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Permalink

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Journal

Bio-Algorithms and Med-Systems, 21(1)

ISSN

1895-9091

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Publication Date

2025-12-31

DOI

10.5604/01.3001.0055.2175

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Peer reviewed



Bio-Algorithms and Med-Systems

WWW.BAMSJOURNAL.COM

ISSN: 1896-530X

REVIEW ARTICLE

Received: 22.05.2025

Accepted: 08.07.2025

Published: 23.07.2025

CITE THIS ARTICLE AS:

Bharathi PG, Abbaszadeh S, Moskal P, Alavi A, "Transformative Advances in PET Imaging: From FDG to Total Body Scanners, Novel Tracers and AI-Driven Precision Medicine," Bio-Algorithms and Med-Systems vol. 21, no. 1, pp. 40-57, 2025, DOI: 10.5604/01.3001.0055.2175

AUTHORS' CONTRIBUTION:

A – Conceptualization
B – Data Curation
C – Formal Analysis
D – Funding Acquisition
E – Investigation
F – Methodology
G – Project Administration
H – Resources
I – Software
J – Supervision
K – Validation
L – Visualization
M – Writing – Original Draft
N – Writing – Review & Editing

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Transformative Advances in PET Imaging: From FDG to Total Body Scanners, Novel Tracers and AI-Driven Precision Medicine

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ABSTRACT

Introduction: Positron emission tomography (PET) has undergone transformative advancements, evolving from a research tool into a cornerstone of precision medicine.

Objective: This review highlights key developments in PET imaging, including the introduction of specialized systems such as brain and breast-dedicated scanners, total-body PET, and hybrid PET/CT and PET/MRI technologies.

Methods: These innovations have significantly enhanced diagnostic accuracy and patient management across oncology, neurology and cardiology. The emergence of novel radiotracers beyond fluorodeoxyglucose (FDG) has expanded PET's clinical applications by targeting specific molecular pathways, improving sensitivity and specificity in disease characterization. Notable tracers include those for tumor proliferation, hypoxia and receptor-specific imaging, which facilitate personalized treatment strategies. The integration of artificial intelligence (AI) has revolutionized PET imaging by improving image reconstruction, noise reduction, motion correction and lesion segmentation. AI-driven tools enhance diagnostic precision while reducing scan times and radiation exposure, making PET safer and more efficient. Furthermore, AI accelerates radiotracer development by optimizing molecular design and enabling personalized dosimetry planning for theranostic applications. Total-body PET scanners represent a technological milestone, offering unparalleled sensitivity, reduced radiation doses, faster scans, the ability to track systemic diseases comprehensively and to enhance diagnosis by novel imaging biomarkers. These advancements enable earlier disease detection, precise monitoring of treatment efficacy and deeper insights into disease mechanisms.

Results: Collectively, these innovations underscore PET's transformative role in advancing precision medicine through early diagnosis, disease monitoring and tailored therapeutic interventions.

Conclusions: This review concludes that ongoing technological progress will continue to redefine the capabilities of PET imaging in clinical practice and research.

KEYWORDS

PET imaging, FDG, total body scanners, radiotracers, AI-driven precision medicine

LIST OF ABBREVIATIONS

AD – Alzheimer's Disease
AI – Artificial Intelligence
Aβ – amyloid-beta
CAD – Coronary Artery Disease
CBD – corticobasal degeneration
CT – Computed Tomography
DAT – dopamine transporters
dbPET – dedicated breast PET
DL – Deep Learning
FBP – Filtered Back Projection
FDG – fluorodeoxyglucose
FET – Fluoro-Ethyl-Tyrosine
FLT – fluoro-thymidine
FTLD-tau – frontotemporal lobar degeneration
IR – Iterative Reconstruction
LSO – Lutetium Scintillator Oxide
LYSO – lutetium-yttrium oxyorthosilicate
MIP – Maximum Intensity Projection
MRI – Magnetic Resonance Imaging
PD – Parkinson's Disease
PEM – Positron Emission Mammography
PET – Positron Emission Tomography
PSMA – Prostate-Specific Membrane Antigens
PSP – Progressive Supranuclear Palsy
RF – radiofrequency
SERT – serotonin transporters
SiPMs – silicon photomultipliers
TOF – Time-Of-Flight
XAI – explainable AI

INTRODUCTION

Positron emission tomography (PET) imaging emerged in the early 1970s as a groundbreaking technique in nuclear medicine, integrating principles from radiation physics and advanced computational technology [1]. The foundation of PET imaging lies in the use of positron-emitting isotopes to capture and visualize metabolic activity within the body [2, 3]. A key milestone in its development occurred through the efforts of Dr. Michael Phelps, Dr. David Kuhl and their team at the University of Pennsylvania [4, 5]. They successfully demonstrated the practicality of PET imaging by constructing the first tomographic scanner capable of detecting positron emissions. This innovation culminated in the introduction of the first human PET scanner in 1975, enabling noninvasive imaging of real-time biological processes within living organisms [6].

The breakthrough in PET imaging came from the utilization of radiotracers, substances labeled with positron-emitting isotopes, which could be injected into the body [7]. One of the key moments in PET development was the synthesis of fluorodeoxyglucose (FDG), a glucose analog labeled with fluorine-18, which has become a standard radiotracer in PET imaging [5, 8–10]. FDG accumulates in areas of high metabolic activity, such as tumors, making it a powerful tool for cancer diagnosis [11]. This allowed PET to offer a noninvasive approach for visualizing physiological processes such as blood flow, oxygen consumption and glucose metabolism [12, 13]. In addition to conventional oncologic applications, PET has also emerged as a valuable tool for treatment verification in particle therapy. PET-based in vivo monitoring of ion beam range during hadron therapy is gaining increasing attention to improve treatment accuracy and safety. This approach enables the visualization of β^+ -emitting isotopes generated by nuclear interactions of the therapeutic ions with patient tissue, allowing assessment of dose delivery and anatomical changes. Recent developments and clinical experiences highlight the growing integration of PET imaging into ion beam therapy workflows and underscore its potential in adaptive treatment strategies [14].

As PET technology advanced it evolved into a hybrid imaging modality by combining PET with computed tomography (CT) or magnetic resonance imaging (MRI), allowing for both functional and anatomical information to be obtained simultaneously [15–17]. To overcome the limitations of standalone systems, an innovative Add-on PET system, an insert-type PET scanner engineered to transform a conventional MRI into a fully integrated PET-MRI, was developed [18]. A key feature of this design is the complete integration of PET detector modules within a head radiofrequency (RF) coil. This strategic placement ensures optimal detector proximity to the brain while eliminating the typical issue of RF coil interference within the PET field of view. The development of PET/CT in the early 2000s revolutionized clinical imaging, particularly in oncology, where it enabled more accurate detection and staging of cancers [19]. Today, PET is an indispensable tool in the fields of neurology, cardiology and oncology, and continues to evolve with the introduction of new radiotracers, improved imaging technologies and better computational methods for image analysis [20, 21].

The advent of time-of-flight (TOF) PET in the 1980s further revolutionized the field, leveraging the precise timing of photon pair detection to enhance image quality and reduce noise [22, 23]. TOF technology improved localization of annihilation events, offering superior signal-to-noise ratios compared to conventional PET [24, 25]. This breakthrough spurred additional research into fast scintillators and photodetectors, such as silicon photomultipliers (SiPMs), which are now integral to modern PET systems [26–28]. These components allow for more compact scanner designs

while delivering enhanced timing resolution, paving the way for innovations like organ-specific and total-body PET systems [29–31]. The high sensitivity of total-body PET systems enabled effective dynamic and model-based kinetic imaging [32–34] has opened prospects for the development of novel imaging biomarkers sensitive to the early stages of the tissue alterations, e.g., positronium imaging [35–42] or the emerging quantum-enhanced PET imaging [43–48]. Due to the high sensitivity of the new-generation PET scanners, simultaneous dual-tracer imaging, requiring multiphoton tomography capability [49–52], becomes also a realistic possibility.

PET/MRI systems emerged in the 2000s, offering superior soft-tissue contrast alongside metabolic imaging, particularly beneficial in pediatric and neurological cases [53–56]. Recent advancements in hybrid PET/MRI systems include the development of MR-compatible preclinical PET inserts such as the ScintoTube, which employs a monolithic LYSO scintillator tube to maximize sensitivity and spatial resolution. Validated for use inside 7T and 9.4T Bruker MRI systems without mutual interference, ScintoTube [57] represents a next-generation approach in simultaneous PET/MRI imaging for small-animal studies. Such hybrid systems continue to drive the evolution of PET technology, facilitating multiparametric imaging and enabling researchers to study disease processes in greater detail [58, 59]. These advancements underscore the ongoing transition of PET from a diagnostic tool to a versatile modality for precision medicine and therapy monitoring [60].

APPLICATION OF PET IMAGING

Over the past decade, PET has transitioned from being predominantly a research-oriented modality to an imaging technique with substantial clinical utility [5, 61]. This evolution has significantly influenced the medical imaging domain, providing exceptional insights into physiological and biochemical processes. Its ability to visualize metabolic activity *in vivo* has made it indispensable in oncology [62–68], neurology [69–73] and cardiology [74–78]. PET utilizes radioactive tracers labeled with short-lived radioisotopes derived from naturally occurring elements present in the biochemical constituents of the human body. PET can identify and measure physiological and receptor activities within the body [79, 80], especially in cancerous cells, a feat that remains unattainable through alternative imaging modalities.

Oncology: Advancing Cancer Diagnosis and Monitoring

In oncology, PET is widely used for tumor detection, staging, and monitoring therapeutic responses, particularly with ^{18}F -FDG [81–84], which highlights regions of increased glucose metabolism often associated with malignancies. FDG-PET remains the benchmark imaging modality for assessing glucose metabolism in cancer, owing to the Warburg effect, which drives elevated glucose uptake by cancerous cells [85]. FDG-PET is particularly integral

in diagnosing lung cancer (Fig. 1.), lymphoma (Fig. 2.) and colorectal cancer [86–88].

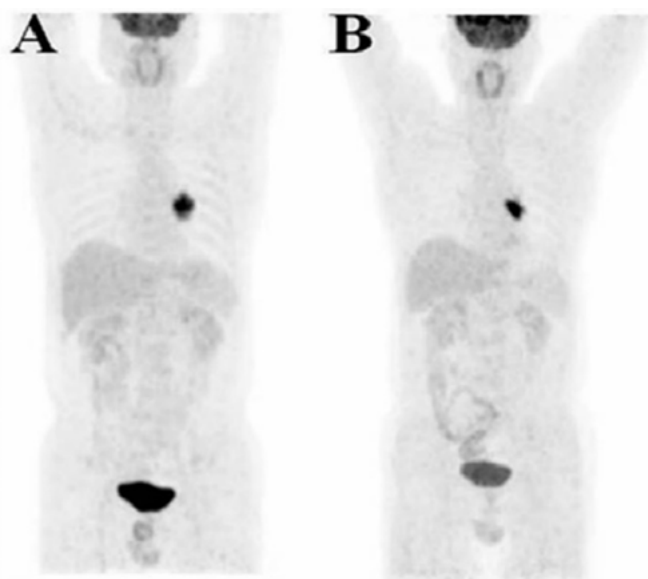


Fig. 1. A 53-year-old man with squamous cell lung cancer. (A, B) Maximum intensity projection (MIP) image of scan-1 and scan-2, respectively. Adapted from [89].

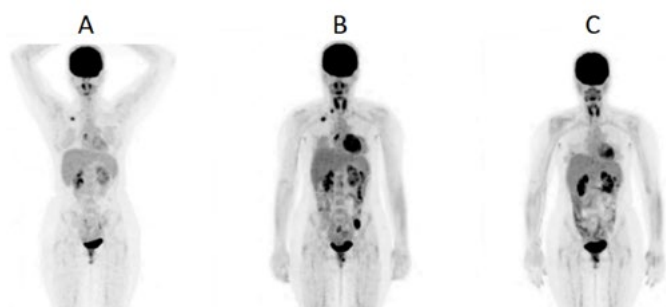


Fig. 2. Serial MIP images of a Hodgkin's lymphoma patient demonstrating pseudo progression pattern during the interim period. (A) Initial scan before Immunotherapy; (B) After 4 cycles of pembrolizumab; (C) Follow-up scan. Adapted from [90].

Neurology: Insights into Brain Function and Disorders

PET imaging has revolutionized the field of neurology by providing detailed insights into the brain's metabolic functions, neurochemical activities and structural alterations associated with neurological disorders [91]. PET offers a unique capability to visualize brain activities in real time, enabling the evaluation of metabolic processes at the neuronal level [80]. This approach is particularly significant in the study of neurological conditions such as Alzheimer's disease (AD; Fig. 3.), Parkinson's disease (PD; Fig. 4.), and epilepsy, which are characterized by disruptions in normal brain function. Through the use of radiolabeled tracers, PET facilitates the quantification of specific molecular targets, including glucose metabolism and neurotransmitter interactions, such as those involving dopamine and serotonin [92].

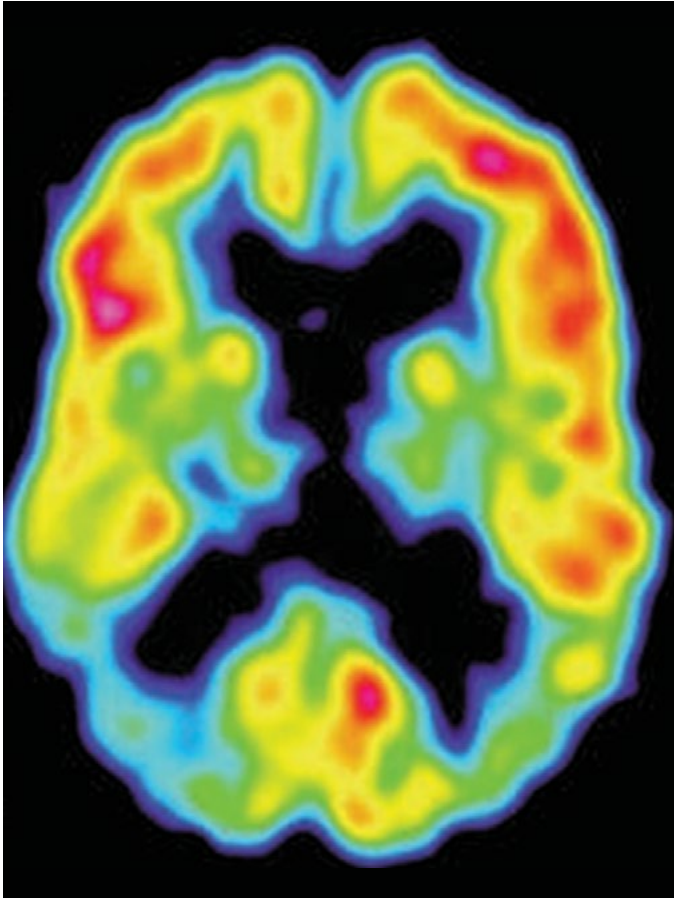


Fig. 3. A patient with mild AD who underwent PET study using ^{18}F -FDG. Adapted from [94].

By providing a comprehensive representation of deviations in these biological processes from standard physiological conditions, PET imaging supports early diagnosis, disease progression monitoring and the evaluation of therapeutic interventions [93].

In the realm of neurodegenerative disorders, PET has established itself as a pivotal imaging modality for the diagnosis and evaluation of conditions such as AD. PET facilitates the detection of alterations in brain metabolism and the Accumulation of amyloid plaques, changes that often precede the onset of clinical symptoms [94–96]. Additionally, PET plays a crucial role in assessing the functionality of the dopamine system in PD, aiding not only in diagnosis but also in monitoring disease progression [97–99]. In epilepsy, PET imaging is utilized to localize brain regions responsible for seizures, providing critical insights into disease management [100, 101]. Furthermore, the application of PET in psychiatric disorders, including depression and schizophrenia, has gained prominence, enabling the monitoring of specific neurotransmitter system activities [102, 103]. By offering a unique capability to visualize brain function and chemistry, PET imaging has significantly advanced the understanding of neurological and psychiatric conditions, surpassing the diagnostic capabilities of traditional imaging modalities such as MRI and CT.

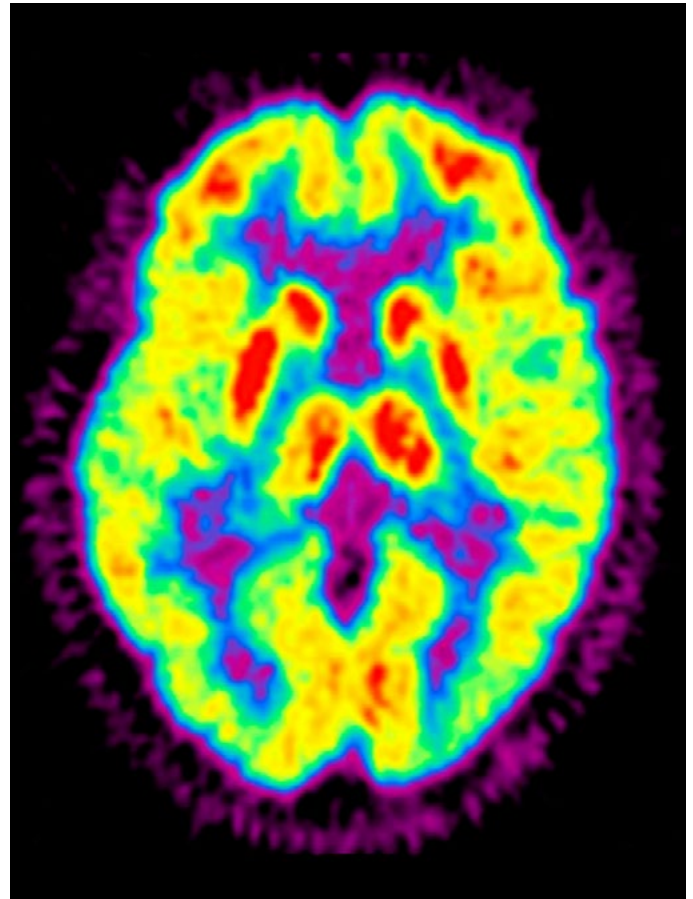


Fig. 4. A patient with PD who underwent PET study using ^{18}F -FDG. Adapted from [104].

Cardiology: Visualizing Myocardial Function and Viability

In the domain of cardiology, PET imaging offers significant advantages in the evaluation of heart diseases, particularly in understanding myocardial function and the underlying pathophysiological mechanisms of cardiovascular disorders [105, 106]. PET provides a noninvasive means to assess coronary blood flow, myocardial metabolism and cardiac tissue viability, which are critical for the diagnosis of conditions such as coronary artery disease (CAD), heart failure and myocardial infarction [107, 108]. The use of FDG in PET imaging enables the detailed evaluation of glucose metabolism in cardiac tissues, offering insights into regions with metabolic dysfunction or compromised viability [109]. This application is particularly essential for detecting hibernating myocardium, a state where cardiac muscle retains viability but demonstrates suboptimal function due to reduced blood flow. Additionally, PET plays a pivotal role in analyzing the heart's metabolic activity and its response to stress, aiding in the assessment of CAD severity and serving as a valuable tool for monitoring treatment effectiveness [110].

Furthermore, PET imaging serves as a critical tool for evaluating the cardiac response to various interventions, including coronary

bypass surgery, angioplasty and pharmacological therapies [111]. By offering real-time assessments of blood flow restoration and myocardial metabolic improvements, PET imaging underscores its transformative role in advancing personalized medicine through enhanced diagnostic precision and therapeutic monitoring.

Regenerative Medicine and Stem Cell Imaging

An emerging application of PET imaging lies in the domain of regenerative medicine and stem cell transplantation. Molecular imaging techniques such as FDG-PET have shown potential in evaluating disease prognosis and treatment response in patients undergoing autologous hematopoietic stem cell transplantation, particularly in hematological malignancies like relapsed/refractory diffuse large B-cell lymphoma [112]. Moreover, PET-based imaging is gaining traction in stem cell research, offering a non-invasive means to monitor stem cell viability, migration, and differentiation in vivo. This approach could significantly enhance the understanding of cell-based therapies and their integration into personalized treatment plans [113].

ADVANCEMENT IN PET TECHNOLOGY

Advanced PET technologies, encompassing developments such as total-body PET scanners [29, 114], hybrid imaging systems [115] and molecularly-targeted tracers [116, 117], are set to transform diagnostic practices in various medical fields, including oncology, neurology, cardiology and immunology. The development of these tools will enable a more precise and rapid understanding of biological processes at the cellular and molecular levels. This advancement will aid in early disease detection, enhance the accuracy of disease staging and support the creation of personalized treatment plans. The incorporation of advanced computational techniques, including artificial intelligence (AI) and sophisticated data-analysis algorithms, is revolutionizing specialized imaging systems.

These technological advancements are enhancing the efficiency of complex image data interpretation, thereby empowering healthcare professionals to reach more rapid and well-informed clinical judgments. This synergy between cutting-edge technology and medical expertise is paving the way for more precise and timely patient care, ultimately improving diagnostic accuracy and treatment outcomes in various medical fields [118]. The ongoing evolution of sophisticated PET systems holds significant promise for improving patient care on multiple fronts. These advancements are expected to yield safer procedures by minimizing radiation exposure; additionally, patients are likely to benefit from shorter scan times and improved comfort [119]. Perhaps most crucially, these technological leaps are poised to dramatically increase the sensitivity of PET imaging. This heightened capability could prove invaluable in identifying subtle alterations in disease states, potentially allowing for earlier intervention and more precise

monitoring of treatment efficacy. Collectively, these improvements represent a significant stride towards more patient-centric and diagnostically powerful imaging protocols.

Dedicated System: Brain and Breast-Specific PET Innovations

PET imaging of the brain has been influential in investigating neurological conditions such as AD, epilepsy and brain tumors [69]. The development of high-resolution, total-body PET scanners (Fig. 5.) [120] represents a significant advancement in this domain, enabling comprehensive imaging of the brain while preserving sensitivity throughout the entire body [29]. Advancements in specialized PET imaging technology have the potential to greatly improve the monitoring of neurodegenerative conditions such as AD [121] and PD [71].



Fig. 5. Explorer total-body PET/CT scanner. Adapted from [120].

An intriguing development in specialized PET technology is the creation of new, highly specific radiotracers. For example, $^{13}\text{C}_6$ or $^{12}\text{C}_6$ -leucine tracers targeting amyloid plaques and tau tangles are already being used in AD research [122], and advancements in radiotracers that bind to dopamine receptors show promise for studying PD [123]. Among these radiotracers, $[18\text{F}]\text{-DOPA}$ and $[18\text{F}]\text{-FMT}$ are commonly used to detect loss of nigrostriatal dopaminergic nerve endings, with $[18\text{F}]\text{-DOPA}$ now clinically approved in the US and EU for PD diagnosis. In addition, $[18\text{F}]\text{-FE-PE2I}$, a PET tracer targeting dopamine transporters (DAT), demonstrates faster kinetics than DaTSCAN and offers high diagnostic accuracy, making it a strong candidate for broader clinical application. Beyond dopaminergic imaging, $[11\text{C}]\text{-DASB}$ binds to serotonin transporters (SERT) and is particularly useful for investigating non-motor symptoms of PD, such as depression and fatigue. The $[18\text{F}]\text{-FDG}$ tracer is employed to assess PD-related alterations in brain metabolism, blood flow and functional connectivity, contributing to the understanding of disease progression and heterogeneity [123].

The shift towards precision neurology, supported by specialized PET imaging, empowers healthcare providers to tailor interventions based on the unique characteristics of each patient's brain pathology,

moving away from a one-size-fits-all approach [124, 125]. This personalized approach is particularly crucial in AD, where PET imaging can help stratify patients who are likely to respond to specific treatments from those who are not. By integrating imaging biomarkers with other diagnostic tools, clinicians can make more informed decisions about treatment plans, enhancing the precision and effectiveness of therapeutic interventions [126].

Tau PET imaging enables the *in vivo* visualization of tau neurofibrillary tangles, a hallmark of AD, which is closely associated with synaptic loss, brain atrophy and cognitive decline. Unlike amyloid-beta (A β) PET, tau PET [127–129] provides a stronger spatial and temporal correlation with clinical symptoms, making it a superior biomarker for staging disease progression and predicting cognitive decline. Recent advancements in tau tracers, such as ^{18}F -flortaucipir [130] and ^{18}F -MK6240 [131], have demonstrated high sensitivity and specificity in detecting tau pathology in AD while differentiating it from other neurodegenerative disorders. These tracers are also valuable for identifying atypical presentations of AD and preclinical stages of the disease, offering insights into the topographical distribution of tau aggregates and their role in disease progression [132–134].

Beyond AD, tau PET imaging holds promise for diagnosing and monitoring non-AD tauopathies, such as frontotemporal lobar degeneration (FTLD-tau) [135], corticobasal degeneration (CBD) [136] and progressive supranuclear palsy (PSP) [137]. However, challenges remain due to weaker tracer binding and off-target uptake in non-AD conditions. Despite these limitations, the use of second-generation tau tracers with improved selectivity has shown potential for advancing differential diagnosis and tracking disease progression. Furthermore, tau PET imaging is increasingly recognized as a critical tool in clinical trials for evaluating therapeutic interventions by assessing target engagement and monitoring treatment effects. As research continues to refine tracer specificity and address methodological issues, tau PET imaging is poised to become an indispensable diagnostic and prognostic tool for both clinical practice and research into neurodegenerative diseases [138, 139].

Recent innovations in brain-dedicated PET systems have led to remarkable advancements in spatial resolution, timing accuracy and integration with other imaging modalities. For example, Yoshida et al. [140] developed a 245 ps TOF PET prototype with a hemispherical detector configuration, significantly enhancing sensitivity and spatial resolution specifically for brain imaging applications. Gonzalez-Montoro et al. [141] introduced the 4D-PET brain system, which enables dynamic imaging and motion tracking, demonstrating its potential for capturing temporal physiological processes in the brain. In a major step toward hybrid imaging, Takahashi et al. conducted the first human study using an add-on PET system integrated within a 3T MRI RF coil, allowing for simultaneous PET/MR imaging without compromising MR performance [18]. These dedicated systems are paving the way for more accurate, high-resolution neuroimaging, with

potential benefits in early diagnosis and therapeutic monitoring of neurological diseases.

The development of dedicated PET systems for breast imaging [142] represents a significant advancement in the early detection and staging of breast cancer. Unlike whole-body PET systems, which often lack the resolution and sensitivity required for small lesion detection, breast-specific PET devices are designed to address these limitations. For example, positron emission mammography (PEM) [143] and dedicated breast PET (dbPET) [144] systems utilize advanced detector technologies to achieve higher spatial resolution and sensitivity, enabling the detection of sub-centimeter lesions and intra-tumoral heterogeneity. These systems have shown promise in improving diagnostic accuracy, particularly in women with dense or fibrocystic breast tissue, where traditional imaging modalities such as mammography and ultrasound may fall short [145, 146].

In addition to enhanced imaging capabilities, dbPET systems are being integrated with biopsy tools to improve clinical workflows. High-resolution PEM/PET devices, for instance, not only detect suspicious lesions but also guide biopsy procedures with precision. These systems use rotating planar detectors and advanced positioning mechanisms to ensure accurate needle placement during tissue sampling. Such innovations reduce the likelihood of sampling errors and enable real-time verification of biopsy needle positions. The integration of PET with other imaging modalities, such as CT or MRI, further enhances diagnostic capabilities by combining metabolic data with detailed anatomical information, making it possible to better characterize lesions and assess their malignancy [145, 147].

Furthermore, dbPET systems are playing an increasingly important role in staging and treatment planning for breast cancer patients. Studies have demonstrated that these systems can detect regional and distant metastases with higher sensitivity compared to conventional imaging methods. For instance, the use of ^{18}F -FDG PET/CT has been shown to significantly alter staging and therapeutic management by identifying previously undetected metastatic disease. This capability is particularly valuable in guiding neoadjuvant chemotherapy decisions and monitoring treatment response. With ongoing advancements in detector technology and tracer development, dbPET systems are expected to further refine their diagnostic accuracy while reducing false positives, ultimately improving outcomes for breast cancer patients [148–151].

Studies have shown that dbPET offers higher sensitivity for early-stage breast cancer compared to whole-body PET/MRI, making it a valuable tool for diagnosing and evaluating breast cancer in patients with dense breasts [146]. When compared to MRI, dbPET systems also present certain benefits and limitations. While MRI provides detailed anatomical images and is highly sensitive in detecting breast cancer, it can sometimes overestimate the extent of disease and produce false positives due to its high sensitivity [152].

dbPET systems complement MRI by offering metabolic insights that can help differentiate between benign and malignant lesions, potentially reducing unnecessary biopsies [153]. Moreover, PEM has been found to have higher specificity than MRI in certain studies, although overall diagnostic accuracy may be similar. This specificity can be particularly beneficial in surgical planning and monitoring treatment response. However, both imaging modalities are often used together to provide a comprehensive assessment, as they can identify different aspects of the disease [152, 154].

Total-Body PET Scanners: A Technological Milestone

Traditional PET scanners typically cover smaller regions, such as the brain or specific parts of the body [155], but with the development of total-body PET technology, the entire body can now be imaged in a single scan [156]. This advancement is primarily driven by innovations in detector technology, such as the use of ultra-high sensitivity detectors such as LSO (lutetium scintillator oxide) and SiPMs, which allow for the efficient detection of even the smallest quantities of radiation emitted by tracers. As a result, total-body PET scanners can deliver higher-resolution images with increased signal-to-noise ratios, providing more precise data on tissue and organ function across the entire body [157–159]. This leap in capability is expected to significantly improve early detection, diagnosis and monitoring of a wide range of diseases, including cancers, neurological conditions and cardiovascular diseases.

The advent of total-body PET scanners represents a significant leap forward in the field of medical imaging, enabling comprehensive and detailed whole-body scans with remarkable speed and sensitivity. Total-body PET scanners, such as the Explorer [160], represent a breakthrough in molecular imaging, enabling full-body scans in a single pass [161]. These scanners allow for faster imaging [162], lower radiation doses and the ability to track systemic diseases over time [156]. The reduced scan time also minimizes the risk of motion artifacts, which can compromise the quality of images and lead to misdiagnosis. Furthermore, there is no need for multiple imaging sessions to assess different regions, making the process more convenient for both patients and healthcare providers. This speed and efficiency also enhance the potential for frequent monitoring, enabling clinicians to track disease progression and evaluate the effectiveness of treatments with greater ease.

The impact of total-body PET scanners extends beyond diagnostic applications, offering exciting possibilities for research and personalized medicine [114, 163]. Researchers can now investigate whole-body metabolic activity, study disease mechanisms in real time and observe how various organs interact on a molecular level [156, 164]. MIP scans acquired using the Explorer Total-Body PET scanner are presented in Fig. 6. In cancer research, for example, these scanners can provide unprecedented insights into the spread of tumors and their response to therapy, facilitating the development of more effective treatment strategies. Similarly,

in neurology, the ability to monitor changes in brain metabolism and neuroinflammation across the entire body could lead to breakthroughs in understanding complex neurological disorders such as AD, PD and multiple sclerosis [165]. Additionally, the high sensitivity of total-body PET scanners [29] allows for the use of lower doses of radiotracers, reducing radiation exposure to patients [156]. This not only makes technology safer but also opens the door for long-term monitoring and more frequent imaging in clinical practice. As these scanners become more widely available, they are expected to revolutionize the field of medical imaging, providing clinicians with a powerful tool for both diagnosis and ongoing patient care.



Fig. 6. FDG-PET scan of a healthy volunteer and ^{68}Ga -PSMA scan of a prostate cancer patient acquired using the Explorer total-body PET scanner.

AI in PET: Enhancing Image Reconstruction and Quantification

AI is revolutionizing the field of PET [166], particularly in enhancing image reconstruction [167–170] and quantification [171–173]. Traditional PET image reconstruction methods, such as filtered back projection (FBP) and iterative reconstruction (IR) [174–176], have been the cornerstone of clinical practice but suffer from limitations such as noise [177], low spatial resolution [178] and long acquisition times [179]. AI, especially deep learning (DL), offers innovative solutions by leveraging neural networks to improve image quality through denoising [180–182], artifact reduction [183, 184], and super-resolution techniques [185, 186]. These advancements not only enhance diagnostic accuracy but also enable reductions in radiation dose [187] and scan duration [188], making PET imaging safer and more efficient for patients. Enhancement of effective sensitivity by the application of AI in image reconstruction will enable the faster

development and translation to clinics of low-cost PET solutions based, e.g., on plastics scintillators, which are less efficient than crystals [189], thus making PET diagnosis more accessible and affordable in low and medium-income countries [190].

AI-based reconstruction techniques utilize large datasets to learn the manifold of realistic PET images, enabling the generation of high-quality images even from “noisy” or incomplete data [167, 191]. For instance, DL algorithms can integrate prior knowledge about PET imaging physics to suppress noise without sacrificing resolution [181, 192, 193]. These methods also facilitate motion correction [194] and parametric imaging, addressing challenges like patient movement during scans [183]. Furthermore, hybrid approaches that combine AI with conventional IR methods have shown promise in improving quantitative accuracy while maintaining computational efficiency [118]. The clinical adoption of AI-enhanced PET imaging is already underway, with some AI-driven tools achieving regulatory approval and integration into routine workflows [19].

Despite its transformative potential, the application of AI in PET imaging faces significant challenges. One major issue is the availability of large, annotated datasets for training robust models. Variability across scanners, imaging protocols and patient populations introduces additional complexities that can affect the generalizability of AI models [195–197]. Federated learning [198–202] has emerged as a promising solution to address data-sharing barriers while preserving patient privacy. However, concerns about the “black box” nature of AI models persist, emphasizing the need for explainable AI (XAI) [203–206] to build trust among clinicians by providing transparency in decision-making processes.

The clinical applications of AI in PET extend beyond image reconstruction to include lesion detection [207–209], tumor segmentation [210–213] and risk stratification [214–216]. For example, AI tools have demonstrated high accuracy in identifying cancer types and predicting treatment responses by analyzing radiomic features [217–221] from PET/CT scans [222]. These capabilities enhance personalized medicine by enabling early diagnosis and tailored treatment plans. Additionally, AI’s ability to harmonize data across different imaging centers supports multicenter studies and facilitates broader clinical adoption.

Looking ahead, the integration of multimodal imaging data – such as combining PET with CT [19, 223–225] or MRI [226–229] offers exciting opportunities for AI-driven advancements in precision medicine. By incorporating diverse clinical data into predictive models, AI can provide holistic assessments of patient health. Emerging trends also highlight the potential for using historical imaging data to improve diagnostic performance over time. However, rigorous validation through phantom studies and clinical trials remains essential to ensure the reliability and safety of these technologies.

EMERGING PET TRACERS

Beyond FDG: Novel Radiotracers for Targeted Imaging

The development of novel PET tracers beyond FDG has been driven by the need to overcome its limitations, such as false positives in inflammatory conditions [230, 231] and false negatives [232] in low-grade tumors [233]. Emerging radiotracers target specific biological processes or molecular markers, enhancing diagnostic accuracy and specificity [234, 235]. For instance, fluoro-thymidine (FLT) has shown promise in imaging cellular proliferation [236, 237], particularly in cases such as solitary pulmonary nodules, where FDG’s specificity is limited due to granulomatous diseases [238]. Similarly, amino acid-based tracers such as ^{11}C -Methionine [239] and [^{18}F] Fluoro-ethyl-tyrosine (FET) have demonstrated superior specificity in brain tumor imaging compared to FDG [240, 241], as they bypass the high glucose uptake of normal brain tissue. These tracers highlight the potential for tailored imaging approaches that align with tumor biology, improving sensitivity and specificity in diverse clinical settings [242–244].

Another significant advancement is the exploration of cancer-specific biomarkers for imaging. Radiotracers targeting choline metabolism (^{18}F -Fluorocholine) [245, 246] or hypoxia (^{18}F -Fluoromisonidazole) [247, 248] have been developed to address cancers with low FDG activity. Additionally, receptor-targeted tracers such as those binding to somatostatin receptors [249] or prostate-specific membrane antigens (PSMA) [250] are increasingly used for neuroendocrine tumors [251] and prostate cancer, respectively [252]. These tracers not only improve diagnostic capabilities but also enable precision medicine by identifying patients who may benefit from targeted therapies [253, 254].

Theranostics: The Dual Role of PET in Diagnosis and Therapy

Theranostics integrates diagnostic imaging with targeted therapy [255], leveraging PET radiotracers to identify disease-specific markers and deliver therapeutic agents [256]. This approach has revolutionized oncology by enabling personalized treatment strategies [257]. For example, radiopharmaceuticals like ^{68}Ga -DOTATATE [258] and ^{177}Lu -DOTATATE are used in neuroendocrine tumors for both diagnostic imaging and radionuclide therapy [259, 260]. Similarly, PSMA-based agents such as ^{68}Ga -PSMA-11 [261] for diagnosis and ^{177}Lu -PSMA-617 for therapy exemplify theranostic applications in prostate cancer [262, 263]. These agents allow patient selection based on target expression, dosimetry calculations, and real-time monitoring of therapeutic response.

The theranostic paradigm is expanding beyond oncology into other fields like cardiovascular diseases [264] and infectious diseases [265]. Advances in radiotracer chemistry [266] have

enabled the development of dual-purpose agents that combine diagnostic precision with therapeutic efficacy while minimizing off-target effects. For instance, alpha-emitting radionuclides like Actinium-225 [267] offer high biological effectiveness for small tumors and micro metastases while sparing healthy tissues. As theranostics evolves it is expected to play a critical role in predictive and preventive medicine by integrating molecular imaging with targeted treatments [268].

Accelerating Radiotracer Development with AI-Driven Tools

AI is transforming radiotracer development by optimizing discovery workflows and enhancing efficiency [269]. AI-driven platforms can analyze large datasets to identify promising molecular targets, predict binding affinities and design novel radiotracers with improved pharmacokinetics [270]. Generative AI models such as deep generative networks have been used to create candidate molecules rapidly, reducing the time required for preclinical validation [271]. For example, platforms such as IBM's RoboRXN integrate AI with automated synthesis techniques to streamline the production of radiotracers from concept to experimental testing [272].

AI also enhances image analysis and clinical implementation by automating tasks such as quantification of tracer uptake or lesion segmentation [273]. Machine-learning algorithms improve the accuracy of PET imaging by reducing noise and optimizing image reconstruction processes. Furthermore, AI tools can predict patient-specific responses to radiopharmaceuticals based on biodistribution data [274], facilitating personalized dosimetry planning [275] in theranostic applications [276]. These advancements underscore AI's potential to accelerate innovation while ensuring safety and efficacy in radiotracer development.

Emerging Radiotracers and Their Applications

Emerging radiotracers are addressing unmet needs across various medical fields by targeting novel biomarkers and physiological processes. In oncology, tracers such as ^{18}F -Flurpiridaz for myocardial perfusion imaging [277–279] or ^{89}Zr -labeled monoclonal antibodies for immune checkpoint visualization [280, 281], are expanding the scope of PET imaging beyond traditional metabolic markers such as FDG. In cardiovascular medicine, tracers targeting inflammation (^{68}Ga -DOTATATE) [282] or thrombosis (^{64}Cu -Fibrinogen) [283] are being developed to improve diagnostic precision in conditions such as atherosclerosis or heart failure.

Additionally, infection-specific tracers such as ^{64}Ga -NOTA-ubiquitin are emerging as tools for distinguishing between

sterile inflammation and bacterial infections [284–286]. These innovations extend PET's utility into areas such as infectious disease management and neurodegenerative disorders [133] by enabling early detection of pathological changes at the molecular level. As these tracers progress through clinical trials they hold promise for enhancing disease characterization, guiding therapeutic interventions and advancing personalized medicine.

CONCLUSIONS

In this survey we have presented a comprehensive overview of transformative advancements in PET imaging, emphasizing its evolution from a research tool to a cornerstone of precision medicine. Key innovations include the development of specialized PET systems such as total-body scanners, brain- and breast-specific devices and hybrid PET/CT and PET/MRI technologies, which enhance diagnostic accuracy and patient outcomes across oncology, neurology and cardiology. The introduction of novel radiotracers targeting specific molecular pathways has expanded PET's clinical applications, enabling more precise disease characterization and treatment planning. Additionally, advancements in AI have revolutionized image reconstruction, quantification and motion correction, and improved image quality while reducing scan times and radiation exposure. These innovations collectively position PET as a vital tool for early diagnosis, disease monitoring and personalized treatment strategies. AI's role in optimizing radiotracer development and harmonizing imaging protocols across centers has accelerated innovation while ensuring safety and reproducibility. Total-body PET scanners represent a significant leap forward, offering unparalleled sensitivity for whole-body imaging, reduced radiation doses and faster scans. This paper highlights the transformative potential of theranostics, which integrates diagnostic imaging with targeted therapy, to revolutionize oncology and extend its applications to areas such as cardiovascular and infectious diseases.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Drs. Lorenzo Nardo and Yasser Gaber Abdelhafez from University of California Davis for generously providing the images featured in Fig. 6. This work was supported by the National Institutes of Health under Award 5R01EB033466-03. Paweł Moskal received support from the National Science Centre of Poland through grants MAESTRO no. 2021/42/A/ST2/00423, OPUS no. 2021/43/B/ST2/02150 and OPUS-LAP no. 2022/47/I/NZ7/03112, and the SciMat and qLife Priority Research Areas budget under the program Excellence Initiative – Research University at Jagiellonian University.

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