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Novel radiopharmaceuticals in endocrinology: a comprehensive review

Mateusz Pociegiel[1], *Tomasz Saniewski*[1], *Kamil Wrzosek*[1], *Piotr Opyd*[1], *Edward Franek*[2], *Michał Lis*[1, 3]

[1]*Clinical Department of Internal Medicine, Endocrinology, Diabetology, and Nephrology, Czerniakowski Hospital, Warsaw, Poland*
[2]*Clinical Department of Internal Medicine, Endocrinology, and Diabetology, National Medical Institute of the Ministry of the Interior and Administration, Warsaw, Poland*
[3]*Faculty of Medicine, Lazarski University, Warsaw, Poland*

Abstract

Endocrinology is the study of hormones and the endocrine glands that are responsible for maintaining homeostasis in the human body. Recently, there has been a surge of interest in the development of novel radiopharmaceuticals for diagnostic and therapeutic purposes in endocrinology. This comprehensive review explores the latest advances in novel radiopharmaceuticals with applications in the diagnosis and treatment of different endocrine disorders, including thyroid, adrenal, and pituitary disorders, as well as neuroendocrine tumours. The article discusses innovative approaches that leverage the decay characteristics of radioisotopes to enhance the accuracy of diagnostic imaging and the therapeutic capability of targeted interventions. It covers the fundamental principles underlying radiopharmaceutical design, synthesis, and imaging modalities, as well as the mechanisms that drive their efficacy in endocrine applications. Furthermore, the clinical implications of these novel radiopharmaceuticals are explored, along with their role in early detection, precise localisation, and personalised treatment strategies. Case studies and clinical trials are cited to highlight the practical utility and potential transformative impact of these advancements in the management of endocrine diseases. This review also notes current challenges, ongoing research and development, and future directions in the field. By providing a comprehensive overview of the evolving landscape of radiopharmaceuticals in endocrinology, this article aims to contribute to the collective knowledge base and foster a deeper understanding of the potential benefits and implications of these innovative technologies for both clinicians and researchers in the field of endocrine health.

Key words: *nuclear endocrinology; NET; theranostics; nuclear imaging*

Introduction

Endocrine disorders pose numerous challenges to treatment, arising from the complexity of the endocrine system, an insufficiency of diagnostic tests, and the need for individualised treatment. The advent of targeted radionuclide therapy has opened new avenues for overcoming these challenges. Theranostics is a revolutionary paradigm in nuclear medicine that leverages the unique properties of radionuclides to seamlessly integrate diagnostic imaging and therapeutic treatment. The level of precision afforded by this combination of nuclear medicine techniques has led to a significant shift toward more personalised therapies for a wide range of endocrine disorders.

Radiopharmaceutical diagnostics utilise radioactively labelled compounds or radiotracers. These can be used to noninvasively probe the function of internal organs, including those of the endocrine system. In conjunction with advanced imaging modalities, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), radiopharmaceuticals can help elucidate intricate molecular pathways, receptor kinetics, and metabolic flux within endocrine tissues. This sophisticated diagnostic armamentarium is particularly useful for nuanced identification and characterisation of endocrine pathologies.

Copper-64, for example, has PET imaging capabilities that support accurate disease diagnosis and staging. Copper-67, when chelated to targeting molecules, delivers targeted radiotherapy that minimises collateral damage to surrounding tissues. Actinium-225, an alpha-particle-emitter, exhibits a localised cytotoxic effect suitable for precision therapy in nuclear medicine. Such theranostic tools enable both high-resolution imaging and personalised, effective treatment strategies capable of advancing patient care.

Nuclear medicine has emerged as the gold standard in endocrinology, providing invaluable tools for the diagnosis, localisation, and treatment of endocrine disorders. This scientific discussion explores the key applications of nuclear medicine techniques in endo-

Mateusz Pociegiel, Clinical Department of Internal Medicine, Czerniakowski Hospital in Warsaw, Stepinska 19/25, 00–739 Warsaw, Poland; e-mail: mateusz.pociegiel@op.pl

Table 1. *Nuclear medicine gold standards for endocrine diagnostics*

Application	Gold standard
Thyroid gland	Radioactive iodine-131 (^{131}I) is widely used for imaging and treating thyroid disorders, such as hyperthyroidism and thyroid cancer ^{131}I is selectively taken up by thyroid cells, allowing for precise imaging of the thyroid gland and targeted therapy by destroying abnormal thyroid tissue
Parathyroid gland	Technetium-99m sestamibi ([^{99m}Tc]Tc-MIBI) is a radiotracer commonly employed for parathyroid imaging This technique aids in the localisation of hyperfunctioning parathyroid glands in cases of hyperparathyroidism, guiding surgeons to perform minimally invasive procedures
Adrenal gland	Iodine-131 metaiodobenzylguanidine ([^{131}I]I-MIBG) is used for imaging of adrenal medulla, to aid in the diagnosis and localisation of neuroendocrine tumours such as pheochromocytomas
Pituitary gland	Radiolabelled analogues of somatostatin, such as indium-111 pentetreotide (Octreoscan), are employed for imaging pituitary tumours, particularly those secreting growth hormone or prolactin
Endocrine oncology	^{18}F-Fluorodeoxyglucose ([^{18}F]FDG) PET is utilised to evaluate and stage endocrine malignancies to provide information on tumour metabolism and aid in treatment planning

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crinology and highlights their significance in advancing patient care (Tab. 1) [1].

The somatostatin receptor (SSTR) is deeply connected to the intricate molecular milieu of endocrine cells. Somatostatin receptors (SSTRs) have therefore become valuable targets for both radiopharmaceutical diagnostics and therapeutic interventions in endocrinology [2]. The orchestrated overexpression of SSTRs, notably subtype 2 ($SSTR_2$) and subtype 5 ($SSTR_5$), on the plasma membranes of cells inside neuroendocrine tumours (NETs) forms the basis of highly targeted imaging and treatment strategies [3]. Radiotracers have been engineered to engage these receptors with unprecedented specificity. This has allowed for a level of precision in delineation and characterisation of neuroendocrine tumours that represents a paradigm shift in diagnostics [3].

The decay characteristics of the various isotopes used in radiopharmaceuticals significantly influences their diagnostic and therapeutic efficacy. For diagnostic purposes, positron-emitting isotopes, such as fluorine-18 (^{18}F) and gallium-68 (^{68}Ga) are used in PET imaging, and the gamma-ray-emitting technetium-99m (^{99m}Tc) is commonly employed for SPECT imaging. Both allow highly sensitive imaging of metabolic and physiological processes. Beta-emitting isotopes are favoured for some therapeutic applications. These include iodine-131 (^{131}I) in radioiodine therapy for thyroid disorders and lutetium-177 (^{177}Lu) in peptide receptor radionuclide therapy (PRRT) for NETs [4].

In PRRT, the connection between the radionuclide and somatostatin analogue occurs through a designated chelator. This complex, known as the radio–analogue complex, attaches to the somatostatin receptor on the cell membrane and undergoes internalisation. Consequently, radioactivity is conveyed into an intracellular, receptor-recycling compartment of the cell, bringing the radionuclide even closer to the nucleus. Recent advancements in clinical practice have involved somatostatin receptor antagonists, which, unlike internalising agents, identify a larger number of binding sites. This leads to higher tumour-absorbed doses (Fig. 1) [5]. Beta radiation released by the radionuclide delivers localised cytotoxic effects to target tissues for precision in therapeutic outcomes while minimising damage to surrounding healthy tissues.

This discussion explores the evolving role of radiopharmaceuticals in diagnosing and treating endocrine disorders. The approach involves enhancing precision medicine by examining the molecular and decay characteristics of radiopharmaceuticals and exploiting them to tailor interventions based on detailed evaluations. As scientific research uncovers new radiotracers and therapeutic options, the application of nuclear medicine to endocrinology promises to improve diagnosis and treatment for a range of endocrine diseases, from thyroid dysfunction to NETs (Tab. 2).

This potential is particularly significant for somatostatin receptor-targeted methods such as PRRT. The use of PRRT for the treatment of pancreatic neuroendocrine neoplasms should be considered as a second-line treatment option for tumours with Ki-67 levels below 10%. PRRT may be a viable alternative to tyrosine kinase inhibitors or chemotherapy. In cases of secreting malignant pancreatic neuroendocrine neoplasms, PRRT can be used as a first-line treatment to manage symptoms, although there is currently limited evidence supporting their effectiveness [4, 6].

Diagnostic radiopharmaceuticals

[^{68}Ga]Ga-DOTATATE

The isotope gallium-68 allows high-resolution imaging via positron emission tomography/computed tomography (PET/CT). [^{68}Ga]Ga-DOTATATE has become a popular radiopharmaceutical in endocrinology [7] for diagnosing and managing neuroendocrine tumours (NETs) and other somatostatin receptor-expressing lesions. DOTATATE consists of the 8-amino-acid peptide octreotate covalently bonded to the bifunctional

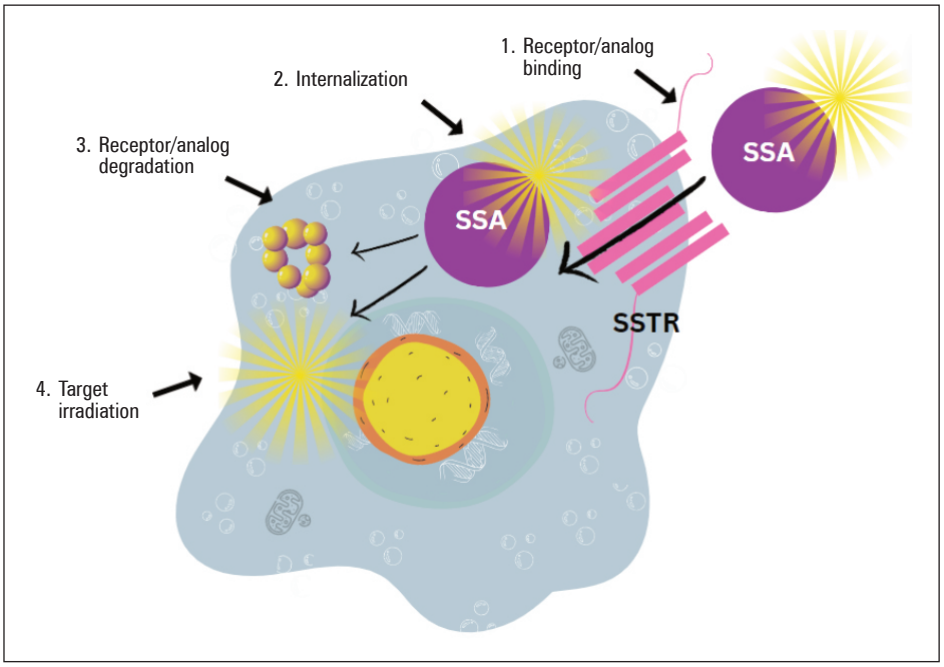

Figure 1. *Mechanism of peptide receptor radionuclide therapy (PRRT). SSA — somatostatin analogue; SSTR — somatostatin receptor*

Table 2. *Summary of applications of novel radiopharmaceuticals in endocrinology*

Compound	Clinical application	Isotope ()	Role
[^{68}Ga]Ga-DOTATATE	GEP-NETs, bronchial and thymic NETs, differentiating between NETs and other lesions	^{68}Ga (68 min)	D
[^{68}Ga]Ga-PSMA	Thyroid carcinoma, pancreatic NETs		
[^{68}Ga]Ga-DOTANOC	NETs, planning of PRRT		
[^{68}Ga]Ga-DOTATOC	NETs, metastatic lesions, whole-body scan		
[^{18}F]F-FDOPA	NETs, primary and metastatic neuroendocrine lesions of pancreas, hyperinsulinism (abnormal pancreatic tissue responsible for the hyperinsulinism)	^{18}F (109.8 min)	D
[^{68}Ga]Ga -Exendin-4	Insulinomas, assessing β-cell function in type 1 and type 2 diabetes, monitoring changes in β-cell mass over time	^{68}Ga (68 min)	D
[^{99m}Tc]Tc-MIBI	Hyperthyroidism and thyroid nodules, parathyroid adenomas, pheochromocytomas and adrenal cortical tumours, adrenal abnormalities, pituitary adenomas and incidentalomas	^{99m}Tc (6 h)	D
^{18}F]F-Fluorocholine	NETs, parathyroid (hyperfunctioning parathyroid tissue in cases of primary hyperparathyroidism)	^{18}F (109.8 min)	D
[^{68}Ga]Ga-Bombesin	Pancreatic NETs	^{68}Ga (68 min)	D
[^{68}Ga]Ga-FAPI	Pancreatic tumours, head and neck tumours, pituitary adenomas		
[^{177}Lu]Lu-DOTATOC	NETs, pheochromocytomas and paragangliomas, endocrine malignancies	^{177}Lu (6.7 d)	T
[^{131}I]I-MIBG	NETs, pheochromocytomas and paragangliomas	^{131}I (8 d)	T
[^{212}Pb]Pb-DOTAMATE	Somatostatin receptor–positive NETs	^{212}Pb (10.6 h)	T
[^{213}Bi]Bi-DOTATOC	Somatostatin receptor–positive NETs	^{213}Bi (45.6 min)	T
[^{64}Cu]Cu-DOTATATE	GEP-NETs, pheochromocytomas and paragangliomas, GISTs, MTC, lung and bronchial NETs	^{64}Cu (12.7 h)	Th
[^{64}Cu]Cu-Cetuximab	Pancreatic cancer, head and neck cancer, monitoring treatment response		
[^{225}Ac]Ac-DOTA-JR11	NETs	^{225}Ac (10 d)	Th

GEP-NET — gastroenteropancreatic neuroendocrine tumour; NET — neuroendocrine tumour; GIST — small intestinal gastrointestinal stromal tumour; MTC — medullary thyroid cancer; $t_{1/2}$ — half-life of isotope; ^{68}Ga — gallium-68; ^{18}F — fluorine-18; ^{212}Pb — lead-212; ^{213}Bi — bismuth-213; ^{64}Cu — copper 64; ^{225}Ac — actinium-225; D — diagnostics; T — therapy; Th — theranostics

chelator 1,4,7,10-tetraazacyclododecane-N, N′, N,″ N′′-tetraacetic acid (DOTA). Octreotate is a somatostatin analogue with a high affinity for SSTRs. SSTRs are overexpressed in many NETs, making them ideal targets for diagnostic purposes. The development of [^{68}Ga]Ga-DOTATATE has led to more accurate and earlier detection of NETs, aiding the selection of appropriate treatment strategies and positioning [^{68}Ga]Ga-DOTATATE as the putative gold standard for NETs [8, 9].

[^{68}Ga]Ga-DOTATATE is prepared through the complexation of ^{68}Ga with DOTATATE. The source of ^{68}Ga is based on the choice of on-site production process, either cyclotron irradiation or radionuclide generator [10].

Expression of SSTRs

This section discusses the mechanism of action of [^{68}Ga]Ga-DOTATATE. The high affinity of radiopharmaceuticals for SSTRs, particularly $SSTR_2$, has been explained [11]. Insulinomas, the most prevalent pancreatic islet cell tumours, often lead to hypoglycaemia due to excessive insulin production. Approximately 90% of insulinomas are benign and solitary, with 99% located in the pancreas [12]. SSTR expression studies have indicated consistent expression of $SSTR_1$ and $SSTR_2$ in insulinomas. Radioligand competition studies revealed $SSTR_2$ and $SSTR_5$ binding sites in 72% of insulinomas, $SSTR_3$ in 44%, $SSTR_1$ in 44%, and $SSTR_4$ in 28%.

Glucagonomas, the third-most-common islet cell tumour, are malignant in 70% of cases. In glucagonomas, $SSTR_2$ shows high expression, whereas $SSTR_5$ expression is lower, consistent with the pattern observed in normal pancreatic α-cells. Due to the rare occurrence of glucagonomas, drawing a generalised conclusion regarding SSTR expression is challenging.

Gastrinomas, which constitute up to 20% of pancreatic endocrine tumours, induce gastric ulcer formation through increased gastric acid secretion. The prevalence of expression of $SSTR_2$ (in up to 100% of tumours) and $SSTR_5$ (in 76–100% of tumours) in gastrinomas correlates with positive clinical responses to octreotide treatment.

Somatostatinomas, which are mostly malignant and pancreatic polypeptide (PP)-producing tumours, are exceedingly rare. Vasoactive intestinal polypeptide–producing tumours (VIPomas), found in endocrine islets, also occur with low incidence. Although limited data hinder generalisation, $SSTR_5$ appears to be predominantly expressed in somatostatinomas, while $SSTR_2$ is prevalent in VIPomas. This molecular insight supports diagnostic and therapeutic targeting using radioactive octreotide for rare tumour entities [13–15].

Clinical applications

Clinical applications of [^{68}Ga]Ga-DOTATATE include tumour localisation, staging and grading, therapeutic planning, response monitoring, and patient selection for PRRT.

Table 3. *Advantages and limitations of [^{68}Ga]Ga-DOTATATE*

Advantages	Limitations
High sensitivity and specificity	Short half-life of ^{68}Ga
Improved patient management	Requirement for on-site sterile radiopharmacy facilities and radionuclide generator or cyclotron
Reduced radiation exposure compared to traditional scintigraphy methods	

^{68}Ga — gallium-68

Table 3 summarises the key advantages and limitations of [^{68}Ga]Ga-DOTATATE in the field of nuclear medicine.

Table 4 highlights the impact of [^{68}Ga]Ga-DOTA-conjugated peptides on the diagnosis and management of NETs [16].

[^{68}Ga]Ga-PSMA

As this article provides an in-depth examination of the development of radiotracers, their radiopharmaceutical characteristics, and emerging applications in endocrinology [17], it is worthwhile discussing the growing role of [^{68}Ga]Ga-PSMA in PET in endocrinology. [^{68}Ga]Ga-PSMA binds prostate-specific membrane antigen (PSMA), it was originally designed for prostate cancer detection, and it is still primarily used for prostate cancer imaging. However, recent studies have demonstrated a wider potential application in endocrinology. [^{68}Ga]Ga-PSMA exhibits affinities for specific receptors expressed in both prostate and certain other endocrine tissues [18]. In addition, some endocrine tumours, such as pheochromocytomas and paragangliomas, express PSMA. [^{68}Ga]Ga-PSMA can be used to visualise and diagnose these tumours with high sensitivity and specificity.

Recent studies have revealed that [^{68}Ga]Ga-PSMA can detect parathyroid gland lesions, neuroendocrine tumours, and thyroid lesions [19]. Compared to conventional endocrine imaging modalities, the ability of [^{68}Ga]Ga-PSMA PET to simultaneously provide functional and anatomical information makes it a potentially valuable tool in certain endocrine scenarios. Despite its promising applications, the use of [^{68}Ga]Ga-PSMA in endocrinology is not without its challenges, including the variability of receptor expression and the need for rigorous standardisation.

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Various malignant conditions other than prostate cancer may result in [^{68}Ga]Ga-PSMA uptake. Several non-prostatic tumours express PSMA, either on their cell membranes or within the endothelial cells of

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Table 4. *Tumours that may be visualised with [^{68}Ga]Ga-DOTA-conjugated peptides using positron emission tomography (PET) imaging*

High expression of receptors	Low expression of receptors
Gastroenteropancreatic tumours (e.g. carcinoids, gastrinoma, insulinoma, glucagonoma, VIPoma, etc.), functioning and nonfunctioning.	Breast cancer
Sympathoadrenal system tumours (phaeochromocytoma, paraganglioma, neuroblastoma, ganglioneuroma)	Melanoma
Medullary thyroid carcinoma	Lymphomas
Pituitary adenoma	Prostate carcinoma
Medulloblastoma	Non-small-cell lung cancer
Merkel cell carcinoma	Sarcomas
Small-cell lung cancer (mainly primary tumours)	Renal cell carcinoma
Meningioma	Differentiated thyroid carcinoma
	Astrocytoma
	Ependymoma

the capillary beds associated with tumour neovasculature. Consequently, these tumours demonstrated PSMA uptake in imaging studies. Examples of non-prostate malignancies displaying PSMA uptake include renal cell carcinoma, pulmonary adenocarcinoma, multiple myeloma, glioblastoma multiforme, hepatocellular carcinoma, urothelial carcinoma, lymphoma, squamous cell carcinomas, colorectal carcinoma, thyroid carcinoma, gastrointestinal stromal tumours, and pancreatic neuroendocrine tumours (PNETs) [20].

[^{68}Ga]Ga-PSMA has evolved from a groundbreaking tool in prostate cancer imaging to become an unexpected protagonist in the field of endocrinology. With its ability to detect various endocrine lesions, [^{68}Ga]Ga-PSMA is a multifaceted diagnostic tool with potential to play a role in endocrine imaging and contribute to the paradigm shift toward more personalised targeted therapies.

[^{68}Ga]Ga-DOTANOC

[^{68}Ga]Ga-DOTANOC is a radiotracer with applications in NET imaging. It has high affinity for $SSTR_2$, $SSTR_3$, and $SSTR_5$ and allows detection of primary and metastatic lesions. Accurate staging is crucial for clinicians developing effective, personalised treatment strategies for NETs. [^{68}Ga]Ga-DOTANOC provides precise information about tumour localisation, a capability that is particularly valuable when conventional imaging modalities do not supply a full understanding of the extent and distribution of NETs, such as with PNETs, gastrointestinal neuroendocrine tumours (GI-NETs), and lung neuroendocrine tumours (LNETs) [21]. [^{68}Ga]Ga-DOTANOC thus plays an important role in staging by identifying distant metastases and characterizing the disease burden. [^{68}Ga]Ga-DOTANOC can also be used to determine the grade of NETs based on the intensity of somatostatin receptor expression, further supporting a more personalised approach to patient management for tumours such as well-differentiated NETs (WD-NETs) and poorly differentiated neuroendocrine carcinomas (PD-NECs) [22]. By precisely delineating the extent of somatostatin receptor-positive lesions, [^{68}Ga]Ga-DOTANOC supports NET treatment planning and therapeutic interventions, including surgery, PRRT, and targeted systemic therapies.

[^{68}Ga]Ga-DOTANOC is also useful in monitoring treatment responses, allowing for timely adjustments to therapeutic regimens based on changes in somatostatin receptor expression. This is applicable to various types of NETs, including gastrointestinal carcinoids, bronchopulmonary carcinoids, and thymic NETs [23]. In certain clinical scenarios, such as insulinomas, gastrinomas, and glucagonomas, distinguishing between benign and malignant lesions or discerning different subtypes of NETs can be challenging. Highlighting patterns of somatostatin receptor expression aids in differentiation of these lesions, which improves diagnostic accuracy and helps inform decisions to tailor the aggressiveness of therapeutic interventions. Somatostatin receptor expression in NETs is associated with prognosis. [^{68}Ga]Ga-DOTANOC, which noninvasively assesses somatostatin receptor density, contributes prognostic information helpful for risk stratification and determination of the overall management approach for patients with NETs of various subtypes and grades [24].

[^{68}Ga]Ga-DOTANOC is useful for NET imaging across diverse tumour types and subtypes. With multiple applications in diagnosis, staging, treatment planning, lesion differentiation, and prognostic assessment, the radiotracer contributes significant information helpful for guiding clinical decisions supporting personalised and targeted therapeutic strategies for NET patients.

[^{68}Ga]Ga-DOTATOC

[^{68}Ga]Ga-DOTATOC is a radiolabelled somatostatin analogue that specifically binds to $SSTR_2$ and is therefore a useful imaging agent for detecting and localising NETs, which commonly overexpress somatostatin receptors. [^{68}Ga]Ga-DOTATOC has superior sensitivity and specificity in detecting and staging neuroendocrine tumours, compared to conventional imaging modalities. It allows for precise localisation and categorisation of both primary tumours and metastatic lesions expressing high concentrations of somatostatin receptors. In addition to its diagnostic role, [^{68}Ga]Ga-DOTATOC PET provides clinicians with information on disease extent and treatment response to support planning and monitoring of personalised therapeutic approaches, such as PRRT, with high precision [25]. [^{68}Ga]Ga-DOTATOC allows for comprehensive whole-body imaging for the detection of both primary and metastatic lesions in a single examination. This feature is particularly useful in the management of NETs, which often present as multifocal and metastatic diseases [26].

[^{68}Ga]Ga-DOTATOC's high sensitivity, specificity, and whole-body imaging capabilities make it an invaluable tool in NET management for diagnosis, staging, treatment planning, and monitoring. As this technology continues to advance, and with ongoing research, [^{68}Ga]Ga-DOTATOC is likely to play an increasingly prominent role in personalised management of NETs.

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[^{18}F]FDOPA

Fluorine-18 3,4-dihydroxyphenylalanine ([^{18}F]FDOPA) has gained significant attention in the field of endocrinology as a PET radiotracer, particularly in the imaging of NETs [27]. [^{18}F]FDOPA is an analogue of the amino acid *L*-DOPA with high specificity for neuroendocrine tissues. The radiotracer exhibits excellent chemical stability and a short half-life (110 min), making it suitable for clinical use [28].

Mechanism of uptake

The mechanism of [^{18}F]FDOPA uptake in neuroendocrine tissue is closely related to the *L*-DOPA metabolic pathway. Neuroendocrine cells, particularly those in NETs, express aromatic *L*-amino acid decarboxylase, leading to the accumulation of [^{18}F]FDOPA in these cells. This uptake mechanism enhances the sensitivity and specificity of [^{18}F]FDOPA PET imaging for the detection of neuroendocrine lesions [29].

Clinical applications

[^{18}F]FDOPA has demonstrated high sensitivity and accuracy for the detection of primary and metastatic neuroendocrine lesions. Its ability to detect lesions in various organs, including the pancreas, gastrointestinal tract, and lungs, can contribute to improved diagnosis and staging [29]. [^{18}F]FDOPA PET/CT with carbidopa premedication resulted in positive detection for 8 of 11 patients (73%) with histologically proven solitary insulinoma. In control patients who underwent PET/CT without carbidopa premedication, none of the confirmed lesions (4 insulinomas, one nesidioblastosis) were detected [30] As previously mentioned, precise localisation of NETs is crucial for treatment planning. [^{18}F]FDOPA aids in identifying and localising lesions that may be missed by other imaging modalities, thereby assisting in guiding therapeutic decisions such as surgery, radiotherapy, or targeted radionuclide therapy. Changes in [^{18}F]FDOPA uptake can provide valuable information about the treatment response, allowing for early adjustments to improve the effectiveness of personalised therapeutic strategies [28].

Comparisons between [^{18}F]FDOPA and other imaging modalities, such as octreotide scintigraphy and CT/MRI, revealed that [^{18}F]FDOPA possesses better sensitivity and specificity in detecting small lesions and those with low somatostatin receptor expression. Research is ongoing to further optimise [^{18}F]FDOPA imaging protocols and explore their applications in other endocrine disorders. Efforts are also underway to develop novel radiotracers that can complement or enhance [^{18}F]FDOPA's diagnostic capabilities in endocrinology [31].

[^{68}Ga]Ga-Exendin-4

[^{68}Ga]Ga-Exendin-4 is a radiopharmaceutical used for imaging pancreatic β-cell function and localisation of insulinomas. It binds to glucagon-like peptide-1 (GLP-1) receptor, and therefore can provide insight into the function and distribution of insulin-secreting cells. Since its applications focus on visualisation of pancreatic β-cells, it has potential implications for noninvasive detection and management of endocrine disorders [32, 33]. The synthesis of [^{68}Ga]Ga-Exendin-4 involves conjugation of exendin-4 with a chelator that can stably complex with gallium-68. Radiolabelling is achieved through the coordination of gallium-68 with the chelator [34]. Common chelators include NOTA (1,4,7-triazacyclononane-N, N′, N′′-triacetic acid) and DOTA (1,4,7,10-tetraazacyclododecane-N, N′, N,″ N′′-tetraacetic acid).

Clinical applications

[^{68}Ga]Ga-Exendin-4 imaging has demonstrated high sensitivity and specificity in visualising pancreatic β-cells. This is particularly relevant in the context of diabetes mellitus, where the ability to noninvasively assess β-cell mass makes early diagnosis and personalised treatment strategies possible [32]. Several clinical stud-

ies have investigated the utility of [^{68}Ga]Ga-Exendin-4 under different endocrine conditions. Notable trials include those evaluating its role in detecting insulinomas, assessing β-cell function in type 1 and type 2 diabetes, and monitoring changes in β-cell mass over time [33, 35].

[^{99m}Tc]Tc-MIBI

[^{99m}Tc]Tc-MIBI, a lipophilic cationic radiopharmaceutical, is widely utilised in nuclear medicine and has proven invaluable for imaging various endocrine organs. [^{99m}Tc]Tc-MIBI is taken up by cells in proportion to their mitochondrial membrane potential. In endocrine tissues, the accumulation of [^{99m}Tc]Tc-MIBI is influenced by metabolic activity and tissue perfusion. This mechanism forms the basis for [^{99m}Tc]Tc-MIBI imaging to detect abnormalities in endocrine organs [36].

Clinical applications

Thyroid disorders, including hyperthyroidism and thyroid nodules, can be effectively evaluated using [^{99m}Tc]Tc-MIBI. The radiotracer accumulates in thyroid tissues, which allows visualisation of functional abnormalities and differentiation of benign and malignant lesions [37]. Primary hyperparathyroidism often necessitates localisation of abnormal parathyroid glands for surgical intervention. [^{99m}Tc]Tc-MIBI scintigraphy, in combination with other imaging modalities, is capable of identifying parathyroid adenomas and hyperplasia [38, 39]. Radiotracer uptake in adrenal tissues aids in the localisation and characterisation of adrenal abnormalities, and functional adrenal lesions such as pheochromocytomas and adrenal cortical tumours can be imaged using [^{99m}Tc]Tc-MIBI [40]. Although less common, [^{99m}Tc]Tc-MIBI has been employed for imaging pituitary adenomas and incidentalomas. In conjunction with other imaging techniques, it contributes to the comprehensive assessment of pituitary disorders [41, 42]. Overall, [^{99m}Tc]Tc-MIBI plays an important role in the imaging of endocrine organs and the diagnosis and management of a wide range of endocrine disorders.

[^{18}F]F-Fluorocholine

[^{18}F]F-Fluorocholine ([^{18}F]-FCH) is a radiopharmaceutical with applications in imaging various tumours, including parathyroid adenomas. It also aids in the surgical management of primary hyperparathyroidism by locating hyperfunctioning parathyroid glands [43]. To correctly interpret imaging results, it is important to understand the radiotracer's mechanism of action. [^{18}F]-FCH mimics choline metabolism and exhibits preferential uptake in tissues with increased cell membrane turnover. Beheshti et al. [44] discuss the molecular processes and factors that influence [^{18}F]-FCH uptake in endocrine tissues.

Clinical applications

The thyroid is a central player in overall endocrine function. However, assessment of thyroid nodules and malignancies can present a diagnostic challenge, which [^{18}F]-FCH can assist by differentiating benign from malignant lesions [45, 46]. [^{18}F]-FCH can also be used to image NETs and other endocrine pathologies [47]. Recent studies have investigated the feasibility of using [^{18}F]-FCH for the localisation and characterisation of parathyroid lesions [48, 49]. Comparisons with conventional imaging modalities, such as CT and magnetic resonance imaging (MRI), are essential for evaluating the added value of [^{18}F]-FCH. Beheshti et al. [44] provide a comprehensive analysis of the diagnostic accuracy and clinical relevance of [^{18}F]-FCH PET compared with other imaging techniques. [^{18}F]-Fluorocholine has emerged as a valuable and versatile tool in the field of endocrinology. Its application in prostate, thyroid, and neuroendocrine imaging has shown clinical significance.

[^{68}Ga]Ga-Bombesin

Bombesin is a 14-amino acid peptide with a high affinity for gastrin-releasing peptide receptor (GRPR). The current state of knowledge, technological advancements, and potential clinical implications of [^{68}Ga]Ga-Bombesin in endocrinology have been previously reviewed [50]. GRPR is overexpressed in certain endocrine tumours, including prostate, breast, and gastrointestinal NETs, a finding that prompted the investigation of [^{68}Ga]Ga-Bombesin for molecular imaging purposes [51].

Clinical applications

Translation of [^{68}Ga]Ga-Bombesin from preclinical research to clinical practice is underway. Numerous preclinical studies have demonstrated the feasibility and specificity of [^{68}Ga]Ga-Bombesin in detecting GRPR-positive tumours. Animal models have provided valuable insights into the pharmacokinetics, biodistribution, and dosimetry of this imaging modality [52]. GRPR is a transmembrane G protein-coupled receptor found in the central nervous system, gastrointestinal tract, and pancreas. The receptor is involved in modulating diverse physiological functions, including synaptic plasticity, hormone secretion, smooth muscle contraction, and cell proliferation [53, 54].

[^{68}Ga]Ga-FAPI

Fibroblast activation protein inhibitors (FAPI) are a class of molecules that bind to fibroblast activation protein, a marker overexpressed in various tumours and tissues associated with endocrine pathology. When complexed with gallium-68, these radiotracers show promise

for high-resolution PET imaging of endocrine pathological changes at the molecular level [55].

Clinical applications

[^{68}Ga]Ga-FAPI holds potential for imaging a diverse spectrum of cancers, including pancreatic, head and neck, colon, lung, and breast cancers. Notably, FAPI imaging demonstrates tumour-to-background contrast ratios that are comparable to or surpass those achieved with [^{18}F]Fluorodeoxyglucose (FDG)-PET imaging [56]. Its sensitivity and specificity can improve diagnostic accuracy for thyroid diseases [57, 58]. NETs, which are often challenging to localise, can also be effectively visualised using [^{68}Ga]Ga-FAPI due to the increased uptake of FAPI in these tumours. [^{68}Ga]Ga-FAPI has potential applications in pituitary imaging, for assessment and characterisation of pituitary adenomas. As a noninvasive diagnostic tool, it may offer additional insights into tumour biology and guide therapeutic decisions [59, 60]. As research on this method continues to evolve, [^{68}Ga]Ga-FAPI may become an integral component of the endocrinologist's diagnostic toolkit [61].

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Therapeutic radiopharmaceuticals

[^{177}Lu]Lu-DOTATOC

[^{177}Lu]Lu-DOTATOC is a therapeutic radiopharmaceutical that has revolutionised the treatment of inoperable and metastatic NETs. It belongs to a class of radiolabelled somatostatin analogues and delivers targeted radiation to tumour cells expressing SSTRs [62]. The success of [^{177}Lu]Lu-DOTATOC in prolonging progression-free survival and improving patient quality of life has made it a valuable addition to the armamentarium of endocrine tumour treatments. [^{177}Lu]Lu-DOTATOC has high affinity for somatostatin receptors, particularly for subtype 2, which is overexpressed in many NETs. The binding of [^{177}Lu]Lu-DOTATOC to $SSTR_2$ initiates internalisation of the receptor-ligand complex, leading to localised emission of beta radiation, induction of DNA damage, and ultimately, targeted tumour destruction [63].

Therapeutic applications

Clinical studies reveal a role for [^{177}Lu]Lu-DOTATOC in the management of NETs, especially those overexpressing $SSTR_2$. PRRT with [^{177}Lu]Lu-DOTATOC showed substantial improvement in progression-free survival and symptomatic relief [64]. Given their expression of somatostatin receptors, pheochromocytomas and paragangliomas are potential therapeutic targets for [^{177}Lu]Lu-DOTATOC. This application is supported by preliminary investigations, but further research is needed on its efficacy and safety for these malignancies [65]. Promising results were obtained for PRRT with ^{177}Lu/^{90}Y (DOTATATE or DOTATOC) in 69 patients, including 46 patients with pancreatic NET. The results were particularly encouraging for patients with a Ki-67 index of ≤ 55%, even for those who had previously failed chemotherapy [4]. Success in [^{177}Lu]Lu-DOTATOC therapy relies on precise patient selection based on somatostatin receptor imaging to ensure optimal receptor avidity and therapeutic response. Advanced imaging modalities, such as [^{68}Ga]Ga-DOTATATE, can be used to characterise receptor expression patterns [65, 66]. Customisation of the [^{177}Lu]Lu-DOTATOC treatment regimen involves meticulous consideration of dosimetry and administration schedule, tumour burden, and kidney function to optimise therapeutic efficacy while mitigating haematological and renal toxicity [67, 68]. Ongoing research is exploring the synergistic potential of combining [^{177}Lu]Lu-DOTATOC with other targeted therapies and immunotherapies. Challenges include optimising dosimetry for therapeutic response and managing renal toxicity and myelosuppression [69].

[^{131}I]I-MIBG

Iodine-131 metaiodobenzylguanidine ([^{131}I]I-MIBG) is a radiolabelled guanethidine analogue that plays a role in both diagnostics and targeted therapeutic interventions for NETs [70]. [^{131}I]I-MIBG exhibits high affinity for the norepinephrine and dopamine transporters in neuroendocrine cells, which is the basis for its diagnostic imaging and therapeutic applications. [^{131}I]I-MIBG also has the potential to provide insights into molecular mechanisms of the complex biochemical web that comprises the adrenergic neuroendocrine signalling pathways [9, 71, 72].

Clinical applications

[^{131}I]I-MIBG scintigraphy, characterised by high-resolution imaging capabilities beyond those of conventional imaging, has emerged as a sophisticated diagnostic tool. The high specificity and sensitivity of [^{131}I]I-MIBG is useful in precise localisation and staging of NETs, in gathering insight into primary lesions and metastatic dissemination [71], and especially in detecting elusive tumours like pheochromocytomas and paragangliomas [73, 74].

Beyond diagnostics, [^{131}I]I-MIBG delivers targeted radiation therapy to neuroendocrine cells expressing norepinephrine and dopamine transporters. Clinical efficacy has been demonstrated for precision therapy of metastatic pheochromocytomas and paragangliomas. The trajectory of endocrinology has been shaped by continual advancements in radiopharmaceutical development and imaging technologies. Newer radiolabelled compounds with high molecular specificity, like [^{131}I]

I-MIBG, combined with high-resolution imaging modalities, can improve diagnosis and address concerns related to radiation exposure [75]. Future research refining the scientific and clinical applications of [^{131}I] I-MIBG has potential to advance the state of the art in the treatment of endocrine malignancies [74, 76, 77].

[^{212}Pb]Pb-DOTAMTATE (AlphaMedix™)

[^{212}Pb]Pb-DOTAMTATE is a radiolabelled compound designed for targeted treatment of NETs. The backbone of the radiopharmaceutical consists of the chelating agent DOTAM, a derivative of DOTA, conjugated to the somatostatin analogue octreotate. This molecular design ensures a high specificity for the somatostatin receptor $SSTR_2$. ^{212}Pb is a radionuclide with a half-life of 10.6 hours, and it emits beta particles. The therapeutic effectiveness of [^{212}Pb]Pb-DOTAMTATE lies in the combined longer-range "crossfire" effect of beta particles combined with shorter-range alpha particles emitted by the daughter radionuclide of ^{212}Pb, ^{212}Bi, which has a half-life of 61 min. This combination enhances the overall radiation dose delivered to the tumour microenvironment [78, 79].

Preclinical studies involving animal models have demonstrated the ability of [^{212}Pb]Pb-DOTAMTATE to specifically bind to somatostatin receptors on NET cells, resulting in efficient internalisation and subsequent alpha particle-induced apoptosis. Notably, these studies have shown promising tumour regression with a minimal impact on non-targeted tissues. Clinical trials evaluating the safety and efficacy of [^{212}Pb]Pb-DOTAMTATE in patients with somatostatin receptor-positive NETs are ongoing. Initial reports indicate a favourable safety profile and encouraging antitumour responses, warranting further investigation into long-term outcomes and potential integration of this novel therapeutic approach into clinical practice [80].

[^{213}Bi]Bi-DOTATOC

Bismuth-213 is a promising alpha-emitting radioisotope with a half-life of 45.6 minutes, making it suitable for targeted alpha-particle therapy (TAT) applications [81]. When ^{213}Bi is coupled with the somatostatin analogue DOTATOC, the resulting [^{213}Bi]Bi-DOTATOC is a potent radiopharmaceutical for the treatment of NETs that express SSTRs. The high linear energy transfer of alpha particles emitted by ^{213}Bi results in a short path length, confining cytotoxic effects to the targeted tumour cells and minimising the damage to adjacent healthy tissues. Preclinical studies have demonstrated the efficacy of [^{213}Bi]Bi-DOTATOC in inhibiting tumour growth and inducing apoptosis in SSTR-positive tumour cells [78]. In terms of dosimetry, investigations have been conducted to optimise the administered activity of [^{213}Bi]Bi-DOTATOC to achieve an effective therapeutic dose while mitigating potential radiation toxicity to surrounding organs [82].

Theranostics applications

[^{64}Cu]Cu-DOTATATE

[^{64}Cu]Cu-DOTATATE is an emerging radiopharmaceutical that is used for the diagnosis of NETs. This positron-emitting radiotracer has the advantages of high-resolution PET with a longer half-life (12.7 h) for extended imaging periods. As with other octreotate-containing radiopharmaceuticals, the action of [^{64}Cu]Cu-DOTATATE is based on $SSTR_2$ targeting, and offers a novel approach for both diagnostic and therapeutic purposes [83].

Diagnostic applications

[^{64}Cu]Cu-DOTATATE allows high-resolution imaging and enables visualisation of $SSTR_2$ expression in endocrine tissues [84], and it has demonstrated remarkable sensitivity and specificity for the detection of NETs. Its ability to identify and localise lesions, especially in cases where conventional imaging modalities may fail, can contribute to more accurate staging and treatment planning [83]. Several studies have highlighted the superiority of [^{64}Cu]Cu-DOTATATE over traditional imaging techniques for the diagnosis of NETs [85].

Therapeutic implications

Beyond its diagnostic role, [^{64}Cu]Cu-DOTATATE is promising as a theranostic agent. The beta-emitting properties of copper-64 can be harnessed for targeted radionuclide therapy, delivering therapeutic doses precisely to $SSTR_2$-expressing tumours [86]. Clinical trials exploring the efficacy and safety of ^{64}Cu-DOTATATE-based theranostics have shown promising results for the management of NETs.

Although the role of [^{64}Cu]Cu-DOTATATE in endocrinology is expanding, some challenges remain. Optimal dosimetry, patient selection, and long-term effects require further investigation. Another area for future research is the exploration of [^{64}Cu]Cu-DOTATATE in endocrine disorders other than NETs. With its dual functionality as a diagnostic imaging tool and a therapeutic agent, [^{64}Cu]Cu-DOTATATE represents a significant advancement in the field of endocrinology, particularly toward personalised medicine.

[^{64}Cu]Cu-Cetuximab

[^{64}Cu]Cu-cetuximab is a radiopharmaceutical used for the imaging and therapy of patients with head and neck squamous cell carcinoma. Cetuximab is a monoclonal antibody targeting epidermal growth factor receptor

(EGFR). Anderson and Ferdani [87] have reviewed the molecular aspects, synthesis, and applications of [^{64}Cu]Cu-Cetuximab. [^{64}Cu]Cu-Cetuximab has high potential in diagnosing and treating endocrine-related disorders and personalised medicine, and it has demonstrated efficacy for various cancer types. The conjugation of copper-64 to cetuximab allows the specific targeting of EGFR-expressing cells for visualisation of EGFR status in endocrine tissues. [^{64}Cu]Cu-Cetuximab is synthesised by chelation of the radionuclide to a bifunctional chelator linked to the antibody [88] .

Clinical applications

Beyond diagnostic imaging, [^{64}Cu]Cu-Cetuximab offers potential for theranostics in endocrinology. [^{64}Cu]Cu-Cetuximab can deliver localized radiation to EGFR-expressing cells of NETs, such as in pancreatic cancer [89]. [^{64}Cu]Cu-Cetuximab represents a promising avenue for targeted therapy of endocrine-related disorders, but clinical studies are needed to validate the diagnostic and therapeutic potential of [^{64}Cu]Cu-Cetuximab for clinical applications in endocrinology, especially in regard to safety, efficacy, and patient outcomes [90].

[^{225}Ac]Ac-DOTA-JR11

[^{225}Ac]Ac-DOTA-JR11 is a novel radiopharmaceutical for diagnosis and targeted radionuclide therapy of NETs. [^{225}Ac]Ac-DOTA-JR11 is a high-affinity antagonist of $SSTR_2$. In contrast to SSTR agonists, which are internalised in vesicles after receptor binding, SSTR–antagonist complexes mostly remain on the surface of the cell. [^{225}Ac]Ac-DOTA-JR11 exhibits excellent stability and favourable pharmacokinetics that allow for specific targeting of tumour cells while minimising off-target effects [91].

Clinical applications

The diagnostic potential of [^{225}Ac]Ac-DOTA-JR11 is rooted in its ability to selectively bind to $SSTR_2$. Molecular imaging with [^{225}Ac]Ac-DOTA-JR11 offers high sensitivity and specificity to aid in precise staging and treatment planning. Actinium-225 has potent alpha-emitting properties and is an ideal radionuclide for targeted therapy [91, 92]. Despite its promising profile, the clinical use of [^{225}Ac]Ac-DOTA-JR11 remains challenging. Ongoing research to optimise dosimetry, manage potential toxicities, and refine patient selection criteria are needed for clinical translation of [^{225}Ac]Ac-DOTA-JR11. Development of personalised treatment regimens and integration of [^{225}Ac]Ac-DOTA-JR11 with other therapeutic modalities may further improve outcomes in patients with NETs. [^{225}Ac]Ac-DOTA-JR11 probably represents a significant milestone in the evolution of targeted radionuclide therapy for neuroendocrine tumours [91, 93].

Other radio compounds

Endocrine tumours, including those originating from the thyroid, pancreas, and parathyroid glands, frequently metastasise to bones, where they cause debilitating pain. Conventional treatments often provide only limited efficacy for pain management, necessitating alternative approaches. Rhenium-188 (^{188}Re) and samarium-153 (^{153}Sm), because of their unique nuclear properties, offer targeted therapeutic options for addressing painful bone metastases.

^{188}Re is well suited for therapeutic applications owing to its favourable decay characteristics. ^{188}Re undergoes beta decay to form stable osmium-188, emitting beta particles with a maximum energy of 2.12 MeV. These high-energy beta particles allow for effective penetration and localised irradiation within the targeted bone metastatic foci. Several studies have demonstrated the efficacy of ^{188}Re-labelled radiopharmaceuticals, such as [^{188}Re]Re-hydroxyethylidene diphosphonate (HEDP), for pain relief of bone metastases from endocrine tumours [94, 95].

^{153}Sm, an emitter of beta particles and gamma rays, has been extensively studied for its use in palliative care of painful bone metastases. For patients with bone metastases and accompanying clinical symptoms, palliative radioisotope therapy with ^{86}Sr or ^{153}Sm should be considered following a positive verification in bone scintigraphy using [^{99m}Tc]Tc-MDP [96]. The beta particles emitted by ^{53}Sm travel shorter distances than those emitted by ^{188}Re, making it suitable for treating smaller lesions or those in close proximity to critical structures. Studies utilizing [^{53}Sm]Sm-ethylene diamine tetramethylene phosphonate (EDTMP) have shown significant pain reduction and improvement in the quality of life of patients with bone metastases from various malignancies, including endocrine tumours [97, 98].

The use of ^{188}Re and ^{53}Sm in multimodal therapeutic approaches is an area of ongoing research. Preliminary studies suggest that combining these radionuclides may provide synergistic effects, enhance overall therapeutic outcomes, and potentially reduce radiation-induced toxicity.

Future directions

The development of novel radiopharmaceuticals in endocrinology is rapidly advancing. Researchers continue to explore, validate, and extend applications of the compounds reviewed in this article as well as new radiolabelled compounds that target different receptors

and biomarkers associated with endocrine disorders. Advancements in radiochemistry and molecular imaging will continue to make possible the creation of more specific and effective radiopharmaceutical tools for targeted therapies and personalised medicine within endocrinology. Integration of artificial intelligence, radiomics, and other emerging technologies with these imaging techniques is likely to profoundly influence diagnostic precision of endocrine disorders.

Conclusion

Exploration of novel radiopharmaceuticals is a promising frontier for improving diagnostics and targeted therapies for clinical endocrinology. This comprehensive review surveys the evolving landscape of molecular imaging and its potential to revolutionise precision medicine. As we navigate the challenges of adoption of these innovative technologies, collaborative efforts among researchers, clinicians, and industry stakeholders are crucial for translating them into tangible advancements that improve patient care. Radiopharmaceuticals are continually being refined, demonstrating a commitment in this field to push the boundaries of medical science and bring us closer to a future in which personalised interventions have redefined the management of endocrine conditions.

Author contributions

M.P.: conceptualisation, investigation, data curation, writing — original draft, writing — review and editing. T.S.: writing — review and editing. K.W.: writing — review and editing. P.O.: editing — review and editing. E.F.: conceptualisation, writing — review and editing. M.L.: writing — review and editing.

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Conflict of interest

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