MSAC Application 1822

F-18 Fluorodeoxyglucose (FDG) positron emission tomography (PET) for evaluation of complex infection

PICO Set 1

F-18 FDG for complex infection

Population

Describe the population in which the proposed health technology is intended to be used:

Patients with persistent fever with absence of diagnosis or resolution despite investigations.

FUO/PUO is defined as:

- Documented fever ≥38.3 °C on at least two occasions; and
- Duration of fever ≥3 weeks

Persistent or recurrent high-risk neutropenic fever is defined as

- Persistent fever: Absolute neutrophil count <0.5 X 109/L and documented fever ≥38.0 °C daily for at least 3 days; OR
- Recurrent fever: Documented fever ≥38.0 °C which has recurred during same neutropenic episode after an initial episode of neutropenic fever (temperature ≥38.0 °C sustained over 1 hour during absolute neutrophil count <0.5 X 109/L)

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:

Fever of Unknown Origin

Patients with suspected fever of unknown origin (FUO) in Australia commonly present to primary care or emergency departments with persistent or recurrent fever lacking an identifiable source. Initial evaluation involves a detailed clinical history, emphasising travel, occupational, zoonotic, and environmental exposures, followed by a systematic physical examination and baseline investigations. These are recommended to include:

- FBC, ESR, CRP, EUC, LFTs,
- ANA, rheumatoid factor and TFT (in adults)
- Sputum culture (in adults)
- MSU microscopy, culture and susceptibility testing
- HIV serology
- CXR
- Echocardiogram if heart murmur present.[1]

In cases where initial investigations are non-diagnostic, patients are referred to hospital-based General Medicine or Infectious Diseases services for further evaluation, which traditionally may incorporate CT or nuclear medicine studies, expanded autoimmune and microbiological testing, and tissue or bone marrow biopsy when indicated.

Within this second-line investigative stage, after obtaining a detailed clinical history and comprehensive laboratory evaluation have been completed, FDG PET/CT is increasingly being proposed as the preferred whole-body imaging modality, superseding conventional CT or nuclear

1- Australian Radiation Protection and Nuclear Safety Agency (ARPANSA). (n.d.). Radiation protection in nuclear medicine and PET: Principles and practice. https://www.arpansa.gov.au/understanding-radiation/radiation-safety-guides/nuclear-medicine-and-pet

2- Australasian Association of Nuclear Medicine Specialists. (2021). Economic cost of lack of indexation for nuclear medicine: Final report to the Australasian Association of Nuclear Medicine Specialists. Synergies Economic Consulting. https://treasury.gov.au/sites/default/files/2021-05/171663_australasian_association_of_nuclear_medicine_specialists_supporting_document.pdf

medicine techniques. This is particularly relevant in the evaluation of neoplastic causes of FUO, which comprise approximately 15–25% of cases[2].

As highlighted by the Royal College of Pathologists of Australasia (RCPA), tumour markers are insufficiently sensitive and non-specific for screening occult malignancy, underscoring the need for tissue diagnosis. Because confirmation of malignancy typically requires fine-needle aspiration or core biopsy, high-yield imaging such as FDG PET/CT plays a critical role in localizing appropriate biopsy targets and facilitating definitive diagnosis.[3]

Persistent or recurrent high-risk neutropenic fever

Patients with persistent or recurrent high-risk neutropenic fever will almost always be inpatients in a haematology ward of a tertiary centre, as they will be under close observation given their tendency to deteriorate. Due to their lack of neutrophils, they often do not have focal signs or symptoms to localize infection, and furthermore, heavily immunocompromised patients are known to have potentially multiple infective and non-infective causes of fever simultaneously that are important to identify[4]. An infectious diseases physician should have reviewed the patient to assess for potential sites of infection. Investigations that should be performed include:

- At least 2 sets of blood cultures (if central line, at least one from central line)
- Other cultures based on clinical suspicion (urine, stool, sputum)
- UEC, LFT, CRP
- Chest X-ray
- Focal imaging based on clinical suspicion (if any)- e.g. MRI brain if concerns for focal CNS infection, CT sinuses if concerns for fungal sinusitis
- +/- HRCT chest

If, based on the above investigations and after review by an infectious diseases physician, the cause of fever is unclear (pathogen and site/s of infection), or there is significant concern for additional undetected infections (e.g. fungal infection) or concern for undetected nidus of infection of a known pathogen (for instance, bacteraemia with concern for deep seated infection), this would be when an FDG-PET/CT would be considered appropriate.

Provide a rationale for the specifics of the eligible population:

Eligible patients are those who have already undergone standard baseline investigations for FUO or neutropenic fever, as recommended in classic FUO definitions[5] and contemporary NF guidance from the Infectious Diseases Society of America[6]. Initial investigations identifies a cause in many cases using low-cost, high-yield methods. Performing FDG PET/CT only after this stage ensures it is used when true diagnostic uncertainty persists, avoiding unnecessary cost.

Scanning later than this window may increase healthcare costs from utilisation of lowered sensitivity scans, delay definitive intervention, and increase morbidity and hospital stay. Therefore, the optimal timing for FDG PET/CT is immediately after negative baseline investigations but before extended empirical management, when whole-body metabolic imaging is most likely to localize occult infection, inflammation, or malignancy and meaningfully alter clinical management.

Are there any prerequisite tests?

Yes

Are the prerequisite tests MBS funded?

Yes

Provide details to fund the prerequisite tests:

Provide a response if you answered 'No' to the question above

Intervention

Name of the proposed health technology:

^{18}F-FDG PET/CT

Describe the key components and clinical steps involved in delivering the proposed health technology:

18F-FDG can be produced on-site in facilities equipped with a cyclotron and radiopharmacy or obtained from a commercial supplier. Patients are required to fast for 4–6 hours prior to administration. The FDG is administered intravenously approximately 60 minutes before imaging, during which patients remain resting quietly in a dimly lit room to minimize muscular and brown fat uptake. After this period, patients are transferred to the PET camera room and positioned on the scanning bed for image acquisition.

The administered activity of 18F-FDG depends on patient body mass and PET scanner specifications. For an average 75 kg individual, typical activity ranges from 180 to 260 MBq, and dosage is generally calculated at approximately 3-5 MBq per kilogram of body weight, with ARPANSA recommending 3.5MBq/kg. Estimated effective doses for patients receiving between 150 and 450MBq of FDG are 3-9mSv.[7]

PET imaging is performed according to a standardized protocol, which typically incorporates a low-dose CT scan for attenuation correction and anatomical localization. These CTs generally add 4-5mSv radiation dose depending on arm position and length of scan. When clinically indicated by the referring physician, a diagnostic-quality CT may be performed concurrently, often with oral and/or intravenous contrast, resulting in a PET/CT diagnostic study whereby the PET images can be directly fused to the diagnostic CT images for additional information. The PET field-of-view is generally determined by the clinical indication but most commonly spans from the base of the skull to the upper thighs or to the toes, offering an entire-body investigation, but can be localised to specific areas of clinical concern if deemed appropriate by referrer and reporting doctor. Acquisition times for modern PET scanners are usually under 30 minutes, although the exact duration depends on the scanner's performance characteristics, the extent of the field-of-view, and the administered FDG activity.

PET images are generally reconstructed using the manufacturer's recommended protocols and software, fusing the acquired PET images to the localisation CT or the diagnostic CT if performed.

Interpretation of the images, including any available correlated imaging, is performed by a nuclear medicine specialist, who prepares a clinical report for the referring clinician.

Identify how the proposed technology achieves the intended patient outcomes:

FDG PET/CT uses 18F-fluorodeoxyglucose (FDG), a radioactive glucose analogue, to detect infection by identifying areas of increased glucose metabolism. During infection, activated immune cells display heightened glycolytic activity, increased blood flow, and inflammatory cell recruitment. FDG accumulates in these metabolically active cells, appearing as “hot spots” on the scan. Due to the metabolic nature of FDG uptake, infection can be detected before structural changes become visible, and the whole-body uptake allows scanning of the entire body without additional radiation dose, allowing detection of unknown foci for patients with infections of unknown origins.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

Provide a response if you answered 'Yes' to the question above

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

No

Provide details and explain:

Patients should only require a single PET scan to establish or exclude diagnosis of infection. As infections can occur multiple times per lifetime, especially in the most vulnerable populations, placing any restrictions on the number of scans allowable can be highly detrimental.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

PET services are provided by credentialled nuclear medicine specialists registered with general or specialist registration and have recognition by AHPRA as a specialist in nuclear medicine.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

PET services are a specialised service that can only be provided by trained and registered Nuclear Medicine specialists, who consult on and obtain consent from the patient, tailor the scan dependent on medical indication, and prepare a report using the relevant clinical data. Equipment handling and radiopharmaceutical administration are performed by trained and registered Nuclear Medicine Technologists. Other staff may be involved, including clerical staff and nurses.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

PET services are provided on request from a medical specialist

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

Provide details and explain:

18-F FDG PET scans for infection imaging will be performed by:

a) a nuclear medicine specialist or consultant physician credentialled under the Joint Nuclear Medicine Specialist Credentialling Program for the Recognition of the Credentials of Nuclear Medicine Specialists for Positron Emission Tomography overseen by the Joint Nuclear Medicine Credentialling and Accreditation Committee of the RACP and RANZCR;

or

b) a practitioner who is a Fellow of either RACP or RANZCR, and who, prior to 1 November 2011, reported 400 or more studies forming part of PET services for which a Medicare benefit was payable, and who holds a current licence from the relevant State radiation licensing body to prescribe and administer the intended PET radiopharmaceuticals to humans

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

Inpatient private hospital

Inpatient public hospital

Outpatient clinic

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:

Provide a response if you answered 'No' to the question above

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:

For fever of unknown origin, where a diagnosis is not achieved through first line testing, a contrast-enhanced CT CAP is often utilised to narrow source of infection to specific category (infective, malignancy, autoimmune or other). Each category of assignment leads to further laboratory and diagnostic tests, including other whole-body nuclear imaging tests such as Ga-67 or labelled WBC Scanning.[8]

Persistent/recurrent neutropenic fever is currently typically investigated with a high-resolution CT chest with option to add CT brain, sinus, abdomen and pelvis based on clinical suspicion

List any existing MBS item numbers that are relevant for the nominated comparators:

56807 - Computed tomography—scan of chest, abdomen and pelvis with or without scans of soft tissues of neck with intravenous contrast medium and with any scans of chest, abdomen and pelvis with or without scans of soft tissue of neck before intravenous contrast injection, when performed

56007 - Computed tomography—scan of brain with intravenous contrast medium and with any scans of the brain before intravenous contrast injection, when performed

56030 - Computed tomography—scan of facial bones, para nasal sinuses or both, with scan of brain, without intravenous contrast medium

61429 – Whole-body Ga 67 study (planar)
61430 – Whole-body Ga 67 study with SPECT
61442 - Whole-body Ga 67 study with SPECT (two or more body regions separately)
61477 - Supplementary item for Ga 67 scans
61462 - Repeat planar and SPECT imaging, or repeat planar imaging or single photon emission tomography imaging on an occasion subsequent to the performance of item , 61429, 61430, 61442, 61450, 61453, if there is no additional administration of radiopharmaceutical and if the previous radionuclide scan was abnormal or equivocal
61433 – Whole-body study using cells labelled with technetium
61434 - Whole-body labelled-cell study + SPECT

Provide a rationale for why this is a comparator:

These modalities are regarded as comparators to FDG PET/CT because they reflect the conventional imaging strategies used to evaluate patients with fever of unknown origin and neutropenic fever. Historically, they have been employed to identify occult infection, inflammation, or malignancy when initial clinical assessment and laboratory investigations fail to reveal a source. They are performed to localize the cause of fever when no clear clinical focus is apparent.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

FDG PET demonstrates high sensitivity for infection and a high negative predictive value in both fever of unknown origin and neutropenic fever.[9,10] A negative scan may justify discontinuation of further diagnostic investigations and support conservative management, whereas a positive scan can identify a focal source, enabling targeted therapy.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

Health benefits

Diagnostic Accuracy

- Higher proportion of patients in whom a definitive diagnosis is established.

- Higher sensitivity and specificity

- Better positive predictive value (PPV) and negative predictive value (NPV).

Time to Diagnosis

- Smaller interval from initial presentation to definitive diagnosis.

Health harms

Invasive Procedures Avoided

- Number of unnecessary biopsies, bronchoscopies, exploratory surgeries, or repeat imaging procedures avoided due to PET/CT findings.
- Lowered risk of procedural morbidity and patient discomfort

- Potential for avoidance of sedation in paediatric patients

Safety and Radiation Exposure

- Lowered cumulative radiation dose

- Less likely adverse events related to contrast agents or radiotracers

- No blood-handling (compared to labelled WBC scanning)

Resources

Health Resource Utilization and Cost-effectiveness

- Lowered total healthcare costs including imaging, hospitalisation, procedures, follow- up due to faster diagnosis and less investigative tests.

Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

FDG PET/CT has been shown to frequently alter clinical management in patients with fever of unknown origin and neutropenic fever. In FUO, prospective and retrospective studies have demonstrated that FDG PET contributes diagnostically in a substantial proportion of cases and leads to management changes in approximately one-third to one-half of patients.[9,10] Similarly, studies in neutropenic fever populations report that FDG PET/CT can identify occult infectious foci and influence antimicrobial strategy or duration of therapy.[11]

FDG PET/CT prognostic effect is generally indirect through earlier diagnosis, more accurate localization of disease, and facilitation of targeted therapy. FDG PET has high diagnostic yield and clinical utility, and outcome benefits are mediated by subsequent management decisions.

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):

Self-funded

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number (where used as a template for the proposed item)	
Category number	Category 5
Category description	DIAGNOSTIC IMAGING SERVICES
Proposed item descriptor	Positron emission tomography study using 18F-fluorodeoxyglucose for the evaluation of fever/pyrexia of unknown origin (FUO/PUO) or persistent or recurrent high-risk neutropenic fever in a patient where initial evaluation has not established a diagnosis.
Proposed MBS fee	$953.00
Indicate the overall cost per patient of providing the proposed health technology	$953.00
Please specify any anticipated out of pocket expenses	N/A
Provide any further details and explain	FUO/PUO is defined as: • Documented fever ≥38.3 °C on at least two occasions; and • Duration of fever ≥3 weeks Persistent or recurrent high-risk neutropenic fever, defined as • Persistent fever: Absolute neutrophil count <0.5 X 109/L and documented fever ≥38.0 °C daily for at least 3 days; OR • Recurrent fever: Documented fever ≥38.0 °C which has recurred during same neutropenic episode after an initial episode of neutropenic fever (temperature ≥38.0 °C sustained over 1 hour during absolute neutrophil count <0.5 X 109/L)

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

Patients who have presented to healthcare departments with fever of unknown origin will undergo the following tests as a baseline:

- FBC, ESR, CRP, EUC, LFTs,
- ANA, rheumatoid factor and TFT (in adults)
- Sputum culture (in adults)
- MSU microscopy, culture and susceptibility testing
- HIV serology
- CXR
- Echocardiogram if heart murmur present.

They will then be referred to hospital-based general specialist or infectious diseases services if these tests fail to yield a diagnosis.

Patients who have presented to healthcare departments (generally with hospital admission) with neutropenic fever will under the following tests as a baseline:

- At least 2 sets of blood cultures (if central line, at least one from central line)
- Other cultures based on clinical suspicion (urine, stool, sputum)
- UEC, LFT, CRP
- Chest X-ray
- Focal imaging based on clinical suspicion (if any)- e.g. MRI brain if concerns for focal CNS infection, CT sinuses if concerns for fungal sinusitis
- +/- HRCT chest

They will then be referred to infectious diseases services if these tests fail to yield a diagnosis.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

Please provide a response if you answered 'Yes' to the question above

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

18F-FDG PET/CT is being proposed as a stand-alone service

Explain what other healthcare resources are used in conjunction with the comparator health technology:

Comparator imaging is used as a stand-alone service

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Both use nil other health resources

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the proposed health technology:

When initial investigations fail to yield a diagnosis, the priority is to use imaging to narrow source of infection into a specific category (infective, malignancy, autoimmune or other) or anatomical site so further investigations can be more targeted. The use of FDG PET/CT as the first advanced investigation after baseline investigations provides a whole-body overview, showing uptake in a vast array of infective, inflammatory, malignant and auto-immune conditions, with a very high negative predictive value. A positive FDG-PET scan will often mean no further exploratory diagnostic tests required, directing targeted investigations such as focused laboratory tests, specialist referral, organ-specific imaging, or image-guided biopsy, whilst a negative FDG PET/CT substantially lowers the likelihood of significant occult disease, allowing clinicians to conclude extensive investigation with confidence and adopt a structured watchful-waiting approach with clinical follow-up, as many cases resolve spontaneously[12].

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

When initial investigations fail to yield a diagnosis, recommended clinical management is to use CT imaging to narrow source of infection into a specific category (infective, malignancy, autoimmune or other) or anatomical site so further investigations can be more targeted. In about 40% of FUO patients[13] and 40-70% of NF patients (CT PAN scans of sinus-pelvis scans displaying higher rates of positive scans)[14], CT demonstrates a focal abnormality, and management proceeds with targeted investigations, such as image-guided biopsy, aspiration and culture of collections, tumour markers, organ-specific laboratory tests, echocardiography, or referral to infectious diseases, oncology, surgery, or other relevant specialties, followed by definitive medical or surgical treatment. However, if CT is negative or non-specific, which occurs in approximately 60% of patients, further evaluation is typically required because CT primarily detects anatomical rather than metabolic changes; this may include advanced functional imaging (e.g., FDG PET/CT, Ga-67 Labelled WBC), specialist-directed serology, autoimmune panels, bone marrow biopsy, or prolonged microbiological testing.

Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:

After FDG PET/CT, healthcare resource utilisation is typically more streamlined and targeted compared with CT. Because FDG PET/CT provides whole-body metabolic imaging with high sensitivity and strong negative predictive value, it more often localises occult inflammatory,

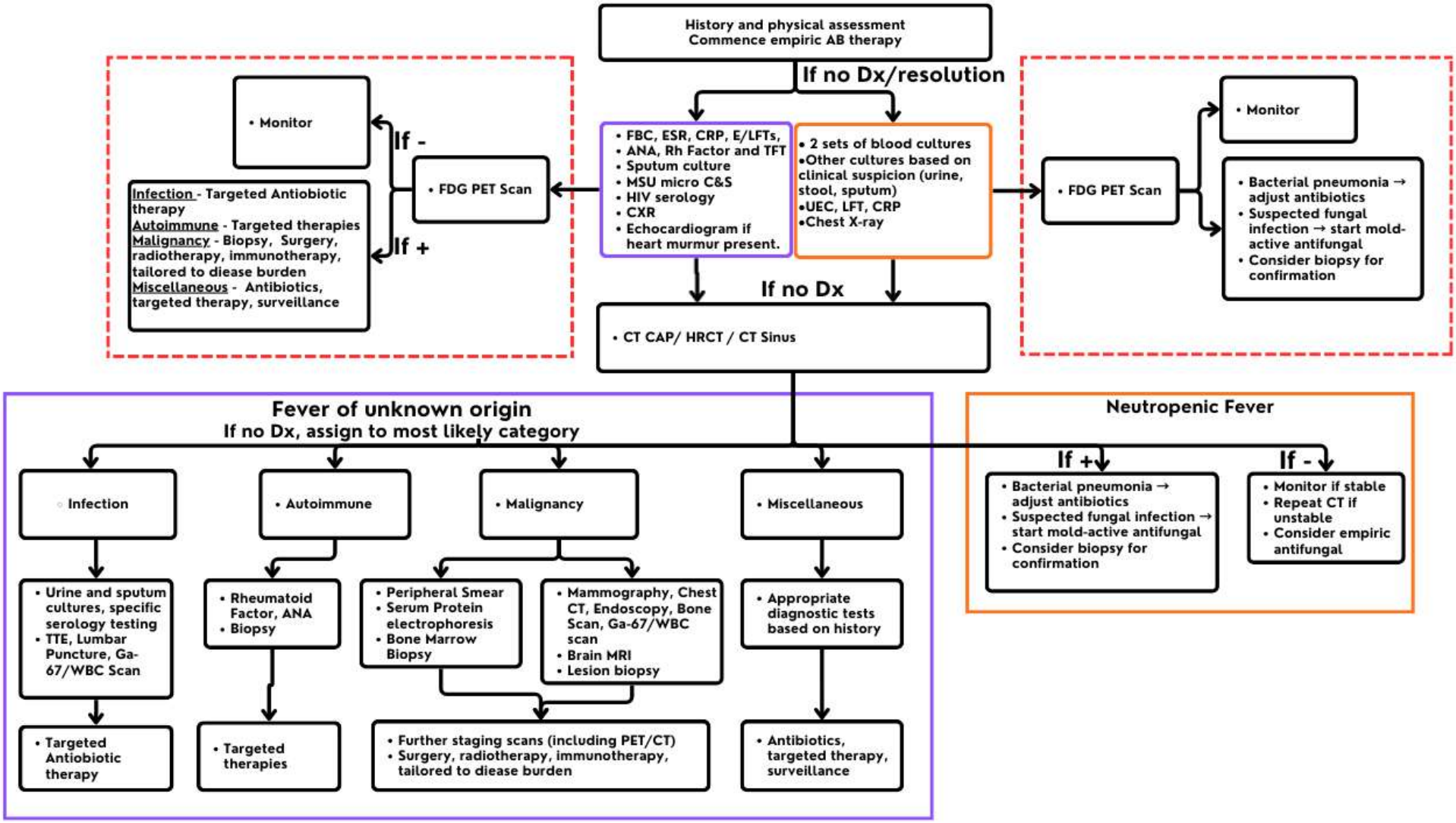
infective, malignant, or autoimmune pathology. A positive scan usually leads directly to focused downstream resources such as image-guided biopsy of PET-avid lesions, limited additional organ-specific imaging, and early referral to the appropriate specialty. A negative FDG PET/CT frequently allows clinicians to avoid further invasive testing and adopt structured clinical observation, reducing cumulative laboratory testing, repeated imaging, and prolonged inpatient stay.

In contrast, CT chest/abdomen/pelvis has a more moderate diagnostic yield in FUO and NF. When positive, it can lead to targeted treatment. However, when CT is negative or non-specific, which occurs in a greater proportion of cases than in FDG PET, additional investigations are required, including further laboratory testing, echocardiography, endoscopy, bone marrow biopsy, or escalation to functional imaging which includes FDG PET/CT. This sequential testing increases cumulative healthcare utilisation, multidisciplinary involvement, and sometimes length of hospital stay, generating greater downstream resource use due to lower sensitivity.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

See next page

Fever of Unknown Origin/Neutropenic Fever diagnosis Pathway



Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Please state what the overall claim is, and provide a rationale:

The clinical claim is that 18F-FDG PET imaging is superior to other second-line advanced imaging techniques for patients with FUO and persistent/recurrent neutropenic fever, resulting in a quicker, more accurate diagnosis, and lowered healthcare burden. This can be broken into radiographical techniques and nuclear imaging techniques.

Radiography Techniques

FDG PET/CT provides standardised whole-body imaging and can be performed as a hybrid study with CT or MRI, integrating functional and anatomical information in a single examination. In the early stages of infectious disease, anatomical imaging alone is frequently limited, as structural changes may only become apparent once significant tissue involvement has occurred, leading to lower sensitivity than FDG PET scan. Reliance on lower-sensitivity anatomical imaging is unlikely to alter clinical management and may instead contribute to diagnostic delay, cumulative radiation exposure, and prolonged inpatient hospitalisation.

Nuclear Imaging Techniques

FDG PET/CT demonstrates diagnostic sensitivity comparable to labelled white blood cell scanning and gallium scintigraphy, with all modalities providing whole-body functional imaging for the detection of infection. Compared with Gallium-67 studies, FDG PET/CT offers important practical advantages, including greater tracer availability, lower overall cost, reduced need for close contact restrictions, shorter interruption to breastfeeding, and substantially faster acquisition. In contrast to labelled white blood cell imaging, PET/CT avoids blood handling, enabling safer and more efficient delivery, and tracer availability is less volatile. Image quality is superior, and increasing scanner availability further supports its role as the preferred functional imaging modality in this setting.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

FDG PET provides whole-body, high-resolution metabolic imaging that can detect active infection, inflammation, or malignancy before structural changes are visible. Unlike CT, which identifies anatomical abnormalities, FDG PET highlights metabolically active lesions, allowing earlier localization of occult disease and guiding targeted interventions such as biopsy or drainage, with higher sensitivity. The high negative predictive value of PET gives clinicians greater confidence when a diagnosis is not achieved, allowing conservative treatment without repeat scans or treatment delays, which is particularly important for high-risk, vulnerable or paediatric patients.

Compared with WBC or Ga-67 scans, FDG PET is faster, offers superior image resolution, and detects a broader spectrum of infectious and inflammatory processes. Where PET is available, scans are performed sooner and with less discomfort for vulnerable patients (only 1 timestamp scanning, less close contact restrictions, nil blood-handling).

Identify how the proposed technology achieves the intended patient outcomes:

FDG PET/CT uses 18F-fluorodeoxyglucose (FDG), a radioactive glucose analogue, to detect infection by identifying areas of increased glucose metabolism. During infection, activated immune cells display heightened glycolytic activity, increased blood flow, and inflammatory cell recruitment. FDG accumulates in these metabolically active cells, appearing as "hot spots" on the scan. Due to the metabolic nature of FDG uptake, infection can be detected before structural changes become visible, and the whole-body uptake allows scanning of the entire body without additional radiation dose, allowing detection of unknown foci for patients with infections of unknown origins.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? Yes

Please provide a rationale, and information on other benefits if relevant:

Change in Clinical Management

- Detection of infection sooner than CT, prompting earlier targeted therapy.
- Identification of the most metabolically active site for biopsy, increasing diagnostic yield.
- Support de-escalation or discontinuation of empiric therapy when negative
- Reduction of the need for further imaging studies

Change in Health Outcomes

- Reduced time to diagnosis
- Higher likelihood of diagnosis (increased sensitivity, less negative/equivocal results)
- Earlier treatment, reducing morbidity and mortality in vulnerable patients
- Lower risk of complications
- Shorter duration of broad-spectrum antimicrobial exposure
- Potential reduction in length of hospital stay

Other Benefits

- Whole body assessment avoiding multiple regional scans, reducing overall radiation exposure
- Quicker scanning, more reliable tracer availability, higher resolution than other metabolic whole body imaging techniques
- Potential long-term cost-effectiveness
- Can shift care from prolonged empiric treatment and repeated testing to directed therapy based on identified pathology.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

More costly

Provide a brief rationale for the claim:

In terms of immediate costs, FDG PET/CT is more costly than CT alone. PET involves radiotracer production, handling and freight, longer scan time, specialized equipment including camera, injection supplies and shielding, and nuclear medicine staff, all of which increase per-scan cost compared with a standard diagnostic CT. CT typically requires only the scanner, radiographer time, and contrast (if used), making it less expensive on a per-test basis. However, while PET has a higher upfront cost, the immediate cost comparison does not account for downstream consequences such as avoiding multiple repeat CT scans, additional nuclear studies, invasive procedures, or prolonged hospitalization.

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

This application relates to the use of 18F-FDG for a new clinical indication. 18F-FDG is already TGA-approved and MBS-rebatable for multiple other indications. The clinical claim presented in this submission is based directly on the published evidence evaluating 18F-FDG PET/CT in Fever of unknown origin and neutropenic fever. The diagnostic performance, clinical utility, and management impact data cited are specific to 18F-FDG and are not extrapolated from other radiopharmaceutical products.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

	Type of study design*	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1	Retrospective Cohort	Fever of unknown origin: a value of 18F FDG PET/CT	Study of 48 PUO patients. Reported sensitivity of 97%, Specificity of 75%	https://doi.org/10.1016/j.ejrad.2008.12.014	2010
2	Retrospective Cohort	Diagnostic value of 18F FDG PET/CT in patients with fever of unknown origin	Study of 48 PUO patients. Reported sensitivity of 89%, Specificity of 33%, positive predictive value of 80% and negative predictive value of 50% Concluded usefulness as second-line imaging	https://doi.org/10.1016/j.ejim.2010.09.015	2011
3	Retrospective single-center study	[18F]FDG-PET/CT for the diagnosis of patients with fever of unknown origin	Study of 112 PUO patients. Reported sensitivity of 72.2%, specificity of 57.5%, PPV 74.2%, NPV 53.5%	https://doi.org/10.1093/qjmed/hcu193	2014
4	Retrospective cohort	The diagnostic value of 18F FDG PET/CT in identifying the causes of fever of unknown origin	Study of 89 PUO patients. Reported sensitivity of 84.5%, Specificity of 25.8%, and accuracy 64.0%. Concluded strong clinical importance in diagnosing PUO when combined with serum CRP levels	https://doi.org/10.7861/clinmed.2020-0268	2020
5	Retrospective cohort	Performance and value of 18F FDG PET/CT in patients with fever of unknown origin	Study of 105 FUO patients. Reported sensitivity of 72%, specificity of 29%, PPV 68%, NPV 33% and accuracy 58%	https://doi.org/10.3892/br.2024.1857	2024

	Type of study design*	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
6	Cost of Illness analysis Retrospective cohort	FDG-PET/CT for investigation of pyrexia of unknown origin: a cost of illness analysis	Reviewed 31 inpatients and 15 outpatients with PUO who underwent FDG-PET/CT PET/CT had "high diagnostic accuracy" and significantly impacted patient management. Performing PET/CT earlier during admission (≤ 7 days) was associated with **shorter length of stay and lower total cost** **Australian Study***	https://doi.org/10.1007/s00259-023-06548-y	2024
7	Meta-analysis / systematic review	A meta-analysis of the value of fluorodeoxyglucose-PET/PET-CT in the evaluation of fever of unknown origin	Analysis of 9 studies, found that for FDG-PET alone: pooled sensitivity was 82.6%, specificity was 57.8% For FDG-PET with diagnostic CT, pooled sensitivity was 98.2%, and specificity was 85.9%	https://doi.org/10.1016/j.ejrad.2010.11.018	2010
8	Meta-analysis	Diagnostic performance of 18F-FDG PET/CT in patients with fever of unknown origin	Analysis of 15 studies including 595 patients for PUO. Reported sensitivity of 85%	https://doi.org/10.1097/MNM.0b013e328361cd0e	2013
9	Meta-analysis	Nuclear Imaging for Classic Fever of Unknown Origin: Meta-Analysis	Analysis of 42 studies including 2058 patients for classic PUO. Reported sensitivity of 86% and specificity of 52%. Diagnostic yield was 58%, which was the highest compared to Ga-67, labelled WBC or monoclonal antibody scanning	https://doi.org/10.2967/jnumed.116.174391	2016
10	Meta-analysis Systematic Review	Diagnostic yield of FDG-PET/CT in fever of unknown origin: a systematic review, meta-analysis, and Delphi exercise	Analysis of 18 studies including 905 patients for PUO. Diagnostic yield was calculated at 56%, with estimated diagnostic yield beyond conventional CT calculated as 32%	https://doi.org/10.1016/j.crad.2017.04.014	2017

	Type of study design*	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
11	Meta-analysis	Contribution of 18F-FDG PET/CT in a case-mix of fever of unknown origin and inflammation of unknown origin: a meta-analysis	Analysis of 23 studies including 1927 patients for PUO. Calculated sensitivity of 84%, specificity of 63%. Positive likelihood ratio reported as 2.3, negative likelihood ratio as 0.25 and diagnostic odds ratio as 9	https://doi.org/10.1177/028418511879512	2018
12	Systematic Review	Molecular Imaging of Fever of Unknown Origin: An Update	Analysis of 63 studies including 5094 patients for PUO. Calculated sensitivity 84.4%, specificity 61.8%, PPV 80.7%, NPV 67.8%, accuracy 76.3% and helpfulness of 61.1%. Labelled FDG PET/CT as preferred molecular diagnostic imaging technique	https://doi.org/10.1053/j.semnuclmed.2022.07.002	2023
13	Prospective Study	Place of the 18F-FDG-PET/ CT in the Diagnostic Workup in Patients With Classical Fever of Unknown Origin (FUO)	Study of 44 patients with FUO. 18F-FDG-PET/CT was helpful for making a final diagnosis (true positive) in 43.6% of all patients. Sensitivity and specificity levels were 85% and 37%, respectively. Authors recommended FDG PET as first imaging study of choice	https://doi.org/10.3390/jcm10173831	2021
14	Prospective cohort	The diagnostic role of FDG PET/CT in patients with fever of unknown origin	Study of 24 patients with FUO. 18F-FDG PET/CT contributed to final diagnosis in 63% of cases. Sensitivity 93%, specificity 45%. Authors concluded FDG PET/CT is valuable early in FUO workup, particularly after inconclusive conventional investigations.	https://doi.org/10.4274/MIRT.20.04	2011

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15	Retrospective observational study	Diagnostic value of F18 FDG PET/CT in fever or inflammation of unknown origin in a large single center retrospective study	Retrospective study of 300 patients with FUO/IUO. FDG PET/CT showed diagnostic contribution in 54% of cases. Sensitivity 83%, specificity 89%. Authors supported PET/CT as a central second-line imaging modality in persistent unexplained fever.	https://doi.org/10.1038/s41598-022-05911-7	2022
16	Narrative literature review	Optimal use of the FDG PET/CT in the diagnostic process of fever of unknown origin (FUO): a comprehensive review	Comprehensive review of FUO literature. Reported pooled sensitivities 80–90% with meaningful management impact in ~30–60% of patients. Recommended FDG PET/CT early after negative baseline evaluation to shorten diagnostic delay.	https://doi.org/10.1007/s11604-022-01306-w	2024
17	Retrospective diagnostic study	Diagnostic value of (18)F-FDG PET/CT in children with FUO or unexplained inflammation	Retrospective study of 44 **paediatric** patients with FUO. FDG-PET contributed to establishing a diagnosis in ~73% of cases when abnormal findings were confirmed, with scans considered clinically helpful in 45% of all scans performed.	https://doi.org/10.1007/s00259-009-1185-y	2009
18	Retrospective single-centre study	Role of FDG-PET/CT in children with fever of unknown origin	Retrospective single-centre study of 110 **paediatric** patients with FUO. FDG-PET/CT identified a true cause of fever in 48% of patients and led to treatment modifications in 53% of cases. Sensitivity was 85.5% and specificity was 79.2%.	https://doi.org/10.1007/s00259-020-04707-z	2020
19	Systematic review & meta-analysis	Quantifying the contribution of 18F-FDG PET to pediatric FUO diagnosis: a systematic review and meta-analysis	Systematic review and meta-analysis including six **paediatric** FUO studies. Abnormal FDG-PET findings were ~17 times more likely to achieve a definitive diagnosis than those with normal scans.	https://doi.org/10.1007/s00247-022-05333-7	2022

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20	Retrospective evaluation	Diagnostic value of FDG-PET/(CT) in children with fever of unknown origin and unexplained fever during immune suppression	Study of 31 **Paediatric** patients with FUO and 12 with unexplained fever during immune suppression. FDG-PET/CT identified the cause in 52% of FUO cases (sensitivity 80%, specificity 78%) and in 75% of unexplained fever cases (sensitivity 78%, specificity 67%).	https://doi.org/10.1007/s00259-014-2801-z	2014
21	Prospective clinical evaluation	Use of FDG PET/CT for investigation of febrile neutropenia: evaluation in high risk cancer patients	Study of 20 high-risk cancer patients with febrile neutropenia. FDG PET/CT detected occult infection in 93% and altered management in 75% of cases. Authors supported PET/CT as useful adjunct in persistent neutropenic fever.	https://pubmed.ncbi.nlm.nih.gov/22584486/	2009
22	Prospective study	Use of FDG PET/CT for investigation of febrile neutropenia: evaluation in high-risk cancer patients.	Study of 20 patients with cancer and persistent neutropenic fever ≥ 5 days where conventional evaluation did not find cause. PET/CT 93% sensitive compared to conventional evaluation, and identified an additional 8 confirmed infection sites in the 20 patients. *** Australian study**	https://doi.org/10.1007/s00259-012-2143-7	2012

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23	Retrospective case-control study	Impact of fluorine-18 fluorodeoxyglucose positron emission tomography on diagnosis and antimicrobial utilization in patients with high-risk febrile neutropenia	Single centre study, N=37 cases where PET/CT performed in neutropenic fever in haematologic malignancy, compared to n=76 controls with conventional workup only. Underlying cause for NF determined in 94.6% of cases, vs 69.7% of controls. FDG-PET had a significant impact on antimicrobial utilization compared to conventional imaging (35.1% vs. 11.8%). *** Australian study**	https://doi.org/10.3109/10428194.2012.677533	2012
24	Prospective study	18F-FDG PET/CT for diagnosing infectious complications in patients with severe neutropenia after intensive chemotherapy for haematological malignancy or stem cell transplantation	28 consecutive patients had PET/CT if NF + CRP>50 in haematologic malignancy or allogeneic transplant. Pathological uptake explaining fever (infection or mucositis) was seen in 26/28 (93%), contributing significantly to management.	https://doi.org/10.1007/s00259-011-1939-1	2012
25	Prospective study	The role of18F-FDG PET/CT for the diagnosis of infections in patients with hematological malignancies and persistent febrile neutropenia	PET/CT prospective performed in 91 episodes of NF of 5-7 days in high risk haematology patients, in 79 patients. Sensitivity of PET was 79.8% compared to 51.7% in chest/sinus CT alone. Specificity 32.1% vs 42.9% respectively. PET/CT resulted in a change from the pre-test diagnosis in 69% of episodes and in modification of patients' management in 55%.	http://dx.doi.org/10.1016/j.leukres.2013.06.025	2013

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26	Prospective study	18F-FDG-PET/CT Imaging in Patients with Febrile Neutropenia and Haematological Malignancies	48 prospective patients had PET/CT in NF >2 days in high risk haematology on intensive chemotherapy. 31 infective foci identified in 24 patients. Sensitivity 61% compared to conventional work up (mucositis was part of denominator of infection, not detected on PET, reducing sensitivity). Specificity 90%	^{18}F-FDG-PET/CT Imaging in Patients with Febrile Neutropenia and Haematological Malignancies - PubMed	2015
27	Multicentre randomisd trial	[^{18}F]FDG-PET-CT compared with CT for persistent or recurrent neutropenic fever in high-risk patients (PIPPIN): a multicentre, open-label, phase 3, randomised, controlled trial	Multicentre RCT of 147 patients comparing PET/CT to CT for investigation of persistent or recurrent neutropenic fever in high risk patients PET/CT met primary endpoint of greater rationalization of antimicrobial therapy at 96 hours post scan (82% vs 65%). More patients had antimicrobials de-escalated in PET/CT arm: 43% vs 25% **Length of stay was 3.5 days lower in PET/CT arm** *** Australian study**	https://doi.org/10.1016/S2352-3026(22)00166-1	2022

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28	Health Economic analysis of the PIPPIN study	Evaluating the cost-effectiveness of [18F]FDG-PET/CT for investigation of persistent or recurrent neutropenic fever in high-risk haematology patients	Formal health economic analysis by health economists of PIPPIN RCT. **Adjusted healthcare costs were lower for PET/CT** (mean $49,563) compared to CT (mean $57,574). When simulated 1000 times, PET/CT was the dominant strategy (cheaper with better outcomes) than CT group in 74% of simulations**. The estimated NMBs at willingness-to-pay thresholds of $50,000 and $100,000 per QALY were positive, thus PET/CT remained cost-effective at these thresholds.**	https://doi.org/10.1186/s40644-023-00647-7.	2023
29	Interventional diagnostic study	Impact of the PET in the Diagnosis Strategy of FUO or Inflammatory Syndrome in Immunocompetent Patients (FUO-TEP)	103 Adults with prolonged FUO or inflammatory syndrome underwent FDG PET/CT and conventional imaging; results were compared for identifying diagnostic clues. PET/CT reached final diagnosis sooner (3.8 vs. 17.6 months).	https://doi.org/10.3390/jcm11020386	2022

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

	Type of study design*	**Title of journal article or research project**	**Short description of research**	**Website link to journal article or research**	**Date of publication**
1.	Retrospective cohort study	Utility of 18F-FDG PET/CT for Suspected Infection in the Inpatient Setting: a Single Centre Retrospective Cohort Study **NCT07430475**	Inpatients undergoing 18F-FDG PET/CT for suspected infection or inflammation. PET/CT utility will be adjudicated as diagnostic and/or associated with a change in management using a structured consensus process. Associations between pre-PET factors and clinical utility will be explored using descriptive and logistic analyses. • 266 enrolled • Completed • Not yet published	https://clinicaltrials.gov/study/NCT07430475?utm	Study completion 29/01/2024