



Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

The application form will be disseminated to professional bodies / organisations and consumer organisations that have will be identified in Part 5, and any additional groups that the Department deem should be consulted with. The application form, with relevant material can be redacted if requested by the Applicant.

Should you require any further assistance, departmental staff are available through the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Fax: +61 2 6289 5540

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation name: Australasian Association of Nuclear Medicine Specialists (AANMS)

ABN: 71 158 642 267

Primary contact name: REDACTED

Primary contact numbers: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers: REDACTED

Email: REDACTED

2. (a) Are you a consultant acting on behalf of an Applicant?

Yes

No

(b) If yes, what is the Applicant(s) name that you are acting on behalf of?

REDACTED

3. (a) Are you a lobbyist acting on behalf of an Applicant?

Yes

No

(b) If yes, are you listed on the Register of Lobbyists? N/A

Yes

No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

This is a resubmission of application number 1357

F-18 Fluorodeoxyglucose (FDG) positron emission tomography (PET) for the evaluation of breast cancer

5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Breast cancer is the most common cancer in women. In determining the best treatment for each patient, it is important to know when there is locally advanced disease, suspected recurrent breast cancer or metastatic spread. Current diagnostic methods are inferior to PET in evaluation of locally advanced disease, recurrence of disease and identification of metastatic spread. PET provides superior information to guide appropriate medical management.

6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

The proposed service is ¹⁸F-FDG PET scanning for the evaluation of breast cancer in patients who have locally advanced disease where other imaging does not provide sufficient information to determine appropriate treatment and in breast cancer patients where recurrent or metastatic disease is suspected and for whom active therapy is likely to be pursued.

PET is a minimally invasive nuclear medicine imaging technique that uses short-lived radiopharmaceuticals to detect and assess perfusion and metabolic activity in various organ systems. It provides information about function and metabolism that is complementary to the structural information provided by anatomical imaging techniques such as x-ray computed tomography (CT).

7. (a) Is this a request for MBS funding?

- Yes
 No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)
 New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Not applicable

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

- i. An amendment to the way the service is clinically delivered under the existing item(s)
- ii. An amendment to the patient population under the existing item(s)
- iii. An amendment to the schedule fee of the existing item(s)
- iv. An amendment to the time and complexity of an existing item(s)
- v. Access to an existing item(s) by a different health practitioner group
- vi. Minor amendments to the item descriptor that does not affect how the service is delivered
- vii. An amendment to an existing specific single consultation item
- viii. An amendment to an existing global consultation item(s)

ix. Other (please describe below):

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

- i. A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii. A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii. A new item for a specific single consultation item
- iv. A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

- Yes
- No

(g) If yes, please advise:

Insert description of other public funding mechanism here

8. What is the type of service:

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):

- i. To be used as a screening tool in asymptomatic populations
- ii. Assists in establishing a diagnosis in symptomatic patients
- iii. Provides information about prognosis
- iv. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions
- vi. Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

- Pharmaceutical / Biological
- Prosthesis or device
- No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

- Yes
- No

(b) If yes, please list the relevant PBS item code(s):

Insert PBS item code(s) here

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

- Yes (please provide PBAC submission item number below)

No

Insert PBAC submission item number here

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: Insert trade name here

Generic name: Insert generic name here

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

Yes

No

(b) If yes, please provide the following information (where relevant):

Billing code(s): Insert billing code(s) here

Trade name of prostheses: Insert trade name here

Clinical name of prostheses: Insert clinical name here

Other device components delivered as part of the service: Insert description of device components here

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

Yes

No

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

Yes

No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Insert sponsor and/or manufacturer name(s) here

13. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: F-18 Fluorodeoxyglucose (FDG)

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

There are two registered entries for 2-deoxy-2-[18F]fluoro-D-glucose (¹⁸F-FDG). One is by Austin Health with ARTG #54251. The other is by PETTECH Solutions Pty Ltd, with ARTG #78935. FDG may also be produced in-house within public hospitals where there are appropriate facilities for the production of radiopharmaceuticals.

ARTG Entry 54251:

Type of therapeutic good: Single Medicine Product

Manufacturer's name:

Sponsor's name: Austin Health

ARTG Entry 78935:

Type of therapeutic good: Single Medicine Product

Manufacturer's name:

Sponsor's name: PETTECH Solutions Australia Pty Ltd

- (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

- Class III
 AIMD
 N/A

15. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

- Yes (If yes, please provide supporting documentation as an attachment to this application form)
 No

- (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

- Yes (if yes, please provide details below)
 No

ARTG listing, registration or inclusion number: 54251

TGA approved indication(s): Diagnostic agent in pet scanning for tumour detection, focus epilepsy, cardiac disorders, neurological disorders, stroke.

ARTG listing, registration or inclusion number: 78935

TGA approved indication(s): Fludeoxyglucose [¹⁸F] injection is indicated in positron emission tomography (PET) imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer. Fludeoxyglucose [¹⁸F] injection is indicated in positron emission tomography (PET) imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function. Fludeoxyglucose [¹⁸F] injection is indicated in positron emission tomography (PET) imaging in patients for the identification of regions of abnormal

glucose metabolism associated with the foci epileptic seizures.

16. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA? N/A

- Yes (please provide details below)
 No

Date of submission to TGA: Insert date of submission here

Estimated date by which TGA approval can be expected: Insert estimated date here

TGA Application ID: Insert TGA Application ID here

TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here

TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

17. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

- Yes (please provide details below)
 No

Estimated date of submission to TGA: Insert date of submission here

Proposed indication(s), if applicable: If applicable, insert description of proposed indication(s)

Proposed purpose(s), if applicable: If applicable, insert description of proposed purpose(s) here

PART 4 – SUMMARY OF EVIDENCE

18. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.

The re-submission proposes to utilise the current PICO formalised through the DAP in June 2014.

To address MSAC concerns from the initial application, a revised systematic literature search was conducted to identify data that could address the following research questions:

- 1) Are there any prospective, randomised well-sized studies available which compare PET scanning and conventional imaging studies?
 - a) Do these studies report the comparative sensitivity and specificity of PET/CT compared to standard confirmatory imaging as it pertains to patients with locally advanced breast cancer, or suspected metastatic or suspected locally or regionally recurrent breast carcinoma where previous standard diagnostic imaging is equivocal or suspicious for metastatic disease.
 - b) Do any of these studies report change in management (clinical efficacy) and provide details of long-term follow-up on whether treatment was concordant with the post-PET management plan?
 - c) Do any of these studies report on patient relevant outcomes, such as morbidity, mortality, overall survival and quality of life?
 - d) Of these studies, are any applicable to the decision question, that is, use of PET scanning and the comparator as a confirmatory test?
- 2) In the absence of studies of greater internal validity (prospective RCTs), do comparative studies (retrospective studies or case-control studies) exist which report long-term follow-up with patient outcomes?

The following table provides details of 23 additional citations identified in the revised literature searches, over and above citations relied upon in the first. Some citations included in the following table were excluded from the original assessment report, but are considered highly relevant to the proposed descriptors, and are specifically included to address MSAC or ESC concerns.

In addressing MSAC's concerns regarding the initial submission, this resubmission will rely on these additional studies to further strengthen the evidence for the diagnostic validity of PET FDG scanning in breast cancer, as well as providing the requested evidence for its clinical utility. The main new components of the resubmission are:

- Inclusion of studies which specifically address the question of suspected recurrent or metastatic disease, a common clinical scenario and explicitly included in the proposed descriptors, but not addressed in the original external assessment report.
- A meta-analysis of all identified evidence (original submission and newly identified evidence) with respect to diagnostic accuracy
- A cost-utility analysis incorporating additional evidence for change in management and patient outcomes

We believe the revised analyses will provide clear evidence of the clinical utility for ¹⁸F-FDG PET in breast cancer, and build on original data which led to approval of ¹⁸F-FDG PET in breast cancer staging and restaging through Health Technology Assessments (HTAs) in multiple overseas countries including the USA and UK.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
An YS et al (2014)	Retrospective Comparative diagnostic accuracy	Diagnostic performance of 18F-FDG PET/CT, ultrasonography and MRI. Detection of axillary lymph node metastasis in breast cancer patients.	Comparative diagnostic accuracy of FDG-PET/CT versus ultrasonography and MRI for axillary lymph node staging in 215 women diagnosed with breast cancer confirmed by pathologic biopsy of breast lesion. Axillary lymph node dissection was performed in all patients and the diagnostic performance was evaluated using histopathologic assessments as the reference standard.	Nuclear Medicine. 53 (3) (pp 89-94), 2014	2014
Caglar M. et al (2016)	Non-randomised Diagnostic accuracy	Detection of bone metastases in breast cancer patients in the PET/CT era: Do we still need the bone scan?	Comparative diagnostic accuracy of PET/CT versus bone scintigraphy in 150 patients with suspected BC metastases	Caglar M. et al. European Journal of Nuclear Medicine and Molecular Imaging. Conference: 27th Annual Congress of the European Association of Nuclear Medicine, EANM 2014 Gothenburg Sweden. Publication: (var.pagings). 41 (pp S204), 2014.	2016
Chang HT et al (2015)	Recurrence Change in management Sensitivity and Specificity	Role of 2-[18F] fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in the post-therapy surveillance of breast cancer.	FDG-PET/CT was performed on patients with increased serum CA 15-3 levels and/or clinical/radiologic suspicion of recurrence. A group of asymptomatic patients who underwent FDG-PET/CT in the post-therapy surveillance of breast cancer served as the controls. The results were analyzed based on the patients' histological data, other imaging modalities and/or clinical follow-up. FDG-PET/CT was able to detect recurrence, and the results altered the intended patient management in the post-therapy surveillance of breast cancer.	PLoS ONE. 9 (12) (no pagination), 2014. Article Number: e115127. Date of Publication: 17 Dec 2014.	2015
Chou CP, Peng NJ, Chang TH,	Prospective Comparative diagnostic	Clinical roles of breast 3T MRI, FDG PET/CT, and breast ultrasound for	53 asymptomatic women whose screening mammograms had a BI-RADS category of 4 or 5 were enrolled in this study. Breast 3T MRI, FDG-	Journal of the Chinese Medical Association. 78 (12) (pp 719-725),	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
et al (2015)	accuracy	asymptomatic women with an abnormal screening mammogram.	PET/CT and breast ultrasound were performed before biopsy and all imaging modalities were compared by lesion-by-lesion analyses.	Dec 2015 http://www.jcma-online.com/article/S1726-4901(15)00218-X/abstract	
Cochet A et al (2014)	Recurrence Retrospective Change in management	The utility of 18 F-FDG PET/CT for suspected recurrent breast cancer: impact and prognostic stratification	Sixty-three patients who were referred to our institution for suspicion of BC relapse were retrospectively enrolled. All patients had been evaluated with CI and underwent PET/CT. At a median follow-up of 61 months, serial clinical, imaging and pathologic results were obtained to validate diagnostic findings. Overall Survival (OS) was estimated using Kaplan Meier methods and analyzed using the Cox proportional hazards regression models.	Cancer imaging: the official publication of the International Cancer Imaging Society. 14 (pp 13), 2014. Date of Publication: 2014.	2014
Dizendorf EV, et al. (2003)	Change in management	Impact of whole-body 18F-FDG PET on staging and managing patients for radiation therapy	Whole-body PET was performed in 202 patients with different malignant tumours before radiation therapy. The alteration of PET on each patient's staging and management decisions for radiation therapy were determined.	Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine. 44 (1) (pp 24-29), Jan 2003 http://jnm.snmjournals.org/content/44/1/24.long	2003
Dong Y et al (2015)	Non-randomised Comparative diagnostic accuracy	The diagnostic value of 18F-FDG PET/CT in association with serum tumor marker assays in breast cancer recurrence and metastasis.	Comparative diagnostic accuracy of PET/CT versus conventional imaging in 26 patients with suspected metastases / recurrence.	Dong Y et al BioMed research international. 2015 (pp 489021) https://www.hindawi.com/journals/bmri/2015/489021/	2015
Evangelista L. et al (2016)	Retrospective Diagnostic accuracy	Diagnostic and Prognostic Value of 18F-FDG PET/CT in Male Breast Cancer: Results from a Bicentric Population.	The diagnostic and prognostic values of FDG-PET/CT in 25 men with a proven breast cancer diagnosis was assessed. The prognostic impact of PET/CT was assessed by using Kaplan-Meier analysis.	Current Radiopharmaceuticals. 9 (2) (pp. 169-177), 2016	2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
Garcia Vicente AM (2014)	non-randomised Diagnostic accuracy	Dual time point 2-deoxy-2-[18F]fluoro-d-glucose PET/CT: Nodal staging in locally advanced breast cancer	Diagnostic accuracy of PET/CT in 75 patients with LABC.	Garcia Vicente AM. Revista espanola de medicina nuclear e imagen molecular. 33 (1) (pp 1-5), 2014 http://www.sciencedirect.com/science/article/pii/S2253808913001481	2014
Hildebrandt et al (2016)	Prospective Comparative Diagnostic accuracy	[18F]Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)/Computed Tomography (CT) in Suspected Recurrent Breast Cancer: A Prospective Comparative Study of Dual-Time-Point FDG-PET/CT, Contrast-Enhanced CT, and Bone Scintigraphy	Diagnostic accuracy of [18F] FDG-PET/CT versus contrast enhanced CT (ceCT), and bone scintigraphy (BS) in patients with suspected breast cancer recurrence. 100 women with suspected recurrence of BC underwent 1-hour and 3-hour FDG-PET/CT, ceCT, and BS within approximately 10 days. The study was powered to estimate the precision of the individual imaging tests. Images were visually interpreted using a four-point assessment scale, and readers were blinded to other test results. The reference standard was biopsy along with treatment decisions and clinical follow-up (median, 17 months).	Hildebrandt MG. et al. Journal of Clinical Oncology, 34(16): 1889-1897, 2016. http://ascopubs.org/doi/full/10.1200/JCO.2015.63.5185	2016
Hogan MP et al (2015)	Retrospective Suspected metastases Change in management	Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma.	Hospital Information System was screened for ILC patients who underwent PET/CT in 2006-2013 before systemic or radiation therapy. Initial stage was determined from examination, mammography, ultrasound, MR, or surgery. PET/CT was performed to identify unsuspected distant metastases. A sequential cohort of stage III IDC patients was evaluated for comparison. Upstaging rates were compared using the Pearson chi(2) test.	Journal of Nuclear Medicine. 56 (11) (pp 1674-1680), 2015. Date of Publication: 01 Nov 2015.	2015
Jung N.Y. et al	non-randomised	Clinical significance of FDG-	Comparative diagnostic accuracy of PET/CT and	Jung N.Y. et al. Breast Cancer. 23 (1)	2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
(2016)	Comparative diagnostic accuracy	PET/CT at the postoperative surveillance in the breast cancer patients.	conventional imaging in 1161 patients with suspected metastases and/or recurrent BC	(pp 141-148), 2016. http://link.springer.com/article/10.1007/s12282-014-0542-2	
Kim YH et al (2015)	Suspected metastases PET prognosis	The clinical significance of standardized uptake value in breast cancer measured using 18F-fluorodeoxyglucose positron emission tomography/computed tomography.	The objective of this study was to investigate the clinical and biological significance of F-FDG uptake levels in breast cancer patients. PATIENTS AND METHODS: F-FDG PET/CT was performed in 206 women with breast cancer, and the standardized uptake value (SUV) in breast cancer was analyzed to test associations with prognostic parameters.	https://www.ncbi.nlm.nih.gov/pubmed/25932535	2015
Koolen BB . et al (2014)	Non-randomised Comparative diagnostic accuracy	Accuracy of 18F-FDG PET/CT for primary tumor visualization and staging in T1 breast cancer.	Comparative diagnostic accuracy of PET/CT versus conventional imaging in 62 patients with LABC.	Koolen BB . et al. Acta Oncologica. 53 (1) (pp 50-57), 2014.) http://www.tandfonline.com/doi/pdf/10.3109/0284186X.2013.783714	2014
Krammer J et al (2015)	Suspected metastases Change in management	(18)F-FDG PET/CT for initial staging in breast cancer patients - Is there a relevant impact on treatment planning compared to conventional staging modalities?	To evaluate the impact of whole-body 18F-FDG PET/CT on initial staging of breast cancer in comparison to conventional staging modalities. N=101 patients. Preoperative whole-body staging with PET/CT was performed in patients with clinical stage>T2 tumours or positive local lymph nodes (n=91). Postoperative PET/CT was performed in patients without these criteria but positive sentinel lymph node biopsy (n=10). All patients underwent PET/CT and a conventional staging algorithm, which included bone scan, chest X-ray and abdominal ultrasound. PET/CT findings were compared to conventional staging and the impact on therapeutic management was evaluated.	European radiology. 25 (8) (pp 2460-2469), 2015. Date of Publication: 01 Aug 2015.	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
Lange M.B. et al (2016)	Retrospective study Comparative diagnostic accuracy	Diagnostic accuracy of imaging methods for the diagnosis of skeletal malignancies: A retrospective analysis against a pathology-proven reference.	Comparative diagnostic accuracy of PET/CT versus conventional imaging in 409 patients with suspected BC metastases	Lange M.B. et al. European Journal of Radiology. 85 (1) (pp 61-67), 2016. http://www.ejradiology.com/article/S0720-048X(15)30133-9/abstract	2016
Ng SP et al (2015)	Non-randomised Comparative diagnostic accuracy	Impact of Pretreatment Combined (18)F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging on Radiation Therapy Treatment Decisions in Locally Advanced Breast Cancer.	Comparative diagnostic accuracy of PET/CT versus conventional imaging in 154 patients with LABC	Ng SP et al. International journal of radiation oncology, biology, physics. 93 (1) (pp 111-117), 2015. http://www.sciencedirect.com/science/article/pii/S0360301615005167	2015
Sahin E et al (2014)	Comparative diagnostic accuracy	Is (99m)Tc-MDP whole body bone scintigraphy adjuvant to (18)F-FDG-PET for the detection of skeletal metastases?	Comparative diagnostic accuracy of PET/CT and bone scintigraphy in 121 patients with suspected BC metastases	Sahin E et al. Journal of B.U.ON. 19 (1) (pp 291-296), 2014. http://europepmc.org/abstract/med/24659678	2014
Sawicki LM, et al (2016)	Prospective Comparative diagnostic accuracy Recurrence	Evaluation of 18F-FDG PET/MRI, 18F-FDG PET/CT, MRI, and CT in whole-body staging of recurrent breast cancer.	The diagnostic performance of FDG-PET/MRI was compared with FDG-PET/CT, MRI and CT in whole-body staging of 21 patients with suspected breast cancer recurrence. The reference standard was based on histopathological results as well as prior and follow-up imaging.	European Journal of Radiology. 85 (2) (pp. 459-465), Feb 2016	2016
Sohn YM, Hong IK, Han	Retrospective	Role of [18F]fluorodeoxyglucose	The diagnostic performance of FDG-PET/CT was compared with sonography and sonographically	Journal of Ultrasound in Medicine: Official Journal of the American	2014

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
K (2014)	Comparative diagnostic accuracy	positron emission tomography-computed tomography, sonography, and sonographically guided fine-needle aspiration biopsy in the diagnosis of axillary lymph nodes in patients with breast cancer: comparison of diagnostic performance.	guided fine-needle aspiration (FNA) in the diagnosis of axillary lymph nodes in 107 patients with breast cancer. The diagnostic performance of the modalities was compared with pathologic reports.	Institute of Ultrasound in Medicine. 33 (6) (pp. 1013-1021), Jun 2014	
Sun Z. et al (2015)	Meta-analysis	Comparison of whole-body PET/PET-CT and conventional imaging procedures for distant metastasis staging in patients with breast cancer: A meta-analysis: To compare the performance of whole-body PET/PET-CT with that of conventional imaging procedures for the overall assessment of distant metastasis in patients with breast cancer.	Comparative diagnostic accuracy of PET/CT versus conventional imaging in 609 patients with LABC.	Sun Z et al. European Journal of Gynaecological Oncology. 36 (6) (pp 672-676), 2015.	2015
Teke F et al (2015)	Retrospective Comparative diagnostic accuracy	Significance of hormone receptor status in comparison of 18F -FDG-PET/CT and 99mTc-MDP bone scintigraphy for evaluating bone metastases in patients with breast cancer: single center experience.	Comparative diagnostic accuracy of PET/CT versus bone scintigraphy in 62 patients with suspected BC metastases.	Teke F et al. Asian Pacific journal of cancer prevention : APJCP. 16 (1) (pp 387-391), 2015.	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
You S et al (2015)	Non-randomised Comparative diagnostic accuracy	Evaluation of lymph node status after neoadjuvant chemotherapy in breast cancer patients: comparison of diagnostic performance of ultrasound, MRI and 18F-FDG PET/CT	Comparative diagnostic accuracy of PET/CT versus conventional imaging in 191 patients with suspected BC metastases	You S et al. The British journal of radiology. 88 (1052) (pp 20150143), 2015. http://www.birpublications.org/doi/full/10.1259/bjr.20150143	2015

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.

*** If the publication is a follow-up to an initial publication, please advise.

19. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

No relevant additional research has been identified.

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

20. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

Australasian Association of Nuclear Medicine Specialists

21. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

A variety of imaging techniques are available for staging and restaging breast cancer: plain radiography, ultrasound, bone scintigraphy, CT and MRI. The imaging test most commonly used for staging breast cancer is CT. MRI may be used to confirm spread to the brain and spine. Radiography (diagnostic mammography and/or CT) can be used to evaluate the primary lesion and search for spread to the lungs and other chest tissues. Ultrasound can be used to characterise breast lesions and abdominal spread. Bone scintigraphy is specific for bone metastases.

Diagnostic imaging studies require the following staff:

- Radiology staff (for CT, ultrasound, and MRI): radiographers, radiologists and clerical staff.
- Nuclear medicine staff (for bone scintigraphy): nuclear medicine technologists, nuclear medicine specialists, and clerical staff.

22. List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

The following organisations are relevant to the proposed medical service. These organisations have been approached by AANMS to provide letters of support, which will be forwarded to the Department of Health on receipt by AANMS.

1. Breast Cancer Institute of Australia <https://www.anzbctg.org/>

PO Box 283, The Junction NSW 2291. T +61 2 4925 3022 or 1800 423 3022

2. Australia & New Zealand Breast Cancer Trials Group

PO Box 155, HRMC NSW 2310. Phone: +61 2 4985 0136

General Enquiries: enquiries@bcia.org.au

3. Cancer Council Australia <http://www.cancer.org.au/>

GPO Box 4708, Sydney, NSW 2001 – T +61 2 8063 4100

4. RANZCR Faculty of Radiation Oncology

<http://www.ranzcr.edu.au/about/faculty-of-radiation-oncology>

Level 9, 51 Druitt Street, Sydney, NSW 2000 – T +61 2 9268 9777

5. Breast Surgeons of Australia and New Zealand inc

<http://www.breastsurganz.com/>

PO Box 243, Botany, NSW, 1455

6. Royal Australasian College of Surgeons

<http://www.surgeons.org>

College of Surgeons' Gardens, 250-290 Spring Street, East Melbourne Vic 3002

T + 61 3 9249 1200

7. Medical Oncology Group of Australia

<http://www.moga.org.au>

145 Macquarie Street, Sydney, 2000. T +61 2 9256 5458

8. National Breast Cancer Foundation

<http://www.nbcf.org.au>

GPO Box 4126, Sydney, 2001 T +61 2 8098 4800

9. Breast Cancer Network Australia

<http://www.bcna.org.au>

293 Camberwell Road, Camberwell. T +61 3 9805 2500

23. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

There is no similar product to FDG-PET

24. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

REDACTED

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

The following information is taken from the original DAP, with updated statistics where relevant.

25. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Proven locally advanced breast cancer:

Locally advanced breast cancer (LABC) is defined by one or more of the following features (American Joint Committee on Cancer [AJCC] Stage III, Appendix 2, Table 16):

- Primary tumour larger than 5cm.
- Spread to several lymph nodes in the axilla or other areas near the breast.
- Spread to other tissue around the breast such as skin, muscles, or ribs.

Burden of disease

The application proposes that confirmatory imaging using 18F-FDG PET be used in patients who have proven locally advanced disease, where prior diagnostic imaging does not provided sufficient information to determine if appropriate treatment for disease up-staging or spread is required. The data on burden of disease are primarily for women, men contribute a small proportion to the data.

Burden of disease estimates in the original DAP were based on 2008 data. Updated data are available from the AIHW. In 2012, 15,166 new cases of breast cancer were diagnosed in Australia (116 males and 15,050 females). In 2016, it is estimated that 16,084 new cases of breast cancer will be diagnosed in Australia (150 males and 15,934 females).¹

Cancer Australia states that between 10 to 20% of new breast cancer diagnoses each year have locally advanced disease.² This means approximately 1,600 to 3,200 women will have locally advanced breast cancer.

Suspected locally or regionally recurrent or suspected metastatic breast cancer:

Locally or regionally recurrent breast cancer is defined by the (re)development of cancer in the same breast (local) or ipsilateral (usually axillary) lymph nodes (regional) after an apparently disease-free interval following treatment. Metastatic (secondary) breast cancer (stage 4 breast cancer) is defined by spread to other parts of the body, either at the first diagnosis of breast cancer, or as a recurrence of a previously treated breast cancer.

Burden of disease

There are complexities in estimating incidence and prevalence of recurrent or metastatic breast cancer. The prevalence of the disease is influenced by the incidence of the initial disease, survival from the initial disease, and the age at which people were diagnosed with the initial disease, type of treatment taken, and site of recurrence or metastasis. Unfortunately, the incidence and prevalence of recurrences and metastases of any type are not notifiable in any jurisdiction, so there is no reliable national data on this.

The data are available primarily from women, as men contribute a small amount. At the end of 2010, there were 176,556 people living who had been diagnosed with breast cancer in the previous 29 years,

¹ Australian Institute of Health and Welfare 2016. Australian Cancer Incidence and Mortality (ACIM) books: breast cancer. Canberra: AIHW. [Accessed January 2016].

² <https://canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/about-breast-cancer/types-breast-cancer/what-locally-advanced-breast-cancer>

including about 61,500 people diagnosed in the previous 5 years.³ Recurrence may occur in these patients. There are only a few studies estimating recurrence in Australian breast cancer patients. Two Australian studies from 1995 on women who had been treated for early breast cancer found that 6-8% of women had recurrent ipsilateral breast cancer and 14-16% had metastatic disease at relapse. A 2012 study using 2001-2002 data from NSW found that 5% with localised node-negative disease and 17% with regional disease at initial diagnosis developed metastatic breast cancer within 5 years. This study highlights the different statistics that occur depending on factors such as initial diagnosis. A 2012 Australian study suggests that diagnosis of metastatic breast cancer peaks 2 years after initial treatment.⁴

The original DAP estimated that, per annum, 5-15% of all patients (women and men) with breast carcinoma would undergo restaging for suspected local or regional recurrence (closer to 5%) or suspected metastatic disease (closer to 15%) - based on HESP and applicant advice. Extrapolating to the breast cancer population, this means that of 176,556 prevalent patients diagnosed with breast cancer and alive up to 2010; between 8,800 to 26,500 could undergo restaging for suspected local or regional recurrence (closer to 8,800) and between 8,800 to 26,500 patients could undergo restaging for suspected metastatic disease (closer to 26,500).

26. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

The population that would be targeted for confirmatory imaging using ¹⁸F-FDG PET are men or women with:

- breast cancer who have locally advanced disease and inconclusive findings on conventional imaging, who require further evaluation;
- breast cancer where recurrent disease is suspected and for whom active therapy is likely to be pursued;
- breast cancer where metastatic disease is suspected and for whom active therapy is likely to be pursued.

Presentation for diagnostic imaging for staging / restaging:

A suspicious breast mass may be identified through a formal breast screening program, or via presentation to a general practitioner by a patient. The breast/s and axillary areas are investigated clinically through palpation and mammography or ultrasound, and MRI in high risk groups, and the presence of malignant tumour confirmed by biopsy. Breast cancer is staged, or classified, to determine the severity of the disease. Staging classification is determined by the American Joint Committee on Cancer's breast cancer staging TNM system. Staging of the disease depends on tumour size ("T"), the number of involved lymph nodes ("N"), and the presence or absence of distant metastases ("M"). Tumour size and axillary metastases can be estimated by clinical examination and imaging techniques, but definitive status/staging is achieved through surgery and histology.

Following and during initial treatment, breast cancer patients continue to have regular examinations and tests to evaluate treatment response and to detect recurrence or metastatic spread. In Australia, from QLD registry data, at initial diagnosis approximately 47% of patients have Stage I and 45% of patients have Stage II-IV disease and unknown in 8% of cases. There are two scenarios where PET/CT may have a role in the assessment of breast cancer patients:

- Proven locally advanced breast cancer
- Suspected locally or regionally recurrent or suspected metastatic breast cancer, particularly when conventional imaging tests are equivocal for spread of disease.

³ Australian Institute of Health and Welfare 2016. Australian Cancer Incidence and Mortality (ACIM) books: breast cancer. Canberra: AIHW. [Accessed January 2016].

⁴ Lord S, Marinovich L, Patterson J, et al. Incidence of metastatic breast cancer in an Australian population-based cohort of women with non-metastatic breast cancer at diagnosis. Medical Journal of Australia 2012; 196(11): 688-92.

27. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

The clinical algorithms developed in the DAP are attached to this resubmission application (Figures 1-3). Three clinical management algorithms are presented – each shows current and proposed algorithms for proven locally advanced breast cancer, suspected locally and regionally recurrent breast cancer, and suspected metastatic breast cancer. Please note that these Protocols present the common pathways, as there are always unique circumstances where variations in practice may occur (e.g. no biopsy after clearly positive findings on initial and confirmatory diagnostic imaging studies). The Protocols do not show the pathways for positive or negative results after conventional staging, as we are only interested in comparing the clinically relevant pathway options for an equivocal result after initial standard diagnostic imaging study.

The treatment options for spread of disease in proven locally advanced breast cancer include:

- Local treatment for treatable disease after a negative biopsy result: Any combination of surgery, radiotherapy, chemotherapy, and/or hormonal therapy.
- Altered local treatment +/- systemic therapy for treatable disease after a positive biopsy result: Any combination of surgery, radiotherapy, chemotherapy, and/or biologic therapy.
- Palliation for incurable disease.

The treatment options for spread of disease in metastatic breast cancer include:

- Observation.
- Further therapy for treatable disease after a positive biopsy: Treatment is based on number of sites, organs involved, and hormonal/HER2+ status of tumour. This would be surgery +/- radiotherapy, hormonal therapy, and/or biologic therapy.
- Palliation for incurable disseminated disease.

The treatment options for spread of disease in locally and regionally recurrent breast cancer include:

- Further therapy for treatable disease after a positive biopsy: Treatment is based on number of sites, organs involved, and hormonal/HER2+ status of tumour. This would be surgery +/- radiotherapy, hormonal therapy, and /or biologic therapy.
- Palliation for incurable disseminated disease.

PART 6b – INFORMATION ABOUT THE INTERVENTION

28. Describe the key components and clinical steps involved in delivering the proposed medical service:

Delivery of ¹⁸F-FDG PET scanning can be broken down into 3 “phases”. These are (1) ¹⁸F-FDG preparation, (2) PET scanning, and (3) image reconstruction and interpretation.

¹⁸F-FDG preparation and administration:

¹⁸F-FDG can be produced either in-house in facilities with a cyclotron and radiopharmacy capability, or sourced from a commercial supplier. Patients must fast for 4 to 6 hours prior to ¹⁸F-FDG administration. ¹⁸F-FDG is administered intravenously 60 minutes prior to scanning. European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) clinical practice guidelines state that the activity of ¹⁸F-FDG will vary according to body mass and PET machine parameters used, but is approximately 180 to 260 MBq for a 75kg patient,⁵ but can be as high as 740 MBq in some circumstances,⁶ and is adjusted accordingly for body weight at around 5 MBq per kilogram of body weight. The activity required is becoming lower with newer advanced machines (e.g. time-of-flight PET scanners would typically require an activity of less than 250 MBq in a small woman according to clinical experts from HESP and the applicant). During the 60 minutes prior to scanning, patients rest quietly in a

⁵ Boellaard R, O'Doherty MJ, Weber WA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging 2010; 37(1):181-200.

⁶ Delbeke D, Coleman RE, Guiberteau MJ, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2006; 47(5): 885-95.

dimly lit room. Following this uptake period, patients are taken to the PET suite and positioned on the scanning bed.

PET scanning:

PET scanning is done using a standard protocol which usually includes low-dose computed tomography (CT) for attenuation correction and anatomical correlation. In some cases, when the referring clinician deems necessary, a diagnostic CT may be done at the time of the PET study, using oral and/or intravenous contrast material (this would be a PET/CT diagnostic study). The field-of-view for PET scans is determined by the clinical indication, but usually extends from the base of the skull to the upper thighs. Typical PET study acquisition times with current scanners are less than 30 minutes, but are determined by performance characteristics of the PET scanner, the field-of-view, and the administered activity of FDG. For attenuation correction and anatomical correlation, an additional CT scanning time of 1 to 2 minutes is added.

PET scanning radiation dose:

In terms of radiation dose delivered, nuclear medicine and PET services abide by the ALARA principle (“as low as reasonably achievable”) with consideration of the clinical situation. The International Commission on Radiological Protection (2008) states that the effective radiation dose for FDG is 0.019mSv/MBq ; the typical effective dose for low-dose CT (for attenuation correction and anatomic correlation) is 2 – 3 mSv.⁷

PET image reconstruction and interpretation:

PET images are usually reconstructed using the PET scanner manufacturer’s recommended reconstruction protocols and software. The nuclear medicine specialist interprets the images (including correlated imaging where available) and generates a clinical report. This report is provided to the requesting clinician. Electronic copies of the PET images are provided to the requesting clinician as appropriate.

29. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

No.

30. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Not applicable

31. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

All nuclear medicine and PET services are provided on the basis of the ALARA principle and in accordance with clinical need.

32. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

¹⁸F-FDG PET is proposed to be used where prior tests have been inconclusive or suspicious for spread of disease. Prior tests may include CT, MRI and bone scintigraphy. However, ¹⁸F-FDG PET is proposed as a stand-alone, defined medical service.

33. If applicable, advise which health professionals will primarily deliver the proposed service:

PET services are provided by credentialed nuclear medicine specialists who also have credentialing for PET, as described in the current DAP:

34. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

⁷ ICRP. Radiation dose to patients from radiopharmaceuticals. Addendum 3 to ICRP Publication 53. ICRP Publication 106. Approved by the Commission in October 2007. Annals of the ICRP 2008; 38(1-2): 1-197.

PET services involve nuclear medicine specialists who consult with the patient, determine the relevant dosage and nature of the scan, review the available relevant clinical data and preparation of the report of the scan. The equipment is operated by trained technologists who operate under the direction of the nuclear medicine specialist. Quality is assured by the nuclear medicine specialists. Other staff involved in the delivery of the service may include nurses and administration staff.

35. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

PET services are provided by credentialed nuclear medicine specialists who also have credentialing for PET; services are provided on request from a medical specialist.

36. If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:

With reference to the regulations on the MBS for delivering PET services for other diseases (i.e. "Note DIN Group 14 – Nuclear Medicine Imaging" for MBS Items 61523 to 61646), it is envisioned that PET services for breast cancer patients must be performed by:

- a) a nuclear medicine specialist or consultant physician credentialed under the Joint Nuclear Medicine Specialist Credentialing Program for the Recognition of the Credentials of Nuclear Medicine Specialists for Positron Emission Tomography overseen by the Joint Nuclear Medicine Credentialing 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;

37. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

- Inpatient private hospital
- Inpatient public hospital
- Outpatient clinic
- Emergency Department
- Consulting rooms
- Day surgery centre
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

PET services may be provided in both an inpatient and outpatient setting. Under the current Medicare funding arrangements, Medicare eligibility for the PET service is linked to a number of criteria that include a link to a comprehensive cancer service.

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Patients with breast cancer requiring the proposed medical service are more likely to be outpatients

38. Is the proposed medical service intended to be entirely rendered in Australia?

- Yes
- No – please specify below

Specify further details here

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. 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 health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

Standard confirmatory diagnostic imaging is the comparator test.

Initial diagnostic imaging tests for diagnosing and staging breast cancers is CT. MRI may also be used to confirm brain and spine tumour involvement and spread. For radiography, diagnostic mammography and CT can be used to evaluate the primary lesion in the breast and search for spread to the lungs and other chest tissues. Ultrasound can be used to characterise breast lesions, where it can be used to differentiate between cysts and solid masses such as a tumour. The more complex diagnostic techniques (i.e. MRI, CT, bone scintigraphy) are discussed below.

MRI:

MRI is used for various imaging purposes, including for oncological investigations. There are MBS items for MRI for breast cancer investigations (MBS #63457 and #63458), brain investigations (MBS #63001 and #63491), and spinal investigations (MBS #63154 and #63491). MRI uses the physical properties of unpaired hydrogen ions (protons) in different chemical, structural and magnetic environments to produce images of tissues. Unlike PET and CT, it does not use ionising radiation. The effectiveness of a given MRI examination is highly dependent on the imaging parameters (pulse sequences) selected. Furthermore, MRI may be conducted with the use of contrast agents, typically intravenous gadolinium attached to a chelating agent such as DTPA (diethylene triamine penta-acetic acid).

CT:

CT is used for various imaging purposes, including for oncological investigations. Most patients will have CT of their chest, abdomen, and pelvis (MBS #56807). Some patients may rarely have CT on their chest only (MBS #56307). Some patients may additionally have brain CT (MBS #56007). CT is a non-invasive imaging modality that involves measuring the x-ray attenuation coefficient of the anatomical part examined. Radiopaque intravenous and oral contrast material is usually given during the examination.

Bone scintigraphy:

Bone scintigraphy is a diagnostic study used to evaluate the distribution of active bone formation in the body. The MBS item is #61425. Radiopharmaceuticals are injected intravenously into the patient to allow clinicians to detect how much radiotracer collects in the bones. These radiolabelled bisphosphonates bind to hydroxyapatite at sites of osteogenesis. To evaluate metastatic bone disease, images are taken 2 - 3 hours after radiotracer injection. There are a few options for using bone scintigraphy. These are:

1. Whole-body bone scintigraphy produces planar images of the skeleton.
2. Bone single-photon emission computed tomography (SPECT) produces a tomographic image of a portion of the skeleton.
3. Multiphase bone scintigraphy usually includes blood flow images, immediate images, and delayed images.

Reference standard

The reference standard to identify breast cancer is a biopsy. Cells from the area of concern are removed so they can be studied in the laboratory. There are several types of biopsies that can be performed. For breast biopsies, these are:

Fine needle aspiration (FNA) biopsy. This is the easiest type of biopsy to have, but it doesn't always give a clear answer.

Core needle biopsy. It is used to remove one or more cores (pieces) of tissue. Because more tissue is removed, a core needle biopsy is more likely than an FNA to provide a clear result.

Vacuum-assisted biopsies. These can be done with various commercial systems under the guidance of a mammogram or MRI. The skin is numbed, a small cut (incision) is made, then a hollow probe is put

through the cut into the breast tissue, and a piece of tissue is sucked out. Several samples can be taken from the same cut. This method usually removes more tissue than core biopsies.

Surgical (open) biopsy: Most often, breast cancer can be found using the other types of biopsy. Surgery is rarely needed to remove all or part of a lump so it can be looked at under a microscope. The whole lump as well as some normal tissue around it may be taken out.

A lymph node biopsy may also need to be done for suspected advanced, metastatic and recurrent breast cancers. Tissue removed during biopsy is analysed by the laboratory, which will report on the breast cancer grade, hormone receptor status (i.e. oestrogen and progesterone), HER2 / neu status, and in some cases gene patterns.

40. Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?

- Yes (please provide all relevant MBS item numbers below)
 No

MBS Item number	Description
56807	Computed tomography (chest, abdomen, and pelvis)
56307	Computed tomography (chest)
56007	Computed tomography (brain)
63457	MRI (breasts)
63458	MRI (breasts – follow-up)
63001	MRI (brain)
63491	MRI (brain – contrast medium)
63154	MRI (spine)
63491	MRI (spine – contrast medium)
61505	CT (with SPECT, for localisation / correction)
61719	CT (with SPECT, for localisation / correction)
61425	Bone study (for bone scintigraphy)
55059	Breast ultrasound
55061	Breast ultrasound

41. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):

As described in response 27, three clinical management algorithms are attached to this re-application. The algorithms were developed in the original DAP and describe current and proposed algorithms for proven locally advanced breast cancer, suspected locally and regionally recurrent breast cancer, and suspected metastatic breast cancer.

42. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

- Yes
 No

(b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:

PET is likely to be used in addition to the nominated comparators, where the comparators provide an equivocal result.

43. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):

The main outcome from a PET scan in the population relevant to this application is a change in management when compared with the clinical information provided by other diagnostic modalities. For many patients with breast cancer, this is most likely to result in upstaging and a change of management that results in avoidance of, or reduction in, futile treatment such as major surgery or chemotherapy.

For the individual patient where a PET scan indicates more advanced disease than previously indicated by other diagnostic modalities, a management change may be indicated, including a recommendation to not proceed with futile radical treatment.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

The clinical claim is that confirmatory ¹⁸F-FDG PET imaging is superior to confirmatory standard diagnostic imaging. ¹⁸F-FDG PET is more effective (for the outcomes listed previously) than standard diagnostic imaging.

45. Please advise if the overall clinical claim is for:

- Superiority
 Non-inferiority

46. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

¹⁸F-FDG PET is considered a safe procedure. A previous MSAC report discussed relevant safety issues on PET for recurrent colorectal cancer.⁸ Patients undergoing ¹⁸F-FDG PET will be exposed to additional radiation on top of the radiation from CT during the initial diagnostic imaging tests, but doses from PET are typically lower than with diagnostic CT.⁹ The potential long-term effects of exposure to diagnostic levels of radiation are unlikely to be a relevant consideration for patients with proven locally advanced, suspected locally or regionally recurrent or suspected metastatic breast cancers. This is due to their likely exposure to radiotherapy and/or chemotherapy either in the past or in the future of their treatments.

Clinical Effectiveness Outcomes:

Diagnostic accuracy:

Sensitivity.

Specificity.

Additional true positive (TP) & false positive (FP), receiver operator characteristic (ROC) area under the curve (AUC), Cochrane Q statistic for testing heterogeneity, diagnostic odds ratio (DOR).

Change in management:

Definitive treatment avoided.

Investigations avoided (eg biopsies from false positives).

Definitive treatment instigated.

Overall change.

Type of change occurring

Patient outcomes:

Morbidity.

Mortality.

Overall survival.

Cancer-specific mortality.

Cancer progression.

Treatment morbidity.

Adverse events.

Quality of life.

⁸ Medical Services Advisory Committee (MSAC). Positron Emission Tomography for recurrent colorectal cancer. Ref 35a. In: Department of Health and Ageing, editor. Canberra, Australia: Commonwealth of Australia; 2007.

⁹ Medical Services Advisory Committee (MSAC). Positron emission tomography for cervical cancer. Ref 35e. In: Ageing DoHa, editor. Canberra: Commonwealth of Australia; 2010.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

47. Estimate the prevalence and/or incidence of the proposed population:

Building on the burden of disease detailed in response to question 25:

Locally advanced disease

Cancer Australia states that between 10 to 20% of new breast cancer diagnoses each year have locally advanced disease.¹⁰ This means approximately 1,600 to 3,200 women will have locally advanced breast cancer. According to clinicians involved in the Austin Report and HESP clinicians, 30% of these patients will have inconclusive conventional imaging staging studies for spread of disease and would therefore be suitable for PET evaluation.

Based on these assumptions, approximately 480 to 960 patients (women and men) per year with locally advanced breast cancer would be eligible for 18F-FDG PET imaging.

Suspected locally or regionally recurrent or suspected metastatic breast cancer:

The original DAP estimated that, per annum, 5-15% of all patients (women and men) with breast carcinoma would undergo restaging for suspected local or regional recurrence (closer to 5%) or suspected metastatic disease (closer to 15%) - based on HESP and applicant advice. Extrapolating to the breast cancer population, this means that of 176,556 prevalent patients diagnosed with breast cancer and alive up to 2010; between 8,800 to 26,500 could undergo restaging for suspected local or regional recurrence (closer to 8,800) and between 8,800 to 26,500 patients could undergo restaging for suspected metastatic disease (closer to 26,500).

According to clinicians involved in the Austin Report and HESP clinicians, 30% of these patients will have inconclusive conventional imaging staging studies for spread of disease and would therefore be suitable for PET evaluation. Therefore approximately 2,640 patients with suspected locally or regionally recurrent breast cancer and 7,950 patients with suspected metastatic breast cancer would access PET scanning annually.

48. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

The PET service will be delivered when conventional staging procedures are equivocal or inconclusive. For any individual patient the PET service may not be required at all or be performed several times during a relatively short period when clinical management decisions are being made and conventional staging procedures have been inconclusive or equivocal.

Patients with locally advanced disease with equivocal findings on conventional imaging would likely only need one PET scan in total.

For restaging of patients with suspected recurrent or metastatic disease, of the 30% of patients with equivocal findings on conventional imaging, these patients could reasonably be expected to have one or two scans per year.

49. How many years would the proposed medical service(s) be required for the patient?

Any individual patient with breast cancer may need to access the PET service at any time during their lifetime, when the patient's medical condition warrants further diagnostic evaluation and conventional imaging provides inconclusive results.

50. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

¹⁰ <https://canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/about-breast-cancer/types-breast-cancer/what-locally-advanced-breast-cancer>

From the financial estimates in the assessment report for application 1357, conducted by the NHMRC clinical trials unit (for the year 2016):

LABC: 717

Recurrent or metastatic: 1,286

Using the epidemiological evidence presented in the original DAP, updated with 2012 AIHW incidence and prevalence estimates. The number of patient with equivocal or suspicious results on prior conventional imaging, per annum:

LABC: 480-960

Recurrent: 2,640

Metastatic: 7,950

51. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

From the assessment report for application 1357:

Description	2015	2016	2017	2018	2019
Number of new cases of breast cancer ¹¹	15,600	15,930	16,250	16,570	16,890
Number of new cases of locally advanced breast cancer ¹²	2,340	2,390	2,438	2,486	2,534
Number of new cases of metastatic breast cancer ¹³	1,092	1,115	1,138	1,160	1,182
Number of new cases of recurrent breast cancer ¹⁴	3,105	3,170	3,234	3,298	3,361
% patients with equivocal prior imaging ¹⁵	30%	30%	30%	30%	30%
LABC	702	717	731	746	760
Recurrent or metastatic	1,259	1,286	1,311	1,337	1,363

¹¹ Australian Institute of Health and Welfare (AIHW) 2012, Cancer incidence projections: Australia, 2011 to 2020, Cat. No. CAN 62, Canberra: AIHW

¹² Cancer Australia 2012, What is locally advanced breast cancer? [Internet 30/10/2013, available from: <http://canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/about-breast-cancer/types-breast-cancer/what-locally-advanced-breast-cancer>]

¹³ Walkington, L, Newsham, A. et al. 2012, Patterns of breast cancer recurrence and associated health care costs of 1000 patients: a longitudinal study. 8th NCRI Cancer Conference, LB91

¹⁴ Cancer Australia 2012 (as above)

¹⁵ DAP – HESP assumption

PART 8 – COST INFORMATION

52. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

For the purposes of this application form, the AANMS notes that:

- The Commonwealth Government has determined the fee for Medicare benefit for PET – currently an average of \$955. The fees for Medicare benefit have not increased since the original Determination (Health Insurance Determination HS/6/01 dated 15 January 2002)
- During this period the cost of delivering services has increased, including the additional capital costs associated with the transition to PET/CT and phasing out of “PET only” equipment;
- Increases in the fees for Medicare benefit for PET have been sought on a number of occasions;
- The present fee for Medicare benefit does not include a capital component (unlike other comparable MBS items); and
- The AANMS has sought a Medicare item, along the lines of item 61505 [CT scan performed at the same time and covering the same body area as single photon emission tomography for the purpose of anatomic localisation or attenuation correction where no separate diagnostic CT report is issued and only in association with items 61302 - 61650 (R)], that would be related to the PET items in the same way item 61505 is related to SPECT items.

While the MSAC application process seeks a full costing as part of the application, the AANMS notes that previous costings* submitted to the Department of Health have not resulted in review of the current fees for Medicare benefit over the past 15 years and thus this application will proceed on the basis of the existing fees for Medicare benefit, but with the addition of a capital component as currently reflected in MBS item 61505 and the caveat that these are considered outdated.

(Included in reports from the national PET Data Collection Project based on costs drawn from data from the eight participating sites which was compiled and analysed by the PET Data Collection Agency.)*

53. Specify how long the proposed medical service typically takes to perform:

See above

54. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Proposed MBS item descriptor for ¹⁸F-FDG PET for proven locally advanced breast cancer

Category 5 – DIAGNOSTIC IMAGING SERVICES

Whole body ¹⁸F-FDG PET study, performed for the staging of locally advanced (Stage III) breast cancer in a patient considered potentially suitable for active therapy, where prior investigations have provided either equivocal results or findings suspicious for metastatic disease.

Fee: see above

Proposed MBS item descriptor for 18F-FDG PET for suspected locally or regionally recurrent or suspected metastatic breast cancer

Category 5 – DIAGNOSTIC IMAGING SERVICES

Whole body 18F-FDG PET study, performed for the evaluation of suspected metastatic or suspected locally or regionally recurrent breast carcinoma in a patient considered suitable for active therapy, where prior investigations have provided either equivocal results or findings suspicious for metastatic disease.

Fee: see above

Application 1357 was considered at the 26-28 November 2014 MSAC meeting. MSAC considered that a resubmission should include:

1. Amendments to the descriptor, better definitions of what constitutes standard prior imaging and equivocal prior diagnostic work-up; and to specify specialist referral

The MSAC executive requested that the populations/item descriptors in the application be revised to ensure that PET/CT will not be used for ‘monitoring’ of patients progress. The proposed item descriptors have been revised. The applicant agrees that specialist referral should be stipulated in the MBS descriptor.

2. An amended decision tree to consider earlier use of PET/CT (noting that PET/CT, not stand-alone PET, is the current standard)

Applicant response:

In standard clinical practice, some form of imaging will always have been performed to establish the initial diagnosis of breast cancer and to stage local spread of disease. Hence, no change to the position of PET/CT in the algorithm for LABC has been considered.

In the case of suspected recurrent or metastatic disease, AANMS does not propose that PET/CT replace conventional imaging, nor would standard clinical practice or currently available clinical evidence support the earlier use of PET/CT in all patients.

Thus, no change to the decision tree is proposed in the resubmission.

3. Any evidence for a consequential change in clinical management and patient outcomes

The MSAC executive has advised that consistent with previous diagnostic imaging applications, improvements in clinical outcomes could be inferred from meaningful changes in management resulting from PET/CT findings. Therefore evidence of change in patient outcomes is not essential in a resubmission.

4. A cost consequence analysis

Applicant response:

The first assessment report presented the cost per diagnostic error avoided. It is planned to present a stepped approach in the resubmission, using the following outcomes:

- Cost per biopsy avoided
- Cost per surgery avoided
- Cost per delayed biopsy / delayed treatment avoided
- Cost per QALY

5. A longer time horizon in the economic evaluation

Applicant response:

A one-year time horizon has been retained for the base case of the economic models. In both locally advanced and suspected recurrent / metastatic breast cancer, clinically relevant outcomes will occur within the first 12 months following the PET imaging, and costs are adequately identified. A longer time horizon is likely to favour PET/CT scanning, but the added complexity and longer extrapolation of the clinical evidence may introduce uncertainty, deleterious to MSAC consideration.

PART 9 – FEEDBACK

The Department is interested in your feedback.

55. How long did it take to complete the Application Form?

Insert approximate duration here

56. (a) Was the Application Form clear and easy to complete?

- Yes
- No

(b) If no, provide areas of concern:

Describe areas of concern here

57. (a) Are the associated Guidelines to the Application Form useful?

- Yes
- No

(b) If no, what areas did you find not to be useful?

Insert feedback here

58. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

- Yes
- No

(b) If yes, please advise:

Insert feedback here

Figure 1: Clinical management algorithm for proven locally advanced breast cancer. Confirmatory standard diagnostic imaging vs confirmatory ¹⁸F-FDG PET.

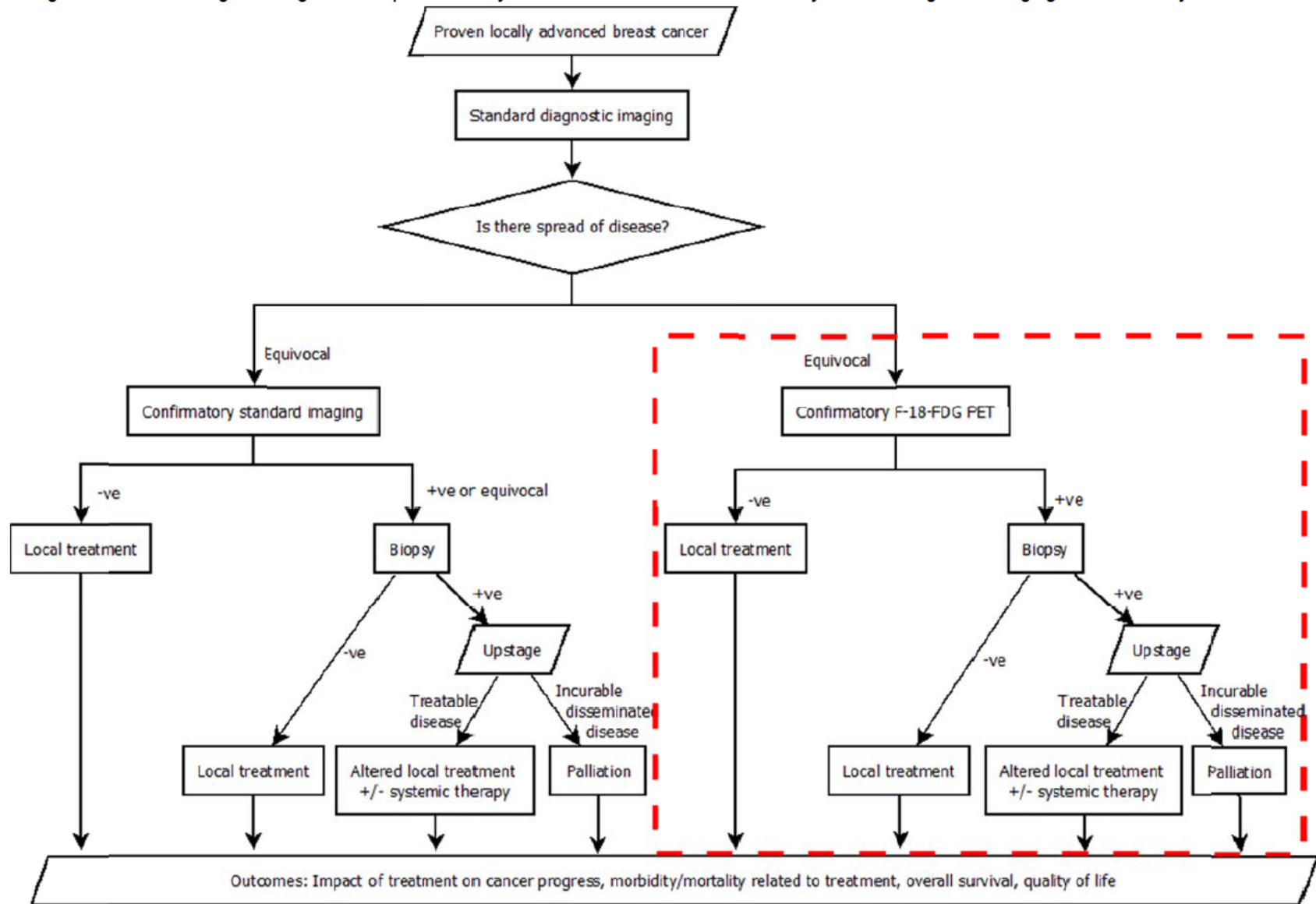


Figure 2: Clinical management algorithm for suspected locally and regionally recurrent breast cancer. Confirmatory standard diagnostic imaging vs confirmatory ¹⁸F-FDG PET.

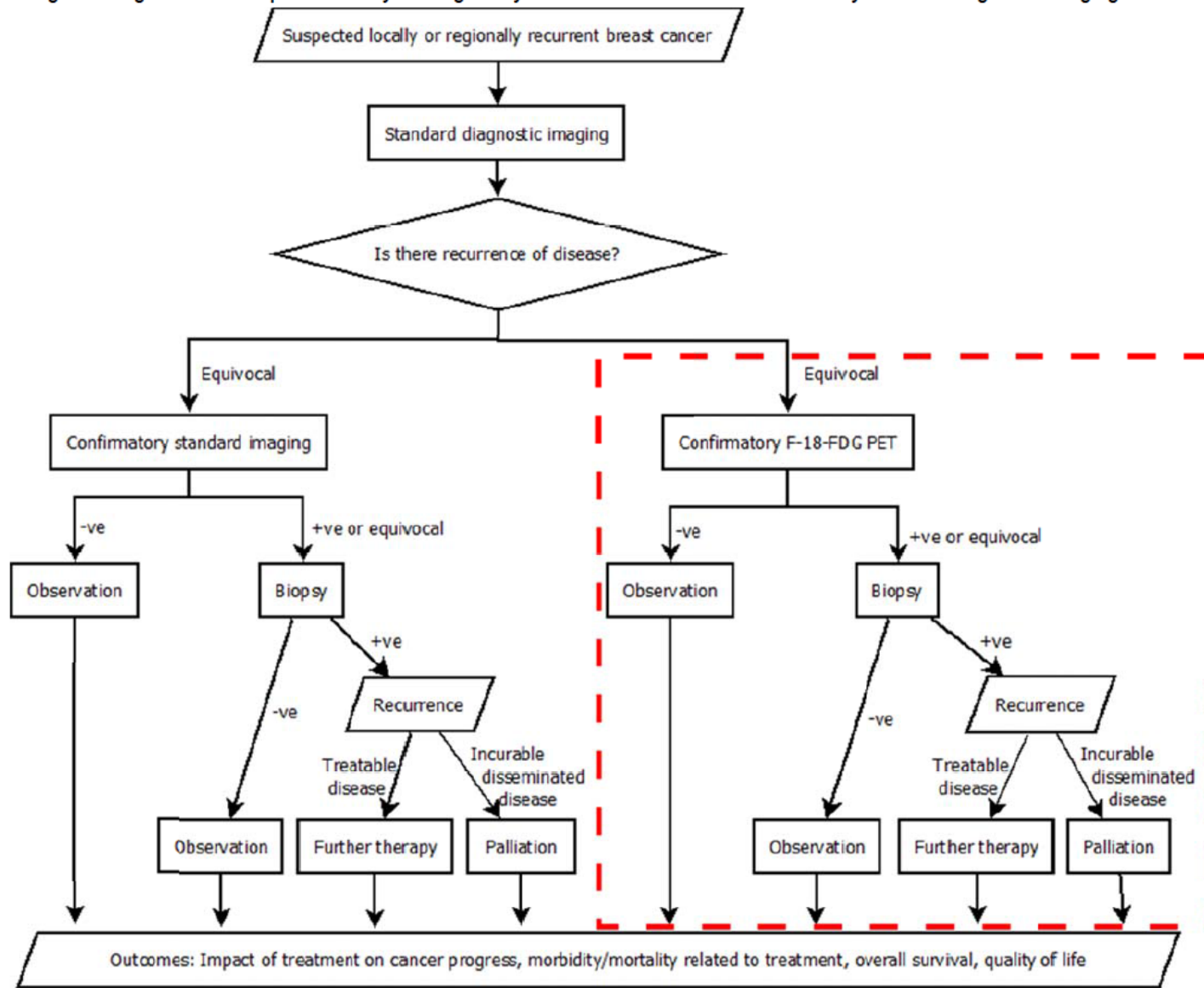


Figure 3: Clinical management algorithm for suspected metastatic breast cancer. Confirmatory standard diagnostic imaging vs confirmatory ¹⁸F-FDG PET.

