NUCLEAR MEDICINE

Abstract

Nuclear medicine is a medical specialty which uses radiopharmaceuticals for diagnosis and treatment. Radiopharmaceuticals are targeted compounds that have radionuclide for obtaining the images of the location of diagnosis and treatment. Using tools like gamma cameras, it is possible to objectively detect, measure and picture the ionizing radiations that come along with the radioactivity that has been injected. Nuclear medicine is used in diagnosis and therapy and has grown from simple *in vitro* test to advanced methods for imaging organ function. These include gamma cameras, SPECT and PET scanners, and single-photon emission computed tomography (SPECT) scanners. This chapter is focused on the history, diagnostic and clinical applications of nuclear medicine and design of radiopharmaceuticals.

Keywords: Nuclear Medicine, Radiopharmaceuticals, PET, SPECT, Radionucleide

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I. INTRODUCTION

Nuclear medicine uses radiopharmaceuticals for diagnosing and treating the diseases (1,2). Radiopharmaceuticals are targeting compounds such as biologicals, chemicals or particles that are radiolabeled (3). Radiopharmaceuticals should be prepared and used in a safe and knowledgeable manner due to risk of ionizing radiations emitted from them (4). In order to design effective nuclear medicine for therapeutic and diagnostic imaging, it is essential to understand the ways and mechanism of interactions of the radioactive elements with different entities such as medicinal compounds, and biologicals especially (5). Nuclear medicine is generally administered via oral, nasal and intravenous route. With the help of gamma cameras, it is possible to detect, measure and image the ionizing radiations which are emitted due to decay of administered radiopharmaceuticals. Single photon emission computed tomography (SPECT), positron emission tomography (PET), PET-CT, micro-PET (with ultra-high resolution), and micro computerized axial tomography are illustrations of nuclear medicine techniques. These techniques are used to investigate the origins of biochemical dysfunctions as early illness indicators, their relationships to a variety of disease states, such as cancer, cardiovascular disease, and mental disorders (6,7,8). Nuclear Medicine imaging offers a number of important advantages in clinical practice, as well as in preclinical and clinical research such as it is non-invasive, quantitative or semiquantitative and having high detection sensitivity as compared to other imaging procedures like computer tomography and magnetic resonance imaging (9). The pictures produced by positron emission tomography (PET) are entirely quantitative and parameterizable according to the quantity of radioactivity present (for instance, in units of MBq/cm3)(10). The type of radiation employed determines the diagnostic and therapeutic applications such as Technetium-99m is the most often utilized agent for gamma emitters in diagnostic procedures and iodine-131 for beta emitters for treatments. (11). For illnesses in oncology, cardiology, neurology, infectious and inflammatory diseases, nuclear medicine has diagnostic, prognostic, predictive, and intermediate endpoint biomarkers (12). This chapter mainly focuses on the history, design of radiopharmaceuticals, diagnostic and clinical applications of nuclear medicine.

II. HISTORY

1. **Artificial radioactivity:** By subjecting stable nuclides to alpha particle radiation in 1934, René and Frédéric Joliot-Curie generated radioactive elements, continuing the work of Pierre and Marie Curie. More specifically, the Joliot-Curies used alpha particles to attack a variety of elements, such as H, He, Li, B, Be, C, N, O, F, Na, Al, Ca, Mg, Ni, and Ag. Aluminum (Z = 13) was blasted by Polonium's alpha particles decay, resulting in the production of (Z = 15) Radioactive phosphorus and a neutron.

$$^{27}Al_{13} + {}^{4}He_{2} \rightarrow {}^{0}P_{15} + {}^{1}n_{0}$$
$$^{30}P_{15} \rightarrow {}^{30}Si_{14} + {}^{0}p_{1}$$

They were able to prove that In fact, they had formed artificially introducing a new element by condensing the radioisotope nitrogen-13, which emits positrons into a different vessel after a similar reaction with boron, which released radiation within a $t_{1/2}$ of ten minutes. But they quickly managed to replicate and validate their finding of the creation of artificial radioactivity (13). The Nobel Prize was given to Irène and Frédéric Joliot-Curie in 1935 for contribution to production of new radioactive elements (14). Lawrence was

using the cyclotron to produce fake radioactivity as well, but he was oblivious to these residual emissions because the lab's Geiger counter was controlled by the same switch as the cyclotron. In 1938 at Berkeley, Emilio Segre and Glenn Seaborg and John Livingood made the discoveries of technetium-99m and iodine-131 owing to the efforts of Lawrence's crew and the early 1930s with the Joliot-Curies. Lawrence earned the Nobel Prize in 1939 for developing and creating the cyclotron and for the investigations he conducted with it, particularly in relation to synthetic radioactive elements" as a result of his diligent work, and it also opened the way for the radionuclide production for SPECT and PET using cyclotron (15). The "father of nuclear medicine," George de Hevesy, initially proposed the radiotracer concept, which supports using radionuclides to examine the stable atoms and molecules' behavior (16). In the first radiotracer experiment on animals, bismuth-210 was used to track the flow of Bi-containing antisyphilitic drugs in rabbits (17, 6).De Hevesy and a colleague used the isotopic dilution technique for the first time in clinical sciences to calculate their bodily water content, which was 43 liters with a 50% turnover every nine days (18). Of course, these were the initial subjects, consuming progressively larger aliquots of water that had been tracer-injected with deuterium. One of the most significant investigations revealed that the skeleton could absorb and release phosphorus, demonstrating for the first time that the bone is an active organ like any other(19).

2. **Iodine radionuclides:** Only a few years after iodine's discovery in seaweed in 1811, the effects of iodine on the thyroid were first researched. Amazingly, it took only 8 years for iodine to be employed as a goiter treatment (20). Saul Hertz, a member (and eventually director) of the MGH Thyroid Clinic, questioned whether iodine could be turned radioactive during a colloquium at Harvard Medical School in 1936. Then-MGH President Karl Compton promised to look into it. The outcome was a cooperative initiative between the Massachusetts Institute of Technology and the Massachusetts General Hospital that was designed to produce iodine -128 ($t_{1/2}$ = 25 min) utilizing a neutron source and research its absorption in rabbits (21). They announced their findings in 1938 after using deuterons from the Berkeley cyclotron to bombard tellurium -128and produce Iodine-130 ($t_{1/2}$: 12 hours) and Iodine-131 ($t_{1/2}$: 8 days)(22). Iodine -131 studies in the future made it possible to trace the radionuclide in living things for extended periods of time (23).They discovered that the therapy of metastases required thyroid ablation, which lessened the thyroid's competition for iodine uptake(24, 25).These groundbreaking trials transformed thyroid carcinoma from a terminal illness to one with an approximate 85% overall survival rate (26).

3. **Carbon radionuclides:** In the late 1930s, carbon-11 (C^{11}; $t_{1/2}$ = 20 min) was frequently produced at the Ernest Lawrence laboratory in Berkeley by blasting boron oxide with deuterons. Later, in the 1970, the Welch lab and Raichle and coworkers actively used the photosynthesis-based technique to produce ^{11}C-labeled glucose (27, 28). The manufacture of carbon-14 was thereafter vigorously pursued by Kamen and Ruben. They could have built it based on calculations, but despite expecting it to have a longer half-life, they had no idea what it would be (29). On Berkeley's 60-inch cyclotron, Kamen created an iron target and attacked it with 5700 Amp Hours of 7 to 8 MeV deuterons in 1940. By precipitating CaCO3, Ruben examined the irradiated target and discovered persistent activity that may be attributed to carbon-14 (30). The estimated half-life of carbon-14 by Kamen and Ruben was 4000 years, which was relatively close to the actual half-life, which was discovered many years later and is 5700 years (31).

4. **The ^{99}Mo/^{99}mTc Generator and Radiopharmaceuticals Labeled with ^{99}mTc**: Segre and Perrier made the discovery of the element technetium in Palermo, Italy, in 1937 (32). In order to examine the element's shorter-lived radionuclides, Segre went back to Berkeley and collaborated with Seaborg. This research resulted in the finding of technetium 99m (t1/2 6 h) (33). In the 1950s and 1960s, Powell Richards strongly promoted the use of technetium-99m as the ideal nuclear material for imaging molecular function in vivo due to its wide chemistry, intermediate photon half-life, photon energy of 140 keV, and lack of particle emissions (34, 35). Beck noted that in the 1960s, 150 keV was the appropriate detection energy for sodium iodide crystals (36). Iodine-132 rather than technetium 99m was the first generator system to be created (from tellurium-132)(54). The radioactive impurity in this tellurium-132, which was produced from fission products, was discovered by chance(37, 38). The tellurium-132 was subsequently shown to be followed by the impurity molybdenum-99 during the separation process, which was later used to create the Mo-99/Tc-99m generator (39).

5. **Instrumentation for imaging development**: The invention of the rectilinear scanner, which during the 1950s and the beginning of the 1970s served as the primary instrument for nuclear imaging and automated the scanner's location, was the next major development. The time it took to photograph big organs was a major drawback of this technology. Hal Anger made a huge advancement in this area using several photomultiplier tubes and a collimated gamma camera to examine the whole of the target organ at once to increase the effectiveness of detection (40, 41.). In 1953, Brownell and Sweet developed a multidetector instrument using positron-emitting radionuclides to detect brain tumors (42, 43, 44).David Kuhl and Roy Edwards introduced the ideas of longitudinal and transaxial tomography and a nuclear medicine tomographic imaging apparatus in the 1960s (45). Transverse axial tomography was used by Godfrey Hounsfield to produce radiography, which he later used to create positron emission tomography (PET)(46).In 1975, Ter-Pogosian-filtered back projection, Phelps, and Hoffman were used to create a PET device (47, 48).The first camera that revolved around the patient wasn't invented until Keyes et al.1977 's study at the University of Michigan (49). Larsson introduced the cantilever system in the 1980s as a result of this (50).

6. **Radionuclide Manufacturing**: After the cyclotron was built at Berkeley and Irene Curie and Frederic Joliet discovered how to create isotopes artificially, carbon-11 ($t_{1/2}$ -20 min), nitrogen-13 ($t_{1/2}$ -10 min), and fluorine-18 ($t_{1/2}$ 120 min) were produced and used as biological radiotracers. Kamen investigated how plants absorb carbon dioxide that had been tagged with carbon-11 in the 1930s (51).Furthermore, Cramer and Kistiakowsky studied metabolic pathways using lactic acid tagged with carbon-11 in the 1, 2, and 3 locations (52).Tobias et al. employed carbon-11 for the first time in people to explore how carbon monoxide behaved in people after being labeled with ^{11}C (53). Rueben et al's initial investigation using nitrogen-13 was aimed at investigating nitrogen fixing by non legume plants. Volker et al. studied the uptake of fluoride by bone and tooth enamel using fluorine-18 in the early 1940s. Nevertheless, despite these early developments, curiosity about these transient radionuclides decreased in the 1940s and 1950s (54). In order to measure the oxygen tension in malignant neoplasms, Powers and Ter-Pogossian created oxygen-15 ($t_{1/2}$ = 2.0 min) in the physics department of Washington University's cyclotron in the 1950s.

This innovation spurred an increase in evaluating cerebral metabolic studies and repertoire using radioactive gases (55, 56).

7. **The Discoveries and Uses of FDG**: 2-Deoxy-2-[^{18}F] Fluoro-D-glucose, often known as [^{18}F], Fig.2.shows that the hexokinase process is prevented by eliminating the hydroxyl in the 2-position.fluorine-18 atom replaces a hydroxyl group in the radiolabeled form of glucose known as FDG, sometimes known as just FDG. FDG was created specifically to track how much glucose is being used by the human brain. The hexokinase reaction is isolated when 2-deoxyglucose is used (57).Louis Sokoloff and Martin Reivich's 1975 science article proved to be a very useful resource in order to research glucose metabolism (58).

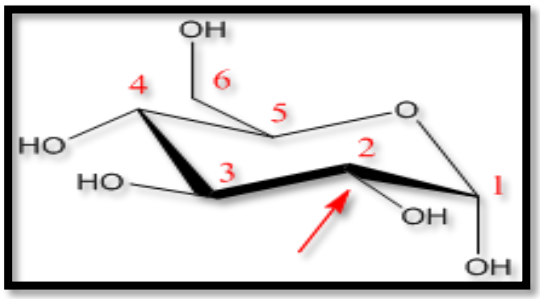

Figure 1: Shows that the hexokinase process is prevented by eliminating the hydroxyl in the 2-position.all carbons in the molecule of glucose are numbered, highlighted by the red arrow that Sokoloff and Reivich have assigned the carbon-14 designation to.

To see the [^{18}F]FDG in a human, it was essential to fly the substance to Philadelphia, , the closest PET scanner at the time. It should come as no surprise that the logistics were difficult. Brookhaven developed the [^{18}F] FDG, driven to the University of Pennsylvania for administration (59). Following this initial delivery, [^{18}F] FDG's clinical application significantly increased. Preclinical research undertaken in the late 1970s and early 1980s found that [18F]FDG, despite initially beingain imaging, may also be effective for monitoring heart metabolism and tumor metabolism (60). Kurt Hamacher made a big development by using [^{18}F] fluoride to synthesize FDG in 1986 (61) (Fig.3).

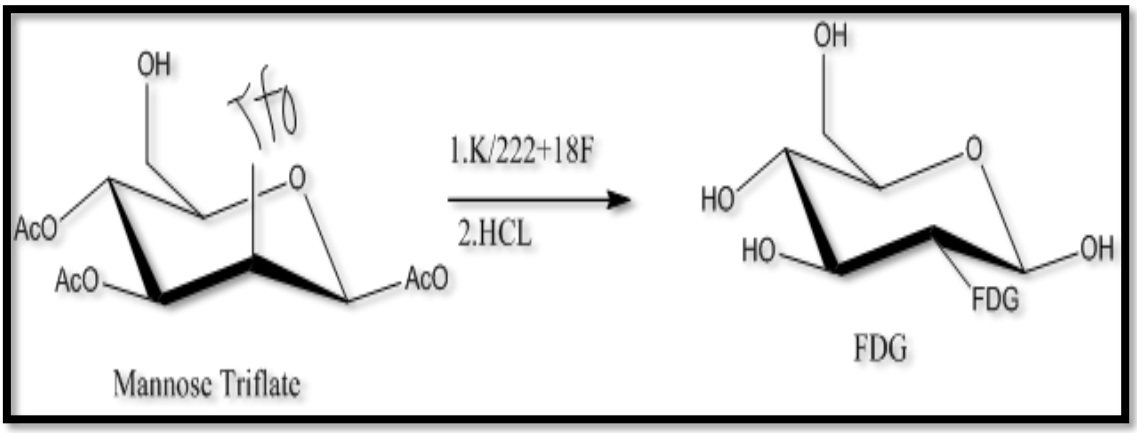

Figure 2: FDG synthesis

8. **A brief history of Indian nuclear medicine:** Considering the development of nuclear medicine in India historically, "Dr. Homi Jehangir Bhabha," known as the "Father of Indian

Nuclear Program," must be mentioned. After India gained its independence, Pandit Jawaharlal Nehru, the nation's first prime minister, gave Dr. Homi Bhabha the responsibility of leading and coordinating the country's ambitious nuclear energy programme (in 1948). Atomic Energy Establishment Trombay (AEET) was constructed by Dr. Bhabha in 1954. a pioneering research reactor in Asia and India outside of the USSR and Russia, APSARA, reached criticality in 1956. In 1960, the site of AEET also saw the operationalization of the second reactor, CIRUS. This resulted in the domestic manufacture and availability of numerous radionuclides with medical applications (^{131}I, ^{32}P, and ^{51}Cr). Particularly, radioiodine (^{131}I) was becoming more and more relevant in clinical studies and practice. Since the early 1960s, the Bhabha Atomic Research Center, later known as the Isotope Division of AEET, has undertaken the enormous challenge of producing and commercially supplying radiopharmaceuticals to hospitals in India (62, 63). In 1956, with approval from the the late Pandit Jawahar Lal Nehru, an Indian Prime Minister, the multidisciplinary study group known as "Radiation Cell" was established within the purview of the Ministry of Defense with the goal of conducting biomedical research utilizing radioisotopes and applying radiation to medicine. India began Allied Sciences and Nuclear Medicine Institute (INMAS) received approval from Delhi University in 1963 to offer the first programme of its kind in the world (64). The early 1960s contributions from the BARC Isotope Division and later the BRIT, the Board of Isotope and Radiation Technology (after 1989) served as the fundamental hub for the development and organization of India's current nuclear medicine culture (64). At KEM Hospital in Mumbai, In 1960, Dr. R. S. Satosker carried out the initial thyroid uptake measuring investigation. Later, at RMC, uptake measurements were standardized (65). The slow rectilinear scanner was purchased by RMC in 1965, and the fast rectilinear scanner took its place in 1969 (66). RMC began offering diploma programmes in radiation medicine and medical radioisotope techniques, both of which are approved by Mumbai University, in 1973. In 1982, the Indian government's National Board of Examination recognised nuclear medicine as a broad field of study and granted RMC accreditation for its Diplomate of National Board training programme. At the Sanjay Gandhi Postgraduate Institute in Lucknow, the MD programme began for the first time in Asia and India in 1990 (67). The Society of Nuclear Medicine, India (SNMI) is the oldest and biggest professional association, with 1425 nuclear medicine specialists as life members. The inaugural Annual Conference of SNMI, which was founded in 1967, was held at RMC in Mumbai in 1968 (65). Since then, SNMI has been holding its Annual Conferences across the nation with the aim of fostering scholarly dialogue and increasing clinician awareness of the modality. RMC hosted the SNMI's first Conference in 1969 (68). There have been 233 operational gamma cameras (SPECT/SPECT-computed tomography [CT] systems) in India since 1969, when the first gamma camera was commissioned at RMC. A revolution in molecular imaging had begun in India with the first PET (2002), first medical cyclotron (2002), and first PET-CT (2004; all of which were performed in Mumbai) (69, 70).Table.1 Nuclear medical facilities in India, categorized [Table data is driven by (71)]:

Facility name	Quantity in numbers
Gamma cameras/SPECT	163
SPECT-CT	70
PET-CT	222
PET-MRI	3
High dose radionuclide therapy ward	92
Cyclotron	19

CT: Computed tomography, SPECT: Single-photon emission CT, PET: Positron emission tomography, MRI: Magnetic resonance imaging Gamma cameras/SPECT.

A PhD in therapeutic nuclear medicine was first made available in 2015 by the Delhi-based All India Institute of Medical Sciences. Nuclear medicine facilities of the nation have rapidly expanded as a result of the design and deployment of affordable generators (Having low specific activity and loaded ^{99}Mo) using locally developed solvent extraction (Methyl Ethyl Ketone) technology. There are 293 nuclear medicine departments nationwide,according to the facilities list released by the Atomic Energy Regulatory Board in July 2018. The remaining 86 percent are privately held companies, of which 14% are owned by the government (71).

III. DESIGN OF RADIOPHARMACEUTICALS

Radiopharmaceuticals consist of two components i.e a radionuclide for permitting external scan, and non radioactive element for acting as a carrier for conducting the radionuclide to the particular organs (72). Radioactive elements are highly energetic unstable nuclides because of excess energy i.e stabilized by emission of electromagnetic radiation (α, β and γ) during the decaying process of radioactive elements (73). For diagnostic applications, Gamma or X-rays are produced by the radioactive element, and their detection allows for the determination of the radiopharmaceutical's concentration. In contrast, the radioactive material can be applied therapeutically, where the ionizing radiation released by the radionuclide's decay is used to kill cells.

Nuclear medicine technologies such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) are used to detect radiations released by radionuclides that are dispersed throughout the body or in a specific area of the body.

The image's contrast will be determined by the difference in radionuclide concentration between the target tissue and the surrounding tissue. When the target/background ratio is normally at its best, static imaging provides a snapshot of the radionuclide distribution at a specific time after the injection of the tracer.

The radiopharmaceutical is made up of a linker between a radionuclide for medical or diagnostic use and a vector molecule, as illustrated in figure.

The radionuclide emits radiation, and tissues or cells that express substances are the target of the vector molecule with a specific intent to perform diagnostic and therapeutic procedures. The vector molecule may be a small molecule, a peptide, protein and nanoparticle. For the diagnostic and therapeutic purpose, the vector should have high specificity and selectivity when it is conjugated with radionuclide. When a radionuclide is present in ionic form, such as when [131I]I is used to treat thyroid cancer or when [89Sr]Sr2+ is used to treat bone pain, the radionuclide may also serve as a vector molecule.

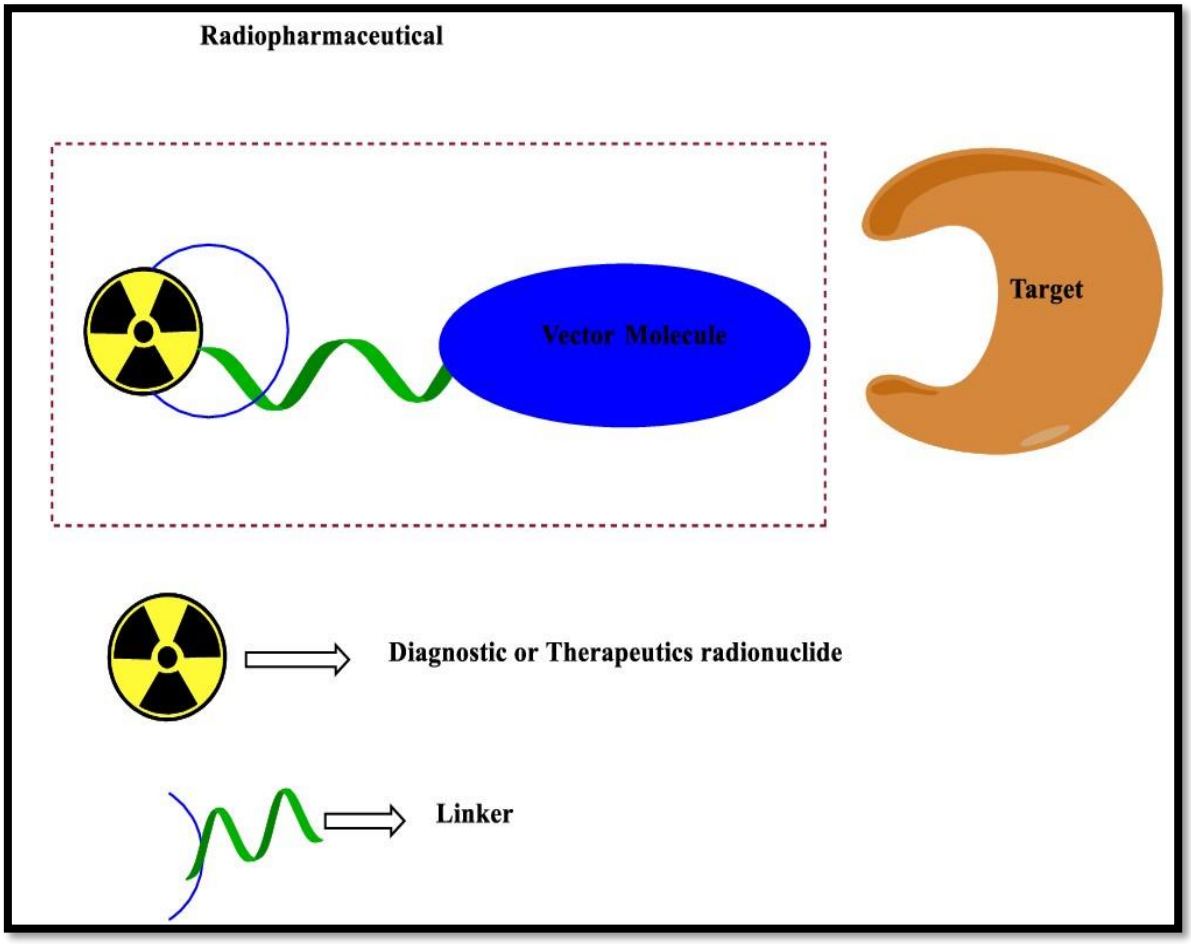

Figure 3: Radiopharmaceutical design

The linker, which is the third component, aids in creating a secure bond between the vector molecule and the radionuclide. Bifunctional chelators are required for radiopharmaceuticals based on radiometals because they guarantee both a stable complex with radiometal nuclei and a covalent link with the vector.

Based on the decaying property of the radionuclide, it is determined that the radiopharmaceutical will be used for diagnostic or therapeutic purposes.

1. **Vector:** For the production of, radiopharmaceutical, vector is the main component as it is responsible for targeting the tissues for maintaining the higher concentration of radionuclide. As a result, therapeutic radiopharmaceuticals can selectively irradiate the target cells while still providing the picture contrast necessary for diagnostic imaging.

Small molecules, peptides and proteins and cells are used as vectors that are explained further. For intracellular targets, small molecules are used as vectors because of having specific characteristics such as membrane permeability and designing molecules within the cytoplasm and nucleus and can cross the blood brain barrier (BBB). Small molecules including Biochemicals Fatty acid, amino acids, nucleosides and xenobiotics are used as vectors.

Peptides are used as vectors because many peptides are present in tumor tissues as compared to normal tissue. Peptides contain less than 50 amino acids and diffusion is higher into the target tissues and long retention period in tumor cells. Peptides are synthesized easily and have favorable pharmacokinetic characteristics such as fast clearance from the blood pool and non-targeted tissues, and high concentration in the target tissue.

2. **Radionuclide:** Radionuclides are unstable and contain excess energy because of heavy nuclei or imbalance in ratio of proton and neutron. The electromagnetic radiations (gamma rays) or particles (alpha and beta particles) are released due to excess energy present in radionuclide. These can be produced artificially or spontaneously via cyclotrons, particle accelerators, or radioactive decay of additional radionuclides.

IV. NUCLEAR MEDICINE TECHNIQUES

In nuclear medicine, the camera will construct a picture taken at the radiation's emission points. The image is observed on the monitor and the anomalies are checked.(74). Two examples of these modalities are Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT).

1. **Single Photon Emission Computerized Tomography (SPECT):** Single-photon emission computed tomography (SPECT) is the most frequently used technique in diagnosis.It generates a three-dimensional image of the distribution of a radioactive tracer throughout the body following its injection into the bloodstream and subsequent uptake by particular organs (75). Utilizing specialized nuclear medicine cameras allows for this. So, using SPECT, a clinician can evaluate the perfusion and functionality of particular tissues. SPECT relies on the spinning detectors' detection of single photons emitted during a radionuclide's decay in order to produce a 3D image of the distribution of the radionuclide in the body (76). For efficient imaging, energies between 100 and 200 keV are required. Technetium (99mTc, T1/2 = 6 hours) in its metastable form is the radioisotope that is most frequently used in SPECT scans. In the clinic, the 99mTc-complexes are frequently used to assess cardiovascular illnesses, renal excretion, identify tumor lesions, and CNS disorders (77).

Table 1: Radionuclides frequently used in SPECT imaging

S No.	Radio Nuclei	Half Life (h)	Type of Emission	Photon emission Energy (MeV)
1	123I	13.2	Electron capture	0.16
2	99mTc	6	Isomeric transition	0.14
3	111In	67.9	Electron capture	0.17/0.25
4	67Ga	78.3	Electron capture	0.09/0.19/0.30
5	201Tl	73.1	Electron capture	0.17

2. PET: PET detects two photons with a combined energy of 511 keV that are released in opposing directions upon the annihilation of positronium, which is produced when an electron and a positron from a neutron-deficient nuclei unite(78).

Table 2: Commonly used radionuclides for PET (79, 80, 81)

S No.	Radio Nuclei	Half Life	Mode of decay	Decay Product	Energy (MeV)
1	11C	20.4 min	β+	11B	0.960
2	13N	10 min	β+	13C	1.199
3	15O	2.0min	β+	15N	1.732
4	18F	109.8 min	β+, Electron Capture	18O	0.634
5	64Cu	12.8h	β+, Electron Capture	64Ni 64Zn	0.653 0.329-1.675
6	68Ga	67.6 min	β+, Electron Capture	68 Zn	1.899 0.227-2.821
7	76Br	16 h	β+, Electron Capture	76Se	3.382 0.599
8	82Rb	1.3 min	β+,	82 Kr	3.378

V. APPLICATIONS OF NUCLEAR MEDICINE

1. Clinical applications

- **Renal and urinary tract disorders:** 1.The renogram acquired using DTPA (Diethylene triamine pentaacetic acid) or ^{99m}Tc can tagged with 123I Hippuran be used to differentiate between urinary blockage and atonic dilatation; measurements of cortical transit and entire kidney, as well as responsiveness to furosemide, can also be obtained (82,83,84). 2.Detection and monitoring of vesicoureteric reflux utilizing a direct cystogram with ^{99m}Tc pertechnetate or an indirect cystogram with ^{99m}Tc DTPA, both of which result in substantially lower gonadal irradiation than a radiological cystogram (85,86,87). 3.When determining creatinine clearance is not necessary, the overall clearance must be evaluated. A ^{99m}Tc DTPA or chromium-51 edetic acid intravenous injection is given between two and four hours later, two to three blood samples could be used to precisely calculate glomerular filtration rate (^{51}Cr EDTA). The latter method is more precise, simpler to use, does not involve collecting urine, and is helpful for renal illnesses that affect both kidneys equally(88). 4. Renal function evaluation of a person: this information is typically available during the initial stages of a ^{99m}Tc DTPA, ^{123}I Hippuran Renogram, or ^{99m}Tc DMSA uptake. This is indicated in the study of uropathies and particular nephropathies, which may inflict unequal damage to the kidneys both before and after surgery (89,90). 5.Accurate topographical description of kidney location, kidney morphology, and parenchymal damage using ^{99m}Tc DMSA static images (acute and chronic pyelonephritis, trauma) (91, 92).

Table 3: Detectors used in kidney and urinary tract conditions (93)

Detectors	Physiology
Diethylene triamine penta-acetic acid	glomerular fraction alone
Technetium 99m-dimercaptosuccinic acid ^{99m}Tc	the tubular cells' uptake
Edetic acid-chromium 51	Only glomerular filtration can remove; in vivo measures are not appropriate
Hippuran ^{123}I	80 percent removed via tubular secretion and 20 percent through glomerular filtering
Pertechnetate technetium 99111	bladder-filling and -voiding tracer

- **Pulmonary diseases:** 1.To confirm or rule out the identification of local long illness when chest x-ray pictures are normal or ambiguous (Small lungs, bronchiectasis, aspiration pneumonia, hyperlucent lungs, foreign body). With a normal scan, the chance of obtaining bronchiectasis or a foreign body is rather low when choosing individuals who need to have more invasive procedures exams, for example (bronchoscopy, bronchography).2. Before performing surgery to remove a lobe, to assess lung function (bronchiectasis, sequestration).3. prior to doing angiography, to identify

intrapulmonary shunts and other vascular irregularities (a negative scintigraphy result could prevent angiography).4. to monitor severe disease, such as cystic fibrosis, bronchiectasis, viral pneumonia after effects.5. The detection of primary arterial disease and pulmonary embolism requires coupled perfusion and ventilation investigations 6. in order to assess mucociliary removal (94, 95, 96, 97, 98)

Table 4: Tracers used in pulmonary diseases (93)

Tracers	Physiology	Comments
Macroaggregates-technetium 99m or human albumin microspheres-technetium 99m	Regional perfusion	high-quality static graphics that are simple to create, affordable, and age-inclusive
Krypton gas 81m	Localized ventilation	Good cost and organizational requirements, static images of high quality when breathing normally with a mask, and low sensitivity for subsegmental abnormalities in infants younger than one year
Xenon gas 133	Localized ventilation	Demands participation from the patient (patients must be over 6 years old), produces static, subpar photographs after a single breath, and is moderately priced.
Millimicrospheres aerosols-technitium 99m	Localized ventilation	Still needs more work standardization

- **Hepatosplenic disorders:** 1) Jaundice to rule out in the child biliary atresia; to evaluate the biliary tree's post-surgical patency; to evaluatethe choledocal cysts' discharge; and to determine the existence of dilated ducts, for example, Caroli's sickness. 2.Detection and monitoring of liver lesions that take up space using other imaging methods (computed tomography, ultrasound). 3) To find anomalies of the spleen and congenital heart disease that are present at birth (asplenia, polysplenia). (4) To identify accessory spleens or splenic trauma (idiopathic thrombocytopenic purpura)(99).

Table 5: Tracers used in Hepatosplenic Disorders

Tracers	Physiology
Colloid-technetium 99m	liver and spleen's reticuloendothelial systems uptake
Damaged red blood cells-technetium 99m	spleen's selective uptake
Iminodiacetic acid (N substituted)- technetium 99m	parenchymal liver cells' early absorption and biliary channels' excretion of the substance into the duodenum

- **Gastrointestinal tract disorders:** 1. Gastroesophageal reflux disease diagnosis and monitoring (including the syndrome of near-miss sudden newborn death, recurrent lung infections, and chronic vomiting)(100).2. Studying conditions including caustic stricture, peptic oesophagitis, achalasia, and impaired neurogenic peristalsis (101, 102). 3.Meckel's diverticulum containing stomach mucosa is diagnosed (103). 4. evaluation of the 24-hour stomach emptying (104).

Table 6 : Tracers used to diagnose digestive system issues:

Colloid-technetium 99m	Static image activity is influenced by osteoblast activity and blood flow
Krypton 81 in glucose	because to the tracer's incredibly brief life, it disappears quickly.
Pertechnetate-technetium 99m	the stomach mucosa actively absorbs

- **Thyroid disorders:** 1. Aplasia, ectopia, and regularly occurring glands are defined.2. Analyzing nodules in the neck and their connections to thyroid tissues.3. (3) Identification of a foliated lesion as a potential hyperactive adenoma in hyperthyroidism (rare in children) (123). A trusted tracer for determining thyroid function is 131 Iodine. Due to the high radiation, youngsters should not use it (105).

- **Heart diseases:** 1) Evaluation of the left to right heart shunt with the help of ^{99M}Tc pertechnetate.2.Using ^{99m}Tc macroaggregates, the right to left cardiac shunt is evaluated (MAA).3. Red blood cells that have been ^{99m}Tc-labeled or iTc pertechnetate (first pass) can be used to measure the function of the left ventricle (equilibrium).4. Right ventricular function can be evaluated with an ^{81m}Kr infusion or ^{99m}Tc pertechnetate (first pass) (106,107).

Table 7: Tracers used in Heart disorders

Tracers	Physiology
Krypton gas-181 m	The moment it makes contact with air, this isotope will leave the solution. If the ^{81m}Kr is administered continuously intravenously, The isotope will first go into the right heart before continuing on to the pulmonary circulation. Considering that the isotope will easily cross the alveolar barrier and discharge, normally it won't get into the left heart or pulmonary veins. Good right ventricular structural delineation can be attained without any left heart superposition, allowing for the assessment of right ventricular contractility.
Macroaggregates-technetium 99m	Following an intravenous injection, the isotope will frequently become caught in the first capillary plexus and stop moving completely across the pulmonary capillary bed. The isotope can be found in the systemic circulation, such as the kidneys, if there is a right-to-left shunt.
Pertechnetate-technetium 99m	Right heart will transport this isotope to the lungs, followed by the left heart and the systemic circulation. The left heart phase isotope will travel to the systemic vascular system as well as to the lungs again when there is left to right shunt. The value of the shunt is quantifiable
Technetium 99m red blood cells	Since the isotope is connected to red blood cells during this time, it is able to take several photographs of the beating heart throughout time to assess ventricular function. Function changes are measurable (ejection fraction).

2. **Diagnostic applications:** The diagnosis of disease is more routinely performed using nuclear medicine.In this instance, the patient is administered a radioactive material, and then its dispersion in the body (7). Following the administration of a radiopharmaceutical, its biokinetics are observed, and the target organ or body system is functionally studied, or the lesion viability and the targeted biological process are characterized and evaluated (3).The tool being utilized determines the mode of observation:1)Imaging technology: shows the temporal distribution of radioactivity that is visible at specific times or over a predetermined period of time.Displays of images can be 2D (static/dynamic whole-body images), 3D (tomograms), or 4D (dynamic/temporal tomograms).2) Calculating tools: Externally, a probe system is utilized to examine in vivo body system and organ function (called radioassay).It is important to remember that radionuclides are administered in such dosages for research and diagnostics that there are no detectable biological side effects (3).To visualize the activities of many organs, including the kidney, lung, thyroid, and heart, as well as bone metabolism and blood circulation, radiopharmaceuticals are administered orally, intravenously, or by inhalation in the imaging modality(108).Although the applications of integrated diagnostic systems have expanded to include cardiology, neurology, and the imaging of inflammatory diseases, they have demonstrated their clinical worth most prominently in the field of oncology (109).

- **Oncology:** Imaging is essential for the accurate staging of the disease and the assessment of therapy response in the early identification of cancer. Contrarily, "conventional" nuclear medical imaging (planar and SPECT) and PET can offer significant additional functional data, albeit with a reduced spatial resolution compared to radiological methods. CT and MRI provide significant anatomical information but do not provide meaningful functional information on the observed lesions. Furthermore, by accurately co-registering anatomical and functional data obtained through the use of hybrid SPECT/CT and PET/CT equipment, complementary information is obtained that, in the field of oncology, translates into greater sensitivity (better ability to localize lesions) and greater specificity (exclusion of false positives caused by the physiological accumulation of radio composed): approach makes it possible to accurately determine the functional significance of uncertain lesions (110).

- **Differentiated thyroid cancer:** The most frequent endocrine neoplasia, differentiated thyroid cancer (CDT), often has one favorable prognosis. The standard course of treatment entails a complete thyroidectomy and iodine-131 ablation of any remaining thyroid tissue. The thyroid gland values are measured as part of the CDT follow-up together with the neck's ultrasonography and, if necessary, Iodine-131 scintigraphy (WBS). Lack of anatomical and physiological references, as well as radioiodine accumulation in thyroid tissue remnants that can mimic metastasis, can make it challenging to interpret the WBS. By finding more lesions, enabling accurate localization of lesions, and excluding lesions in regions of normal radioiodine accumulation, using hybrid SPECT/CT imaging, radioiodine scintigraphy in CDTs improves both sensitivity and specificity (110,111).

- **Diagnostic application of nuclear medicine in urology:** Between 50% and 60% of kidney tumors have been reported to be detectable with ^{18}F-FDG PET/CT as a first diagnosis. It has not been demonstrated to significantly improve on traditional imaging techniques like CT and MRI for this purpose. Although dual-phase delayed imaging and after forced diuresis imaging were undertaken to lessen the impact of physiological urine activity, neither strategy outperformed the standard imaging protocol. After the main tumor was surgically removed, Additionally, it was found that the uptake of 18F FDG and the amount of GLUT 1 expression were not correlated (112,113,114). Standard procedures and recommendations do not advocate the regular staging of kidney tumors with ^{18}F-FDG PET/CT. The main cause of this is that due to the intensive physiological urine activity, 18F-FDG frequently gives false-negative results for the underlying tumor. Nevertheless, it has been argued in patients who are at risk, it may be helpful in demonstrating extrarenal metastatic illness (115, 116).

- **Myocardial imaging of perfusion test:** Traditional methods cannot differentiate between benign and malignant conditions in 14% of T1 kidney tumor surgeries (4 cm), while the pathology results of 20–30% of operated cases are benign. As a result, a SPECT agent may be helpful for preoperative characterisation of primary renal masses even though no PET agent can be demonstrated to do so. Tc-99m Traditional gamma cameras employ MIBI, a non-specific tumor agent, for imaging. It is maintained in benign and cancerous tumours with increased metabolic rate in the mitochondria of the cell (117). Oncocytomas have higher Tc-99m MIBI absorption than other forms of RCC because they include more mitochondria (118). According to the findings of the limited

research on this topic, nearly all of the patients who had a pathologically confirmed oncocytoma and underwent a Tc-99m MIBI SPECT/CT evaluation before surgery were positive for the radioactive substance. Patients showed no Tc-99m MIBI uptake, who were determined to have other RCC subtypes. Oncocytoma sensitivity was shown to range from 83 to 100% (119).When staging a high-risk condition in RCC patients with metastatic disease, 18F-FDG PET/CT is helpful for assessing treatment response. However, more research on common use is required. High sensitivity and specificity are provided by Tc^{99m} MIBI SPECT/CT for the malignant-benign distinction of ambiguous renal tumours.Testicular tumor staging, restaging, and follow-up are all aided by ^{18}F-FDG PET/CT , while not being engaged in the metabolic characterisation of original scrotal masses, particularly when evaluating seminoma patients who have a persistent retroperitoneal lesion larger than 3 cm after treatment. Ga^{68} PSMA PET/CT has good sensitivity in all stages of prostate cancer, Its use is expanding, particularly in individuals with biochemical recurrence (120).

- **Cardiology:** For measuring and evaluating the signs and symptoms of ischemic heart disease, the main method for functional cardiac imaging is radioactive myocardial perfusion scintigraphy (MPS). For examining IHD, a popular noninvasive nuclear image acquisition method is SPECT(single-photon emission tomography) of the heart . Currently, SPECT is suitable for detecting and controlling IHD in all its facets, consisting of diagnostic, risk assessment and classification, myocardial viability testing, and left ventricular function testing (121). More recently, individuals who may have coronary artery disease have been able to receive better diagnosis, risk assessment, and treatment planning thanks to hybrid images that integrate coronary angiography with computed tomography (CT) and SPECT functional imaging (122). The first radiopharmaceutical used extensively in clinical myocardial perfusion imaging was tl-201 chloride (123). Two technetium-based agents, sestamibi and tetrofosmin, are presently utilised frequently .I^{123} MetaiodobenzylGuanidine (MIBG) is a guanethidine derivative having characteristics similar to those of the heart's adrenergic system transmitter norepinephrine. The ratio of uptake in the mediastinum to the myocardium (heart) is used to semi-quantitatively measure sympathetic innervation of the myocardium (124). I -123 15- (p-Iodophenyl) The beta-methyl fatty acid analogue 3-R, S-Methylpentadecanoic Acid (BMIPP) 15- (p-iodophenyl) S-Methyl-3-R, 3-Pentadecanoic Acid (BMIPP), Since the drug is retained in the myocardium for a while, SPECT imaging with a conventional gamma camera is more advantageous (125). Stress-only imaging was advised in a recent information statement from the American Society of Nuclear Cardiology (ASNC) when utilized on carefully chosen individuals (126). Over the past few years, major cardiac societies including the American College of Cardiology and American Heart Association, along with other imaging associations, have taken proactive steps to reduce the usage of cardiac imaging. To guarantee that doctors are, in the majority of cases, performing the right test on the right patient at the right time, for nuclear cardiology, acceptable use criteria have been created (127). This has brought about a number of quick advancements that have improved the hardware in nuclear cardiology scanners' photon sensitivity. Furthermore, software that uses innovative SPECT reconstruction techniques on established and specialized systems has retained or even enhanced SPECT image quality with reduced count statistics. To minimize radiation exposure while retaining diagnostic performance, MPI procedures should be improved. This development includes the use of radionuclides with shorter

half-lives, like Tc-99m and PET tracers, stress-only imaging when practical, and weight-based dose.(124).

- **Thyroid disease**: The iodine intake by the thyroid gland is controlled by the sodium-iodide symporter (NIS), which was initially identified by Kaminsky et al. in 1993 (128).Through the use of thyroid scintigraphy and radioiodine uptake tests, the thyroid cells' ability to absorb iodine is still frequently utilized to assess thyroid function (129). Thyroid scintigraphy shows the location of thyroid tissue that is actively producing thyroid hormones in addition to the morphological knowledge obtained by ultrasonography (130). The assessment of technetium-99m absorption in the thyroid is given much attention. ^{99m}Tc uptake ranges from 0.5-2.0% in euthyroidism with typical iodine intake. Similar to iodine intake, this proportion falls in hypothyroidism, iodine pollution, and iodine insufficiency, while rising in Graves' illness. By comparing the number of counts in the regions of interest above the thyroid with the number of counts above the syringe carrying the ^{99m}Tc-pertechnetate before injection, this straightforward measurement is carried out as an addition to thyroid scintigraphy (131, 132, 133). Patients are photographed in a planar fashion when they are lying or sitting. ^{123}I, ^{131}I, and ^{99m}Tc. Technetium-99m (^{99m}Tc), obtained from a molybdenum-technetium generator, is delivered intravenously in the form of pertechnetate. In a way similar to that of iodine isotopes, NIS delivers an analogue of iodine, ^{99m}Tc-pertechnetate, to thyroid cells. It is important to keep in mind that ^{99m}Tc absorption is not just restricted to thyroid tissue when interpreting scintigraphic pictures acquired with the radioactive substance. Thyroid imaging is another procedure that makes use of the iodine isotopes ^{123}I and ^{131}I (130,132). The most often utilized radioactive isotope of iodine is ^{131}I, sometimes known as radioiodine, with a half-life of 8.1 days; this nuclide emits both beta and gamma radiation. The energy of gamma rays is 364 keV and is employed in diagnostic procedures. Because of these drawbacks vs ^{99m}Tc and ^{123}I, ^{131}I scintigraphy should only be used to track treatment in people with differentiated thyroid cancer (130,132). With PET and ^{18}F-FDG, differentiated thyroid carcinoma can be detected. There are clinical situations in which a thyroid issue is unintentionally discovered during a PET/CT scan, despite the fact that it is not recommended to utilize PET to identify benign thyroid disease. For instance, a PET/CT scan using 18F-FDG can be used to distinguish between benign and malignant tumors when a single pulmonary nodule is present. Identifying the surgical indications in cases of a follicular neoplasm or an unclear biopsy is a difficulty that frequently arises in thyroid management. The positive predictive value (PPV) of an image of a metabolically active thyroid nodule ranged from 33 to 50% in different prospective investigations. Furthermore, the standardized uptake value (SUV) for glucose metabolism in the focal lesion did not improve PET's ability to diagnose (134,135). If a thyroid nodule is accidentally discovered to be metabolically active, a biopsy should be performed to rule for thyroid cancer. If there is diffuse 18F-FDG absorption, it is also advisable to prescribe TSH and thyroid antibodies (aTPO, aTg) tests. Compared to conventional ^{131}I scintigraphy, the PET/CT with ^{124}I provides better accurate pictures with the benefit of having no influence on thyroid stunning (136). With this method, only differentiated thyroid carcinoma may be detected (137).

- **Pulmonary embolism:** If left untreated, PE has a significant fatality rate. The diagnosis cannot be made merely only on clinical findings or the results of straightforward tests

like Blood chemistry, simple chest radiography, or ECG. Therefore, imaging studies are necessary to support or disprove a PE diagnosis. The following products are utilized for mapping regional ventilation: radiolabelled aerosols ^{99m}Tc-DTPA and ^{99m}Tc-labeled Technegas, inert gases ^{133}Xe and ^{81m}Kr. Historically, the agent utilized for ventilation research was ^{133}X e (138,139). By administering radioactive tracers to a vein in the arm, perfusion scintigraphy is carried out. The particles that are used in commerce are called MAA and are ^{99m}Tc-labeled (140). A dual or triple head gamma camera with a wide field of view is required for V/PSPECT in order to decrease acquisition time and the possibility of patient movement. Palmer et al. thoroughly investigated the correlations between SPECT imaging activities, acquisition periods, collimators, and matrices (141). V/PSPECT is highly advised since it enables accurate PE detection even when pneumonia and diseases like COPD are present. In COPD patients, Technegas is preferable over DTPA. When offered, ^{81m}Kr is beneficial. Reduce the radiation dose as much as possible without clinically significant image deterioration.. This means that before the perfusion scan, which uses 100-120 MBq for both the V/ PLANAR and V/PSPECT, the ventilation scan should use 30 MBq of 99mTc-aerosol. Only a perfusion scan is advised during pregnancy. Holistic interpretation should take the place of probability interpretation as it is no longer relevant. Mismatch in more than one subsegment is an essential PE criteria (141).

VI. FUTURE OF NUCLEAR MEDICINE

Applications of radioisotopes in nuclear medicine include both diagnostic and therapeutic procedures as we have already discussed in this chapter. Actually, the key factors that led to the development of nuclear medicine as a distinct medical field were the accomplishments in using radioiodine to treat thyroid issues, both benign and cancerous.

1. **Oncology:** Since 1990, the real number of cancer diagnoses has risen by 73%, despite the fact that In an age-standardized population, the incidence of invasive cancers has steadily decreased throughout the 1990s (142). This trend is caused by several factors, including an older population, higher incidence of cancer, and the detection of tumors through screening that would not have manifested as symptoms or resulted in death throughout the anticipated lifetime of a patient. From 469,000 in 1990 to 606,000 in 2020, 609,360 in 2022 number of cancer-related fatalities in the US has climbed more gradually (143,144).As a result, a lot more patients are coping with a cancer diagnosis. In light of this, it is all but likely that cancer imaging will continue to be a key area of nuclear medicine practise in the years to come.Currently, oncologic imaging investigations' interpretation is almost entirely a manual, subjective procedure, including the scrolling through many stacks of images by nuclear medicine specialists or radiologists with appropriate training to find and define anomalies. Given how quickly machine learning-based approaches to picture classification are developing, it is likely that this procedure may soon be aided by or even replaced by computer systems (145).Because tumor and normal tissue generally contrast greatly, nuclear oncology imaging investigations appear to be especially well adapted for AI-based interpretation. This is already the case due to the use of tracers in therapeutic settings, such as PSMA ligand, 18F-FDG, and somatostatin analogues .Presently, patient staging and restaging before and after therapeutic intervention predominate oncologic imaging. Nuclear imaging has been used in oncologic research to evaluate the pharmacokinetics of therapeutic drugs for many years.Two significant challenges were the inability to radiolabel

medications in time for clinical use and the limited sensitivity of PET scanners, which only allowed imaging investigations a few hours after drug administration. Significant advancements made in recent years may help to get beyond both constraints. New total body systems exhibit previously unheard-of sensitivity and expand the time window for pharmaceutical research(146).Oncologic research will benefit greatly from the combination of radiolabeled antibodies and more sensitive PET devices (147).Initial efforts like pre-targeting and cutting-edge antibody labeling techniques show potential for minimizing radiation exposure and lowering the time between antibody injection and imaging (148).In oncologic molecular imaging, PET imaging of the dynamic TME following immune modulation therapy has emerged as the next frontier. It has been shown that using CD8-positive T cells and antibodies against programmed death ligand 1 labeled with ^{89}Zr for PET imaging improves the precision of predicting the results of immunotherapy and is superior to biopsy and immunohistochemistry (149). The targeting of immune cell markers using ^{89}Zr-labeled antibodies is the only restriction on their use.FAP inhibitors, which target the tumor stroma, can be used alone (150); they can be used in conjunction with cell-based therapies that target PSMA, such as CAR-T cells, that have reporter genes transfected into them, which can target both prostate cancer tumor cells and the PSMA-expressing tumor neovasculature, or they can be added to pretargeted strategies (like bispecific antibodies or bioorthogonal click chemistry) (151).Through the development of hybrid imaging methods like SPECT/CT, PET/CT, and PET/MRI, as well as the advent of PET, nuclear medicine technology has evolved during the past 20 years (152, 153).The development and commercialization of PSMA-targeted theranostics were spurred on by the success of peptide receptor radionuclide treatment. Major clinical guidelines for the detection of biochemical recurrence now include PSMA-directed PET imaging as a key component(154).The FDA just received a new medication application for ^{68}Ga-PSMA11, and approval is anticipated soon. The ^{18}F-labeled PSMA ligand registration studies are still ongoing.

2. **Neurology:** In the years to come, it is anticipated that a number of current research applications in the field of molecular brain imaging will become common therapeutic tools. This shift encompasses both technological and radiotracer developments. Additionally, innovative and interesting research methodologies will develop. It is reasonable to suppose that brain PET tracers in the future would be available to imaging the majority of neurodegenerative diseases, if not all of them. This would be an example of effective research translation from the bench to the bedside. This progression began with the known b-amyloid PET tracers' acceptance some time ago and continued with the first authorized tau PET tracer(155). As the clinical use of molecular brain imaging significantly develops, the criteria and diagnostic methods now used for neurodegenerative illnesses are expected to be scrutinised. This alteration in perspective is primarily driven by the inability to offer disease-modifying therapies for any of these conditions up to this point given the way they are currently diagnosed. It was recently proposed to begin with AD and replace the disease's current classification as a syndromal construct with a biologic definition that includes running diagnostic tests for neurodegeneration, tau, and amyloid (the so-called ATN concept) (156).Growing evidence indicates that the role of PET imaging in the context of treatment stratification and therapy monitoring will increase, which is consistent with the anticipated paradigm change on how to identify neurodegenerative illnesses. There is optimism that the most innovative disease-modifying treatment approach for neurodegeneration, aducanumab, a human monoclonal antibody, will be granted a license

for clinical usage in anti-amyloid drugs for AD (157).Experts believe that in order to justify drug administration, a positive PET scan for amyloid demonstrating the actual existence of therapeutic target will be necessary because such medications will be highly expensive and may have important adverse effects. Based on the knowledge gained from drug testing trials conducted on individuals with a suspected AD clinical diagnosis, such an application seems reasonable. About 20% of these individuals had baseline amyloid PET results that were negative despite standard evaluation by experienced doctors(158).In terms of technical developments, in the years to come, there will surely be additional research addressing the critical question of the clinical use of the use of AI and hybrid PET/MRI in molecular brain imaging (despite the value proved in research).Many experts anticipate that once disease-modifying medicines are available, AD will be the first clinical application for hybrid PET/MRI. For example, there is optimism that AI will be able to distinguish between different illness subtypes, which will improve differential diagnosis and treatment choices. Both in terms of academic study and therapeutic application, the future of molecular brain imaging appears promising (159).

3. **Cardiology:** Nuclear medicine has been utilized in cardiovascular applications to measure ischemic heart disease's myocardial perfusion, function, and viability, as well as to guide revascularization operations. True molecularly focused imaging has not yet made an impact on clinical cardiovascular care comparable to oncology or neurology, despite continual advancements in imaging technology. This discrepancy is best explained by the fact that targeted molecular imaging—which is most effective when combined with targeted molecular therapies—has not always been required in cardiology, where mechanical interventional techniques and widely applicable, generalizable pharmacological therapies have generally predominated. However, molecular imaging will be the key to the development of cardiovascular nuclear medicine. This will be closely related to the advancement of cardiovascular medicine in the future, when molecularly focused approaches will become increasingly important (160).One excellent example of how molecular imaging will become clinically relevant when targeted medicines define a particular need is the recent radionuclide imaging's success in detecting cardiac amyloidosis (161).Nuclear imaging makes it simple to see chemokine receptors like CXCR4, also known as CC-motif chemokine receptor 2, is a kind of chemokine receptor (CCR2) and profibrotic proteins like FAP.The heart is the focal point of the circulatory system, but it also has an impact on a number of other systems, including the immunological and neurohumoral systems, therefore systems-based, holistic methods will increasingly dictate cardiovascular therapy. A systemic, targeted solution should take into account all of the impacts on the intended area and surrounding tissues because cardiovascular disorders are closely linked to disease of other organs and tissues.As a whole-body method, radionuclide-based molecular imaging is ideally suited to find such systemic networks. One current illustration is the connection between inflammation and the kidneys, the brain, the hematopoietic system, the arterial wall, and the heart (162).Another instance is the recent focus on cardio oncology, which focuses on assessing how tumors affect the body and tumor therapies on the circulatory system (163).Therefore, new, targeted imaging methods that are created to guide particular molecular therapies in cardiovascular target tissues as well as the concurrent condition of networking distant organs and tissues will influence the future of cardiovascular nuclear medicine.

4. **Radiopharmaceutical chemistry:** In order to best select molecular targets for radiopharmaceutical development, biologists from all disease fields must work closely with doctors to determine and prioritize clinical needs and open questions. This will be accurate for the creation of PET imaging with fresh radiotracers and theranostics (in oncology, cardiology, neurology, infection, and other domains).The use of radiometals, most notably ^{64}Cu and ^{89}Zr, has likely had the greatest expansion in terms of fundamental, translational, and clinical studies over the past few decades, despite the emergence of novel techniques for labeling molecules with ^{11}C and ^{18}F.Despite the substantial advancements previously made in the ^{68}Ga field, this should be a focus in the upcoming years. Given the promising clinical outcomes with ^{225}Ac-PSMA, future advances may focus on the usage of a-emitters (164).It is also possible to employ a well-designed tracer to non-invasively check on the efficacy of therapeutic medications that are used after the drug target. One illustration of this is the use of human epidermal growth factor receptor 2 imaging for drugs that target tyrosine kinase and block human epidermal growth factor receptor 2 (165).

5. **Instrumentation and Analysis:** From simple, single-channel, position-sensitive probes with rectilinear scanning to complex detectors with great energy, spatial, and time resolution, nuclear imaging detectors have advanced. Planar cameras have given way to tomographs that can produce high-quality 3- and 4-dimensional data as a result of advances in imaging technology. Nuclear imaging equipment was coupled with CT and then MRI to provide precisely matched anatomic information to enhance that information. Parallel developments in mathematics and computing for the reconstruction and analysis of PET and SPECT images accompanied these improvements in hardware. Iterative image reconstruction methods based on statistical and physical models have brought about a new era of image quality and are currently the industry standard for both PET and SPECT. The development of novel data analysis techniques that can quantify intricate molecular processes like enzymatic activity and receptor binding as well as sophisticated image analysis techniques like pharmacokinetic models has significantly improved our ability to measure regional tracer concentration, first for PET and more recently for SPECT. Faster, more compact, and more precise detectors are now possible thanks to developments in material science and electronics (166).The creation of molecular imaging biomarkers is now possible thanks to the advancement of imaging technology and image-generating algorithms, which has created a setting with a wealth of biological and clinical data (167).The aim of published criteria like PERCIST for Cancer and ^{18}F-FDG PET and of organizations specializing in quantitative imaging in the US and Europe has been to establish standards for quantitative molecular imaging (168).

6. **Artificial intelligence:** Among the many research and development fields that AI is actively transforming, nuclear medicine and molecular imaging are just two. Early in the 1990s, publications that demonstrate concepts in the realms of cardiac and brain imaging demonstrated the potential of AI and neural network-based technologies for image processing and pattern recognition (169,170,171,172).Total-body PET scanner data that we begin to gather regarding physiologic and pathologic pathways may potentially be advantageous for training AI-based reconstruction algorithms. Thus, these methods could produce total-body PET-like images obtained with contemporary scanners without ultralong axial field of view, AI might serve an important part in maximizing impact of technological investments in nuclear medicine clinical practise (the same would be true for ultrafast PET detectors).If true, the modest spatial and temporal resolution that has always

been regarded as a drawback of PET and SPECT imaging would be resolved, and readily available scanners would soon be able to provide an unmatched sensitivity combined with great spatial and temporal resolution. AI is likewise influencing the analysis and interpretation of nuclear medicine pictures.

At the beginning of the 2000s, a number of doctors legitimately questioned whether PET/CT systems were clinically necessary (173). To increase access to clinical PET imaging, SPECT/PET systems were considered a possible tactic(174).Until recently, it was thought that imaging radiolabeled PSMA for prostate cancer inhibitors was not possible(175).There were also convincing arguments that creating novel imaging agents is typically too expensive to be profitable(176).Radioisotopes are frequently used in nuclear medicine to diagnose and treat human illnesses. However, the relative relevance of nuclear medicine's diagnostic and therapeutic applications has fluctuated throughout time. Internal medicine gave rise to nuclear medicine, which was initially used in clinical settings primarily for investigations of the pathophysiology of various diseases and the management of thyroid conditions (177,178).The American Board of Nuclear Medicine advocated for the removal of nuclear medicine as a separate medical specialty in the early 2010s because clinical nuclear medicine was so similar to radiology (179).The majority of people believed that the only financially viable task for nuclear medicine doctors was the precise ^{18}F-FDG PET/CT scan interpretation. On the basis of this premise, it seemed obvious that nuclear medicine should be added to the list of radiology's subspecialties.

In the interim, the FDA has approved a number of additional imaging products, consequently, it seems unlikely that nuclear medicine will be limited to reading 18F-FDG PET/CT readouts in the future. The FDA's clearance of the theranostic pair ^{68}Ga-DOTATATE and ^{177}Lu-DOTATATE for use in imaging and treating neuroendocrine tumors, as well as the extremely encouraging outcomes from the use of radiolabeled PSMA ligands in imaging and treating prostate cancer, are even more significant.Therefore, it is very possible that therapeutic uses of radioisotopes will become increasingly important in future developments in clinical nuclear medicine. Simply said, nuclear radiology will retake nuclear medicine's place in the profession.

VII. CONCLUSION

An essential instrument for a comprehensive approach to medical radiation science is provided by nuclear medicine. It is established historically and in the evolution of contemporary best practice that nuclear medicine and both radiography and radiation treatment complement one another. Clinical practitioners in all branches of the medical radiation sciences benefit from knowledge of the technical and clinical elements of integrated modalities. To enhance the skills of radiographers, radiation therapists, and other healthcare professionals working in the diagnostic imaging sector, this article offers a fundamental understanding of nuclear medicine. Since the area of nuclear medicine has been so inventive and quick to adapt to new scientific discoveries and clinical requirements, its development has been unexpected. Nuclear medicine will surely have a promising future if this success is sustained.

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