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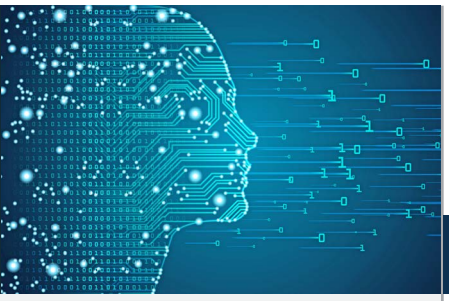

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A vision to increase the availability of PET diagnostics in low- and medium-income countries by combining a low--cost modular J-PET tomograph with the $^{44}Ti/^{44}Sc$ generator

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ABSTRACT

Objectives: This paper presents the prospects for increasing the availability of PET diagnostics by combining low-cost, lightweight and easily portable modular J-PET with the $^{44}Ti/^{44}Sc$ generator.

Methods: J-PET is constructed based on the low-cost axially arranged plastic scintillators that may enable the construction of PET scanners 5 to 10 times less expensive compared to current PET systems, which are based on crystal scintillators. Development of the radionuclide $^{44}Ti/^{44}Sc$ generator with the 60-year half-lifetime would enable long-term onsite production of ^{44}Sc labelled radiopharmaceuticals, eliminating the need for extensive and costly infrastructure typically associated with nuclear medicine. Presently applied $^{68}Ge/^{68}Ga$ generators with the 270 days half--lifetime require renewal every year. The $^{44}Ti/^{44}Sc$ generator could, in principle, be purchased once every half century.

Results: The lightweight and portable J-PET scanner, combined with the $^{44}Ti/^{44}Sc$ generator, can be deployed in remote and underserved regions, thus democratising access to advanced medical-imaging techniques.

Conclusions: This novel concept shows the transformative potential of combining innovative J-PET technology with the $^{44}Ti/^{44}Sc$ generator to make advanced diagnostics more accessible and affordable worldwide, especially benefiting millions of patients in low- and medium-income countries, and driving further innovations in medical imaging.

KEYWORDS

positron emission tomography, PET, modular J-PET, scandium, $^{44}Ti/^{44}Sc$ generator

LIST OF ABBREVIATIONS

CT – computed tomography
GATE – Geant4 Application for Tomographic Emission
HER2 – human epidermal growth factor receptor 2
J-PET – Jagiellonian positron emission tomography
LYSO – lutetium-yttrium oxyorthosilicate
MRI – magnetic resonance imaging
NEMA – National Electrical Manufacturers Association
PET – positron emission tomography
SiPMs – silicon photomultipliers

BRIEF DESCRIPTION OF THE WORK

This paper explores how the integration of the cost-effective modular J-PET scanner with the long-lasting $^{44}Ti/^{44}Sc$ generator can make PET imaging more accessible and affordable in low- and medium-income countries. This innovation holds significant potential to improve the early detection of disease and treatment planning, especially in remote and underserved regions, resulting in improved public health outcomes.

INTRODUCTION

Positron emission tomography (PET) is a powerful tool in modern diagnostic imaging, providing unique insights into cellular and molecular processes within the human body [1]. Since achieving the first blurry brain tumour images in the mid-20th century [2] and initiating its clinical application in the 1970s [3], PET technology has significantly transformed. It has benefited from continuous improvements in radiation detection [4] and radio-pharmacy [5], which have enhanced its role in medical diagnostics.

Unlike conventional imaging methods, such as X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), PET offers both anatomical and functional insights into the human body [6]. This dual capability is crucial for early disease detection and tracking metabolic changes over time, facilitating precise treatment planning [1]. PET achieves this by detecting gamma rays emitted from a radiopharmaceutical tracer injected into the patient's body, which accumulates in areas of high biochemical activity indicative of disease sites, such as tumours [7]. Moreover, PET scans are instrumental in diagnosing nervous system disorders, including sclerosis, memory disorders and neurodegenerative diseases such as Parkinson's and Alzheimer's [8]. They are also crucial in cardiological assessments, aiding in the evaluation of heart functions, effects of myocardial infarction, blood flow and abnormalities in heart muscle structure [9].

Despite its advantages, the widespread adoption of PET is challenged by the high cost of the scanner and the required infrastructure of the traditional, crystal scintillator-based PET scanners, as well as the availability of the imaging agents, which both limit the spread of the PET technique to well-equipped medical centres [1, 10, 11]. As illustrated in Fig. 1., almost half of the world's countries still lack access to PET imaging, with many others having far fewer scanners per million people compared to nations such as the United States or those in Europe. According to the IAEA Medical Imaging and Nuclear Medicine (IMAGINE) database [12], the average number of PET scanners globally is approximately 0.7 per million people, with 5,672 PET scanners spread across 109 countries. In contrast, the United States has about 5.41 PET scanners per million people [13], which is more than seven times the global average. This disparity highlights the challenges faced by countries with limited healthcare infrastructure, where access to advanced diagnostic tools such as PET is often restricted. Such limitations affect the technique's potential in early diagnosis, where timely and accurate detection can significantly alter disease treatment and patient outcomes. Additionally, the infrastructure required to support traditional PET operations is extensive, requiring onsite or regional cyclotrons for radionuclide production, and rapid transport systems for radiopharmaceutical distribution, restricting PET's availability, especially in less developed regions.

Efforts to overcome these barriers include developing more cost--effective and portable PET systems. Innovations such as the Modular Jagiellonian Positron Emission Tomography (J-PET) scanner [10, 14–16] are extending PET technology to a broader range of settings, potentially reaching underserved areas. Advances in radiopharmaceuticals also contribute to this shift by improving tracer production efficiency and developing longer--lasting tracers, thereby reducing costs and logistical complexities. One promising solution in this direction is the use of scandium-44 (^{44}Sc) radionuclide [17], which offers longer half-life and stable decay properties suitable for labelling radiopharmaceuticals in PET imaging. These developments not only aim to enhance PET's diagnostic accuracy but also broaden its accessibility.

MATERIALS AND METHODS

Modular J-PET

The modular J-PET scanner represents a significant innovation in PET technology, using plastic scintillator strips instead of the traditional crystal scintillator-based detectors [10, 14–16] (Fig. 2.). This choice of material significantly reduces scintillation light attenuation – which is more than an order of magnitude lower than in crystal scintillators – allowing effective light transport even over a few meters [10, 18]. The scintillators are arranged axially and are each read at both strip ends by four Silicon Photomultipliers (SiPMs), as shown in Fig. 3. When gamma quanta interact within a scintillator strip, this interaction generates scintillation photons, which, after reaching the end of the scintillator, generate electric signals in eight SiPMs – four at each scintillator end. The electric signals are used to determine timestamps by the dedicated electronics units – two timestamps at each leading and trailing edge of each SiPM signal. These timestamps are crucial for accurately reconstructing the position and time of a 511 keV

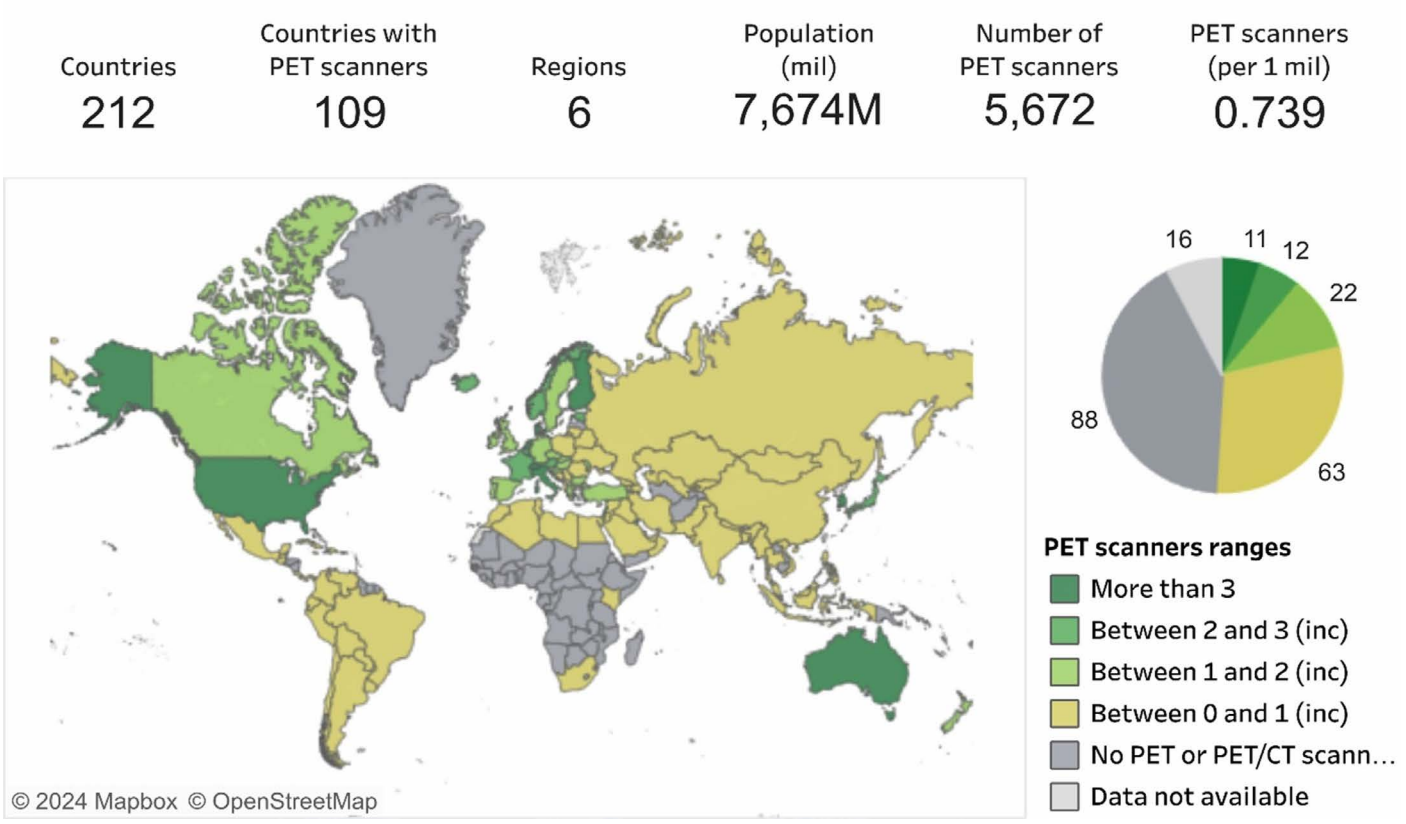

Fig. 1. Global distribution of PET and PET/CT scanners. The map illustrates the availability of PET scanners, emphasising disparities between countries. The pie chart on the right categorises countries based on the number of the devices per million inhabitants. Data sourced from [12].

annihilation photon (produced in the PET detection process) interactions. The signal energy data from the SiPMs are precisely measured to a timing accuracy of about 20 ps by state-of-the-art electronics [19, 20] and then recorded by an innovative, triggerless and adaptable data acquisition system [21, 22]. More details about the system and data selection are available in references [23, 24]. The possibility of multi-photon imaging with the J-PET scanner may also help in improving the specificity of the imaging by the application of positronium imaging [25–32] and quantum entanglement imaging [33–42].

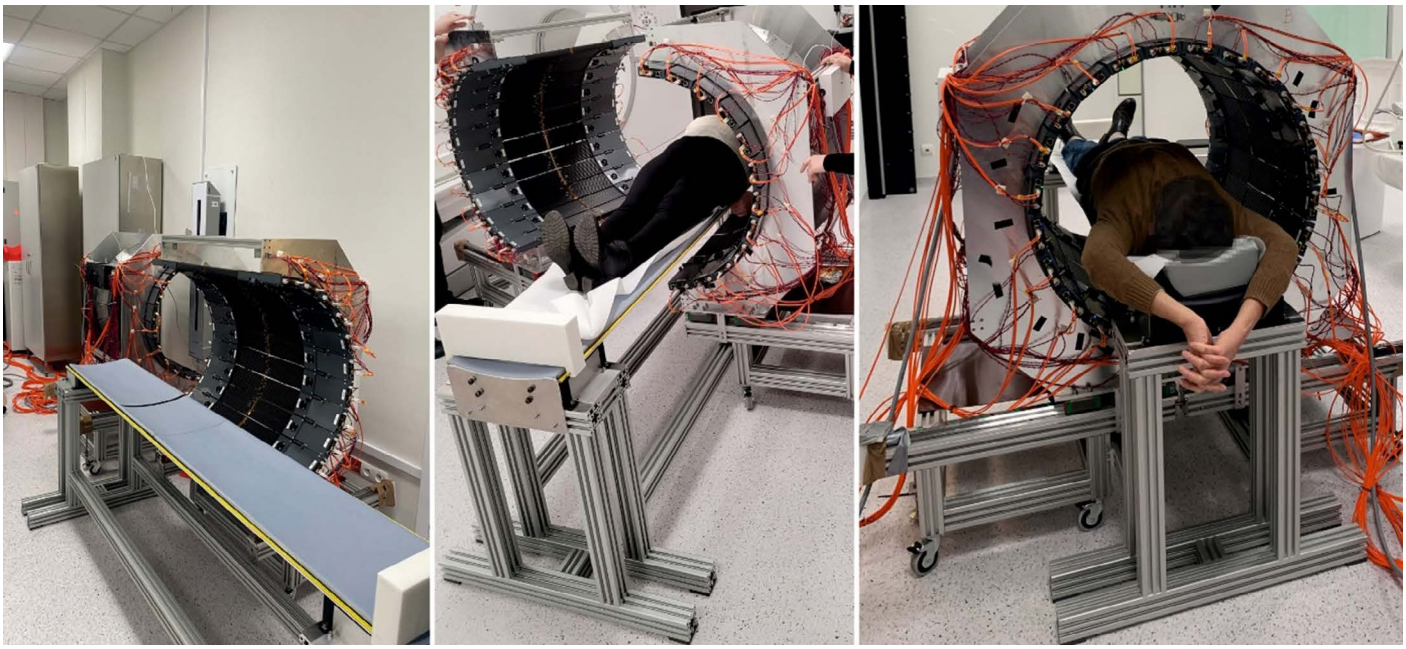

Fig. 2. Photographs of the J-PET scanner during clinical testing on patients in Jagiellonian University Hospital, conducted in the spring of 2024. These images illustrate the practical application and operational setup of the economical J-PET system.

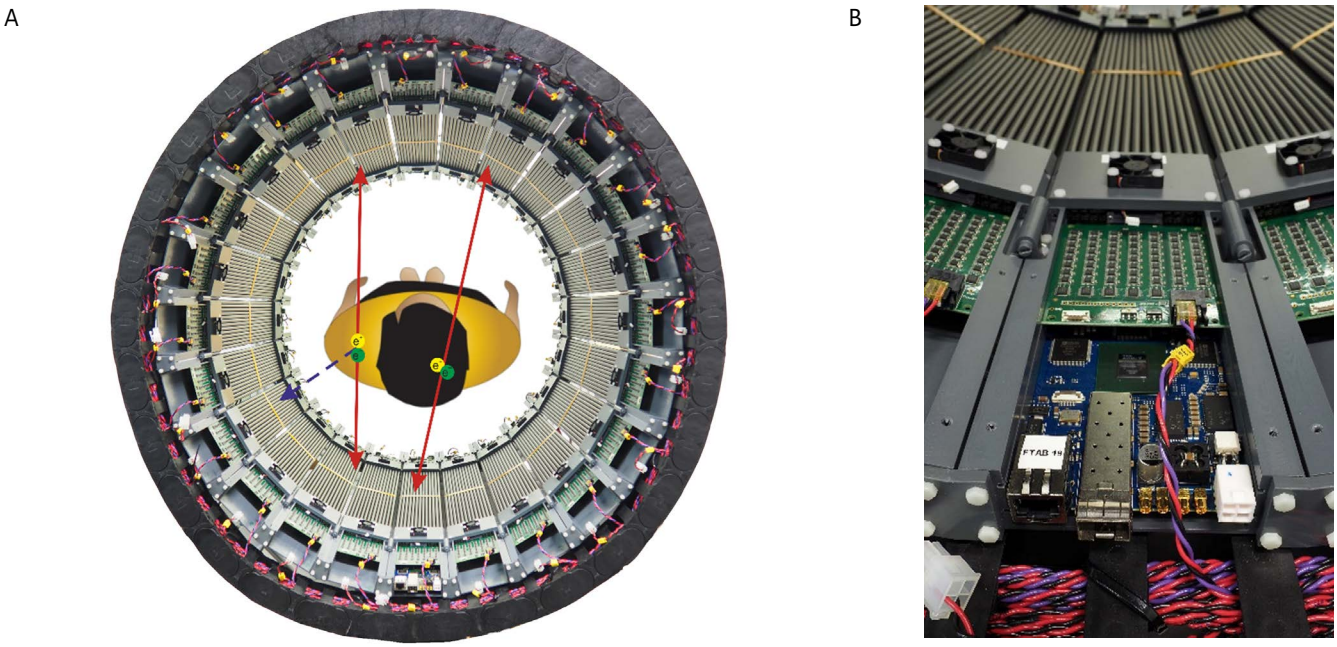

Fig. 3. (A) Photograph of the modular J-PET detector prototype, consisting of 24 modules, each containing 13 scintillator strips read out by a 1 × 4 SiPM array at both ends. These modules can be easily removed for maintenance, and the prototype, with a 50-cm axial field-of-view, weighs approximately only 60 kg, enhancing its mobility and portability [10, 23, 29]. The image includes superimposed representations of electron-positron annihilation in the patient's body, showing two-photon events (red solid arrows) and the associated prompt gamma rays (blue dashed arrow) emitted by $\beta^+\gamma$ radionuclides, such as ^{44}Sc, also indicating the potential for positronium imaging [29] and simultaneous double tracer imaging [43]; (B) Depicts the power supply board (green), which supplies voltage individually to each SiPM, and the TDC board (blue), which converts analogue signals into digital format, retaining information regarding signal crossings at two preselected constant thresholds [23].

The J-PET system, while currently using a single-layer detector configuration (Fig. 2., 3.), is designed with the potential to incorporate a multilayer, concentric detector setup in future iterations [44]. This multilayer configuration would compensate for the lower photon detection efficiency of plastic scintillators, which is primarily due to their lower density of 1.0 g/cm³ [45], compared to the much denser LYSO crystals (7.0–7.4 g/cm³) [46]. The axial arrangement of plastic strips, read out by SiPMs at both ends, could optimise the registration efficiency of annihilation photons [44].

The overall imaging sensitivity of J-PET was estimated using GATE simulation software, following standards set by the National Electrical Manufacturers Association (NEMA), ensuring that it meets clinical and research requirements [16].

The J-PET triggerless data acquisition system [21, 22] allows for the detection of all events, including multiphoton annihilations and prompt gammas, expanding the potential for flexible event selection at the software level [29, 47, 48]. This capability is particularly beneficial when using isotopes such as ^{44}Sc, which emit prompt gamma rays [49, 50]. The system's ability to register and identify signals from prompt gammas and from both two- and three-photon annihilations allows the J-PET to classify events by their originating isotopes. This is crucial for conducting multi-tracer diagnostics [43, 51, 52] within a single PET scan. Furthermore, the detection of an additional prompt gamma from $\beta^+\gamma$ emitters not only improves spatial resolution but also supports the implementation of new tissue-sensitive imaging techniques such as positronium lifetime imaging [24–32].

These advanced features have enabled J-PET to demonstrate the potential for groundbreaking progress in medical diagnostics, particularly in positronium imaging. By simultaneously detecting annihilation photons and prompt gamma rays emitted by radiolabelled pharmaceuticals, the system provides detailed insights into positronium formation and decay. This innovative approach enhances PET diagnostics by revealing differences in positronium lifetimes between healthy and diseased tissues. Key achievements of J-PET include the first ex vivo positronium imaging using a phantom composed of cardiac myxoma and adipose tissue [28], the first multi-photon PET imaging [47] and, more recently, successful in vivo positronium imaging of a glioblastoma brain tumour in a clinical setting [29]. These achievements highlight the potential of J-PET to open new possibilities for clinical and research applications.

^{44}Sc radiopharmaceutical labelling and applications

The J-PET's potential for diagnostic imaging is set to be significantly enhanced by the development of a ^{44}Ti/^{44}Sc generator [53] (Fig. 4A.). This generator enables the onsite production of ^{44}Sc-labelled radiopharmaceuticals and reduces the dependency on extensive and costly infrastructure typically required in nuclear medicine. The parent isotope, ^{44}Ti, has a long half-life of almost 60 years, compared to the 270-day half-life of ^{68}Ge [54] used in conventional ^{68}Ge/^{68}Ga generators, which require yearly replacement [55]. The introduction of the ^{44}Ti/^{44}Sc generator could streamline operations, offering a once-in-a-half-century solution that promises to lower operational costs and simplify logistics in PET imaging facilities.

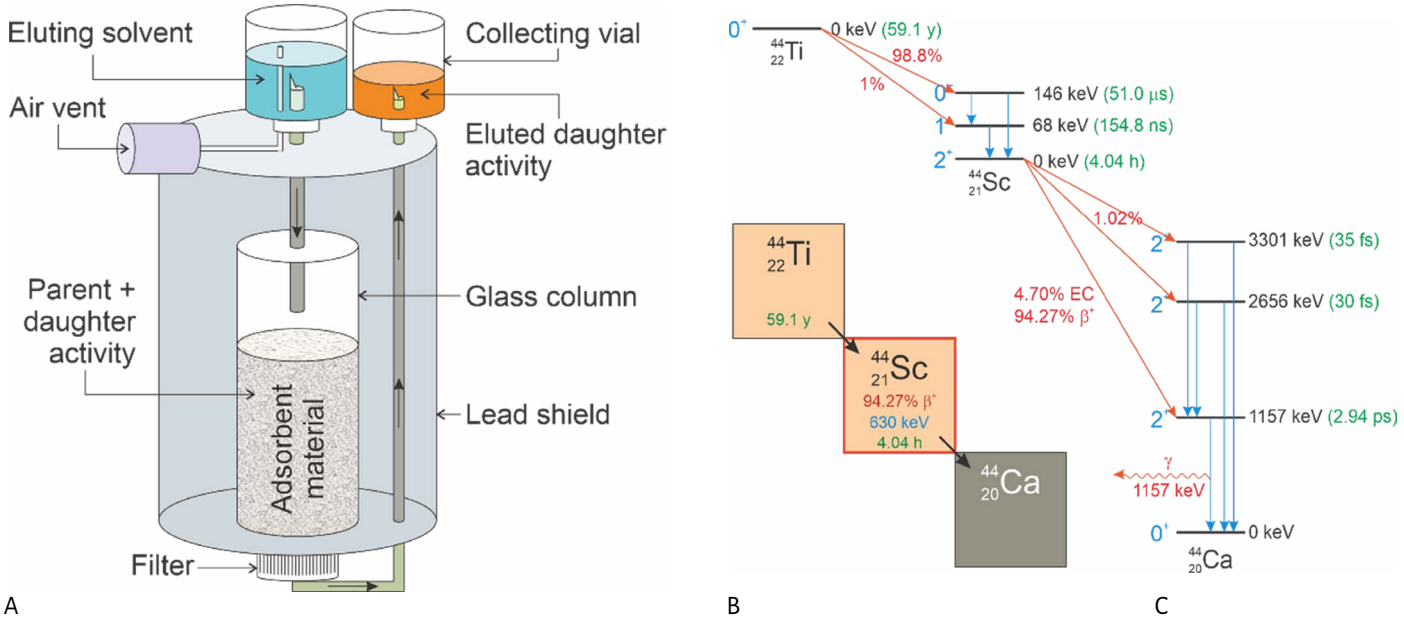

Fig. 4. (A) The principle functional diagram of the ^{44}Ti/^{44}Sc radionuclide generator illustrates the key components and process flow. The generator consists of a column filled with an adsorbent material that contains ^{44}Ti while allowing the elution of ^{44}Sc when a suitable eluent is passed through the system [53]. The eluent carries the ^{44}Sc into a collection vial, where it can be used to label radiopharmaceuticals for PET imaging [57, 58] (B) and (C). The decay scheme for ^{44}Ti shows its transformation through ^{44}Sc to the stable ground state of ^{44}Ca [54]. The figure presents the simplified decay process (B) and a detailed decay scheme (C), illustrating the emission of prompt gamma. ^{44}Ti decays to ^{44}Sc with a half-life of 59.1 years. Subsequently, ^{44}Sc decays with a half-life of about four hours.

This feature is particularly beneficial for medical facilities without direct access to a cyclotron, providing a stable and cost-effective source of high purity ^{44}Sc for diagnostic imaging.

The ^{44}Sc radionuclide has a half-life of 3.97 hours (recent measurements have slightly adjusted it to 4.04 hours [56]), which is almost four times longer compared to the commonly used ^{68}Ga [54]. The longer half-life of ^{44}Sc allows for more flexible scheduling of radiopharmaceutical preparation and imaging procedures, minimising radiation exposure to the patient and personnel. Moreover, ^{44}Sc decays (Fig. 4B., 4C.) by emitting positrons with a branching ratio of 94.27%, coupled with prompt gamma emissions [54]. Its stable decay product, ^{44}Ca, supports the safe use of ^{44}Sc in clinical settings [57], eliminating concerns related to radioactive residues post-imaging.

One of the key strengths of ^{44}Sc is its ability to form stable complexes with various chelators, such as DOTA, DTPA, EDTA and NOTA, which are essential for labelling different biomolecules, including peptides, proteins and small molecules [57, 58]. This versatility extends the utility of ^{44}Sc-labelled radiopharmaceuticals across a wide range of diagnostic applications. For instance, ^{44}Sc-labelled DOTATOC (a DOTA-conjugated peptide) has shown high radiochemical purity and stability, which are crucial for the accurate imaging of neuroendocrine tumours [57, 59]. In addition, ^{44}Sc-PSMA-617 has demonstrated its effectiveness in targeting a prostate-specific membrane antigen in prostate cancer, offering high-contrast PET images that are essential for early and precise disease detection [60, 61]. The evaluation of ^{44}Sc-labelled Affibody molecules for imaging HER2-expressing tumours has shown promising results, highlighting the broad potential of ^{44}Sc in personalised medicine [62].

Our vision is that the integration of ^{44}Sc-labelled radiopharmaceuticals with J-PET scanner technology could represent a significant advancement in nuclear medicine. The ^{44}Ti/^{44}Sc generator enables onsite production of radiopharmaceuticals, reducing the need for extensive infrastructure and frequent replacements. The ability to label a variety of biomolecules with ^{44}Sc [57–62] enhances the range of diagnostic applications and supports the development of targeted imaging agents tailored to individual patient needs. This integration not only promises high-quality affordable imaging but also facilitates personalised diagnostic approaches, improving treatment planning and monitoring therapeutic outcomes. The combined use of ^{44}Sc and the J-PET scanner thus offers a comprehensive and cost-effective high performance frugal [63] global diagnostic solution for a wide range of imaging applications.

DISCUSSION

The integration of the modular J-PET scanner with the ^{44}Ti/^{44}Sc generator represents a visionary approach to PET diagnostics. This combination could aim to address the high costs and logistical complexities that have limited the global accessibility of advanced diagnostics. By using cost--effective plastic scintillators and a modular design, the J-PET scanner could significantly reduce production (by 5 to 10 times) and operational expenses [10], making PET imaging

more accessible in diverse settings, including underserved and remote areas.

The development of the $^{44}Ti/^{44}Sc$ generator [53, 63] enhances this vision by enabling the onsite/regional production of ^{44}Sc-labelled radiopharmaceuticals [64]. The long half-life of ^{44}Ti [54] ensures a stable, long-term source of ^{44}Sc, reducing the dependency on cyclotrons and isotope logistics. This capability could streamline operations, lower operational costs, and simplify and lower the costs of the imaging facilities, particularly benefiting regions without advanced infrastructure.

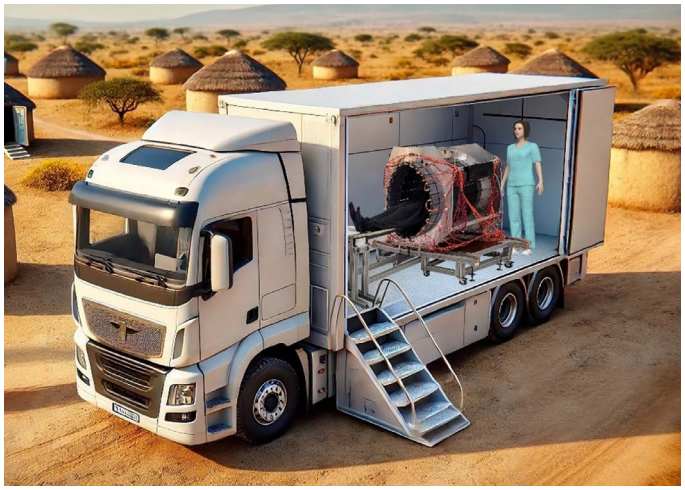

Fig. 5. Visualisation of a potential modular J-PET mobile unit (PEToBUS), demonstrating the integration of advanced imaging technology into a versatile, transportable platform for medical diagnostics. This illustration presents a simplified concept. A practical realisation would require a more detailed design addressing logistical, technical and contextual requirements.

The combination of these technologies could transform PET imaging into a more affordable and accessible diagnostic tool. The portability of the J-PET system supports its deployment in mobile units, such as specialised vehicles (Fig. 5.), further extending its reach to remote regions. This increased accessibility could lead to earlier disease detection, improved treatment planning and better healthcare outcomes globally.

CONCLUSIONS

Our vision of the combined use of the low-cost modular J-PET scanner and the $^{44}Ti/^{44}Sc$ generator articulates a forward-looking solution to global healthcare challenges. This innovative approach not only envisions reduced costs and logistical complexities but also broadens the potential accessibility of high-quality PET imaging, particularly in underserved regions. By facilitating earlier disease detection and improving treatment planning, this technology holds the promise to significantly enhance healthcare outcomes worldwide.

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