, minimizing damage to surrounding healthy tissue. Several types of therapy can be distinguished:

- **Radioimmunotherapy (RIT)**: This therapy uses antibodies tagged with radioactive isotopes (such as ^{90}Y or ^{131}I) to selectively target cancer cells. RIT treats certain types of lymphoma, prostate cancer, and neuroendocrine tumours, with other potential uses currently in development or clinical trials [5], [6].

[5] Radioimmunotherapy (RIT) (RadiologyInfo.org, reviewed Aug 2023) (access link)

[6] Fact Sheet: What is Radioimmunotherapy (Society of Nuclear Medicine and Molecular Imaging, SNMMI-Patients) (access link)

- **Peptide Receptor Radionuclide Therapy (PRRT)**: This method employs radiolabeled [7] peptides to bind to specific receptors on tumors. For example, neuroendocrine tumors are treated with a drug containing ^{177}Lu administered intravenously. The ^{177}Lu binds to receptors present on the surface of cancer cells, delivering targeted radiation [8].

- **Radioligand Therapy (RLT)**, also known as Targeted Radionuclide Therapy, utilizes ligands that specifically bind to cell markers, such as PSMA ligands, targeting prostate cancer cells. These ligands are typically low-molecular-weight compounds, allowing **rapid tumour penetration and fast clearance from non-target tissues**. Once bound, the ligand directs the attached radioisotope to the cancer cells, delivering localized radiation even when tumour lesions are small, heterogeneous, or widely disseminated throughout the body.

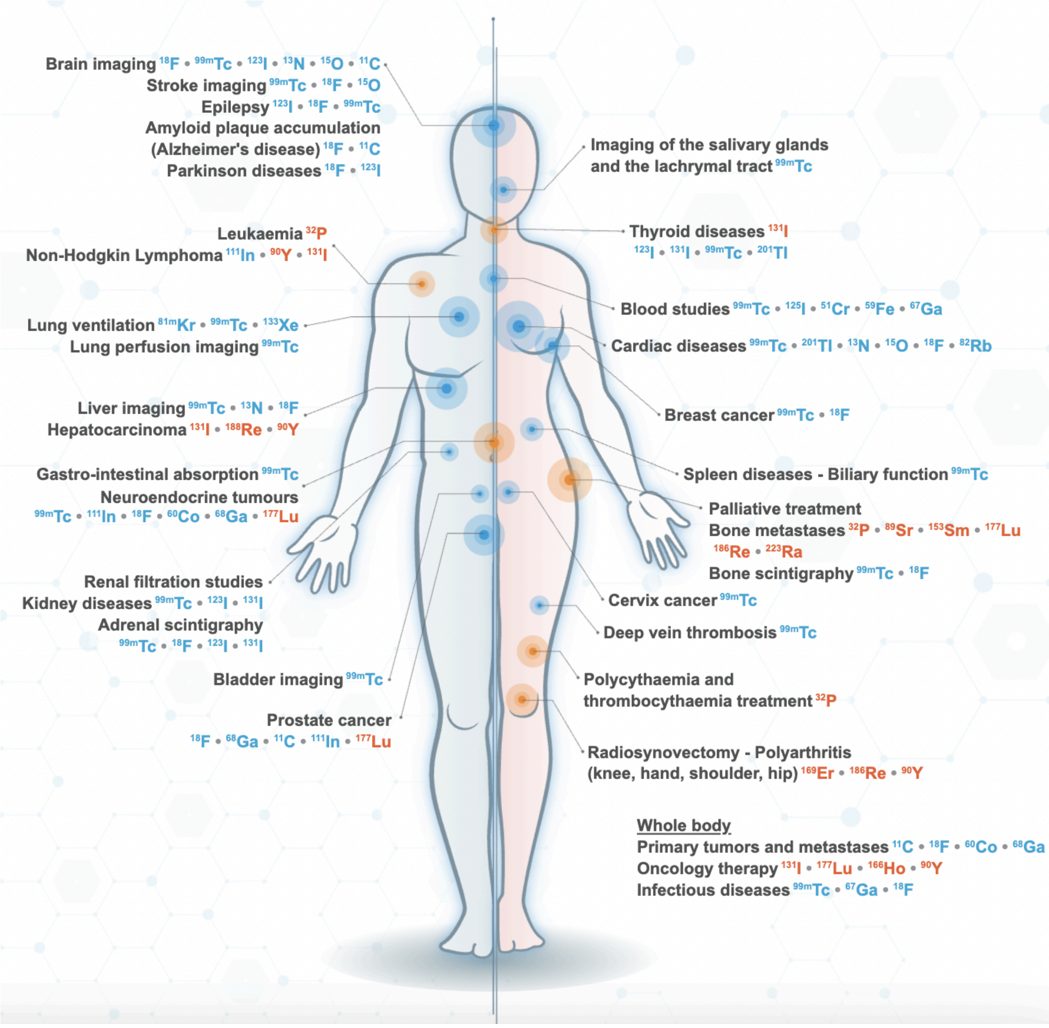

Figure 4: Diagnostic and therapeutic isotopes. The displayed isotopes are all present in products that have been granted E.U. marketing authorization. Experimental molecule treatments have not been included [9]

[7] Radiolabeling is the process of chemically incorporating a radionuclide into a compound

[8] Fact Sheet: What is Peptide Receptor Radionuclide Therapy (PRRT) (Society of Nuclear Medicine and Molecular Imaging) (access link)

[9] Hygieia – Interactive Data on Diagnostic and Therapeutic Isotopes (Nuclear Medicine Europe) (access link)

In radiopharmaceutical therapy, various specific solutions offer particular benefits. In oncology, RIT and PRRT provide targeted approaches for cancers that may not respond well to other treatments. Certain radiopharmaceuticals can relieve bone pain in metastatic cancers by selectively irradiating the affected bone areas, offering significant pain reduction. The radioisotope ^{131}I remains a standard therapy for thyroid disorders, including hyperthyroidism and thyroid cancer. It selectively targets thyroid tissue, facilitating therapeutic removal of abnormal cells.

Radiopharmaceutical therapies have gained importance thanks to their manageable side effects relative to their therapeutic benefits across various conditions. Studies show that PRRT, for example, can significantly prolong survival in patients with neuroendocrine tumors, with mild toxicity compared to conventional chemotherapy. **Overall clinical outcomes, including tumor reduction, pain relief, and improved quality of life, underscore the therapeutic benefits of radiopharmaceuticals**.

Emerging Trends and Innovations

1. Theranostics: versatility and personalized treatment potential

Radiopharmaceuticals can be tailored for diagnostic, therapeutic, or combined, making them highly versatile. Their adaptability enables personalized medicine, where treatments are adjusted to a patient's specific condition and response, improving outcomes and minimizing side effects.

Theranostics (or theragnostics) is an innovative and rapidly evolving field in nuclear medicine that combines **two radiopharmaceuticals using the same ligand/vector, one for nuclear imaging/diagnostics, the other for radiation therapy**. This concept allows clinicians to select the most effective vector for a specific tumour type, monitor the response to treatment, and adjust the therapy as needed to enhance therapeutic efficacy and reduce adverse effects [10]. While the theranostics approach is **still developing and requires further clinical trials, it has already demonstrated promising results**, particularly in treating cancers such as prostate cancer (using PSMA-targeted therapy) and neuroendocrine tumors (with peptide receptor therapy, PRRT).

As research progresses, theranostics proves its significance and future prospects and is poised to revolutionize how we diagnose and treat cancers, offering a more precise and patient- centered approach [11].

2. Advances in radiopharmaceutical production techniques

Medical radioisopes used in **radiopharmaceuticals** are produced by irradiating target materials with charged particles in particle accelerators (predominantly cyclotrons), or with neutrons in nuclear reactors, as can be seen in Figure 1.

[10] Nuclear Medicine – A Brief Introduction (Nuclear Medicine Europe) (access link)

[11] *Ibid*. (access link)

Cyclotrons and other particle accelerator systems are particularly advantageous for producing **short-lived isotopes such as ^{68}Ga and ^{99m}Tc**, improving availability and reducing costs, while nuclear **reactors** are essential for **longer-lived isotopes like ^{131}I, ^{117}Lu, and ^{99}Mo**, which are vital for both diagnostic imaging and targeted radiotherapy.

For patients, these complementary production routes translate into more reliable access to essential diagnostic and therapeutic procedures, reduced delays in care, and improved continuity of treatment, particularly for time-critical or personalized therapies.

Recent advancements in further steps of radiopharmaceutical production move forward especially in the field of production methods, radiolabelling, yield and quality enhancement.

Advances in production methods:

- **Microfluidics technology**, manipulating small volumes of fluids within microscale channels to enable precise control of chemical reactions, is emerging as a powerful tool in radiopharmaceutical synthesis. This approach allows to miniaturize and automate the synthesis of radiopharmaceuticals, enhancing efficiency and reducing reagent use.
- **Automated synthesis platforms** have become increasingly important for standardizing radiopharmaceutical production. These systems streamline production process, while minimizing human error, facilitating compliance with Good Manufacturing Practices (GMP) and improving reproducibility.

Advancements in radiolabeling chemistry:

Radiolabelling is the process of **chemically incorporating a radioisotope** into a compound, creating a **radiotracer**. This allows the compound to be tracked using nuclear imaging techniques such as **PET** or **SPECT**. Among the recent advancements are:

- The development of **novel ligands/vectors, and chelators** has significantly enhanced radiotracer conjugation techniques [12], offering improved biological targeting and in-vivo stability of radiopharmaceuticals.
- Recent breakthroughs in **click chemistry and bioorthogonal reactions** [13] **have enabled rapid and highly selective radiolabeling processes under mild conditions, protecting bioactivity and structural integrity of sensitive biological molecules.**
- **Bifunctional chelators** have been introduced to allow for the incorporation of both imaging and therapeutic isotopes into a single molecule.

Enhancing radiopharmaceutical yield, purity and stability:

In terms of enhancing quality, following advancements are visible in the field:

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[12] Radiotracer Conjugation Techniques - the process of joining two molecules together to form a complex, i.e. to attach a radioactive isotope to a ligand/vector

[13] Click chemistry –near-perfect synthesis reactions for assembling fragments into more complex structures. Bioorthogonal reactions occur rapidly and under biological conditions

- Optimization of target material processing and irradiation parameters in cyclotron and reactor production to **maximize radioisotope yield**.

- . Advances in **purification techniques** at both the radioisotope and radiopharmaceutical levels, including solid-phase extraction and high-performance liquid chromatography (HPLC), are applied first to separate the desired radioisotope from irradiated target materials and radionuclidic impurities, and subsequently to purify the final radiopharmaceutical formulation after radiolabelling. These purification steps are essential to ensure radionuclidic, radiochemical, and chemical purity, which are critical for clinical safety and regulatory compliance.

- Development of **stabilizing agents and nanocarriers**, which enhances shelf-life and biodistribution properties of a radiopharmaceutical.

3. Novel radiopharmaceuticals and their applications

Many novel radiopharmaceuticals are currently entering the market **targeting specific biomarkers and molecular pathways** involved in various diseases.

Innovative ligands/vectors designed for oncology are able to target specific issues like:

- PSMA in prostate cancer,
- Somatostatin receptors in neuroendocrine tumors,
- HER2 receptors in breast cancer,
- Fibroblast activation protein (FAP) in various epithelial tumors,
- CXCR4 receptors in hematological malignancies,
- Epidermal Growth Factor Receptor (EGFR) in lung cancer,
- Vascular Endothelial Growth Factor Receptor (VEGFR) in angiogenesis-related tumors.

> **"The applications of novel radiopharmaceuticals include improvement of early disease detection and their treatment. Targeted radioisotope therapies show promise in late-stage cancers with minimal systemic toxicity."**

We also observe further expansion of radiopharmaceuticals into non-cancer applications, including **amyloid and tau imaging for Alzheimer's disease** (imaging of two key pathological hallmarks of the disease) and **inflammatory biomarkers** for autoimmune and cardiovascular disorders.

3.1. On the way to implementation:

The novel radiopharmaceuticals, on their way to implementation, must undergo **preclinical and clinical studies:**

- Preclinical research explores new vectors/ligands, isotopes, and delivery systems to enhance efficacy and reduce off-target effects.

- Ongoing clinical trials are evaluating pharmacokinetics, safety profiles, and treatment outcomes, with many substances progressing from experimental to clinical use.
- Studies also aim at identifying the potential in addressing radiation resistance and combining radiopharmaceuticals with immunotherapy or chemotherapy.

In general, the diagnostic and therapeutic applications of novel radiopharmaceuticals include improvement of early disease detection, particularly in hard-to-diagnose conditions, and of their treatment. Finally, targeted radioisotope therapies show promise in late-stage cancers with minimal systemic toxicity.

4. Integration of artificial intelligence and data analytics in optimizing radiopharmaceutical design and usage

AI and data analytics are revolutionizing nuclear medicine by enhancing radiopharmaceutical design, imaging interpretation, treatment planning, and patient management. Machine learning models can also improve image analysis by identifying subtle patterns in PET and SPECT scans that may escape human detection.

Several major examples of the use of AI in the field of radiopharmaceuticals include:

- **Support for radiopharmaceuticals development**, e.g.:
  o **Virtual screening** of radiotracer candidates, that accelerates discovery by predicting **binding affinity, stability**, and **pharmacokinetics**.
  o Support in optimization of radiolabeling strategies, ensuring better targeting and reducing off-target radiation.

- Personalized dosimetry and treatment **optimization**, e.g.:
  o AI-driven models, that enable **patient-specific dose calculations**, adaptive treatment planning, and predicting treatment responses based on individual imaging biomarkers.
  o Personalized treatment approaches, that improve efficacy and reduce side effects in **Targeted Radionuclide Therapy (TRT)**.

- Integration in **nuclear imaging modalities**, e.g.:
  o AI algorithms enhance nuclear imaging (PET/SPECT) by automating lesion detection, quantifying radiotracer uptake, and analyzing patterns for disease progression.
  o Automated image analysis reduces interpretation time while maintaining or improving diagnostic accuracy.

Examples of AI-driven solutions already demonstrate increased efficiency in clinical workflows, better treatment response prediction, and improved resource allocation. Studies showcase also improved outcomes in oncology, cardiology, and neurology due to optimized dosimetry and adaptive treatment strategies. However, its implementation also presents **challenges**, such as issues with data quality, algorithm robustness, regulatory compliance, and ethical concerns related to transparency and patient privacy.

Conclusion

Radiopharmaceuticals represent a powerful convergence of nuclear science and modern medicine, offering precision in diagnosis and treatment across a range of conditions. Their capacity to visualize and target diseases at the molecular level improves clinical outcomes and paves the way for personalized medicine. Innovations like new isotopes, production techniques and the use of AI drive further efficiency and personalization of the treatments.

The European Union, with its strong research base and clinical infrastructure, is positioned at the forefront of this field, contributing to innovations that are transforming patient care. However, the full potential of radiopharmaceuticals can only be realized by addressing key challenges—technological, logistical, regulatory, and safety-related. As such, **Part 2 of this position paper will focus on the supply chain, policy considerations, and expert recommendations** necessary to secure and strengthen Europe's leadership in this critical domain of healthcare.

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