Substitution of ^{68}Ga-DOTA-peptide PET/CT scanning in lieu of Octreotide for patients undergoing somatostatin receptor diagnostic imaging under MBS item 61369

February 2017

Mini assessment report

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The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This min-assessment was prepared by Dr Judy Morona and Dr Ruchi Mittal from Adelaide Health Technology Assessment (AHTA). Clinical advice was provided by A/Prof Paul Roach, Dr David Wyld and Prof Nick Pavlakis. The mini-assessment was commissioned by the Australian Government Department of Health. It was edited by Dr Debra Gum and Ms Skye Newton.

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EXECUTIVE SUMMARY

Substitution of ^{68}Ga-DOTA-peptide PET/CT scanning in lieu of ^{111}In-octreotide SPECT/CT for patients undergoing somatostatin receptor diagnostic imaging under MBS item 61369

This contracted mini assessment examines the evidence to the support listing of ^{68}Gallium-1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid-peptide (^{68}Ga-DOTA-peptide) positron emission tomography (PET) / computed tomography (CT) scanning for the diagnosis of gastroenteropancreatic neuroendocrine tumours (GEP NETs) on the Medicare Benefits Schedule (MBS). The target population are people with clinically suspected GEP NETs. The applicant has claimed that the successful listing of the technology in the target population and setting will lead to a reduction in the number of repeated tests and superior safety in terms of faster acquisition time and lower radiation exposure.

A systematic literature review was not undertaken for this mini-assessment; and therefore, the evidence base is incomplete. No comparative studies were identified to inform on therapeutic efficacy or effectiveness

ALIGNMENT WITH AGREED PICO CONFIRMATION

This contracted mini assessment of ^{68}Ga-DOTA-peptide PET/CT scanning for the diagnosis of GEP NETs addresses all of the PICO[1] elements that were pre-specified in the draft PICO Confirmation submitted to the PICO Confirmation Advisory Sub-Committee of the MSAC.

PROPOSED MEDICAL SERVICE

The proposed medical service is a combined PET/CT scan for functional (PET) and anatomical (CT) imaging of GEP NETs using a ^{68}Ga-DOTA-labelled somatostatin analogue. Similar to ^{111}Indium (^{111}In)-octreotide, these analogues are also derived from octreotide, a somatostatin octapeptide that binds to the somatostatin receptor. Three different DOTA-peptides—DOTA–D-Phe^{1}-Tyr^{3}-Thr^{8}-octreotate (DOTATATE), DOTA–D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC), and DOTA-Phe^{1}-Nal^{3}-octreotide (DOTANOC)—are currently used in conjunction with ^{68}Ga for PET/CT imaging of GEP NETs.

In Australia, the DOTATATE peptide is coupled to ^{68}Ga. This peptide is supplied by Auspep, which is licensed by the TGA to manufacture active pharmaceutical ingredients (licence MI-07122005-LI-001046-11). The ^{68}Ga-DOTA-peptide is not listed on the Australian Register of Therapeutic Goods

[1] Population, Intervention, Comparator, Outcomes

(ARTG), as it is reconstituted from its components. While several ^{68}Ga generators are available commercially, none are currently registered in Australia. TGA registration is still under review.

^{68}Ga-DOTATATE PET scanning has been performed in lieu of ^{111}In-octreotide SPECT for several years in a number of Australian public hospitals (under the public hospital exemption), so there is local experience and expertise with its use at several hospitals. The Australasian Association of Nuclear Medicine Specialists is requesting that public funding should be provided for Good Manufacturing Practice compliant ^{68}Ga generators.

PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 1. This is proposed to replace the existing MBS item number 61369.

Table 1 Proposed replacement for MBS item number 61369

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS item number 61369 (replacement)
Whole body 68Ga-DOTA-peptide PET scan where:
(a) there is a suspected gastro-entero-pancreatic endocrine tumour, based on biochemical evidence, with negative or equivocal conventional imaging; or
(b) a surgically amenable gastro-entero-pancreatic endocrine tumour has been identified based on conventional techniques, in order to exclude additional disease sites
Fee: $ 953.00 **Benefit:** 75% = $714.75, 85% = $872.80

For a patient undergoing a ^{68}Ga-DOTA-peptide PET/CT scan, the PET procedure is very similar to a fluorodeoxyglucose (FDG) PET scan (MBS item number 61523) with respect to the acquisition time, the processing time for the technologists and the reporting time for the nuclear medicine specialist.

The $953 fee is the same as the cost of FDG PET. However, as PET rebates have not increased for 10 years, a more realistic cost of a ^{68}Ga-DOTA-peptide PET scan (based on CPI and other cost increases) should now exceed $1,100. The CT scan undertaken at the same time is reimbursed separately under MBS item 61505 (Fee: $100.00 Benefit: 75% = $75.00 85% = $85.00).

POPULATION

GEP NETs are a heterogeneous group of tumours arising from the diffuse endocrine system of the gastro-intestinal tract or pancreatic islet cells. Most commonly, the primary lesion is located in the gastric mucosa, small or large intestine, rectum or pancreas. While the majority of GEP NETs are sporadic, they can also occur in familiar syndromes such as multiple endocrine neoplasia type 1 syndrome and von-Hippel-Lindau disease (Kizilgul & Delibasi 2014). The defining characteristic of GEP NETs is the expression of somatostatin receptors, enabling the imaging of these tumours with radiolabelled somatostatin analogues.

Approximately two-thirds of GEP NETS are carcinoid tumours, originating in the enterochromaffin cells of the gut. Many do not cause symptoms, but the metastases from some carcinoid GEP NETs (mostly mid-gut originating in the small intestine, appendix or proximal large bowel) may secrete serotonin and other vasoactive substances, causing carcinoid syndrome. Approximately one-third of GEP NETS are pancreatic tumours, originating from the islet cells. The majority of pancreatic cancers are adenocarcinomas, which arise from the exocrine pancreas. Up to 60% of pancreatic NETs are non-functional. The functional tumours are often classified by the hormone most strongly secreted.

The only population in scope for this assessment is the subgroup of patients with GEP NETs who are currently eligible for item 61369:

- Patients with a suspected GEP NET based on biochemical evidence with negative or equivocal conventional imaging;
- Patients with a surgically amenable GEP NET that has been identified based on conventional techniques, where somatostatin receptor scintigraphy (SRS) is performed in order to exclude additional disease sites.

Patients with other types of NETs that are not GEP in origin are out of the scope of this evaluation, noting that SRS is postulated to have value in a broader cohort of NET patients.

COMPARATOR DETAILS

In Australia, the only approved diagnostic radiopharmaceutical for SRS is OctreoScan® (^{111}In-octreotide), which was listed on the ARTG in 1996 (number 55928). It is covered by MBS item 61369, with a schedule fee of $2015.75 (Table 6 in section A6). This item was included in the MBS in the early 2000s following a recommendation by MSAC in 1999 (Application 1003). Item 61369 is usually performed using SPECT with a gamma camera. If a concomitant CT is performed, it is reimbursed under MBS item 61505 (Fee: $100.00 Benefit: 75% = $75.00 85% = $85.00).

The gold standard for the diagnosis of GEP NETs is histopathology. Most guidelines, such as those from The Clinical Oncological Society of Australia (COSA 2008), European Society for Medical Oncology (Öberg et al. 2012) and the Canadian evidence-based consensus recommendations (Singh et al. 2016), stipulate that histology of surgical or biopsy tissue is mandatory in all cases for the diagnosis of GEP NETs. However, the systematic reviews (SRs) that provide the evidence base for diagnostic accuracy all used a composite reference standard, which included the results from histopathology and/or conventional imaging and/or clinical follow-up of at least 1 year. Thus, this composite reference standard has been used for this mini-assessment.

CLINICAL MANAGEMENT ALGORITHM

Currently, functional SRS assessment of the suspected GEP NET using ^{111}In-octreotide SPECT±CT imaging is funded on the MBS. In the proposed pathway ^{111}In-octreotide SPECT±CT imaging is replaced by ^{68}Ga-DOTA-peptide PET/CT imaging for functional assessment. The current and proposed diagnostic pathways are shown in Figure 2 in section A6.

KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

The key differences between the two tests are:

- The time taken to complete the test is 90 minutes to 2 hours for ^{68}Ga-DOTATATE PET/CT compared with 2 days for ^{111}In-octreotide SPECT/CT.
- The radiation dose from ^{68}Ga-DOTATATE PET (2–3 mSv, 28–41 MBq) is less than that received with ^{111}In-octreotide SPECT (8–16 mSv, ^{111}–222 MBq).
- The cost of ^{111}In-octreotide SPECT/CT is much higher than ^{68}Ga-DOTATATE PET/CT.

CLINICAL CLAIM

A claim has been made that introducing ^{68}Ga-DOTA-peptide PET/CT scanning in lieu of ^{111}In-octreotide SPECT/CT will reduce the amount of repeat testing that supposedly occurs with ^{111}In-octreotide SPECT. ^{68}Ga-DOTA-peptide PET/CT scanning is also claimed to have superior safety over the comparator in terms of faster acquisition time and lower radiation exposure.

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

This mini assessment of the effectiveness of ^{68}Ga-DOTA-peptide PET/CT scanning in lieu of ^{111}In-octreotide SPECT/CT scanning is constrained by a lack of information. A systematic search of the literature is required to properly assess these technologies. To complement the limited evidence provided by the applicant, a quick literature search of the PubMed database to identify recent publications to help evaluate these technologies was undertaken. Therefore, the conclusions drawn from this mini-assessment are based on an incomplete evidence base.

CHARACTERISTICS OF THE EVIDENCE BASE

The characteristics of the evidence informing each step of the linked analysis are shown in Table 2.

There was no direct evidence. Whilst some studies were identified to provide evidence for each step of the linked evidence, data that directly compared the outcomes for ^{68}Ga-DOTA-peptide PET/CT with those for ^{111}In-octreotide SPECT/CT were not available for either therapeutic efficacy or therapeutic effectiveness.

Table 2 Key features of the included linked evidence

Type of evidence	Description	Number
Diagnostic accuracy and clinical validity Reference standard: histopathology and/or conventional imaging and/or clinical follow-up	**^{68}Ga-DOTA-peptide PET/CT versus reference standard** Systematic reviews with a low risk of bias	SRs=2: k=10, n=479 k=22, n=2.098
	^{111}In-octreotide SPECT versus reference standard Diagnostic accuracy studies from the non-SR	k=11, n=523
	^{111}In-octreotide SPECT/CT versus reference standard Diagnostic accuracy studies from the quick literature search	k=9, n=811
Therapeutic efficacy	Systematic review (high risk of bias) non-comparative cohort studies before and after case series Before and after case series (2 low, 3 medium risk of bias) Case series (medium risk of bias)	SR=1 k=14, n=2,091 k=4, n=279 k=5, n=319 k=3, n=102
Therapeutic effectiveness	**Surgery:** retrospective cohort studies (1 low, 2 medium risk of bias) **SSA:** retrospective cohort studies (2 low, 1 medium risk of bias) **PRRT:** cohort study (medium risk of bias)	k=3, n=252 k=3, n=369 k=1, n=450

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; k = number of studies; n = number of patients; PET = positron emission tomography; PRRT = peptide receptor radionuclide therapy; SPECT = single-photon emission computed tomography; SR = systematic review; SSA = somatostatin analogue

RESULTS

On the basis of the benefits and harms reported in the evidence base (summarised below), **it is suggested that, relative to ^{111}In-octreotide SPECT/CT, ^{68}Ga-DOTA-peptide PET/CT has superior safety and superior effectiveness.**

SAFETY

Test adverse events

Short term: Only six mild adverse events associated with injection of the ^{68}Ga-DOTA-peptide have been reported in the literature included in this assessment. Two patients with gastritis and abdominal pain were effectively treated with an antispasmodic drug. The remaining four cases all resolved spontaneously in less than 48 hours (section B7.1).

Long term: Hofman et al. (2012) reported that ^{68}Ga-DOTATATE PET resulted in a significantly lower radiation dose (approximately 3–4 mSv) compared with ^{111}In-octreotide SPECT (approximately 12 mSv). Austin Health[2] concluded that multiple MSAC assessments of FDG PET have stated that it is generally accepted that PET is a non-invasive and relatively safe diagnostic procedure, and that the potential long-term effects of exposure to ionising radiation are unlikely to be of major concern to patients with GEP NETs, given their reduced life expectancy.

[2] 'Report on the Use of Positron Emission Tomography (PET) and Radiopharmaceuticals' (August 2012) commissioned by The Commonwealth Government Department of Health and Ageing.

DIRECT EFFECTIVENESS

There was no direct evidence in inform of the effectiveness of ^{68}Ga-DOTA-peptide PET/CT compared with ^{111}In-octreotide SPECT/CT.

EFFECTIVENESS FROM LINKED EVIDENCE

Diagnostic accuracy and clinical utility

The diagnostic accuracy results for ^{68}Ga-DOTATATE PET/CT (SR by Deppen et al. 2016b[3]), ^{68}Ga-DOTA-peptide PET/CT (SR by Geijer and Breimer 2013[4]) and ^{111}In-octreotide SPECT/CT (meta-analysis, section B3.6.2), compared with the composite reference standard of histopathology and/or conventional imaging and/or clinical follow-up of at least 1 year are shown in Table 3.

Table 3 Pooled summary estimates for ^{68}Ga-DOTATATE PET/CT and ^{68}Ga-DOTA-peptide PET/CT compared to ^{111}In-octreotide SPECT/CT, against the composite reference standard

Accuracy	^{68}Ga-DOTATATE PET/CT	^{68}Ga-DOTA-peptide PET/CT	^{111}In-octreotide SPECT/CT
Pooled sensitivity, %	91% (95%CI 81, 96) range 79–100%	93% (95%CI 91, 94) range 70–100%	80% (95%CI 77, 84) range 52–96%)
Pooled specificity, %	91% (95%CI 79. 96) range 86–100%	96% (95%CI 95, 98) range 67–100%	94% (95%CI 89, 100) range 89–100%)
PPV, %	35%: 84.5% 59%: 93.6% 76%: 97.0%	35%: 92.6% 59%: 97.1% 76%: 98.7%	35%: 87.8% 59%: 95.1% 76%: 97.7%
NPV, %	35%: 94.9% 59%: 87.5% 76%: 76.2%	35%: 96.2% 59%: 90.1% 76%: 81.2%	35%: 89.7% 59%: 76.6% 76%: 59.8%

^{68}Ga = ^{68}Gallium; CI = confidence interval; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; NPV = negative predictive value; PET = positron emission tomography PPV = positive predictive value

^{68}Ga-DOTATATE PET/CT and ^{68}Ga-DOTA-peptide PET/CT were more sensitive than ^{111}In-octreotide SPECT/CT with respect to the reference standard (91% and 93% versus 80%), but the specificity of the tests was similar (91% and 96% versus 94%). The positive predictive value (PPV) and negative predictive value (NPV) of the tests were calculated assuming that the proportion of patients tested in Australia who are diagnosed with a GEP NET ranges from 35% to 76% of those tested, with a median of 59%.

[3] Deppen, SA, Blume, J, Bobbey, AJ, Shah, C, Graham, MM, Lee, P, Delbeke, D & Walker, RC 2016b, '68Ga-DOTATATE Compared with ^{111}In-DTPA-Octreotide and Conventional Imaging for Pulmonary and Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis', J Nucl Med, vol. 57, no. 6, pp. 872-878.

[4] Geijer, H & Breimer, LH 2013, 'Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis', European Journal of Nuclear Medicine and Molecular Imaging, vol. 40, no. 11, pp. 1770-1780.

With a prevalence of 59%, the PPV for ^{111}In-octreotide SPECT/CT was very similar to that for ^{68}Ga-DOTATATE PET/CT and ^{68}Ga-DOTA-peptide PET/CT (95.1% versus 93.6% and 97.1%), the NPV values varied by more than 10% (76.6% versus 87.5% and 90.1%). Thus, 23% of people who had a negative ^{111}In-octreotide SPECT/CT result would actually have a GEP NET compared with 10–12% of those scoring negative after ^{68}Ga-DOTA-peptide PET/CT. Thus, approximately twice as many people with a negative result would actually have disease after ^{111}In-octreotide SPECT/CT scanning compared with ^{68}Ga-DOTA-peptide PET/CT scanning. This is likely to be of clinical significance.

Therapeutic efficacy (change in management)

Barrio et al. (2017) concluded that management changes as a result of ^{68}Ga-DOTATATE PET/CT occurred in 44% of all patients. An updated meta-analysis found 38% of patients who had had a prior ^{111}In-octreotide SPECT/CT had a change in management after having a ^{68}Ga-DOTATATE PET/CT. Even though these data were non-comparative and no data were available to determine whether or not the initial management decisions would have differed in the absence of the ^{111}In-octreotide SPECT±CT, the results of the ^{111}In-octreotide SPECT±CT appeared to be of little value when determining a patient's management plan.

Only two patients (2/322; 0.6%) for whom ^{68}Ga-DOTATATE PET/CT may have resulted in a suboptimal treatment plan were identified from the six studies investigating a change in management after ^{68}Ga-DOTATATE PET/CT in patients who had a prior ^{111}In-octreotide SPECT±CT (Hofman et al. 2012; Srirajaskanthan et al. 2010).

Taken together, the non-comparative studies forming the evidence base for the therapeutic efficacy of ^{68}Ga-DOTA-peptide PET/CT found that a change in management was usually a direct consequence of the improved spatial resolution and clarity of the ^{68}Ga-DOTA-peptide PET/CT image compared with the ^{111}In-octreotide SPECT/CT image. There were four main scenarios that led to a potentially major impact on patient management from ^{68}Ga-DOTA-peptide PET/CT imaging:

1. Approximately half of histopathology-positive GEP NET patients who were falsely negative with ^{111}In-octreotide SPECT/CT could become eligible for somatostatin analogue (SSA) therapy or peptide receptor radionuclide therapy (PRRT) after ^{68}Ga-DOTA-peptide PET/CT imaging due to its better NPV compared to ^{111}In-octreotide SPECT/CT (section B4.6);
2. Histopathology-positive GEP NET patients who are SRS-negative with ^{68}Ga-DOTA-peptide PET/CT would most likely be directed away from PRRT and SSA therapy due to the lack of somatostatin receptors on the tumour cell surface;
3. Identification of the primary tumour site with ^{68}Ga-DOTA-peptide PET/CT imaging in patients in whom it is otherwise not detected could lead to surgical resection; and
4. Identification of more metastases with ^{68}Ga-DOTA-peptide PET/CT imaging may lead to patients receiving PRRT instead of, or in addition to, any planned surgical procedures.

Therapeutic effectiveness (health benefit from change in management)

The most common management decisions resulting from ^{68}Ga-DOTA-peptide scanning were referral for surgery, PRRT or SSA therapy.

As a whole, the non-comparative evidence base for the treatment effectiveness of surgery and PRRT supported the findings in the review by Bodei et al. (2014). This review included an indirect comparison of the 5-year survival rates for patients who had various treatments and found that surgery had better survival outcomes compared to other therapies (Figure 1). However, it should be noted that this category would include most patients with early stage disease who would generally be expected to live longer than those with advanced late-stage disease. As PRRT is used as an alternative to chemotherapy, the patients groups are likely to have similar disease characteristics. Bodei et al. (2014) reported that PRRT was an efficient and relatively safe treatment with patients surviving longer compared to chemotherapy (Figure 1). The non-comparative evidence base for the effectiveness of long-acting release (LAR) SSA therapy supported the findings by Saglam et al. (2015) who reported an estimated 5-year survival rate of 58% for therapy with LAR SSAs. This was included in Figure 1. The literature suggests that LAR-SSAs are used at all stages of disease and, as seen in Figure 1, the estimated 5-year survival rate for LAR SSA therapy was second only to surgical resection in improved survival outcomes (Figure 1).

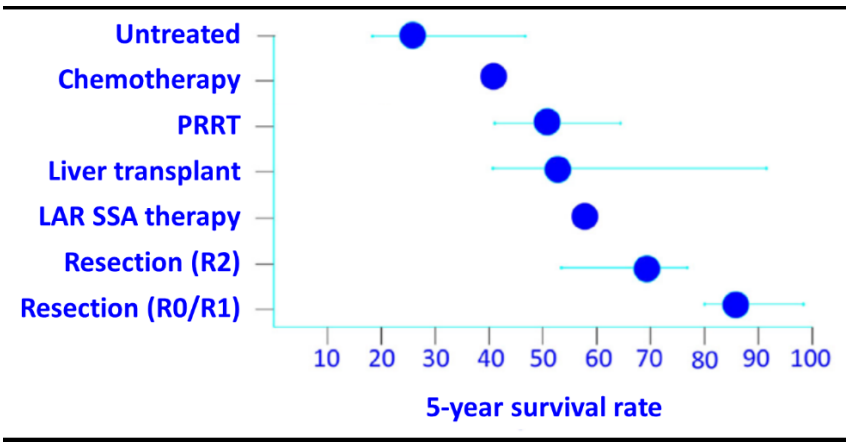

Figure 1 The 5-year survival rate of patients with NETs undergoing various tretaments

Source: adapted from Bodei et al. (2014); LAR SSA therapy from Saglam et al. (2015)

PRRT = peptide receptor radionuclide therapy; R0 = resection for cure or complete remission; R1 = microscopic residual tumour; R2 = macroscopic residual tumour; SSA = somatostatin analogue

Thus, treatment of GEP NETs with surgery, SSA therapy or PRRT appears to be more effective than no treatment or chemotherapy and relatively safe. However, randomised controlled trials are needed to determine if these conclusions are accurate.

Estimated Extent of Use and Financial Implications

An epidemiological approach (combined with additional data from the literature review and clinical expert advice) has been used to estimate the number of services and financial implications associated with the substitution of ^{68}Ga-DOTA-peptide PET for ^{111}In-octreotide SPECT in MBS item

61369. Table 4 summarises the financial implications to the MBS resulting from the proposed listing of ^{68}Ga-DOTA-peptide PET.

Table 4 Total costs to the MBS associated with ^{68}Ga-DOTA-peptide PET/CT service, 2017–18 to 2021–22

	2017–18	2018–19	2019–20	2020–21	2021–22
Number of services estimated to be MBS funded	445	566	691	819	951
Costs to MBS	**$438,794**	**$557,793**	**$680,469**	**$806,816**	**$936,765**

CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; ^{68}Ga = ^{68}GalliumPET = positron emission tomography; MBS = Medical Benefits Schedule;

CONSUMER IMPACT SUMMARY

Not applicable.

OTHER RELEVANT CONSIDERATIONS

None identified.

ACRONYMS AND ABBREVIATIONS

^{111}In	^{111}Indium
^{177}Lu	^{177}Lutetium
^{68}Ga	^{68}Gallium
^{90}Y	^{90}Yttrium
AANMS	Australasian Association of Nuclear Medicine Specialists
ABS	Australian Bureau of Statistics
ARTG	Australian Register of Therapeutic Goods
CI	confidence interval
CT	computed tomography
CUP	carcinoma with unknown primary
DOTA	1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid
DOTANOC	DOTA-Phe1-NaI3-octreotide
DOTATATE	DOTA–D-Phe1-Tyr3-Thr8-octreotate
DOTATOC	DOTA–D-Phe1-Tyr3-octreotide
DTPA	diethylene-triamino-penta-acetic acid
ESMO	European Society for Medical Oncology
FDG	fluorodeoxyglucose
GEP	gastroenteropancreatic
GMP	Good Manufacturing Practice
HIAA	hydroxyindoleacetic acid
HTA	health technology assessment
IHC	immunohistochemical
LAR	long-acting release
MBS	Medicare Benefits Schedule
MR	magnetic resonance

MSAC	Medical Services Advisory Committee
NET	neuroendocrine tumour
NPV	negative predictive value
PET	positron emission tomography
PFS	progression-free survival
PICO	population, intervention, comparator, outcomes
PPV	positive predictive value
PRRT	peptide receptor radionuclide therapy
SPECT	single-photon emission computed tomography
SR	systematic review
SROC	summary receiver operator characteristic
SRS	somatostatin receptor scintigraphy
SSA	somatostatin analogue
TGA	Therapeutic Goods Administration
TTP	time to progression
WHO	World Health Organization

SECTION A CONTEXT

This contracted mini assessment of ^{68}Gallium-1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid-peptide (^{68}Ga-DOTA-peptide) positron emission tomography (PET) / computed tomography (CT) scanning for the diagnosis of gastroenteropancreatic neuroendocrine tumours (GEP NETs) is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The proposal originated from the Australasian Association of Nuclear Medicine Specialists (AANMS) and was referred to MSAC for consideration by the MBS Review Taskforce for targeted assessment. Adelaide Health Technology Assessment has been commissioned by the Australian Government Department of Health to conduct a mini assessment of the management/health outcomes of the incremental diagnostic information obtained from ^{68}Ga-DOTA-peptide PET/CT scanning compared to ^{111}Indium (^{111}In)-labelled octreotide study (^{111}In-octreotide SPECT/CT) in patients with GEP NETs. This assessment has been undertaken in order to inform MSAC's decision-making regarding whether the proposed medical service should be publicly funded.

Appendix A provides a list of the people involved in the development of this assessment report, including clinical expertise.

The proposed use of ^{68}Ga-DOTA-peptide PET/CT scanning in Australian clinical practice was outlined in a draft PICO Confirmation that was prepared by the department in response to a request from MSAC Executive Teleconference on 24 November 2016.

A1 ITEMS IN THE AGREED PICO CONFIRMATION

This contracted mini assessment of MBS item number 61369 has primarily drawn upon material provided to the Department of Health by the applicant, as well as the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines published by Oberg et al. (Öberg et al. 2012).

This mini assessment addresses all of the PICO elements that were pre-specified in the draft PICO Confirmation submitted to the PICO Confirmation Advisory Sub-Committee of the MSAC. **PROPOSED MEDICAL SERVICE**

The proposed medical service is a combined PET/CT scan for functional (PET) and anatomical (CT) imaging of GEP NETs using a ^{68}Ga-DOTA-labelled somatostatin analogue. The current ESMO clinical

guidelines recommend that preoperative staging of GEP NETs should include somatostatin receptor scintigraphy (SRS) (Öberg et al. 2012). However, the guidelines also say that conventional SRS with ^{111}In-octreotide single-photon emission computed tomography (SPECT) with or without CT and/or a gamma camera can be replaced by SRS using ^{68}Ga-DOTA-peptide PET/CT for higher spatial resolution and quantification, resulting in higher sensitivity and specificity. ^{68}Ga-DOTA-peptide PET also has a faster acquisition time than conventional SRS (2 hours compared to 2 days with SPECT) and the patients are exposed to less radiation (see section B7.2). However, not all GEP NETs express a significant number of somatostatin receptors; in the later stages of disease, the tumour characteristics change from being well differentiated to being poorly differentiated with greatly increased metabolic activity and reduced levels of somatostatin receptor expression. Therefore, anatomical imaging (e.g. CT) should always be done in conjunction with ^{68}Ga-DOTA-peptide PET functional imaging (Öberg et al. 2012).

THE RADIOPHARMACEUTICAL ^{68}GA-DOTA-PEPTIDE

Three different DOTA-peptides—DOTA–D-Phe^{1}-Tyr^{3}-Thr^{8}-octreotate (DOTATATE), DOTA–D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC), and DOTA-Phe^{1}-Nal^{3}-octreotide (DOTANOC)—are currently used in conjunction with ^{68}Ga for PET/CT imaging of GEP NETs. Similar to ^{111}In-octreotide, these peptides are also derived from octreotide, a somatostatin octapeptide that bind to the somatostatin receptor.

In Australia, the DOTATATE peptide is coupled to ^{68}Ga. This peptide is supplied by Auspep, which is licensed by the TGA to manufacture active pharmaceutical ingredients (licence MI-07122005-LI-001046-11).

The ^{68}Ga-DOTA-peptide is not listed on the Australian Register of Therapeutic Goods (ARTG), as it is reconstituted from its components. The radioactive isotope is eluted from a Good Manufacturing Practice (GMP)-compliant ^{68}Ga generator. ^{68}Ga is then coupled with the non-radioactive (or cold) DOTA-peptide. This 'radiolabelling' process is routine, and is done on a daily basis in most Australian nuclear medicine departments for the preparation of commonly used radiopharmaceuticals. Examples include: Tc-99m MDP (bone scans), Tc-99m MAA (perfusion lung scans), Tc-99m DTPA (renal scans) and Tc-99m sestamibi (cardiac perfusion scans and parathyroid scans).

THE USE OF ^{68}GA FOR PET/CT SCANNING FOR DIAGNOSIS OF GEP NETS IN AUSTRALIA

While several ^{68}Ga generators are available commercially, none are currently registered in Australia. The TGA has yet to decide whether radiopharmaceutical generators will be fully exempt from regulation in Australia. **The issue of TGA registration is out of scope for the purpose of this assessment and is an issue that will be progressed in parallel with this assessment. When MSAC considers this assessment the Department will separately provide the committee with an update on the TGA status of the Ga-68 generators.**

AANMS accepts that public funding should only be provided when the ^{68}Ga generator used is GMP compliant but does not consider registration by a respected overseas regulator mandatory given that these generators have been used for many years both locally and internationally and, as a result, the safety profile is well established.

In Australia, ^{68}Ga-DOTATATE PET scanning has been performed in lieu of ^{111}In-octreotide SPECT for several years in a number of public hospitals (under the public hospital exemption), so there is local experience and expertise with its use at several hospitals. AANMS is requesting that public funding should be provided for GMP compliant ^{68}Ga generators.

A3 PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 5. This will replace the existing MBS item number 61369.

Table 5 Proposed replacement for MBS item number 61369

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS item number 61369 (replacement) Whole body 68Ga-DOTA-peptide PET scan where: (a) there is a suspected gastro-entero-pancreatic endocrine tumour, based on biochemical evidence, with negative or equivocal conventional imaging; or (b) a surgically amenable gastro-entero-pancreatic endocrine tumour has been identified based on conventional techniques, in order to exclude additional disease sites **Fee:** $ 953.00 **Benefit:** 75% = $714.75, 85% = $872.80

For a patient undergoing a ^{68}Ga-DOTA-peptide PET/CT scan, the PET procedure is very similar to a fluorodeoxyglucose (FDG) PET scan (MBS item number 61523). Following injection of the radiopharmaceutical, there is an uptake period of 45-60 minutes, after which the patient undergoes a scan on a PET/CT scanner. The acquisition time of the scan as well as the processing time for the technologists is comparable to a FDG PET scan, as is the reporting time for the reporting nuclear medicine specialist.

The $953 fee is the same as the cost of FDG PET. However, as PET rebates have not increased for 10 years, a more realistic cost of a ^{68}Ga-DOTA-peptide PET scan (based on CPI and other cost increases) should now exceed $1,100. The CT scan undertaken at the same time is reimbursed separately under MBS item 61505 (Fee: $100.00 Benefit: 75% = $75.00 85% = $85.00).

Due to the short half-life of ^{68}Ga (68 minutes), the commercial sale of individual patient doses of the radiopharmaceutical ^{68}Ga-DOTA-peptide will not be feasible in nearly all circumstances. As a result, nuclear medicine facilities offering this service will need to have a ^{68}Ga generator on site, a synthesis

module to perform the labelling and quality control, as well as consumables (including chemicals, cartridges and the DOTA-peptide).

A4 PROPOSED POPULATION

GEP NETs are a heterogeneous group of tumours arising from the diffuse endocrine system of the gastro-intestinal tract or pancreatic islet cells. Most commonly, the primary lesion is located in the gastric mucosa, small or large intestine, rectum or pancreas. While the majority of GEP NETs are sporadic, they can also occur in familiar syndromes such as multiple endocrine neoplasia type 1 syndrome, von-Hippel-Lindau disease, tuberosclerosis and neurofibromatosis type 1 (Kizilgul & Delibasi 2014). The defining characteristic of GEP NETs is the expression of somatostatin receptors, enabling the imaging of these tumours with radiolabelled somatostatin analogues.

The 2010 World Health Organization (WHO) classification splits GEP NETs into 3 categories with different malignant potential and histology: well-differentiated neoplasms or tumours that are usually low grade (G1, Ki67 <2%) as well as intermediate grade (G2, Ki67 3–20%), and poorly differentiated neoplasms or carcinomas that represent late stages of disease (G3, Ki-67 >20%) (Berardi et al. 2016a). The Ki67 protein is a cellular marker for proliferation. A higher percentage suggests a faster-growing, more aggressive tumour.

GEP NETs are characterized by their ability to synthesize, store, and secrete a variety of neuro-amines and peptides. They can be functioning (hormone secreting and symptomatic), or non-functioning. They are usually slow-growing malignancies that can be difficult to diagnose because of vague and diffuse clinical presentations. Hence, approximately 65% of patients with GEP NETs present with metastatic disease (Modlin et al. 2010).

Approximately two-thirds of GEP NETS are carcinoid tumours, originating in the enterochromaffin cells of the gut. Many do not cause symptoms even when they have metastasized. However, the metastases from some carcinoid GEP NETs (mostly mid-gut originating in the small intestine, appendix or proximal large bowel) may secrete serotonin and other vasoactive substances causing carcinoid syndrome. The symptoms include flushing, wheezing, diarrhoea, abdominal cramping, peripheral oedema, heart palpitations and eventual congestive heart disease. Congestive heart failure is due to chronic exposure to high levels of serotonin, which causes thickening of the heart valves (Oladejo 2009).

Approximately one-third of GEP NETS are pancreatic tumours, originating from the islet cells. The majority of pancreatic cancers are adenocarcinomas, which arise from the exocrine pancreas. Up to 60% of pancreatic NETs are non-functional. The functional tumours are often classified by the hormone most strongly secreted, such as: insulinomas, glucagonomas, gastrinomas and somatostatinomas (Kizilgul & Delibasi 2014).

The only population in scope for this assessment is the subgroup of patients with GEP NETs who are currently eligible for item 61369:

- Patients with a suspected GEP NET based on biochemical evidence with negative or equivocal conventional imaging;
- Patients with a surgically amenable GEP NET that has been identified based on conventional techniques, where SRS is performed in order to exclude additional disease sites.

Patients with other types of NETs that are not GEP in origin are out of the scope of this evaluation, noting that SRS is postulated to have value in a broader cohort of NET patients.

IDENTIFICATION OF PATIENTS ELIGIBLE FOR SRS - PRIOR TESTS REQUIRED TO DIAGNOSE GEP NET

Patients with clinical symptoms suggestive of neuroendocrine GEP NET are usually referred to a tertiary specialist centre with knowledge of these diseases. Histological diagnosis is usually obtained by surgical or endoscopic biopsies or ultrasonography guided liver biopsies (Öberg et al. 2012).

Macroscopic, microscopic and immunohistochemical (IHC) findings are required to support the diagnosis, classification, staging and grading of GEP NETs. IHC for Ki67 is required to grade the tumour according to the WHO classification (G1-3, see above). Additionally, IHC staining for chromogranin A and synaptophysin is useful to confirm the diagnosis because all GEP NETs are immunoreactive to these pan-neuroendocrine markers (Öberg et al. 2012). A survey among French pathologists found that WHO classification was available or feasible in 94.1% of GEP NETs and the Ki-67 index was measured in 80.7% of cases. For confirmation of the neuroendocrine nature of the tumour, chromogranin A and synaptophysin were tested in 93.5% and 79.9% of GEP NET cases, respectively (Scoazec et al. 2016).

Specific IHC staining for hormones in pancreatic NETs, such as serotonin, gastrin, insulin and glucagon, can be applied to confirm the source of clinical symptoms, but the detection of a hormone by IHC alone is not proof of functionality of a NET. The chromogranin A blood test is a useful marker to help detect and monitor the activity of carcinoid tumours in general. For patients with a carcinoid tumour of the small intestinal, a urine test for 5-hydroxy-indole-acetic acid (a breakdown product of serotonin) is important, especially to monitor serotonin release associated with liver metastases and/or carcinoid syndrome (Scoazec et al. 2016).

Endoscopy (gastroscopy, endoscopic ultrasonography, colonoscopy, capsule endoscopy) can often provide additional information along with anatomical imaging (e.g. CT) to evaluate the extent of the tumour spread (staging).

THE INCIDENCE AND PREVALENCE OF GEP NETS

The annual incidence of NETs varies worldwide. It was estimated to be 5.25/100,000 people in the USA in 2004 (Öberg et al. 2012), and 5.86/100,000 people in Canada in 2009 (Patel et al. 2016). In Australia the estimated incidence was lower, at 3.3/100,000 people in 2006 (Luke et al. 2010). The

estimated prevalence in the USA was 35/100,000 people in 2004 (Öberg et al. 2012). The most common primary site for NET was GEP (60% of all NETs), with patients generally diagnosed in their late 50s or early 60s, but those with familial NET syndromes may have a clinical onset of disease 15–20 years earlier than patients with sporadic disease (Yao et al. 2008).

NETs comprised 0.6% of all invasive cancers recorded on the South Australian Cancer Registry from 2000–2006 (Luke et al. 2010). The annual age-standardised incidence per 100,000 people increased by 86.8% from 1.74 between 1980 and 1989 to 3.25 between 2000 and 2006. The NETs originated in the lung in 25.9% of cases, 54.1% were GEP NETs, and 20% had an unknown or other origin (Luke et al. 2010). The most common primary sites for GEP NETs were the small intestine (38.1%), large bowel (21.2%), appendix (17.6%), pancreas (12.0%), and stomach (6.8%).

The 5-year survival rate for patients diagnosed with GEP NETs in South Australia between 1980 and 2006 was higher for those whose tumour originated in the appendix (93.8%), rectum (85.9%) or small intestine (74.6%) compared with the pancreas (42.4%), colon excluding appendix (64.6%) or stomach (66.4%). An increase in survival was seen in later calendar years, with the 5-year survival rate for patients diagnosed with NETs in South Australia between 2000 and 2006 being 73.4% ± 3.0% for all NETs, 84.8% ± 0.1% for stomach, 80.9% ± 8.8% for colon and 100% for appendix NETs (Luke et al. 2010).

The 5-year survival rate for patients with pancreatic NETs is estimated to be 60–100% for localized disease, 40% for regional, 25% for metastatic and 80% for all stages.

A5 COMPARATOR DETAILS

In Australia, the only approved diagnostic radiopharmaceutical for SRS is OctreoScan® (^{111}In-octreotide), which was listed on the ARTG in 1996 (number 55928). It is covered by MBS item 61369, with a schedule fee of $2015.75 (Table 6). This item was included in the MBS in the early 2000s following a recommendation by MSAC in 1999 (Application 1003). Item 61369 is usually performed using SPECT with a gamma camera. If a concomitant CT is performed, it is reimbursed under MBS item 61505 (Fee: $100.00 Benefit: 75% = $75.00 85% = $85.00).

Table 6 MBS item descriptor for the comparator

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS item number 61369
INDIUM-LABELLED OCTREOTIDE STUDY - including single photon emission tomography when undertaken, where:
(a) there is a suspected gastro-entero-pancreatic endocrine tumour, based on biochemical evidence, with negative or equivocal conventional imaging; or
(b) a surgically amenable gastro-entero-pancreatic endocrine tumour has been identified based on conventional techniques, in order to exclude additional disease sites. (R)
Fee: $2,015.75 **Benefit:** 75% = $1,511.85 85% = $1,935.55

Octreotide is a long-acting somatostatin analogue and has been an important agent in the initial evaluation and management of NETs for nearly 30 years. Octreotide is conjugated with diethylene-triamine-pentaacetic acid (DTPA) and labelled with ^{111}In to form ^{111}In-DTPA-D-Phe^{1}-octreotide, also known as ^{111}In-pentetreotide (^{111}In-octreotide). The radiotracer is injected intravenously, followed by imaging at several time-points over the next 1-2 days, usually using SPECT to obtain both two-dimensional 'planar' imaging and three-dimensional cross-sectional images (Rufini, Calcagni & Baum 2006). The results from SRS are easiest to interpret when hybrid SPECT/CT scanners are used to provide both functional (SPECT) and anatomical (CT) information. SRS provides information on the primary tumour location and the extent of disease, as well as predicting the response to therapy with unlabelled or labelled somatostatin analogues (Rufini, Calcagni & Baum 2006).

The use of item 61369 in Australia has decreased in recent years (Table 7) as treating clinicians and nuclear medicine specialists increasingly use ^{68}Ga-DOTA-peptide PET/CT for SRS. Additionally, the increasing costs of performing SRS with ^{111}In-octreotide SPECT compared with the MBS fee makes the test less economical to perform.

Table 7 MBS utilisation for item 61369 2010/11 through to 2015/16

Financial year	**2010/11**	**2011/12**	**2012/13**	**2013/14**	**2014/15**	**2015/16**
Total number of services for item 61369	693	484	419	236	146	106

A6 CLINICAL MANAGEMENT ALGORITHM(S)

The current and proposed diagnostic pathways are shown in Figure 2. Currently, functional SRS assessment of the suspected GEP NET using ^{111}In-octreotide SPECT/CT imaging is funded on the MBS (shown in green). In the proposed pathway ^{111}In-octreotide SPECT/CT imaging is replaced by ^{68}Ga-DOTA-peptide PET/CT imaging (shown in red) for functional assessment.

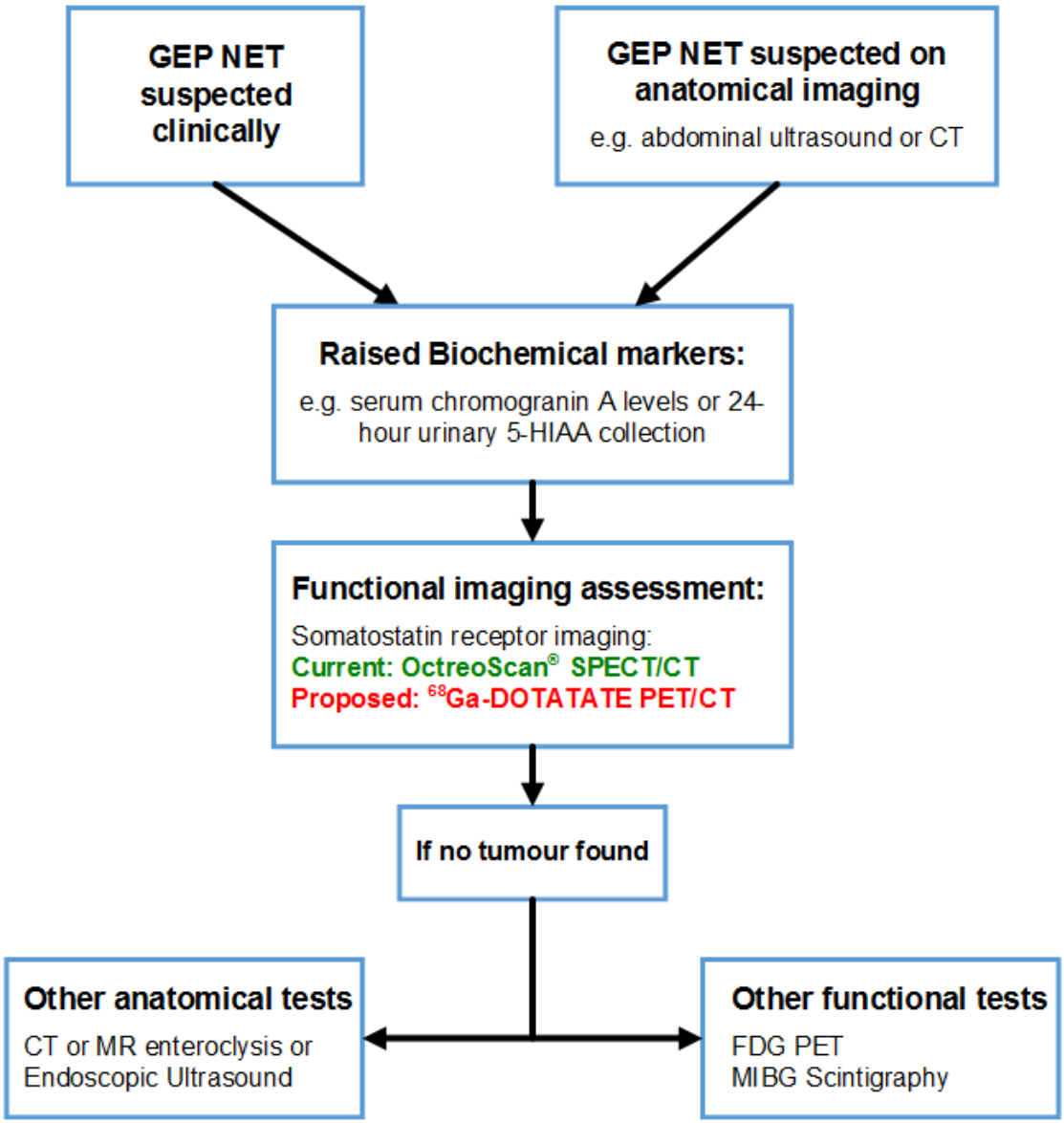

Figure 2 Clinical management algorithm for the diagnosis of GEP NETs

Source: Neuroendocrine Tumours Working Party (2013).

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; FDG = fluorodeoxyglucose; GEP = gastroenteropancreatic; HIAA = hydroxyindoleacetic acid; NET = neuroendocrine tumour; MIBG = ^{123}Iodine-meta-iodobenzylguanidine; MR = magnetic resonance; PET = positron emission tomography; SPECT = single-photon emission computed tomography

A7 Key Differences in the Proposed Medical Service and the Main Comparator

The key differences between the two tests are:

- The time taken to complete the test is 90 minutes to 2 hours for ^{68}Ga-DOTATATE PET/CT compared with 2 days for ^{111}In-octreotide SPECT/CT.
- The radiation dose from ^{68}Ga-DOTATATE PET (2–3 mSv, 28–41 MBq) is less than that received with ^{111}In-octreotide SPECT (8–16 mSv, ^{111}–222 MBq).
- The cost of ^{111}In-octreotide SPECT/CT is much higher than ^{68}Ga-DOTATATE PET/CT.

The US Library of Medicine website[5] provides information on the use and safety of both (^{111}In-octreotide and ^{68}Ga-DOTATATE (marketed as NETSPOT).

The indication for ^{111}In-octreotide is as an agent for the scintigraphic localization of primary and metastatic NETs bearing somatostatin receptors. ^{68}Ga-DOTATATE is indicated by the US Food and Drug Administration for use with PET for localization of somatostatin receptor positive NETs in adult and paediatric patients. There are no contra-indications for either radiopharmaceutical.

The safety of ^{68}Ga-DOTATATE was evaluated in three single centre studies (Deppen et al. 2016a; Haug et al. 2014; Haug et al. 2012) and in a survey of the scientific literature. No serious adverse reactions were identified. As both ^{68}Ga-DOTATATE and ^{111}In-octreotide are derivatives of octreotide, they are likely to have similar adverse reactions and precautions.

The adverse reactions and precautions listed in the TGA product information[6] for ^{111}In-octreotide are:

- Octreotide therapy can produce severe hypoglycaemia in patients with insulinomas and in diabetic patients receiving high doses of insulin. An intravenous solution containing glucose should be administered just before and during administration of ^{111}In-octreotide.
- Since ^{111}In-octreotide is eliminated primarily by renal excretion, use in patients with impaired renal function should be carefully considered.
- As with any other radioactive material, appropriate shielding should be used to avoid unnecessary radiation exposure to the patient, occupational workers, and other persons.
- Evidence of mutagenicity was not found when ^{111}In-octreotide was evaluated in an in vivo mouse micronucleus assay.
- Safety and effectiveness in pregnant women, lactating mothers and paediatric patients have not been established.

A8 CLINICAL CLAIM

A claim has been made that introducing ^{68}Ga-DOTA-peptide PET/CT scanning in lieu of ^{111}In-octreotide SPECT/CT will reduce the amount of repeat testing that supposedly occurs with ^{111}In-octreotide SPECT. ^{68}Ga-DOTA-peptide PET/CT scanning is also claimed to have superior safety over the comparator in terms of faster acquisition time and lower radiation exposure.

[5] Available from URL: https://dailymed.nlm.nih.gov/dailymed/index.cfm [accessed 20 December 2016].

[6] Available from URL: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&k=O&r=https://www.ebs.tga.gov.au/ [accessed 20 December 2016].

A9 SUMMARY OF THE PICO

The guiding framework of a PICO Confirmation is recommended by MSAC for each assessment. The PICO Confirmation describes current clinical practice and reflects the likely future practice with the proposed medical service. The PICO that were pre-specified in the PICO confirmation are presented in Table 8.

Table 8 Criteria for identifying and selecting studies to determine the safety and direct effectiveness of ^{68}Ga-DOTA-peptide PET/CT scanning in patients with GEP NETs

Selection criteria	Description
Population	Patients with GEP NETs, specifically those patients with this tumour currently eligible to receive item 61369.
Prior tests	Conventional imaging, histopathology and various sophisticated biomarkers in a specialised tertiary setting
Intervention	^{68}Ga-DOTA-peptide PET±CT scanning (direct substitution to comparator)
Comparator	Indium labelled octreotide study (^{111}In-octreotide SPECT±CT) currently covered by MBS items 61369 (SPECT) and 61505 (CT)
Outcomes	• Relative Safety • Relative Diagnostic accuracy (sensitivity/specificity) • Impact on clinical management including net change on clinical management arising from differential accuracy • Impact on clinical utility through a linked evidence approach (in the absence of direct evidence) as per Investigative Guidelines • Health resource impacts and cost/consequence analysis
Questions for direct evidence	What is the safety and effectiveness of ^{68}Ga-DOTA-peptide PET/CT scanning compared with ^{111}In-octreotide in patients with GEP NETs?
Questions for linked evidence	What is the diagnostic accuracy of ^{68}Ga-DOTA-peptide PET/CT scanning compared with ^{111}In-octreotide SPECT±CT in patients with GEP NETs? What is the clinical validity of ^{68}Ga-DOTA-peptide PET/CT scanning compared with ^{111}In-octreotide SPECT±CT in patients with GEP NETs? Is there a change in management from ^{68}Ga-DOTA-peptide PET/CT scanning in patients with GEP NETs compared with ^{111}In-octreotide SPECT±CT? Does the change in management due to ^{68}Ga-DOTA-peptide PET/CT scanning improve patient outcomes?

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; GEP = gastroenteropancreatic; NET = neuroendocrine tumour; PET = positron emission tomography; SPECT = single-photon emission computed tomography

A10 CONSUMER IMPACT STATEMENT

Not applicable.

SECTION B CLINICAL EVALUATION

This mini assessment evaluates the management/health outcomes of incremental diagnostic information obtained from ^{68}Ga-DOTA-peptide PET/CT scanning compared to ^{111}In-octreotide SPECT/CT in patients with GEP NETs.

Determination of the clinical effectiveness of an investigative medical service requires either:

- evidence of the effectiveness of ^{68}Ga-DOTA-peptide PET/CT scanning from high-quality comparative studies evaluating the use of ^{68}Ga-DOTA-peptide PET/CT scanning and subsequent treatment compared to ^{111}In-octreotide SPECT/CT and treatment (direct evidence). Randomised controlled trials provide the highest quality evidence for this comparison. Or, if this is not available:

- evidence of the treatment effectiveness from high-quality comparative studies evaluating the treatment for GEP NET, linked with applicable and high-quality evidence of the accuracy of ^{68}Ga-DOTA-peptide PET/CT scanning compared to ^{111}In-octreotide SPECT/CT for the diagnosis of GEP NET. This is called 'linked evidence'.

The Department of Health stipulated that a systematic literature review was not required for this mini assessment. The evidence base consisted of material published by the ESMO, primarily Oberg et al. (2012), The 'Report on the Use of Positron Emission Tomography (PET) and Radiopharmaceuticals' (August 2012) by Austin Health[7], as well as material provided to the Department of Health by AANMS.

To supplement the limited evidence base provided, a quick search of the literature in the PubMed database was undertaken to identify recent systematic reviews (SRs) and studies reporting on the use of ^{68}Ga-DOTA-peptide PET/CT in the diagnosis and management of patients with or suspected of having GEP NETs.

B1 DIRECT EVIDENCE

No studies were provided or identified in the quick literature search that reported on the safety or effectiveness of ^{68}Ga-DOTA-peptide PET/CT scanning directly compared with ^{111}In-octreotide SPECT/CT in patients with GEP NETs.

[7] The Commonwealth Government Department of Health and Ageing contracted Austin Health to undertake a review of the Broader Use of Positron Emission Tomography (PET) and Radiopharmaceuticals in 2012.

B2 LINKED EVIDENCE APPROACH

B2.1 BASIS FOR LINKED EVIDENCE

As there was no direct evidence identified, a linked evidence approach was undertaken.

B2.2 STEPS FOR LINKED ANALYSIS

To construct a linked evidence analysis, different evidence requirements are required.

- Consideration of the diagnostic performance and clinical validity (where relevant) of the investigative medical service (sections B3 and B4);
- Consideration of the clinical utility of the investigative medical service in terms of impact of positive versus negative test results on patient management, the contribution and clinical importance of false negatives versus false positives and direct impact of each therapeutic model service option on health outcomes (section B5);
- Considerations of the impact of repeat testing (if appropriate) (section B6); and
- Consideration of the relative safety of performing the investigative service, both immediate safety issues of directly performing the test and 'flow on' safety issues that arise as a result of conducting the investigative service (section B7).

Conclusions linking these steps are made in section B8.

B3 DIAGNOSTIC PERFORMANCE

B3.1 REFERENCE STANDARD

Most guidelines, such as those from The Clinical Oncological Society of Australia (COSA 2008), ESMO (Öberg et al. 2012) and the Canadian evidence-based consensus recommendations (Singh et al. 2016), stipulate that histology of surgical or biopsy tissue is mandatory in all cases for the diagnosis of GEP NETs. The histopathology tests include:

- Routine haematoxylin and eosin-staining to identify the typical morphology of GEP NETs ;
- IHC for neuroendocrine markers, including synaptophysin and chromogranin A.
  Although GEP NETs are a heterogeneous in nature, they are all immune-reactive to neuroendocrine markers;
- IHC for the cell-cycle-dependent marker, Ki67 antigen, to determine the aggressiveness of the tumour. The Ki67 index serves as the basis for WHO grading of tumours (G1-3);
- Additional biochemical pathology tests verifying increased hormone levels may also be performed, especially in symptomatic patients.

Thus, the gold standard for the diagnosis of GEP NETs is histopathology.

However, the SRs that provide the evidence base for diagnostic accuracy all used a composite reference standard, which included the results from histopathology and/or conventional imaging and/or clinical follow-up of at least 1 year. Thus, this composite reference standard will be used for this mini-assessment.

B3.2 EVIDENCE BASE

The evidence base for this review was provided by the Department of Health and the applicant. A quick search of the PubMed database was conducted for recent publications to supplement the provided evidence when needed.

DIAGNOSTIC ACCURACY OF ^{68}GA-DOTA-PEPTIDE PET/CT COMPARED WITH THE COMPOSITE REFERENCE STANDARD

The 'Report on the Use of Positron Emission Tomography (PET) and Radiopharmaceuticals' (August 2012) by Austin Health[8] conducted a systematic search of the literature for original research papers, including SRs, using PubMed and Cochrane databases, and a search of websites of international health technology assessment (HTA) agencies for existing HTA reports. This report included a SR that

[8] The Commonwealth Government Department of Health and Ageing contracted Austin Health to undertake a review of the Broader Use of Positron Emission Tomography (PET) and Radiopharmaceuticals in 2012.

evaluated the diagnostic accuracy of ^{68}Ga-DOTA-peptide PET/CT compared with histology and/or morphological imaging (Treglia et al. 2012). The applicant provided an additional two SRs that compared the diagnostic accuracy of ^{68}Ga-DOTA-peptide PET/CT with the composite reference standard (Geijer & Breimer 2013; Mojtahedi et al. 2014).

A quick search of the PubMed database identified another 2 SRs that looked at diagnostic accuracy; both Deppen et al. (2016b) and Yang et al. (2014) compared ^{68}Ga-DOTA-peptide PET/CT with the composite reference standard.

DIAGNOSTIC ACCURACY OF ^{68}GA-DOTA-PEPTIDE PET/CT COMPARED WITH ^{111}IN-OCTREOTIDE SPECT±CT

The Report by Austin Health[9] and three of the SRs mentioned above provided a narrative review of the diagnostic accuracy of ^{68}Ga-DOTA-peptide PET/CT compared with ^{111}In-octreotide SPECT/CT using the composite reference standard (Deppen et al. 2016b; Geijer & Breimer 2013; Mojtahedi et al. 2014).

A quick search of the PubMed database identified a non-systematic review that compared the diagnostic accuracy of ^{111}In-octreotide SPECT±CT with the composite reference standard (Koopmans et al. 2009). An additional 9 studies were also identified that compared ^{111}In-octreotide SPECT/CT with the composite reference standard.

B3.3 RISK OF BIAS ASSESSMENT

The five SRs that reported on the diagnostic accuracy of ^{68}Ga-DOTA-peptide PET/CT compared with the composite reference standard and the non-SR comparing the diagnostic accuracy of ^{111}In-octreotide SPECT±CT with composite reference standard were evaluated using the AMSTAR checklist (Shea et al. 2007). A summary of the risk of bias for each SR is shown in Table 9.

[9] The Commonwealth Government Department of Health and Ageing contracted Austin Health to undertake a review of the Broader Use of Positron Emission Tomography (PET) and Radiopharmaceuticals in 2012.

Table 9 Quality appraisal and risk of bias for the SRs

Study	*A priori* protocol for PICO and research question	Quality appraisal of included studies	Number of studies included in the analysis	Quality of SR and risk of bias
Deppen et al. (2016b)	Yes	Quality appraisal using QUADAS Individual scores for each study	k=10	Good quality (7/11) Low risk of bias
Geijer and Breimer (2013)	No Update of Treglia et al. (2012)	Quality appraisal using QUADAS-2 Individual scores for each study	k=22	Good quality (7/11) Low risk of bias
Mojtahedi et al. (2014)	No	Not appraised	k=5	Poor quality (2/9) High risk of bias
Treglia et al. (2012)	No	Quality appraisal using QUADAS Overall result given	k=16	Moderate quality (6/11) Moderate risk of bias
Yang et al. (2014)	No	Quality appraisal using QUADAS Overall result given	k=10	Moderate quality (6/11) Moderate risk of bias
Koopmans et al. (2009)	Non-SR	Not appraised	k=14	Poor quality (1/10) High risk of bias

k = number of studies; PICO = population, intervention, comparator, outcomes; SR = systematic review

B3.4 CHARACTERISTICS OF THE EVIDENCE BASE

A summary of the extent of the database searches and the types and quality of the studies included in the evidence base of the SRs is provided in Table 34 in Appendix B.

The populations in all five SRs and the non-SR were slightly broader than the proposed PICO, which was limited to patients with GEP NETs. Three SRs included patients with thoracic NETS (Deppen et al. 2016b; Geijer & Breimer 2013; Treglia et al. 2012) and the other two studies included all NET patients (Mojtahedi et al. 2014; Yang et al. 2014). However, it should be noted that the majority of patients had GEP NETs. The non-SR by Koopmans et al. (2009) included subgroups of studies that enrolled NET patients with abdominal carcinoids and pancreatic islet cell carcinoma.

The reference standard used in all five SRs and the non-SR included histopathology, conventional anatomical imaging and/or clinical follow-up of at least 1 year.

B3.5 OUTCOME MEASURES AND ANALYSIS

Table 10 summarises the analysis methods used to determine the sensitivity and specificity of the indicated test compared with the reference standard for each of the included SRs.

Table 10 Outcomes reported by the SRs

Study	Test	Reference standard	Method of analysis
Deppen et al. (2016b)	^{68}Ga-DOTATATE PET/CT	Composite reference standard [a]	Meta-analysis (k=10) Narrative synthesis (k=3)
Geijer and Breimer (2013)	^{68}Ga-DOTA-peptide PET/CT	Composite reference standard [a]	Meta-analysis (k=22)
Mojtahedi et al. (2014)	^{68}Ga-DOTATATE PET/CT	Composite reference standard [a]	Narrative synthesis (k=3) Narrative synthesis (k=3)
Treglia et al. (2012)	^{68}Ga-DOTATATE PET/CT	Composite reference standard [a]	Meta-analysis (k=16) SROC analysis (k=6)
Yang et al. (2014)	^{68}Ga-DOTATOC PET/CT ^{68}Ga-DOTATATE PET/CT	Composite reference standard [a]	SROC and meta-analysis (k=6) SROC and meta-analysis (k=4)
Koopmans et al. (2009)	^{111}In-octreotide SPECT±CT	Composite reference standard [a]	Forest plot

[a] Composite reference standard = histopathology and/or conventional imaging and/or clinical follow-up of at least 1 year

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; DOTATOC = DOTA–D-Phe1-Tyr3-octreotide; k = number of studies; PET = positron emission tomography; SPECT = single-photon emission computed tomography; SR = systematic review; SROC = summary receiver operator characteristic

To assess the diagnostic accuracy of the proposed test, each of the SRs only included studies if they provided data that could be extracted into a classic 2 x 2 table (Table 11), in which the results of the index test or the comparator were cross-classified against the results of the reference standard (Armitage, Berry & Matthews 2002; Deeks 2001), and Bayes' Theorem was applied.

Table 11 Diagnostic accuracy data extraction

		Reference standard		
		Disease +	*Disease –*	
Index test	*Test +*	true positive	false positive	Total test positive
Or comparator	*Test –*	false negative	true negative	Total test negative
		Total with disease	Total without disease	

Primary measures

Test sensitivity was calculated as the proportion of people with a confirmed NET diagnosis who were identified by either ^{68}Ga-DOTA-peptide PET/CT or ^{111}In-octreotide SPECT±CT:

Sensitivity (true positive rate) = number with true positive result / total with GEP NETs

Test specificity was calculated as the proportion of people with no NETs distinguishable by the composite reference standard who had no tumours detected by either ^{68}Ga-DOTA-peptide PET/CT or ^{111}In-octreotide SPECT±CT:

Specificity (true negative rate) = number with true negative result / total without GEP NETs

The 95%CI was calculated by the exact binomial method.

Summary measures

Diagnostic test accuracy meta-analysis was undertaken to assess the accuracy of ^{111}In-octreotide SPECT±CT compared with the composite reference standard in the diagnosis of GEP NETs using Stata version 14.1 (StataCorp 2015). Only studies that provided raw (2 × 2) data were included. Forest plots were generated using the 'midas' command in Stata, which requires a minimum of 4 studies for analysis and calculates summary operating sensitivity and specificity (with confidence and prediction contours in summary receiver operator characteristic (SROC) space). Heterogeneity was calculated using the formula I^2 = 100% x (Q – df)/Q, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom (Higgins et al. 2003). Summary estimates for sensitivity and specificity were also calculated.

B3.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE?

Summary – What is the diagnostic accuracy of ^{68}Ga-DOTA-peptide PET/CT scanning compared with ^{111}In-octreotide SPECT±CT in patients with GEP NETs?

Diagnostic accuracy of ^{68}Ga-DOTA-peptide PET/CT compared with the composite reference standard

Two good quality SRs conducted meta-analyses to determine the accuracy of ^{68}Ga-DOTA-peptide PET/CT compared with the composite reference standard. The SR by Geijer and Breimer (2013) included 22 studies with a pooled sensitivity and specificity of 93% (95%CI 91, 94; range 70–100%) and 96% (95%CI 95, 98; range 67–100%), respectively. The SR by Deppen et al. (2016b) included 10 studies comparing ^{68}Ga-DOTATATE PET/CT with the composite reference standard. The pooled sensitivity and specificity were 91% (95%CI 81, 96; range 79–100%) and 91% (95%CI 79. 96, range 86–100%), respectively. The results for ^{68}Ga-DOTA-peptide PET/CT and ^{68}Ga-DOTATATE PET/CT compared with the composite reference standard were similar.

Diagnostic accuracy of ^{111}In-octreotide SPECT±CT compared with the composite reference standard

Meta-analysis of 11 studies that compared ^{111}In-octreotide SPECT with the composite reference standard estimated the pooled sensitivity and specificity to be 84% (95%CI 80, 87; range 54–96%) and 75% (95%CI 59, 91; range 60–84%), respectively. Meta-analysis of 9 studies that compared ^{111}In-octreotide SPECT/CT with the composite reference standard estimated the pooled sensitivity and specificity to be 80% (95%CI 77, 84; range 52–96%) and 94% (95%CI 89, 100; range 89–100%), respectively. The addition of CT to ^{111}In-octreotide SPECT had little effect on the pooled estimate for sensitivity (84% versus 80%) but markedly improved the specificity (75% versus 94%).

^{68}Ga-DOTATATE PET/CT compared with ^{111}In-octreotide SPECT/CT using the composite reference standard

When the pooled estimates for ^{68}Ga-DOTATATE PET/CT (relevant to Australian clinical practice) and ^{111}In-octreotide SPECT/CT were compared, ^{68}Ga-DOTATATE PET/CT was more sensitive than ^{111}In-octreotide SPECT/CT (91% versus 80%) with respect to the reference standard but the specificity of the tests were similar (91% versus 94%).

B3.6.1 DIAGNOSTIC ACCURACY OF ^{68}GA-DOTA-PEPTIDE PET/CT COMPARED WITH THE COMPOSITE REFERENCE STANDARD

Five SRs were identified that investigated the diagnostic accuracy of ^{68}Ga-DOTA-peptide PET/CT compared with the composite reference standard (Table 12). The pooled sensitivities calculated in the SRs ranged from 91% to 96% and the pooled specificities ranged from 85% to 100%. However, after evaluation of the quality and the applicability of the reported outcomes in the five SRs, only the results from the two good quality SRs with a low risk of bias have been discussed further.

Table 12 Overview of the SRs

Study	SRS test	Reference standard	Pooled sensitivity (95%CI) Pooled specificity (95%CI)	Quality and applicability of results
Deppen et al. (2016b)	^{68}Ga-DOTATATE PET/CT	Composite reference standard [a]	91% (81, 96), I^2=62.4%, k=10 91% (79, 96), I^2=0%, k=5	Good quality Relevant to the Australian context
Geijer and Breimer (2013)	^{68}Ga-DOTA-peptide PET/CT	Composite reference standard [a]	93% (91, 94), I^2=72.2%, k=22 96% (95, 98), I^2=68.3%, k=11	Good quality An update of the SR by Treglia et al. (2012) with relevant outcomes
Mojtahedi et al. (2014)	^{68}Ga-DOTATATE PET/CT	Composite reference standard [a]	Not reported	Poor quality Narrative synthesis of results
Treglia et al. (2012)	^{68}Ga-DOTATATE PET/CT	Composite reference standard [a]	93% (91, 95), I^2=66.0%, k=16 91% (82, 97), I^2=61.6%, k=6	Moderate quality Superseded by Geijer and Breimer (2013)
Yang et al. (2014)	^{68}Ga-DOTATOC PET/CT ^{68}Ga-DOTATATE PET/CT	Composite reference standard [a]	DOTATOC: 93% (89, 96), I^2=80.9%, k=6 85% (74, 93), I^2=56.8%, k=6 DOTATATE: 96% (91, 99), I^2=60.5%, k=4 100% (82, 100), I^2=0.0%, k=4	Moderate quality Limited number of included studies Partly superseded by Deppen et al. (2016b)

[a] Composite reference standard = histopathology and/or conventional imaging and/or clinical follow-up of at least 1 year
^{68}Ga = ^{68}Gallium; CI = confidence interval; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; DOTATOC = DOTA–D-Phe1-Tyr3-octreotide; k = number of studies; PET = positron emission tomography; SR = systematic review

The SR by Geijer and Breimer (2013) included 22 studies that compared ^{68}Ga-DOTA-peptide PET/CT with the composite reference standard (Table 34 in Appendix B). The sensitivity for the individual studies ranged from 70% to 100%, with a pooled estimate of 93% (95%CI 91, 94). The pooled specificity was 96% (95%CI 95, 98; range 67–100%). There was substantial heterogeneity between studies (I^2 = 72% and 68% for sensitivity and specificity, respectively). The authors found that there was unlikely to be any publication bias. The area under the SROC curve, which describes the relationship between the 'true positive fraction' (sensitivity: benefits) and the 'false positive fraction' (1– specificity: costs) was 0.98 (95%CI 0.95, 1.0), indicating a high level of test performance.

The SR by Deppen et al. (2016b) included 10 studies comparing ^{68}Ga-DOTATATE PET/CT with the composite reference standard. The pooled sensitivity was 91% (95%CI 81, 96) and ranged from 79% to 100% for the individual studies. There was substantial heterogeneity between studies (I^2 = 62%) but there was no evidence for publication bias (p = 0.3 for the Deek's funnel plot asymmetry test). The pooled specificity was 91% (95%CI 79. 96, range 86–100%), with no heterogeneity between studies.

There was little difference in the pooled sensitivity values for ^{68}Ga-DOTATATE PET/CT and ^{68}Ga-DOTA-peptide PET/CT, compared with the composite reference standard (91% versus 93%) but the pooled specificity was slightly better for ^{68}Ga-DOTA-peptide PET/CT than for ^{68}Ga-DOTATATE PET/CT (96% versus 91%). The results for comparison of ^{68}Ga-DOTATATE PET/CT with the composite

reference standard is more relevant in the Australian clinical context as only DOTATATE is currently available for use in Australia.

It should be noted that the patients included in both of these SRs were not limited to those with proven or suspected GEP NETs. Although the majority of the patients had GEP NETs, a significant proportion had thoracic NETs, NETs of unknown origin and other NETs (Table 34 in Appendix B). Although the population is broader than that specified in the PICO, it is likely that this had little effect on the diagnostic accuracy of ^{68}Ga-DOTA-peptide PET/CT compared with the composite reference standard.

B3.6.2 DIAGNOSTIC ACCURACY OF ^{111}IN-OCTREOTIDE SPECT±CT COMPARED WITH THE COMPOSITE REFERENCE STANDARD

^{111}In-octreotide SPECT has been successfully used for over 2 decades, and it has been reported that the sensitivity of the test is increased when the functional SPECT is combined with an anatomical CT (Deroose et al. 2016). However, no meta-analyses comparing the diagnostic accuracy of this test with the composite reference standard, or any other test, were identified during a quick literature search of PubMed. One non-systematic review by Koopmans et al. (2009) did present a forest plot showing the sensitivity of the test compared with the composite reference standard for subgroups of patients with different NETs, but did not provide a pooled estimate. Eleven studies that compared ^{111}In-octreotide SPECT with the composite reference standard in patients with GEP NETs, sourced form Koopmans et al. (2009), and 9 studies that compared ^{111}In-octreotide SPECT/CT with the composite reference standard that were identified in a quick search of PubMed, were meta-analysed (Figure 7 and Figure 8, Appendix C). The pooled estimates are summarised in Table 13.

Table 13 Pooled sensitivity and specificity of ^{111}In-octreotide SPECT±CT compared with the composite reference standard

SRS test	Pooled sensitivity (95%CI)	Pooled specificity (95%CI)
^{111}In-octreotide SPECT	84% (80, 87), range 54–96%, I^2=72.3%, k=11	75% (59, 91), range 60–84%, I^2=0%, k=3
^{111}In-octreotide SPECT/CT	80% (77, 84), range 52–96%, I^2=85.4%, k=9	94% (89, 100), range 89–100%, I^2=0%, k=6

^{111}In = ^{111}Indium; CI = confidence interval; CT = computed tomography; k = number of studies; SPECT = single-photon emission computed tomography

Although the pooled sensitivity and specificity values were not derived from a systematic literature search, they are more robust than the estimated sensitivity range published in reviews of between 80% and 100%. The meta-analysis showed that the addition of CT to ^{111}In-octreotide SPECT had little effect on the sensitivity of the test but did markedly improve the specificity (94% versus 75%).

B3.7 EXTENDED ASSESSMENT OF RELIABILITY EVIDENCE

Deppen at al. (2016a) reported that the bias-corrected Fleiss kappa was 0.82 (95%CI 0.74, 0.89) between the 3 blinded reviewers in their interpretation of 97 ^{68}Ga-DOTATATE PET/CT scans,

demonstrating a high level of inter-observer reproducibility. No other study reported on intra- or inter-observer reproducibility.

B3.8 CONCORDANCE ANALYSIS

Not required.

B3.9 INTERPRETATION OF EVIDENCE ON DIAGNOSTIC PERFORMANCE

The pooled sensitivity and specificity estimates for ^{68}Ga-DOTATATE PET/CT were compared to ^{111}In-octreotide SPECT/CT. ^{68}Ga-DOTATATE PET/CT combines both functional and anatomical imaging, therefore its accuracy against the composite reference standard will be compared with ^{111}In-octreotide SPECT/CT, which also combines functional and anatomical imaging.

When the pooled estimates for ^{68}Ga-DOTATATE PET/CT and ^{111}In-octreotide SPECT/CT were compared, ^{68}Ga-DOTATATE PET/CT (91%) was more sensitive than ^{111}In-octreotide SPECT/CT (80%) with respect to the composite reference standard but the specificity of the tests was similar (91% versus 94%).

The increased sensitivity is largely due to the increased spatial resolution of ^{68}GA-DOTA-peptide PET compared with ^{111}In-octreotide SPECT[10]. Etchebehere et al. (2014) reported that the spatial resolution for PET was 3–6 mm versus 10–15 mm for SPECT. Krausz et al. (2011) also found that ^{68}GA-DOTATOC PET images were clearer than ^{111}In-octreotide SPECT images. PET was especially useful in detecting small lesions (Etchebehere et al. 2014), particularly in the bones (Frilling et al. 2010; Putzer et al. 2009), as well as identifying the primary tumour site in patients where it was unknown (Prasad et al. 2010).

A preliminary clinical study by Hofman et al. (2001) in a small patient cohort of 8 patients with histologically proven metastatic NET (6 with GEP NET) demonstrated that ^{68}GA-DOTATOC PET achieved higher tumour to non-tumour binding ratios than ^{111}In-octreotide SPECT. ^{68}Ga-DOTATOC PET identified all previously known lesions, whereas ^{111}In-octreotide SPECT identified only 85%. In addition, ^{68}Ga-DOTATOC PET detected previously unknown small lesions, including brain metastases.

[10] Austin Health. 'Report on the Use of Positron Emission Tomography (PET) and Radiopharmaceuticals' (August 2012)

B4 CLINICAL VALIDITY

B4.1 MEASURES OF CLINICAL VALIDITY

The positive predictive value (PPV) and negative predictive value (NPV) are clinically relevant statistical measures that indicate how likely individuals who screen positive (or negative) have (or do not have) the disease. PPV and NPV depends on both the test performance and on the prevalence of the condition in the population tested. The PPV and NPV of the ^{68}Ga-DOTA-peptide PET/CT and ^{111}In-octreotide SPECT/CT tests were calculated using the proportion of patients who were suspected of having GEP NETs that were actually diagnosed with the disease in the included studies.

B4.1.1 TO B4.1.4

As for B3.1 to B3.4

B4.1.5 OUTCOME MEASURES AND ANALYSIS

The pooled sensitivity and specificity estimates and the prevalence of test-positive patients in the included studies were used to assess the positive predictive value (PPV) and negative predictive value (NPV) of ^{68}Ga-DOTA-peptide PET/CT and ^{111}In-octreotide SPECT/CT.

PPV was calculated as the proportion of people with histopathologically-confirmed NETs who were identified by ^{68}Ga-DOTA-peptide PET/CT out of all patients positive by ^{68}Ga-DOTA-peptide PET/CT:

PPV = number true positives / total test positive

$$= \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$$

NPV was calculated as the proportion of people with no NETs distinguishable by histopathology who had no tumours detected by ^{68}Ga-DOTA-peptide PET/CT out of all patients negative by ^{68}Ga-DOTA-peptide PET/CT:

NPV = number true negatives / total test negative

$$= \frac{\text{specificity} \times (1 - \text{prevalence})}{(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})}$$

B4.1.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE IN THE TARGET POPULATION?

Summary – What is the clinical validity of ^{68}Ga-DOTA-peptide PET/CT scanning compared with ^{111}In-octreotide SPECT/CT in patients with GEP NETs?

The PPV and NPV of the tests were calculated assuming that the proportion of patients undergoing SRS testing in Australia who actually have a clinically-diagnosed GEP NET was similar to that in the included studies, which ranged from 35% to 76% of those tested, with a median of 59%.

With a prevalence of 59%, the PPV for ^{111}In-octreotide SPECT/CT (95.1%) was very similar to that for ^{68}Ga-DOTATATE and ^{68}Ga-DOTA-peptide PET/CT (93.6% and 97.1%, respectively). Thus, the difference in the proportion of people with a positive test result who were correctly diagnosed between the three tests is unlikely to be clinically relevant.

However, the NPV varied by more than 10% (76.6% versus 87.5% and 90.1%). Thus, 23% of people who had a negative ^{111}In-octreotide SPECT/CT result would actually have a GEP NET compared with 10–12% of those who are negative after ^{68}Ga-DOTA-peptide PET/CT. This means that almost twice as many people with a negative result would actually have disease after ^{111}In-octreotide SPECT/CT scanning compared with ^{68}Ga-DOTA-peptide PET/CT scanning. This is likely to be of clinical significance.

Fourteen of the included studies enrolled patients suspected of having GEP NETs. Among these patients the proportion who had a clinical diagnosis (including histopathology) ranged from 35% to 76% of the patient cohort, with a median of 59%. Due to the lack of Australian data, the PPV and NPV of both tests were calculated using these prevalence estimates to represent the proportion of patients tested in Australia who would be diagnosed with a GEP NET (Table 14).

Table 14 PPV and NPV of ^{68}Ga-DOTATATE PET/CT, ^{68}Ga-DOTA-peptide PET/CT and ^{111}In-octreotide SPECT/CT

Test	Pooled sensitivity	Pooled specificity	PPV	NPV
^{111}In-octreotide SPECT/CT (section B3.6.2)	80% (95%CI 77, 84)	94% (95%CI 89, 100)	35%: 87.8% 59%: 95.1% 76%: 97.7%	35%: 89.7% 59%: 76.6% 76%: 59.8%
^{68}Ga-DOTATATE PET/CT (Deppen et al. 2016b)	91% (95%CI 81, 96)	91% (95%CI 79, 96)	35%: 84.5% 59%: 93.6% 76%: 97.0%	35%: 94.9% 59%: 87.5% 76%: 76.2%
^{68}Ga-DOTA-peptide PET/CT (Geijer & Breimer 2013)	93% (95%CI 91, 94)	96% (95%CI 95, 98)	35%: 92.6% 59%: 97.1% 76%: 98.7%	35%: 96.2% 59%: 90.1% 76%: 81.2%

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CI = confidence interval; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; k = number of studies; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; SPECT = single-photon emission computed tomography

By definition, as the prevalence of disease among the tested population increases the PPV increases and the NPV decreases. The size of the relative increase and decrease is dependent on the sensitivity

and specificity of the test. When 59% of those tested were assumed to have a GEP NET, the PPV of ^{111}In-octreotide SPECT/CT (95.1%) was very similar to that for ^{68}Ga-DOTATATE PET/CT and ^{68}Ga-DOTA-peptide PET/CT (93.6% and 97.1%, respectively). The difference between tests does not increase greatly if the prevalence decrease to 35% (Table 14). Thus, the difference in the proportion of people with a positive test result who were correctly diagnosed with a GEP NET using the ^{111}In-octreotide SPECT/CT and ^{68}Ga-DOTA-peptide PET/CT tests is unlikely to be clinically relevant.

However, with a prevalence of 59% the NPV varied by more than 10% (76.6% versus 87.5% and 90.1%). Thus, 23% of people who had a negative ^{111}In-octreotide SPECT/CT result would actually have a GEP NET compared with 10–12% of those scoring negative after ^{68}Ga-DOTA-peptide PET/CT. With a higher prevalence of 76% the difference in the proportion of people who are true negatives increases from 11-13% to 16–21%. The difference in the proportion of patients who would have a negative test result but actually have disease is likely to be of clinical significance.

It should also be noted that a proportion of those patients who have histologically proven GEP NET will be true negative with respect to ^{68}Ga-DOTA-peptide PET/CT imaging as some patients with poorly differentiated (WHO grade G3) disease have tumours that do not express high levels of the somatostatin receptor, and therefore, would not bind sufficient ^{68}Ga-DOTA-peptide ligand for detection by PET.

B4.2 PROGNOSIS OR PREDISPOSITION

Not required.

B5 CLINICAL UTILITY

Clinical utility refers to how likely the test is to significantly impact on patient management and health outcomes.

B5.1 IMPACT ON CLINICAL MANAGEMENT (THERAPEUTIC EFFICACY)

B5.1.1 EVIDENCE BASE

The Report by Austin Health[11] included one before and after study that reported on changes in clinical management of GEP NET after ^{68}Ga-DOTA-peptide PET/CT compared with ^{111}In-octreotide SPECT/CT (Hofman et al. 2012) and one case series that looked at the impact of identifying the unknown primary tumour site on management of GEP NETs (Prasad et al. 2010).

The applicant provided a SR by Mojtahedi et al. (2014) that included three before and after studies reporting on the change in management after ^{68}Ga-DOTA-peptide PET/CT compared with ^{111}In-octreotide SPECT±CT (Deppen et al. 2016a; Hofman et al. 2012; Srirajaskanthan et al. 2010). The applicant also provided an additional study reporting on clinical management outcomes after ^{68}Ga-DOTA-peptide PET/CT scanning compared to other tests (Skoura et al. 2016). As the comparator did not include ^{111}In-octreotide SPECT±CT, this study was not included in the evidence base.

During the quick literature search a recent SR was identified that reported on the impact of ^{68}Ga-DOTA-peptide PET/CT scanning on the management of patients with NETs (Barrio et al. 2017). This SR included fourteen before and after studies that reported on the change in management after ^{68}Ga-DOTA-peptide PET/CT compared with all prior tests with or without ^{111}In-octreotide SPECT±CT, four of which included ^{111}In-octreotide SPECT±CT (Deppen et al. 2016a; Krausz et al. 2011; Sadowski et al. 2016; Srirajaskanthan et al. 2010). Another case series that reported on the impact of identifying the unknown primary tumour site using ^{68}Ga-DOTA-peptide PET/CT on clinical management was also identified (Alonso et al. 2014).

[11] The Commonwealth Government Department of Health and Ageing contracted Austin Health to undertake a review of the Broader Use of Positron Emission Tomography (PET) and Radiopharmaceuticals in 2012.

B5.1.2 RISK OF BIAS ASSESSMENT

The SR by Mojtahedi et al. (2014) provided by the applicant was assessed in section B3.3 and was found to be of poor quality with a high risk of bias. The SR by Barrio et al. (2017) was assessed using the AMSTAR checklist (Shea et al. 2007). A summary of the risk of bias shown in Table 15.

Table 15 Quality appraisal and risk of bias for the SRs

Study	*A priori* protocol for PICO and research question	Quality appraisal of included studies	Number of studies included in the analysis	Quality of SR and risk of bias
Barrio et al. (2017)	No	Not assessed	k=14 vs conventional imaging k=4 vs ^{111}In-octreotide SPECT±CT	Poor quality (2/11) High risk of bias

k = number of studies; PICO = population, intervention, comparator, outcomes; SR = systematic review

Five before and after studies reporting on the change in management after ^{68}Ga-DOTA-peptide PET/CT compared with ^{111}In-octreotide SPECT±CT were assessed using the Institute of Health Economics (IHE) Case Series checklist (IHE 2014). Two case series reporting on the impact of identifying the unknown primary tumour site on management of GEP NETs were also assessed using the IHE checklist. The risk of bias for all studies was either low or medium (Table 36 in Appendix B).

B5.1.3 CHARACTERISTICS OF THE EVIDENCE BASE

See Table 35 and Table 36 in Appendix B for details on the individual studies included in the evidence base.

The populations in all included studies were slightly broader than the proposed PICO, which was limited to patients with GEP NETs. Although the majority of patients in the studies had GEP NETs, a small proportion of patients had thoracic or other NETS, or NETs with an unknown primary tumour site. In the two case series reporting on the identification of previously unknown primary tumour sites, the majority of NET sites found were GEP.

B5.1.4 OUTCOME MEASURES AND ANALYSIS

See Table 35 and Table 36 in Appendix B for details on the outcomes measured in the included studies.

The studies that were included for assessment of the impact of testing on clinical management all reported on resulting changes in the treatment pathway. The outcomes were reported as the proportion of patients in whom management was changed as a result of testing, which was appropriate.

Meta-analysis of the proportion of patients who had a change in management after ^{68}Ga-DOTATATE PET/CT compared to ^{111}In-octreotide SPECT±CT was undertaken using Stata version 14.1 (StataCorp 2015). Forest plots were generated using the 'metan' command in Stata.

B5.1.5 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

DOES IT IMPACT ON CLINICAL MANAGEMENT?

Summary – Is there a change in management from ^{68}Ga-DOTA-peptide PET/CT scanning in patients with GEP NETs compared with ^{111}In-octreotide SPECT±CT?

Barrio et al. (2017) concluded that management changes as a result of ^{68}Ga-DOTATATE PET/CT occurred in 44% of all patients whether or not they had had a prior ^{111}In-octreotide SPECT±CT. Meta-analysis found 38% of patients who had a prior ^{111}In-octreotide SPECT/CT had a change in management after ^{68}Ga-DOTATATE PET/CT. None of the included studies reported on whether or not the initial management decisions would have differed in the absence of ^{111}In-octreotide SPECT±CT. Thus, no direct comparison between management changes as a result of ^{68}Ga-DOTA-peptide PET/CT and those resulting from ^{111}In-octreotide SPECT±CT can be made. Nevertheless, the available evidence suggests that ^{111}In-octreotide SPECT±CT may add little value to patient management.

Hofman et al. (2012), Sadowski et al. (2016) and Srirajaskanthan et al. (2010) noted that the most frequent consequence of ^{68}Ga-DOTATATE PET/CT scanning was to increase the number of lesions detected. This resulted in a change in management for many patients, who often received systemic therapy rather than undergoing surgery. Alonso et al. (2014), Prasad et al. (2010) and Sadowski et al. (2016) found that ^{68}Ga-DOTA-peptide PET/CT imaging was useful in identifying the primary lesion (mostly GEP) in NET cases where it was previously unknown. These findings also had implications for surgical management in 17–41% of identified cases.

Only two studies reported on any patient for whom the ^{68}Ga-DOTATATE PET/CT result may have resulted in a suboptimal treatment plan. Hofman et al. (2012) reported on one false positive case with moderately increased uptake in the pancreas which was concordant with earlier ^{111}In-octreotide imaging. The patient underwent surgery and histology revealed no evidence of a NET. Srirajaskanthan et al. (2010) reported that ^{68}Ga-DOTATATE PET/CT was false-negative in 1 intermediate-grade non-functional pancreatic tumour. ^{111}In-octreotide imaging showed faint uptake in the region corresponding to the site of liver metastases. The effect on clinical management for this patient was not discussed. This suggests that few patients would be likely to receive inappropriate treatment after ^{68}Ga-DOTA-peptide PET/CT.

Most of the identified changes in management are as a direct consequence of the improved spatial resolution and clarity of the ^{68}Ga-DOTA-peptide PET/CT image compared with the ^{111}In-octreotide SPECT/CT image. There are four main scenarios that lead to a potentially major impact on patient management from ^{68}Ga-DOTA-peptide PET/CT imaging: histopathology-positive GEP NET patients who were falsely negative with ^{111}In-octreotide SPECT/CT and are positive with ^{68}Ga-DOTA-peptide PET/CT could become eligible for either somatostatin analogue (SSA) therapy or peptide receptor radionucleotide therapy (PRRT); histopathology-positive GEP NET patients who are negative with ^{68}Ga-DOTA-peptide PET/CT would be appropriately directed away from PRRT and SSA therapy; identification of the primary tumour site for patients in whom it is otherwise not detected could lead to appropriate surgical resection; and identification of more metastases may lead to patients receiving PRRT instead of or in addition to any planned surgical procedures.

Barrio et al. (2017) conducted a meta-analysis to determine the impact of ^{68}Ga-DOTATATE PET/CT on the management of patients with NETs compared with prior tests with or without ^{111}In-octreotide SPECT±CT. The results of the meta-analysis are summarised in Table 16.

Table 16 Meta-analysis of the impact of ^{68}Ga-DOTATATE PET/CT compared to ^{111}In-octreotide on patient management

Study	Intervention/comparator	Number of studies	Change in treatment
Barrio et al. (2017)	^{68}Ga-DOTATATE PET/CT vs all prior tests with or without ^{111}In-octreotide SPECT±CT	k=9 implemented changes k=5 intended changes k=14 all studies	44% (95%CI 35, 55), range 19–71% 41% (95%CI 28, 57), range 16–60% 44% (95%CI 36, 51), range 16–71%
	^{68}Ga-DOTATATE PET/CT vs ^{111}In-octreotide SPECT±CT	k=4	39% (95%CI 22, 59), range 16–71%

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CI = confidence interval; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; k = number of studies; PET = positron emission tomography; SPECT = single-photon emission computed tomography

Barrio et al. (2017) concluded that management changes as a result of ^{68}Ga-DOTA-peptide PET/CT occurred in 44% of all patients, whether or not they had a prior ^{111}In-octreotide SPECT±CT. The authors also found that management changed in 39% of the subgroup of patients who had a prior ^{111}In-octreotide SPECT±CT. The meta-analysis was repeated with subgroup data for Deppen et al. (2016a), the addition of another study (Hofman et al. 2012) and the exclusion of the study by Srirajaskanthan et al. (2010) that enrolled only ^{111}In-octreotide SPECT negative patients. This meta-analysis of the proportion of patients with a change in management after ^{68}Ga-DOTA-peptide PET/CT in patients who had either a prior ^{111}In-octreotide SPECT/CT or ^{111}In-octreotide SPECT±CT is shown in Figure 3. The results indicate that 38% of patients who had a prior ^{111}In-octreotide SPECT/CT scan and 36% who had a prior ^{111}In-octreotide SPECT±CT had a change in management after having ^{68}Ga-DOTA-peptide PET/CT imaging. These pooled estimates are similar to the 39% reported by Barrio et al. (2017) in Table 16, and indicate that ^{111}In-octreotide SPECT±CT may add little value to patient management.

Barrio et al. (2017) also concluded that management changes resulting in a change in the type of therapy (inter-modality change, e.g. surgery to chemotherapy) occurred 3-times more frequently than changes in dose/approach/technique within a treatment modality (intra-modality change, e.g. change in surgical strategy), as shown in Figure 4. The treatment changes that occurred in the five before and after studies that investigated the change in management due to ^{68}Ga-DOTA-peptide PET/CT imaging compared with ^{111}In-octreotide SPECT±CT are summarized in Table 17. All five studies found that ^{68}Ga-DOTA-peptide PET/CT changed management in a significant proportion of the patients with prior ^{111}In-octreotide SPECT±CT scans.

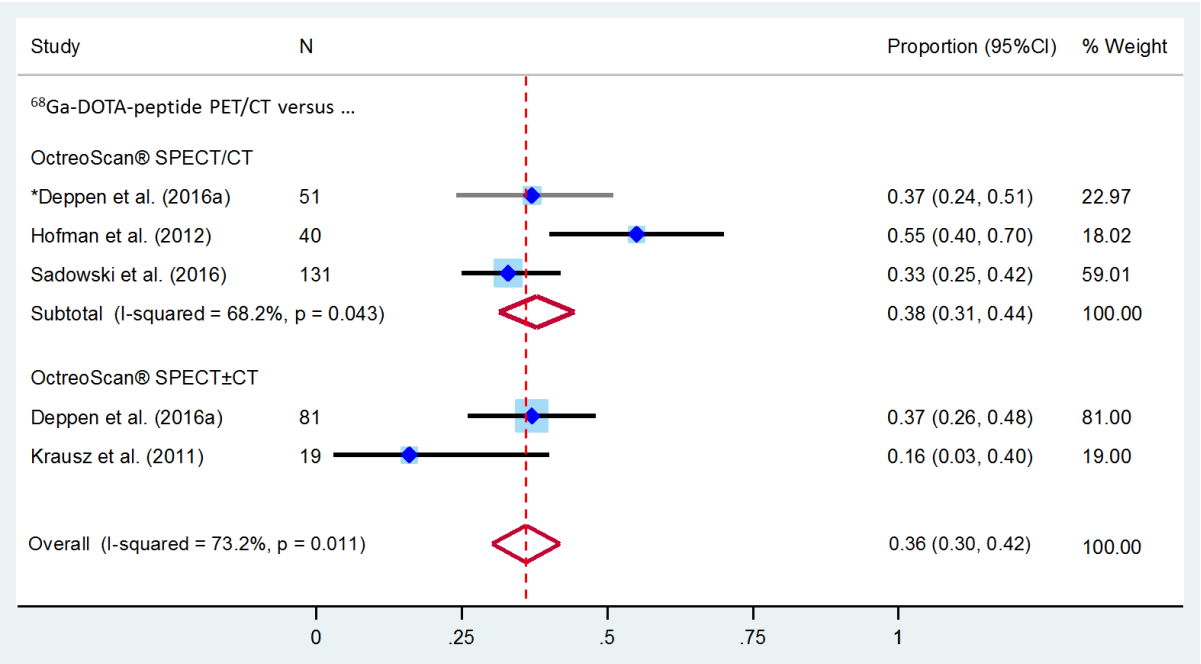

Figure 3 Meta-analysis of the proportion of patients who had a change in management after ^{68}Ga-DOTATATE PET/CT compared to ^{111}In-octreotide SPECT±CT

*The Deppen et al. (2016a) SPECT/CT subgroup was not included in the overall meta-analysis as these patients are included in the total SPECT±CT population.

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CI = confidence interval; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; PET = positron emission tomography; SPECT = single-photon emission computed tomography

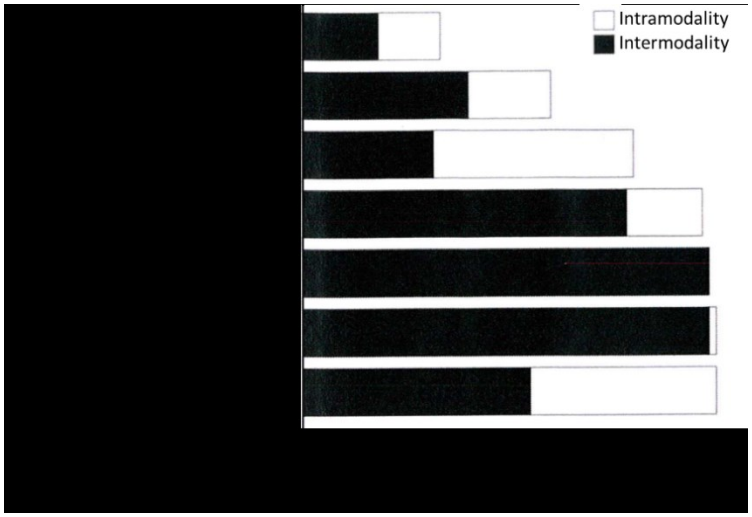

Figure 4 The proportion of management decisions that resulted in either an intra-modality or an inter-modality change

Reproduced from Barrio et al. (2017). An intra-modality change is defined as a change in dose/approach/technique within a treatment modality and an inter-modality change is defined as a change in the type of therapy.

Table 17 Change in management due to ^{68}Ga-DOTA-peptide PET/CT results compared to ^{111}In-octreotide SPECT±CT

Study Time between scans	Intervention/comparator	Number of patients	Change in treatment
Deppen et al. (2016a) 58% and 50% between 6 months and	^{68}Ga-DOTATATE PET/CT vs ^{111}In-octreotide SPECT±CT (n=81)	11 (14%)	Minor change within a treatment modality

Study Time between scans	Intervention/comparator	Number of patients	Change in treatment
3 years Remainder less than 6 months	vs ^{111}In-octreotide SPECT/CT (n=51)	19 (23%) 8 (16%) 11 (22%)	Major change of treatment modality (8 surgery cancelled, 12 PRRT) Minor change within a treatment modality Major change of treatment modality
Hofman et al. (2012) 40% 6–18 months 60% within 6 months	^{68}Ga-DOTATATE PET/CT vs ^{111}In-octreotide SPECT/CT (n=40)	33 (83%) 22 (55%)	Identified additional lesions High impact changes (PRRT, SSA therapy, chemotherapy, surgery)
Krausz et al.(2011) Median 24 days (range 10–65)	^{68}Ga-DOTANOC PET/CT vs ^{111}In-octreotide SPECT±CT (n=19 patients who were ^{111}In-octreotide SPECT±CT positive)	4 (21%) 3 (16%) 2 referred for PRRT 1 more intensive follow-up	Implications for disease staging Implications for patient management
Sadowski et al. (2016) Within 3 months	^{68}Ga-DOTATATE PET/CT vs ^{111}In-octreotide SPECT/CT (n=131)	93 (71%) 44 (34%) 15 (11%) 43 (33%) 19 (15%) 24 (18%)	Detected additional lesions Detected metastatic lesions Detected evidence of disease Change in management Additional patients had surgery Additional patients had targeted chemotherapy or PRRT
Srirajaskanthan et al. (2010) Median 4 months (range 1–8)	^{68}Ga-DOTATATE PET/CT vs ^{111}In-octreotide SPECT (n=47 with evidence of disease) (n=51 patients who were ^{111}In-octreotide SPECT negative or equivocal)	41 (80%) 36 (71%) 20 (39%) 4 (8%) 7 (14%) 3 (6%) 1 (2%) 1 (2%)	Identified lesions Change in management Patients had PRRT Excluded from PRRT due to negative PET/CT Patients commenced SSA therapy Patients had surgery Refused recommended surgery Confirmation of no disease (No CT or biochemical evidence of disease but some uptake with ^{111}In-octreotide SPECT)

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTANOC = DOTA-Phe1-Nal3-octreotide; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; PET = positron emission tomography PRRT = peptide receptor radionuclide therapy; SPECT = single-photon emission computed tomography; SSA = somatostatin analogue

Even though Deppen et al. (2016a) reported that after reviewing patient records, ^{111}In-octreotide SPECT±CT did not add value compared with histopathology and anatomical tests in any patient, no information supporting this statement was provided. None of the other four studies reported on whether or not the initial management decisions would have differed in the absence of the ^{111}In-octreotide SPECT±CT. Thus, no direct comparison between management changes as a result of ^{68}Ga-DOTA-peptide PET/CT and those resulting from ^{111}In-octreotide SPECT±CT can be made.

The study by Deppen et al. (2016a) had the longest time frame between the two SRS tests of up to three years. For these patients, it is reasonable to expect that the difference between the tests and any resultant change in management may be at least partially due to disease progression. However, the authors found that when the time between tests was broken into 3 categories (0–90. 91–180, and >180 days), the highest proportion of scans having an impact on treatment were in the 0–90 day category (44% versus 36% for >180 days), though the differences between categories were not

significant. The study by Hofman et al. (2012) with up to 18 months between tests also found that the greatest proportion of patients with a high management impact had both SRS tests within 3 months (71% versus 50% for >6 months). This suggest that the results have not been confounded by disease progression between SRS tests in these studies.

Three studies reported that ^{68}Ga-DOTA-peptide PET/CT provided additional information for disease staging (Hofman et al. 2012; Krausz et al. 2011; Sadowski et al. 2016). Hofman et al. (2012) and Sadowski et al. (2016) noted that the most frequent consequence of ^{68}Ga-DOTATATE PET/CT scanning was to increase the number of lesions detected (Table 17), and this resulted in many patients receiving systemic therapy rather than undergoing surgery. Srirajaskanthan et al. (2010) found that in many patients with negative or equivocal ^{111}In-octreotide SPECT findings, ^{68}Ga-DOTATATE PET/CT identified additional lesions and altered management in most cases. Sadowski et al. (2016) concluded that ^{68}Ga-DOTATATE PET/CT imaging should be implemented in the initial management and follow-up of patients with GEP NETs as it significantly improves patient care decisions.

Three studies found that ^{68}Ga-DOTA-peptide PET/CT imaging was useful in identifying the primary lesion in NET cases where it is unknown (Table 18). It should be noted that the patients had a prior ^{111}In-octreotide SPECT/CT in only one of these studies (Sadowski et al. 2016). This study identified only 29% of the unknown primary tumour sites, compared with 59% in the other two studies. This suggests that for a proportion of the patients, both ^{68}Ga-DOTA-peptide PET/CT and ^{111}In-octreotide SPECT/CT imaging would have identified the primary tumours. Nevertheless, the additional patients having their primary tumour site identified after ^{68}Ga-DOTA-peptide PET/CT imaging is likely to be of clinical significance.

These findings had implications for surgical management in 17–41% of identified cases. The authors of these studies also concluded that ^{68}Ga-DOTATATE PET/CT is a clinically useful imaging technique for the localization of primary tumours and can play a major role in patient management.

Table 18 Identification of primary tumour site in patients with NETS of unknown origin using ^{68}Ga-DOTA-peptide PET/CT

Study	Study population	Primary lesion identified	Change in treatment
Alonso et al. (2014) DOTATATE	29 patients with negative conventional imaging studies (contrast enhanced CT and MRI) for primary tumour identification	17 (59%) – all GEP 9 midgut: 7 ileum, 1 duodenum, 1 colon 8 foregut: 7 pancreas, 1 stomach	7 (41%) patients had surgery
Prasad et al. (2010) DOTANOC	59 patients with negative physical examination and conventional imaging (multislice CT, MRI and ultrasonography)	35 (59%) 32 (91%)GEPs: 14 ileum/jejunum, 16 pancreas, 2 rectum/colon, 3 (9%) other: 2 lung and 1 paraganglioma	6 (17%) patients had surgery 29 (83%) had advanced metastases and were not suitable for surgery
Sadowski et al. (2016) DOTATATE	14 patients with negative ^{111}In-octreotide SPECT/CT and conventional (CT or MRI) imaging	4 (29%) 1 small bowel, 3 site not reported	Not reported

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid;

DOTANOC = DOTA-Phe1-Nal3-octreotide; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; GEP = gastroenteropancreatic; MRI = magnetic resonance imaging; NET = neuroendocrine tumour; PET = positron emission tomography

Only two studies reported on any patient for whom the ^{68}Ga-DOTATATE PET/CT result may have resulted in a suboptimal treatment plan. Hofman et al. (2012) reported on one false positive ^{68}Ga-DOTATATE PET/CT result for a case that had been confirmed histologically. In this case, there was moderately increased uptake of ^{68}Ga-DOTATATE in the pancreas which was concordant with earlier ^{111}In-octreotide imaging. Although it is now known that such uptake can be physiological, the patient underwent surgery and histology revealed no evidence of a GEP NET. Srirajaskanthan et al. (2010) reported that ^{68}Ga-DOTATATE PET/CT was false-negative in one intermediate-grade non-functional pancreatic tumour. In this patient, ^{111}In-octreotide SPECT imaging showed faint uptake in the region corresponding to the site of liver metastases. The effect on clinical management for this patient was not discussed. Nevertheless, it seems that few patients would receive inappropriate treatment as a result of a ^{68}Ga-DOTA-peptide PET/CT scan.

SUMMARY OF THE TYPES OF CHANGES IN MANAGEMENT RESULTING FROM ^{68}GA-DOTA-PEPTIDE PET/CT

Most of the identified changes in management are as a direct consequence of the improved spatial resolution and clarity of the ^{68}Ga-DOTA-peptide PET/CT image compared with the ^{111}In-octreotide SPECT/CT image. There are four main scenarios that lead to a potentially major impact on patient management:

1. Histopathology-positive GEP NET patients who were falsely negative with ^{111}In-octreotide SPECT/CT are suspected of having low levels of the somatostatin receptor expressed on the tumour cell surface, and would therefore be limited to surgical and/or chemotherapy treatment options. Due to the better NPV of ^{68}Ga-DOTA-peptide PET/CT compared to ^{111}In-octreotide SPECT/CT (section B4.6), approximately half of these patients are likely to be positive after ^{68}Ga-DOTA-peptide PET/CT and could become eligible for either SSA therapy or PRRT, depending on their disease status.

2. Histopathology-positive GEP NET patients who remain SRS negative after ^{68}Ga-DOTA-peptide PET/CT are likely to have poorly differentiated disease that does not express the somatostatin receptor; and therefore, would not benefit from either SSA therapy or PRRT. These patients would appropriately be directed towards other surgical or chemotherapy options.

3. ^{68}Ga-DOTA-peptide PET/CT can identify the primary tumour sites for many patients in whom it is otherwise not detected (Table 18). This could lead to resection of the primary tumour.

4. ^{68}Ga-DOTA-peptide PET/CT can identify smaller lesions than ^{111}In-octreotide SPECT/CT and hence can identify patients who have more extensive metastatic disease than previously realised. These patients may receive PRRT instead of, or in addition to, any planned surgical procedures.

Figure 5 shows the management algorithm from the ESMO Clinical Practice Guidelines indicating at what stage of disease surgery, SSA therapy and PRRT treatments (boxed in red) are implemented.

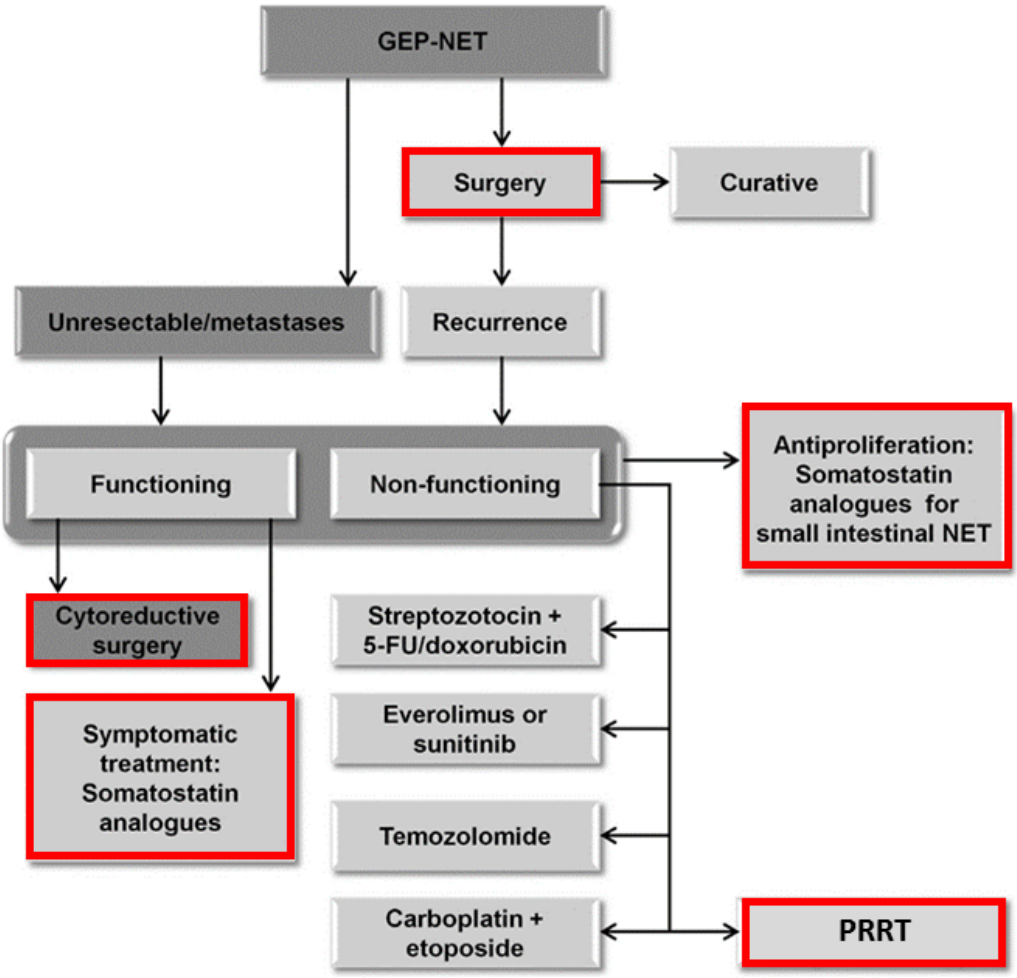

Figure 5 Algorithm for the treatment of GEP NET from the ESMO Clinical Practice Guidelines.

Source: Oberg and Lamberts (2016)

ESMO = European Society for Medical Oncology; GEP = gastroenteropancreatic; NET = neuroendocrine tumour; PRRT = peptide receptor radionuclide therapy

B5.2 THERAPEUTIC EFFECTIVENESS (INCLUDING IMPACT OF EFFECT MODIFICATION)

^{68}Ga-DOTATATE PET/CT is proposed to replace ^{111}In-octreotide SPECT±CT in diagnosing GEP NETs. Most studies found that ^{68}Ga-DOTATATE PET/CT provided additional information for disease staging that was of value in determining clinical management. The most common management changes were referral for surgery, PRRT or SSA therapy.

In order to determine the likely impact of these therapies on patient outcomes, the effectiveness of these therapies are discussed below.

B5.2.1 EVIDENCE BASE

The 'Report on the Use of Positron Emission Tomography (PET) and Radiopharmaceuticals – Part 2' (August 2012) was based on a systematic search of the literature using PubMed and Cochrane databases for original research papers, including SRs and websites of international HTA agencies for existing HTA reports. This report included two studies investigating SSA therapy (di Bartolomeo et al. 1996; Townsend et al. 2010) and two reviews investigating PRRT (Bodei et al. 2009; van Essen et al. 2009). The study by di Bartolomeo et al. (1996) was excluded as several updated studies and reviews were identified in a quick literature search.

A quick literature search of the PubMed database identified five reviews: an updated review on PRRT by Bodei et al. (2014), a review that looked at the safety of PRRT (Sabet, Biersack & Ezziddin 2016), three reviews that looked at the effectiveness and safety of SSA therapy (Oberg & Lamberts 2016; Sidéris, Dubé & Rinke 2012) and a review on surgical management (Tamburrino et al. 2016). Six retrospective studies were also identified: an Australian study by Townsend et al. (2010) that investigated the changing patterns of care over two decades for patients diagnosed with carcinoid tumours in the North West Adelaide Health Service, a multi-centre study that looked at the effectiveness and safety of PRRT (Horsch et al. 2016), two retrospective studies investigating the effectiveness of long-acting release (LAR)-SSAs (Laskaratos et al. 2016; Saglam et al. 2015), and two studies on surgical treatments for GEP NETs (Keck et al. 2017; Pasqual et al. 2016).

B5.2.2 RISK OF BIAS ASSESSMENT

While the reviews provided an overview of the literature and provided useful information in the lack of primary studies, they were not systematic and could not be critically appraised.

The six non-comparative studies were assessed for their risk of bias using the IHE Case Series checklist (IHE 2014). The risk of bias for all studies was either low or medium (Table 37 in Appendix B).

B5.2.3 CHARACTERISTICS OF THE EVIDENCE BASE

See Table 37 in Appendix B for details on the individual studies included in the evidence base.

B5.2.4 OUTCOME MEASURES AND ANALYSIS

See Table 37 in Appendix B for details on the outcomes measured in the included studies.

Two studies reported survival over a fixed time period as a proportion, which was appropriate. The remaining four studies reported time to radiological progression, partial response rate, overall survival and progression-free survival. The analysis used in these studies included Cox univariate and multi-variate regression analysis and Kaplan–Meier techniques, which were appropriate.

B5.2.5 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

DOES THE CHANGE IN MANAGEMENT IMPROVE HEALTH OUTCOMES?

Summary – Does the change in management due to ^{68}Ga-DOTA-peptide PET/CT scanning improve patient outcomes?

The most common management changes resulting from ^{68}Ga-DOTA-peptide PET/CT scanning were referral for SSA therapy, PRRT or surgery.

Effect of SSA on survival in patients with GEP NETs

^{68}Ga-DOTA-peptide PET/CT scanning has a better negative predictive value than ^{111}In-octreotide SPECT/CT. Those patients who would have been falsely classified as negative on ^{111}In-octreotide SPECT/CT, but receive positive results on ^{68}Ga-DOTA-peptide PET/CT scanning, would be eligible to receive SSA therapy or PRRT. Additionally, patients with multiple small metastatic lesions are more likely to have these detected with ^{68}Ga-DOTA-peptide PET/CT scanning than ^{111}In-octreotide SPECT/CT. The detection of more extensive disease in these patients may result in treatments such as PRRT or SSA therapy instead of, or in addition to, any planned surgical procedures.

Three reviews found that SSA therapy with octreotide controlled clinical symptoms arising from hormone secretion in somatostatin receptor-expressing NETs and two of them also report that recently published data have established an anti-proliferative effect for SSAs. Approximately half of the patients with GEP NET on SSA therapy achieved stabilization of tumour growth with a duration of 8–16 months and 10–20% showed tumour regression. Stable disease was achieved in 15–67% patients with poorly differentiated, functioning or non-functioning GEP NETs treated with octreotide and up to 26–88% in those receiving long-acting release (LAR) octreotide. Two recent retrospective non-comparative studies supported the findings (Laskaratos et al. 2016; Saglam et al. 2015).

Saglam et al. (2015) reported an estimated 5-year survival of 58% for patients treated with LAR SSA therapy. When this was compared with the 5-year survival rates for other treatments reported by Bodei et al. (2014), only surgical resection had a longer 5-year survival rate (70–85%). Patients receiving chemotherapy and PRRT had 5-year survival rates of 40% and 50%, respectively. These patients would be expected to have similar disease profiles (metastatic disease) to the patients enrolled in the study by Saglam et al. (2015), suggesting that LAR SSA therapy may be an effective treatment option in these patients.

A retrospective study by Townsend et al. (2010) found that the median overall survival was 112 months for patients receiving octreotide LAR compared with 53 months for those who received SSA therapy using non-LAR analogues (p=0.021, hazard ratio: 2.46), and 10 year survival was 40% compared with 22%, respectively. Thus, LAR SSA therapy appears to provide some survival benefits over non-LAR SSAs to GEP NET patients.

Octreotide has a well-established favourable safety profile with mild to moderately severe gastrointestinal-related complaints, which mostly resolve after a few weeks of therapy, were the most frequently reported side effects. Almost half of all patients with advanced GEP NET are at risk of developing gallstones and/or biliary sludge while receiving SSA therapy, but only 1% of patients develop symptoms sufficiently acute to require a cholecystectomy.

Effect of PRRT on survival in patients with GEP NETs

Bodei et al. (2014) reviewed PRRT and concluded that it was an efficient and relatively safe treatment of unresectable or metastatic NETs. They found that the median time to progression ranged from 10–29 months for ^{90}Y-DOTATOC compared with 36 months for ^{177}Lu-DOTATATE, and the median progression-free survival ranged from 16–29 months and 29–33 months, respectively. Horsch et al. (2016) also found that overall survival and progression-free survival were significantly inferior in the patients treated with solely ^{90}Y-DOTATOC compared to ^{177}Lu-DOTATATE.

Bodei et al. (2014) also reported on the proportion of patients surviving for longer than 5 years after PRRT. Approximately 50% of patients undergoing PRRT survived for at least 5 years compared with 40% of those undergoing chemotherapy. As these patients groups are likely to have similar disease characteristics, PRRT may be more effective than chemotherapy. However, as the evidence base was non-comparative, the indirect comparisons between treatments are likely to be confounded, so randomised controlled trials are needed to determine any true differences between treatments.

Sabet et al. (2016) reported that the high radiation doses associated with ^{90}Y-DOTATOC PRRT can lead to renal impairment and/or delayed end-stage renal disease and significant bone marrow toxicities. When ^{177}Lu-DOTATATE is used instead of ^{90}Y-DOTATOC the number of patients with both haematological and renal toxicities are reduced. Thus, ^{177}Lu-DOTATATE is likely to be safer than ^{90}Y-DOTATOC. The safety of ^{177}Lu-DOTATATE also compares favourably with reported toxicities for common chemotherapy regimens including 5-fluorouracil orstreptozocin (20%-30%, grades 3/4) and sunitinib (>30%, grades 3/4) for pancreatic NET.

Effect of surgery on survival in patients with GEP NETs

Patients with unknown primary tumour sites are more likely to have these detected with ^{68}Ga-DOTA-peptide PET/CT scanning than ^{111}In-octreotide SPECT/CT, enabling these patients to have surgical resections.

A review by Tamburrino et al. (2016) concluded that surgical resection improves survival compared with no surgery. Another review by Bodei et al. (2014) reported that the proportion of patients whose primary tumours were surgically resected surviving for longer than 5 years was approximately 70–85% compared with 25% of untreated patients, 40% of those receiving chemotherapy and 50% of patients on PRRT. However, it should be noted that there are large differences in the patient characteristics between treatments. Those receiving "curative" surgery would have earlier stage disease compared to those receiving chemotherapy or PRRT, confounding the results. Nevertheless, surgery remains the only "curative" treatment and the promising long-term survival of these patients suggests that surgery is an effective treatment for GEP NET.

B5.2.5.1 EFFECT OF SSA THERAPY ON SURVIVAL IN PATIENTS WITH GEP NETS

Histopathology-positive GEP NET patients who were falsely negative with ^{111}In-octreotide SPECT/CT would be limited to surgical and/or chemotherapy treatment options as they would be expected to have low levels of the somatostatin receptor expressed on the tumour cell surface. The better NPV of ^{68}Ga-DOTA-peptide PET/CT compared to ^{111}In-octreotide SPECT/CT (section B4.6) indicates that approximately half of these patients are likely to be positive after ^{68}Ga-DOTA-peptide PET/CT and could become eligible for either SSA therapy or PRRT, depending on their disease status. Furthermore, as ^{68}Ga-DOTA-peptide PET/CT can identify smaller lesions than ^{111}In-octreotide SPECT/CT, it can identify patients who have more extensive metastatic disease than previously realised. These patients may receive PRRT or SSA therapy instead of, or in addition to, any planned surgical procedures.

Three reviews found that SSA therapy controlled clinical symptoms arising from hormone secretion in somatostatin receptor-expressing NETs (Narayanan & Kunz 2016; Oberg & Lamberts 2016; Sidéris, Dubé & Rinke 2012). Two of these reviews also reported that recently published data have established an anti-proliferative effect for SSAs. Oberg and Lamberts (2016) stated that the clinical use of octreotide has contributed to improved patient survival since 1987. Sideris et al. (2012) concluded that stable disease in patients with poorly differentiated, functioning or non-functioning GEP NETs was achieved in 15–67% of patients treated with octreotide and in 26–88% of those receiving octreotide LAR.

Two recent retrospective studies agreed with the findings in the reviews. The study by Laskaratos et al.(2016) looked at the response to SSA therapy using octreotide LAR in 254 treatment naïve patients with advanced NETs and found that a partial response occurred in 5% of patients and the median time to radiological progression was 37 (95%CI 32, 52) months. The study by Saglam et al. (2015) found that patients with locally inoperable or metastatic well-differentiated non-functional NETs who received octreotide LAR treatment had a progression-free survival of 25.0±3.4 months (95%CI 18.4, 31.5) and an overall survival of 71.3±9.5 months (95%CI 52.7, 89.9). The estimated 5-year survival rate for patients receiving Lar SSA therapy was 58%. A study by Townsend et al. (2010) found that patients who received octreotide LAR had improved outcomes; the median overall survival was 112 months compared with 53 months for those who received SSA therapy using non-

LAR analogues (p=0.021, hazard ratio: 2.46), and 10 year survival was 40% compared with 22%, respectively. Thus, SSA therapy with LAR SSAs is more effective than with non-LAR analogues.

When the 5-year survival for LAR SSA therapy was compared with the 5-year survival rates reported by Bodei et al. (2014), only surgical resection had a longer 5-year survival rate (Figure 6). Patients receiving chemotherapy and PRRT would be expected to have similar disease profiles to the patients enrolled in the study by Saglam et al. (2015), suggesting that LAR SSA therapy may be an effective treatment option in these patients.

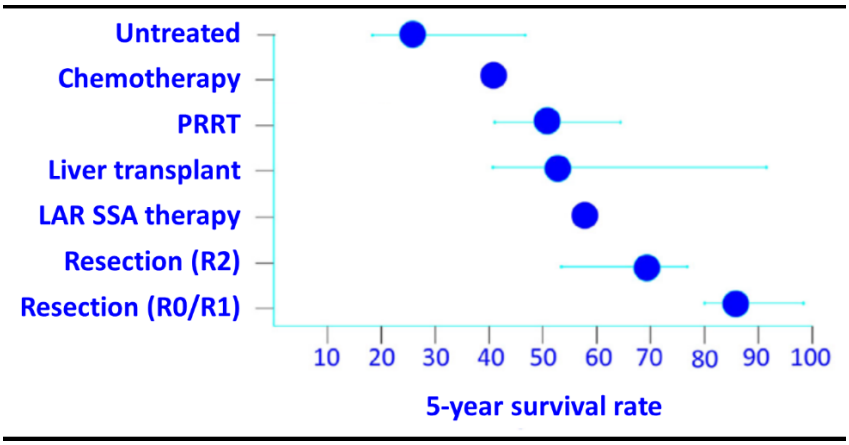

Figure 6 The 5-year survival rate of patients with NETs undergoing various tretaments

Source: adapted from Bodei et al. (2014); LAR SSA therapy from Saglam et al. (2015)

PRRT = peptide receptor radionuclide therapy; R0 = resection for cure or complete remission; R1 = microscopic residual tumour; R2 = macroscopic residual tumour; SSA = somatostatin analogue

Safety of SSA therapy

The review by Oberg and Lamberts (2016) found that SSA therapy with octreotide had a well-established favourable safety profile. Mild to moderately severe gastrointestinal-related complaints were the most frequently reported side effects, and are directly attributable to drug-induced disruption of GEP hormone signalling and reduced secretion of digestive enzymes. Narayanan and Kunz (2016) noted that most of these symptoms were dose dependent, and resolved within the first few weeks of treatment. Both reviews noted that almost half of all patients with advanced GEP NET developed cholelithiasis and were at risk of developing gallstones and/or biliary sludge while receiving SSA therapy. Narayanan and Kunz (2016) reported that this side effect was also dose dependent with only 1% of patients developing symptoms sufficiently acute to require a cholecystectomy.

The retrospective study by Saglam et al. (2015) found that of the 23 patients who had SSA therapy, one patient developed a skin reaction, one had cholestasis, one had grade 1 diarrhoea, and three patients had newly onset diabetes. The authors concluded that SSA therapy seemed to be an effective treatment option with acceptable tolerability for patients.

B5.2.5.2 EFFECT OF PRRT ON SURVIVAL IN PATIENTS WITH GEP NETS

Bodei et al. (2014) reported that initial PRRT studies with ^{90}Yttrium (^{90}Y)-DOTATOC were undertaken in individuals with very advanced disease. However, the documented effectiveness of the therapy, even in these situations, led to the usage of PRRT in earlier phases of disease progression with the key issues in predicting optimal PRRT response being tumour load, especially in the liver, and performance status.

Bodei et al. (2014) reviewed PRRT with either ^{90}Y-DOTATOC or ^{177}Lutetium (^{177}Lu)-DOTATATE and concluded that it was an efficient and relatively safe treatment of unresectable or metastatic NETs. The results of the phase I–II studies identified by the authors that reported clinical outcomes for PRRT are shown in Table 19. These studies all showed promising responses to SSA therapy despite having heterogeneous NET populations and treatment schemes that are not directly comparable. The median time to progression across the studies ranged from 10–29 months for ^{90}Y-DOTATOC compared with 36 months for ^{177}Lu-DOTATATE, and the progression-free survival ranged from 16–29 months for ^{90}Y-DOTATOC compared with 29–33 months for ^{177}Lu-DOTATATE. The review also reported on the proportion of patients surviving for longer than 5 years after PRRT (see Figure 6 above). Approximately 50% of patients undergoing PRRT survived for at least 5 years compared with 40% of those undergoing chemotherapy. As the patients groups are likely to have similar disease characteristics, PRRT may be more effective than chemotherapy but randomised controlled trials are needed to determine if this is the case.

Table 19 Clinical results of PRRT with either ^{90}Y-octreotide or ^{177}Lu-octreotate in GEP NETs

Study	Ligand	Number of patients	Objective response / stable disease (criteria)	Outcome
Waldherr et al. (2001)	^{90}Y-DOTATOC	37	13% / 49% (WHO)	Median TTP > 26 months
Bodei et al. (2003)	^{90}Y-DOTATOC	21	29% / 55% (WHO)	Median TTP 10 months
Valkema et al. (2006)	^{90}Y-DOTATOC	58	9% / 50% (SWOG)	Median TTP 29 months
Bushnell et al. (2010)	^{90}Y-DOTATOC	90	4% / 74% (SWOG)	PFS 16 months
Pfeifer et al. (2011)	^{90}Y-DOTATOC	53	23% / 62% (WHO)	PFS 29 months
Cwikla et al. (2010)	^{90}Y-DOTATOC	58	23% / 77% (WHO)	PFS 17 months
Kwekkeboom et al. (2008)	^{177}Lu-DOTATATE	310	29% / 51% (SWOG)	PFS 33 months
Bodei et al. (2011)	^{177}Lu-DOTATATE	42	31% / 53% (RECIST)	Median TTP 36 months
Sansovini et al. (2013)	^{177}Lu-DOTATATE	52	29% / 52% (SWOG)	PFS 29 months

Source: Bodei et al. (2014)

^{177}Lu = ^{177}Lutetium; ^{90}Y = ^{90}Yttrium; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SWOG = Southwest Oncology Group; TTP = time to progression; WHO = World Health Organisation

One registry study with a prospective follow-up directly compared the effectiveness of ^{90}Y-DOTATOC with ^{177}Lu-DOTATATE (Horsch et al. 2016). The authors found that overall survival and progression-free survival were significantly inferior in the patients treated with solely ^{90}Y-DOTATOC compared to ^{177}Lu-DOTATATE, both solely or in combination with ^{90}Y-DOTATOC. There was no difference in survival when ^{177}Lu-DOTATATE PRRT was compared with ^{177}Lu-DOTATATE in combination with ^{90}Y-DOTATOC. The results are summarised in Table 20. However, as no studies were identified that

directly compared the effectiveness of PRRT compared to chemotherapy, their relative effectiveness could not be assessed.

Table 20 Overall survival and progression-free survival for patients having PRRT using ^{90}Y-octreotide compared with ^{177}Lu-octreotate

Outcome	Number of patients	Number of events	Median	HR (95%CI), p-value
Overall survival		(death)		
^{177}Lu-octreotate	241	29	Not reached	1.13 (0.66, 1.9), p=0.64
^{90}Y-DOTATOC	76	26	38 months	3.22 (1.83, 5.64), p= 0.00004
Combined	130	48	58 months	1
Progression-free survival		(progression)		
^{177}Lu-octreotate	241	55	40 months	1.37 (0.87, 2.13), p>0.05
^{90}Y-DOTATOC	76	37	27 months	2.79 (1.71, 4.55), p<0.05
Combined	130	67	50 months	1

Source: Horsch et al. (2016)

^{177}Lu = ^{177}Lutetium; ^{90}Y = ^{90}Yttrium; CI = confidence interval; HR = hazard ratio; PRRT = peptide receptor radionuclide therapy

Safety of PRRT

A review by Sabet et al. (2016) reported that the high radiation doses associated with ^{90}Y-DOTATOC PRRT can lead to renal impairment and/or delayed end-stage renal disease. Across the studies included in the review, the reported rate of significant renal toxicities (Grade 3 or greater) after either ^{90}Y- or ^{177}Lu- labelled PRRT and ranged from 3% to 9.2% of patients (Table 21). In fact, the 9.2% of patients with nephrotoxicity in the study by Imhof et al. (2011) were all Grade 4/5 leading to permanent renal toxicity or death. PRRT with ^{177}Lu-DOTATATE resulted in less renal impairment (range 0.4–1.9%), probably due to less irradiation of the radiosensitive glomeruli during each course of treatment. Similarly, the review indicated that there were less patients with significant bone marrow toxicities when ^{177}Lu-DOTATATE was used instead of ^{90}Y-DOTATOC; however, the data presented showed little difference (0–11.3% compared with 1.7–15.5%). Bodei et al. (2015), a large retrospective study on 807 patients, found ^{177}Lu-DOTATATE to be safer than ^{90}Y-DOTATOC regarding both haematological and renal toxicity (0% versus 6.1% and 3.1% versus 14%, respectively). In fact, the safety of ^{177}Lu-DOTATATE compared favourably with reported toxicities for common chemotherapy regimens including 5-fluorouracil orstreptozocin (20%-30%, Grade 3/4) and sunitinib (>30%, Grade 3/4) for pancreatic NET (Sabet, Biersack & Ezziddin 2016).

Table 21 Long-term toxicity of PRRT with either ^{90}Y-octreotide or ^{177}Lu-octreotate

Study	Ligand	Number of patients	Number of Tx cycles	Median follow-up	Nephrotoxicity Grade >3	Haematotoxicity Grade >3
Valkema et al. (2006)	^{90}Y-DOTATOC	54	2–4	18 months	3%	1.7%
Bushnell et al. (2010)	^{90}Y-DOTATOC	90	2–4	<33 months	3.3%	15.5%
Imhof et al. (2011)	^{90}Y-DOTATOC	1109	2	23 months	9.2%	12.8%
Pfeifer et al. (2011)	^{90}Y-DOTATOC	53	2	17 months	5.6%	>9%
Bodei et al. (2015)	^{90}Y-DOTATOC	358	~4	30 months	6.1%	14.2%
Kwekkeboom et al. (2008)	^{177}Lu-DOTATATE	504	3–4	19 months	0.4%	9.5%

Study	Ligand	Number of patients	Number of Tx cycles	Median follow-up	Nephrotoxicity Grade >3	Haematotoxicity Grade >3
Bodei et al. (2008)	^{177}Lu-DOTATATE	51	3–4	60 months	1.9%	0%
Sabet et al. (2013) Sabet et al. (2014)	^{177}Lu-DOTATATE	203 74	3 3	31 months 21 months	1.3%	11.3%
Bodei et al. (2015)	^{177}Lu-DOTATATE	290	~5	30 months	0%	3.1%

Source: Sabet et al. (2016)

^{177}Lu = ^{177}Lutetium; ^{90}Y = ^{90}Yttrium; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; DOTATOC = DOTA–D-Phe1-Tyr3-octreotide; Grade 3 = grades of toxicity according to Common Terminology Criteria for Adverse Events; Tx = treatment

B5.2.5.3 EFFECT OF SURGERY ON SURVIVAL IN PATIENTS WITH GEP NETS

^{68}Ga-DOTA-peptide PET/CT can identify the primary tumour sites for many patients in whom it is previously unknown. These patients could potentially become candidates for surgical resection of the primary tumour. In addition, histopathology-positive GEP NET patients who remain SRS negative after ^{68}Ga-DOTA-peptide PET/CT are likely to have poorly differentiated disease that does not express the somatostatin receptor; and therefore, would not benefit from either SSA therapy or PRRT. These patients would appropriately be directed towards other surgical or chemotherapy options.

Oberg and Lamberts (2016) stated that "radical surgery is the only 'curative' treatment for GEP NET" but noted that more than half of tumours were considered to be unresectable at diagnosis.

A review on the surgical management of NETs concluded that surgical resection improves survival compared to no surgery (Tamburrino et al. 2016). Tumour diameter was found to be one of the main parameters in the decision making process for non-functioning NETs. Whereas small lesions can be treated conservatively, larger tumours should be surgically resected, including a lymphadenectomy. The authors found that functioning tumours should be resected regardless the dimension of the lesion. Tamburrino et al. (2016) also reported that locally advanced and metastatic disease should be treated with extensive resections, keeping in consideration the grading, size, Ki67, and presence of extra-abdominal disease. In the case of metastases, the surgical treatment options include resection, ablation and liver transplantation.

A very recent non-comparative study by Keck et al. (2017) reported that among patients presenting with metastases and unresected primaries who had an operation the median survival for those with small bowel and pancreatic tumours was 145 and 71 months, respectively. Another recent non-comparative study by Pasqual et al. (2016) found that the 5-year survival rate for patients that underwent hepatic resections and liver transplantation were 45% (95%CI 26, 78%) and 50% (95%CI 13, 100), respectively. A study by Townsend et al. (2010) retrospectively assessed the treatment trends and their impact over time in a single unit [North West Adelaide Health Service) for 49 patients diagnosed with metastatic carcinoid GEP NETs between 1 January, 1985 and 1 March, 2007. The authors reported that the median survival for those who underwent surgical resection (n=38) was 93 months compared with 33 months for those with intact primary tumour (n=11; p=0.025).

However, the decision for surgery was based on standard clinical practice indicating that those who did not have surgery most likely had unresectable tumours, making the two groups not directly comparable. Pasqual et al. (2016) concluded that although the results are encouraging, randomized clinical trials are necessary to more adequately evaluate the effect of surgery on survival in GEP NET patients.

The review by Bodei et al. (2014) reported on the proportion of patients surviving for longer than 5 years after surgical resection, liver transplantation, chemotherapy, and PRRT compared to untreated patients (Figure 6). Approximately 70–85% of patients whose primary tumours are surgically resected survived for at least 5 years compared with 25% of untreated patients and 40% of those receiving chemotherapy. The median 5-year survival rate is similar (approximately 50%) for patients who have a liver transplant and for patients on PRRT. However, it should be noted that there are large differences in the patient characteristics between treatments. Those receiving "curative" surgery would have earlier stage disease compared to those receiving chemotherapy or PRRT. These differences would confound the results making a direct comparison between surgery and other treatments uncertain. Nevertheless, surgery remains the only "curative" treatment and the promising long-term survival of these patients suggests that surgery is an effective treatment for GEP NET.

B6 IMPACT OF REPEAT TESTING/MONITORING

The clinical claim in the PICO Confirmation was that introducing ^{68}Ga-DOTA-peptide PET/CT scanning in lieu of ^{111}In-octreotide SPECT/CT will reduce the number of tests that would need to be repeated. No evidence was provided by the Department of Health, or identified in the quick literature search to inform on repeat testing. The studies included in the meta-analyses to determine the pooled sensitivity and specificity of ^{111}In-octreotide SPECT±CT did not report any patients in whom the test was inconclusive. Similarly, no reports of failed ^{68}Ga-DOTA-peptide PET/CT scans were identified in the evidence base.

However, the accuracy data did indicate that almost twice as many patients with histologically proven GEP NETs will have a negative ^{111}In-octreotide SPECT/CT compared with a negative ^{68}Ga-DOTA-peptide PET/CT. Thus, fewer patients with suspected GEP NET would need additional anatomical or functional tests, as shown in the clinical algorithm (Figure 2 in section A6), to obtain a final diagnosis.

Some of the studies included in the evidence base tested patients who had recurrent disease, or required follow-up after surgical or other treatments with ^{68}Ga-DOTA-peptide PET/CT. Thus, repeated testing may be of clinical importance for long-term management of these patients. However, the effectiveness of follow-up testing was not evaluated as it was outside the scope of this assessment.

B7 EXTENDED ASSESSMENT OF COMPARATIVE HARMS

The 'Report on the Use of Positron Emission Tomography (PET) and Radiopharmaceuticals' (August 2012) by Austin Health[12] reported on the safety of ^{68}Ga-DOTA-peptide PET/CT compared with ^{111}In-octreotide SPECT/CT and included the safety results reported by Hofman et al. (2012). The applicant provided a recent study by Deppen et al. (2016a) that looked at the safety and efficacy of ^{68}Ga-DOTATATE PET/CT.

The US Library of Medicine website[13] provides information on the use and safety of both ^{111}In-octreotide® and ^{68}Ga-DOTATATE (marketed as NETSPOT). This site reported that the safety of ^{68}Ga-DOTATATE was evaluated in three single centre studies (Deppen et al. 2016a; Haug et al. 2014; Haug et al. 2012) and that no serious adverse reactions were identified. Of these three studies, only Deppen et al. (2016a) published any adverse event data.

The SR by Deppen et al. (2016b) also identified three studies that reported on adverse events (Deppen et al. 2016a; Etchebehere et al. 2014; Kunikowska et al. 2014).

B7.1 SHORT-TERM SAFETY

Austin Health found that there were no documented serious adverse events associated with injection of the ^{68}Ga, or with performing the PET/CT scan and that the studies included in their review did not raise any new safety concerns. Austin Health also concluded that multiple MSAC assessments of FDG PET have stated that it is generally accepted that PET is a non-invasive and relatively safe diagnostic procedure.

Only six mild adverse events associated with injection of the ^{68}Ga-DOTA-peptide were reported in the studies included in this assessment (adverse events associated with ^{111}In-octreotide SPECT±CT were not reported in any study). Deppen et al. (2016a) reported that minor adverse events occurred in three patients. One had minor itching at the ^{68}Ga-DOTATATE injection site the next day. One patient had an unexplained drop in post-scan oxygen saturation on room air from 98% before injection to 90% after scanning. Both of these resolved spontaneously. The third patient had an asymptomatic post-scan tachycardia of 112 beats/minute (baseline 87 beats/minute), spontaneously returning to less than 100 beats/minute within an hour. Kunikowska et al. (2014) reported that two patients with a history of gastritis had abdominal pain associated with ^{68}Ga-DOTATATE

[12] The Commonwealth Government Department of Health and Ageing contracted Austin Health to undertake a review of the Broader Use of Positron Emission Tomography (PET) and Radiopharmaceuticals in 2012.

[13] Available from URL: https://dailymed.nlm.nih.gov/dailymed/index.cfm [accessed 20 December 2016].

administration, which was effectively treated with an antispasmodic drug. The SR by Deppen et al. (2016b) reported that one patient had an adverse event in the study by Etchebehere et al. (2014); this patient had unilateral whole-body oedema ipsilateral to the injected arm occurring within 24 hours of injection, which resolved spontaneously in less than 48 hours. However, this adverse event was not reported in the published study and the source for this information was not reported in the review.

B7.2 LONG-TERM SAFETY

Hartmann et al. (2009) found that ^{68}Ga-DOTA-peptide PET resulted in a significantly lower radiation dose (approximately 3–4 mSv) compared with ^{111}In-octreotide SPECT (approximately 12 mSv). Walker et al. (2013) found similar results with patients undergoing ^{68}Ga-DOTA-peptide PET being exposed to 3.1–4.8 mSv compared with 5.9 mSv for ^{111}In-octreotide SPECT. The use of low dose CT for anatomical localisation of the PET or SPECT data delivers radiation exposure up to 1 mSv (Hartmann et al. 2009). McLean et al. (1989) reported that ^{111}In also causes radiation damage via emission of Auger electrons, which may be underestimated by traditional dosimetry models. Austin Health concluded that the potential long-term effects of exposure to ionising radiation are unlikely to be of major concern to these patients, given their reduced life expectancy.

B8 INTERPRETATION OF THE CLINICAL EVIDENCE

This mini assessment of the effectiveness of ^{68}Ga-DOTA-peptide PET/CT scanning in lieu of Octreotide SPECT/CT scanning is constrained by a lack of information. To comprehensively assess these technologies a systematic search of the literature is required. To complement the limited evidence provided by the applicant a quick literature search of the PubMed database to identify recent publications to help evaluate these technologies was undertaken. Therefore, the conclusions drawn from this mini-assessment are based on an incomplete evidence base and the implications of this are unknown.

On the basis of the evidence presented in section B, **it is suggested that, relative to ^{111}In-octreotide SPECT/CT, ^{68}Ga-DOTA-peptide PET/CT has superior safety and superior effectiveness.**

Barrio et al. (2017) found that management changes occurred in 44% of patients as a result of ^{68}Ga-DOTATATE PET/CT. A change in the type of therapy (inter-modality change) occurred 3-times more frequently than a change in dose/approach/technique within a treatment modality (intra-modality change). An updated meta-analysis found 38% of patients who had had a prior ^{111}In-octreotide SPECT/CT had a change in management after having a ^{68}Ga-DOTATATE PET/CT. The most common management changes were referral for surgery, PRRT or SSA therapy. No data were available to determine whether or not management decisions would have differed in the absence of the ^{111}In-octreotide SPECT±CT. Thus, no direct comparisons between management changes as a result of ^{68}Ga-DOTA-peptide PET/CT and those resulting from ^{111}In-octreotide SPECT±CT can be made. Nevertheless, as the proportion of patients whose management changed after ^{68}Ga-DOTA-peptide PET/CT with or without a prior ^{111}In-octreotide SPECT±CT are similar, the results of the ^{111}In-octreotide SPECT/CT appear to be of little value when determining a patient's management plan.

^{68}Ga-DOTATATE PET/CT was found to be more sensitive, with less false negative results, than ^{111}In-octreotide SPECT/CT when compared to the composite reference standard (91% versus 80%). At an assumed diagnostic yield of 59%, the NPV values for the two tests indicated that 23% of people who had a negative ^{111}In-octreotide SPECT/CT would actually have a GEP NET compared with 13% of those who were negative after ^{68}Ga-DOTA-peptide PET/CT. Thus, almost twice as many people who actually have a GEP NET would have a negative result after ^{111}In-octreotide SPECT/CT compared with ^{68}Ga-DOTA-peptide PET/CT. This difference is likely be of clinical significance and would have implications for patient management.

Without a ^{68}Ga-DOTA-peptide PET/CT scan, the clinicians would have considered that these patients expressed the somatostatin receptor poorly based on the negative ^{111}In-octreotide SPECT/CT scan. As a result, these patients would have been incorrectly directed away from targeted therapies such as PRRT or SSA therapy as they not be expected to benefit from them and would have probably

received chemotherapy. The 13% of patients with a negative ^{111}In-octreotide SPECT/CT scan who had a positive ^{68}Ga-DOTA-peptide PET/CT scan would become eligible for PRRT or SSA therapy.

Even though the evidence base was subject to confounding, both of these therapies appear to be effective treatment options in patients with GEP NETs. Saglam et al. (2015) reported that the 5-year survival rate for patients on LAR SSA therapy was 58%. When the 5-year survival for LAR SSA therapy was compared with the 5-year survival rates reported by Bodei et al. (2014), only surgical resection had a longer 5-year survival rate (Figure 6). Patients receiving chemotherapy and PRRT would be expected to have similar disease profiles to the patients enrolled in the study by Saglam et al. (2015), suggesting that LAR SSA therapy may be an effective treatment option in these patients.

Bodei et al. (2014) reviewed PRRT and concluded that it was an efficient and relatively safe treatment for unresectable or metastatic NETs. The authors also reported on the proportion of patients surviving for longer than 5 years after PRRT (see Figure 6 above). Approximately 50% of patients undergoing PRRT survived for at least 5 years compared with 40% of those undergoing chemotherapy. As these patient groups are likely to have similar disease characteristics, PRRT may be more effective than chemotherapy but randomised controlled trials are needed to determine if this is the case.

Thus, patients with negative ^{111}In-octreotide SPECT/CT scans and positive ^{68}Ga-DOTA-peptide PET/CT scan would most likely have a change in management leading to improved health outcomes.

Conversely, histopathology-positive GEP NET patients who were negative with ^{68}Ga-DOTA-peptide PET/CT are actually likely to have tumours expressing low levels of the somatostatin receptor, and would be appropriately directed away from PRRT and SSA therapy towards surgery and/or chemotherapy options.

The main advantage with ^{68}Ga-DOTANOC PET appeared to be the increased clarity of the images in comparison with ^{111}In-octreotide SPECT making them easier to interpret (Krausz et al. 2011). This increased clarity resulted in an increase in the number of lesions detected (Hofman et al. 2012; Sadowski et al. 2016; Srirajaskanthan et al. 2010). The detection of more lesions also had implications for patient management in a large number of cases. The detection of more advanced disease than previously realised would result in clinicians treating patients with PRRT or SSA therapy instead of, or in addition to, any previously planned surgical procedures.

^{68}Ga-DOTA-peptide PET/CT imaging was also useful in identifying the site of the primary lesion in NET cases where it was previously unknown (Alonso et al. 2014; Prasad et al. 2010; Sadowski et al. 2016). These studies were non-comparative, and it is likely that the primary tumour site for a proportion of these patients would have been detected by both ^{68}Ga-DOTA-peptide PET/CT and ^{111}In-octreotide SPECT/CT. Nonetheless, the additional patients having their primary tumour site identified by ^{68}Ga-DOTA-peptide PET/CT but not by ^{111}In-octreotide SPECT/CT is likely to be of clinical

significance. These patients may be eligible for surgical resection instead of or in addition to other systemic therapies.

The review by Oberg and Lamberts (2016) stated that "radical surgery is the only 'curative' treatment for GEP NET". A review by Bodei et al. (2014) reported that the proportion of patients whose primary tumours were surgically resected surviving for longer than 5 years was approximately 70–85% compared with 25% of untreated patients, 40% of those receiving chemotherapy and 50% of patients on PRRT. However, it should be noted that there are large differences in the patient characteristics between treatments. Those receiving "curative" surgery would have earlier stage disease compared to those receiving chemotherapy or PRRT, confounding the results. Nevertheless, surgery remains the only "curative" treatment and the promising long-term survival of these patients suggests that surgery is an effective treatment for GEP NET.

Only two studies reported on any patient for whom the ^{68}Ga-DOTATATE PET/CT result may have resulted in a suboptimal treatment plan. Hofman et al. (2012) reported on one false positive case with moderately increased uptake in the pancreas which was concordant with earlier ^{111}In-octreotide SPECT/CT. The patient underwent surgery and histology revealed no evidence of a NET. Srirajaskanthan et al. (2010) reported that ^{68}Ga-DOTATATE PET/CT was false-negative in 1 intermediate-grade non-functional pancreatic tumour. ^{111}In-octreotide SPECT showed faint uptake in the region corresponding to the site of liver metastases. The effect on clinical management for this patient was not discussed. Thus, very few patients (2/322; 0.6%) are likely to be managed incorrectly based on their ^{68}Ga-DOTA-peptide PET/CT results.

There were no studies identified that reported on the safety of surgery, but surgery remains the only potentially curative therapy available to patients with GEP NETs. Several reviews reported that octreotide has a well-established favourable safety profile. The most frequently reported adverse events were mild to moderately severe gastrointestinal-related complaints, which mostly resolve after a few weeks of therapy. Almost half of all patients with advanced GEP NET developed cholelithiasis while receiving SSA therapy, but only 1% of patients developed symptoms sufficiently acute to require a cholecystectomy. Of the two main PRRT radiopeptides, ^{177}Lu-DOTATATE has a superior safety profile compared to ^{90}Y-DOTATOC. The higher radiation doses associated with ^{90}Y-DOTATOC PRRT leads to more renal impairment and/or delayed end-stage renal disease and significant bone marrow toxicities than ^{177}Lu-DOTATATE. The safety of ^{177}Lu-DOTATATE also compares favourably with reported toxicities for common chemotherapy regimens including 5-fluorouracil orstreptozocin (20%-30%, grades 3/4) and sunitinib (>30%, grades 3/4) for pancreatic NET (Sabet, Biersack & Ezziddin 2016). Thus, treatment of GEP NETs with surgery, SSA therapy or PRRT appears to be more effective than no treatment or chemotherapy and relatively safe.

Only six patients with mild adverse events associated with injection of the ^{68}Ga-DOTA-peptide were reported in the studies included in this assessment. Two patients with gastritis and abdominal pain were effectively treated with an antispasmodic drug. The remaining four cases all resolved

spontaneously in less than 48 hours. Austin Health[14] concluded that multiple MSAC assessments of FDG PET have stated that it is generally accepted that PET is non-invasive and relatively safe. Additionally, ^{68}Ga-DOTA-peptide PET resulted in a significantly lower radiation dose (approximately 3–5 mSv) compared with ^{111}In-octreotide SPECT (approximately 6–12 mSv). An extra 1 mSv exposure occurs from the use of low dose CT for transmission correction of the PET or SPECT data. Thus, ^{68}Ga-DOTA-peptide PET/CT was found to be a relatively safe procedure in comparison to ^{111}In-octreotide SPECT/CT. Furthermore, Austin Health concluded that any potential long-term effects of exposure to ionising radiation from ^{68}Ga-DOTA-peptide PET/CT are unlikely to be of major concern to these patients, given their reduced life expectancy.

In conclusion, ^{68}Ga-DOTA-peptide PET/CT is more sensitive, with an improved NPV indicating that there are fewer false negative patients compared with ^{111}In-octreotide SPECT/CT. Additionally, increased clarity of the ^{68}Ga-DOTA-peptide PET images in comparison with ^{111}In-octreotide SPECT enabled a more accurate detection of the extent of disease and localisation of the primary tumour. The increased accuracy and clarity resulted in a change in management in approximately 40% of all patients, irrespective of whether or not the patients had had prior ^{111}In-octreotide SPECT/CT imaging. These changes in management resulted in more patients being directed towards surgery, SSA therapy or PRRT rather than chemotherapy. Treatment of GEP NETs with surgery, SSA therapy or PRRT appear to be more effective than no treatment or chemotherapy and are relatively safe. ^{68}Ga-DOTA-peptide PET/CT is also safer with lower radiation exposure and quicker (2 hours versus 2 days) than ^{111}In-octreotide SPECT/CT. When taken together, these results suggest that replacement of ^{111}In-octreotide SPECT/CT with ^{68}Ga-DOTA-peptide PET/CT is likely to lead to better patient outcomes in up to 30% of patients; i.e. those who had an inter-modality change in management (Barrio et al. 2017).

[14] The Commonwealth Government Department of Health and Ageing contracted Austin Health to undertake a review of the Broader Use of Positron Emission Tomography (PET) and Radiopharmaceuticals in 2012.

SECTION C TRANSLATION ISSUES

Not applicable.

SECTION D ECONOMIC EVALUATION

Not applicable.

SECTION E FINANCIAL IMPLICATIONS

E.1. JUSTIFICATION OF THE SELECTION OF DATA SOURCES

^{68}Ga-DOTA-peptide PET is proposed as a replacement test (replacing existing listing for ^{111}In-octreotide SPECT, MBS item 61369), for diagnostic clarification in patients with suspected GEP NETs (*subgroup 1*) or to exclude additional disease sites in patients identified with surgically amenable disease (*subgroup 2*).

To estimate the target patient population, an epidemiological approach (combined with additional data from the literature review and clinical expert advice) has been used to estimate the number of services and financial implications associated with the substitution of ^{68}Ga-DOTA-peptide PET for ^{111}In-octreotide SPECT in MBS item 61369. This is difficult to validate with a market-based estimate, as the use of existing comparator ^{111}In-octreotide SPECT has decreased in recent years despite the increasing incidence and prevalence of GEP NETs. Table 40 in Appendix D shows the MBS utilisation for item 61369 since 2002–03. This may be attributed to treating clinicians and Nuclear Medicine specialists increasingly using ^{68}Ga-DOTA-peptide PET/CT for SRS in lieu of ^{111}In-octreotide SPECT±CT.

Beginning with an estimate of the number of new cases of GEP NETs anticipated each year, using population projections by Australian Bureau of Statistics and published/advised incidence and prevalence rates, the estimated number of ^{68}Ga-DOTA-peptide PET services required to obtain the number of diagnoses is back-calculated using an estimate of diagnostic yield.

The data sources used to calculate the financial impact of the MBS listing of ^{68}Ga-DOTA-peptide PET are summarised in Table 22.

Table 22 Parameters and data sources used in the financial analysis

Data source	Purpose	Value
Epidemiological data		
Expert advice and Fraenkel et al. (2014)	Estimate of incidence of GEP NETs in Australia	3.0–3.6 per 100,000 per year[a]
Fraenkel et al. (2014) and Patel et al. (2016)	Estimate of prevalence of GEP NETs in Australia	21 per 100,000 [a]
Table 14 in Section B.4	Estimated diagnostic yield in the target population to derive the suspected number of cases eligible for diagnostic clarification with the proposed test	Base case: 59% Sensitivity analysis: 35% and 76%
ABS data catalogue no. 3222, series B (2013)	Projection of Australian population, all ages in 2017–2022	Row A, Table 23
Market data		
Medicare item reports	Number of octreotide services (item 61369) that are currently MBS funded	Table 40, Appendix D
Expert advice	Proportion of new cases receiving a follow-up scan in the same year before being considered	Base case: 10% Sensitivity analysis: 20% and 30%

Data source	Purpose	Value
	for surgery	
Expert advice	Proportion of older cases (prevalence minus new cases) identified with surgically amenable disease	Base case: 20% Sensitivity analysis: 10% and 30%
MBS data for current ^{111}In-octreotide SPECT, PET and CT services (MBS items 61369, 61529 and 61505)	Average MBS benefit paid per service, 2015–16	MBS item 61369: $1,942 Proposed item: $896 MBS item 61505 : $90
	Estimated average bulk-billing rate	MBS item 61369: 90% Proposed item: 90%[b] MBS item 61505 : 91%
	Average co-payment per service	MBS item 61369: $45 Proposed item: $15[b] MBS item 61505: $3
MSAC report 1003 (1999), MBS data services for item 61369 and Expert advice	Proportion of services expected to be MBS funded	Base case: 20%–30% Sensitivity analysis: 30%–50%

[a] Incidence of NETs is estimated to be 5–6 per 100,000 per year and the prevalence is 35 per 100,000. It is assumed that 60% of the NETs are GEP NETs (Patel et al. 2016)

[b] Average bulk-billing rate for the proposed item is considered the same as that for item 61369 and the average co-payment per service is estimated by accounting for bulk-billing incentives.

^{111}In = ^{111}Indium; ABS = Australian Bureau of Statistics; GEP = gastroenteropancreatic; MBS = Medicare Benefit Schedule; MSAC = Medicare Services Advisory Committee; NET = neuroendocrine tumour; PET = positron emission tomography; SPECT = single-photon emission computed tomography

E.2. USE AND COSTS OF ^{68}GA-DOTA-PEPTIDE PET/CT

EXPECTED USE

In the PICO confirmation, the applicant claimed that introduction of ^{68}Ga-DOTA-peptide PET/CT scanning in lieu of ^{111}In-octreotide SPECT±CT will reduce the number of tests that would need to be repeated. No evidence was found supporting this claim (see section B.6). However, some of the patients who have recurrent disease, or require follow-up after surgical or other treatments with ^{68}Ga-DOTA-peptide PET/CT may receive repeat testing as a part of long-term management. However, the impact of the proposed test on the rate of follow-up testing is not included in the financial analysis as it was outside the scope of this assessment.

The steps taken to derive the estimated number of eligible services for proposed subgroups 1 and 2 are discussed below.

Subgroup 1

Clinical expert advice suggests that the incidence of NETs has risen in Australia from 3–4 per 100,000 per year in 2000–12 to 5–6 per 100,000 at present. It is unclear, whether this is a true increase in incidence, better detection with imaging and endoscopy, or better histological classification.[15]

[15] Email communication with clinical experts; response received on 10 February 2017.

Approximately 60% of the NETs are estimated to be GEP NETs, with an incidence of approximately 3–3.6 per 100,000 per year (Fraenkel et al. 2014; Patel et al. 2016).

Applying this to the projected Australian population allows an estimate of the total number of new patients diagnosed with GEP NETs in Australia in the next five years. The number of ^{68}Ga-DOTA-peptide PET services associated with new diagnoses of GEP NETs can be estimated by dividing the number of new cases by the diagnostic yield of the test in the clinical setting. Estimates of the diagnostic yield are presented in Table 14 in section B.4. The median estimate of 59% (range 35–76%) is used in the base-case financial analysis. The upper and lower values of diagnostic yield are assessed in the sensitivity analysis (section E.6).

The calculations described above, as applying to Australian data from 2017–18 to 2021–22, are presented in a stepped manner in Table 23.

Table 23 Estimated number of patients who would be eligible for ^{68}Ga-DOTA-peptide PET/CT to provide diagnostic clarification to confirm/refute a diagnosis of GEP NET (subgroup 1), 2017–18 to 2021–22

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
A	Projected Australian population [a]	24,781,121	25,201,317	25,619,895	26,037,356	26,452,147
B	New cases of GEP NET (Row A * 3 / 100,000)	743	756	769	781	794
C	Associated number of ^{68}Ga-DOTA-peptide PET/CT scans anticipated to yield new diagnoses (Row B ÷ diagnostic yield (59%))	1,260	1,281	1,303	1,324	1,345

[a] Australian Bureau of Statistics, catalogue number 3222.0 – Population Projections, Australia, Series B, males + females, all ages (ABS 2013).

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; GEP = gastroenteropancreatic; NET = neuroendocrine tumour; PET = positron emission tomography;

Subgroup 2

According to clinical expert advice, approximately 80% of the patients targeted in subgroup 2 would be newly diagnosed and therefore, would be included in subgroup 1. However, around 10% of the incident cases with potentially resectable disease may be monitored, and then have a repeat scan at 3–6 months to ensure that the disease remains localised before being considered amenable to surgery. Additionally, approximately 20% of the old cases (prevalent cases excluding incident cases) may be reconsidered for surgery after chemotherapy and various other treatments, and would need a ^{68}Ga-DOTA-peptide PET/CT to aid in disease restaging and ruling out other disease sites (Modlin et al. 2010).[16]

[16] Email communication with clinical experts; response received on 10 February 2017.

Since the prevalence of GEP NETs in Australia is unknown, it is assumed to be the same as in the USA with a prevalence of 21 per 100,000 [17] (Fraenkel et al. 2014; Patel et al. 2016).

Table 24 Estimated number of patients who would be eligible for ^{68}Ga-DOTA-peptide PET in surgically amenable patients to exclude additional disease sites (subgroup 2), 2017–18 to 2021–22

Row		2017–18	2018–19	2019–20	2020–21	2021–22
A	Projected Australian population [a]	24,781,121	25,201,317	25,619,895	26,037,356	26,452,147
D	Incident cases having repeat scan (Row B * 10%)	74	76	77	78	79
E	Prevalent cases of GEP NET (Row A * 21/100,000)	5204	5292	5380	5468	5555
F	Estimated number of old cases (Row E – B) * 20%)	892	907	922	937	952
G	**Total number of ^{68}Ga-DOTA-peptide PET/CT scan anticipated to be performed (Row D + F)**	**966**	**983**	**999**	**1015**	**1032**

[a] Australian Bureau of Statistics, catalogue number, 3222.0 – Population Projections, Australia, Series A, males + females, all age(ABS 2013)s (ABS 2013).

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; GEP = gastroenteropancreatic; NET = neuroendocrine tumour; PET = positron emission tomography;

Number of services expected to be MBS funded

The majority of PET scanners are available in the public sector. Only large private hospitals or practices with relatively high throughput could offer ^{68}Ga-DOTA-peptide PET/CT services given the radiochemistry infrastructure required on site (eg, ^{68}Ga / ^{68}Ge generator, a synthesis module to perform the labelling and quality control, as well as consumables including chemicals, cartridges and the DOTA-peptide). Clinical advice suggested that due to the infrastructure limitations mentioned above, approximately 80% of these scans would be performed in the public sector and 20% in the private sector.

Most outpatients in public hospitals would have the cost of ^{68}Ga-DOTA-peptide PET/CT covered by state healthcare budgets. In contrast, ^{68}Ga-DOTA-peptide PET/CT performed in private hospitals would have charges associated with Medicare services, with the costs to MBS and private sector (patients and /or health insurerer). Only costs associated with procedures done in private settings are considered in the financial analysis.

It is assumed that if ^{68}Ga-DOTA-peptide PET is MBS listed, the number of scans in the private settings would increase gradually from 20% in year 1 to 40% in year 5 of the proposed listing. As these estimates are uncertain, sensitivity analyses are performed by varying the uptake rates in private

[17] Prevalence of NETs is reported to be 35/100,000 in USA (Fraenkel et al. 2014) and it is estimated that approximately 60% of the NETs are GEP NETs (Patel et al. 2016) which equates to the prevalence of 21/100,000 for GEP NETs.

settings from 30%–50% (section E.6). An uptake rate of 30% was suggested in the MSAC report 1003 (MSAC 1999) to estimate the number of services expected to be MSAC funded.

Table 25 provides an estimate of the number of services expected to be MBS funded over the next five years of the proposed listing, 2017–18 to 2021–22.

Table 25 Estimated number of services expected to be MBS funded, 2017–18 to 2021–22

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
C	Number of ^{68}Ga-DOTA-peptide PET/CT scans anticipated to yield new diagnoses	1,260	1,281	1,303	1,324	1,345
G	Number of ^{68}Ga-DOTA-peptide PET/CT scans anticipated to be performed under subgroup 2	880	895	910	924	939
H	**Total number of services eligible (Row C + G)**	**2,227**	**2,264**	**2,302**	**2,339**	**2,377**
I	Uptake rate (% of services expected to be MBS funded)	20%	25%	30%	35%	40%
J	**Estimated number of ^{68}Ga-DOTA-peptide PET/CT services to be MBS funded (Row I * H)**	**445**	**566**	**691**	**819**	**951**

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; MBS = Medicare Benefits Schedule; PET = positron emission tomography

EXPECTED COSTS

The proposed MBS fee for the listing is $953 (consistent with the scheduled fee for other FDG PET listings). It is intended that the item be co-claimed with MBS item 61505, with a fee of$100 (which covers the cost of a CT scan).

It is assumed that if ^{68}Ga-DOTA-peptide PET were MBS listed, patterns for MBS subsidy, bulk-billing and co-payments would be similar to those that occur with ^{111}In-octreotide SPECT. Data on the average of fees charged, benefits paid, patient co-payments and bulk-billing rates per service for MBS items 61369 and 61505 were provided by the Australian Government Department of Health and are summarised in Table 26.

Table 26 MBS data and cost of ^{111}In-octreotide SPECT and CT scan, 2015–16

Row	Description	MBS item 61369	MBS item 61505
K	Proportion of services performed as outpatient	98%	95%
L	Scheduled fee	$2,015.75	$100
M	Average fee charged per service	$1,988	$92
N	Average benefit paid (cost to MBS)	$1,942	$90
O	Bulk billing rate	90%	91%
P	Average patient contribution per outpatient service	$449	$31
Q	Average co-payment per service [Row P * (1 – O)]	$45	$3
R	**Total cost (including co-payment) (Row N + Q)**	$1,987	$90

Source: Data provided by Australian Government Department of Health

^{111}In = ^{111}Indium; CT = computed tomography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

Applying a similar pattern to ^{68}Ga-DOTA-peptide PET/CT services, it is assumed that all tests would be conducted in an out-of-hospital setting (98% of ^{111}In-octreotide SPECT±CT services were in outpatient settings, Table 26), and 90 per cent services would be bulk-billed (with a 100% rebate due to the bulk-billing incentive).

The total cost to the MBS per service is calculated as $985.38, derived from the average benefit paid per outpatient service for ^{68}Ga-DOTA-peptide PET/CT (average benefit paid; $895.82) and the associated use of CT scan (MBS item 61505, average benefit paid; $89.56)[18].

The proportion of patients that are bulk-billed (90%) and the patient contribution ($145.81) for proposed service are estimated based on the data for current MBS services (item 61369 and items for FDG PET in 2015–16). Therefore, the estimated patient contribution per ^{68}Ga-DOTA-peptide PET test is $14.58[19] and for the CT scan is $2.75. The total patient contribution associated with each ^{68}Ga-DOTA-peptide PET/CT service is thus $17.33 ($14.58 + $2.75). Application of these costs to the usage estimates are shown in Table 27, disaggregated by payer (the MBS and the patient). The average total cost of ^{68}Ga-DOTA-peptide PET/CT testing is estimated to reach $953,000 in year five of the proposed listing.

Table 27 Estimated MBS and patient contribution costs of the proposed ^{68}Ga-DOTA-peptide PET/CT service, 2017–18 to 2021–22

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
J	Number of services estimated to be MBS funded	445	566	691	819	951
S	Total MBS contribution costs (Row J × $985.38)	$438,794	$557,793	$680,469	$806,816	$936,765
T	Total patient contribution costs (Row J × $17.33)	$7,717	$9,810	$11,968	$14,190	$16,475
U	**Total costs of listing (Row Row S + T)**	**$446,511**	**$567,603**	**$692,436**	**$821,006**	**$953,240**

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; MBS = Medical Benefits Schedule; PET = positron emission tomography

The average benefit paid per outpatient service may differ for the proposed item than used for other FDG-PET services taken as a referral standard. Therefore, a sensitivity analysis is presented in section E.6 assuming the cost to the MBS is 85 per cent of the proposed fee, and the co-payments is 15 per cent of the proposed fee.

[18] Average benefit paid for ^{68}Ga-DOTA-peptide PET is estimated based on the Medicare statistics data available for FDG-PET items, and take into account the bulk-billing incentives; <http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp>; accessed on 8 February 2017.

[19] $145.48 × (1 – 90%)

E.3. CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

ESTIMATED SERVICES OFFSET

The comparator, ^{111}In-octreotide SPECT, is currently MBS listed as item number 61369 which has a scheduled fee of $2,015.75. If listed, ^{68}Ga-DOTA-peptide PET would fully replace ^{111}In-octreotide SPECT. Also, it will result in cost shifts from state government healthcare budgets to the MBS, primarily through an extension of services in the private sector.

An exponential curve was fitted to the number of ^{111}In-octreotide SPECT services that were MBS funded from 2010–11 to 2015–16 (Table 40 in Appendix D). It is assumed that in the absence of ^{68}Ga-DOTA-peptide PET listing, exponential reduction of ^{111}In-octreotide SPECT services would continue. A graph showing a fitted exponential curve and the derived regression equation is presented in Figure 9 in Appendix D.

Table 28 presents the estimated number of ^{111}In-octreotide SPECT±CTs that would be offset over the next five years if ^{68}Ga-DOTA-peptide PET/CT is listed on the MBS.

Table 28 Estimation of the number of comparator services offset

Row		2017–18	2018–19	2019–20	2020–21	2021–22
J	Number of ^{68}Ga-DOTA-peptide PET/CT services expected to be MBS funded	445	566	691	819	951
V	Projected number of ^{111}In-octreotide SPECT±CT (Figure 9 in Appendix D) services	73	50	34	23	16
W	**Total number of services offset (100% × V)**	**73**	**50**	**34**	**23**	**16**

^{68}Ga = ^{68}Gallium; ^{111}In = ^{111}Indium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; MBS = Medicare Benefits Schedule; PET = positron emission tomography; SPECT = single-photon emission computed tomography

ESTIMATED COSTS OFFSET

Data for the average benefit paid and the associated patient contributions for ^{111}In-octreotide SPECT±CT services are summarised above in the Table 26. In summary, the total cost to the MBS per service (including the associated use of CT scan) is calculated as $2,031.33, and the average patient contribution per service is $47.66. Table 29 presents the estimated total costs offset by the replacement of comparator services.

Table 29 Total costs offset by replacement of ^{111}In-octreotide SPECT±CT services

	2017–18	2018–19	2019–20	2020–21	2021–22
Total number of services offset	73	50	34	23	16
Total offsets to the MBS [a]	$148,525	$100,862	$68,495	$46,514	$31,587
Total offsets to patients [b]	$3,485	$2,366	$1,607	$1,091	$741
Total costs offset	**$152,010**	**$103,228**	**$70,101**	**$47,605**	**$32,328**

[a] Total offsets to the MBS are calculated by multiplying number of services offset with average benefit of $2,031.33 paid for ^{111}In-octreotide SPECT and CT.

[b] Total offsets to the patients are calculated by multiplying number of services offset with average patient co-payment of

$47.66 for ^{111}In-octreotide SPECT and CT.

^{111}In = ^{111}Indium; CT = computed tomography; MBS = Medicare Benefits Schedule; SPECT = single-photon emission computed tomography

E.4. FINANCIAL IMPLICATIONS FOR THE MBS

The financial implications to the MBS resulting from the proposed listing of ^{68}Ga-DOTA-peptide PET over the next five years are summarised in Table 30.

Table 30 Net costs to the MBS associated with ^{68}Ga-DOTA-peptide PET/CTs

-	2017–18	2018–19	2019–20	2020–21	2021–22
^{68}Ga-DOTA-peptide PET/CTs					
Number of services	445	566	691	819	951
Cost to the MBS	$438,794	$557,793	$680,469	$806,816	$936,765
Tests offset					
Number of services offset	73	50	34	23	16
Costs offset	$148,525	$100,862	$68,495	$46,514	$31,587
Net cost to the MBS	**$290,269**	**$456,931**	**$611,974**	**$760,302**	**$905,177**

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; MBS = Medicare Benefit Schedule; PET = positron emission tomography

Proposed listing of ^{68}Ga-DOTA-peptide PET/CT is expected to increase the net cost to the MBS, exceeding $900,000 in year five of the listing. This is primarily due to the trended reductions in the usage of ^{111}In-octreotide SPECT±CT in the private sector.

E.5. FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

There may be some financial implications (cost-savings) for state and territory government health budgets, such as for public hospitals due to the extension of ^{68}Ga-DOTA-peptide PET/CT services in the private sector. Quantification of such cost shifts (from state and territory health budgets to MBS) is harder because ^{68}Ga-DOTA-peptide PET/CTs are already being performed in Australian public hospitals, however data regarding its utilisation are not available.

It is assumed that in the absence of the proposed listing, the number of ^{68}Ga-DOTA-peptide PET/CT services not offset by ^{111}In-octreotide SPECT±CT would be performed in the public hospitals. The cost associated with each ^{68}Ga-DOTA-peptide PET/CT service in public sector is assumed to be the total of the schedule fee for FDG PET and CT ($953 + $100 = $1,053).

Table 31 presents the estimated financial implications of the proposed listing for other healthcare budgets. These estimates should be interpreted with caution as it is uncertain how many ^{68}Ga-DOTA-peptide PET/CT services would shift to private sector due to the limitations associated with required infrastructure.

Table 31 Cost implications for other healthcare budgets[a]

	2017–18	2018–19	2019–20	2020–21	2021–22
State and territory governments: number of ^{68}Ga-DOTA-peptide PET/CT services offset	372	516	657	796	935
Cost savings to state and territory governments	**$391,913**	**$543,785**	**$691,658**	**$838,070**	**$984,674**

[a] It is assumed that there will be extension of ^{68}Ga-DOTA-peptide PET/CT services in the private settings due to MBS funding. Thus, a cost shift from public sector to Medicare and private sector.

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; PET = positron emission tomography

Table 32 presents the financial implications to the patients of listing ^{68}Ga-DOTA-peptide PET/CT.

Table 32 Net costs to patients associated with listing of ^{68}Ga-DOTA-peptide PET/CT

	2017–18	2018–19	2019–20	2020–21	2021–22
Number of ^{68}Ga-DOTA-peptide PET/CT services	445	566	691	819	951
Cost to patients	$7,717	$9,810	$11,968	$14,190	$16,475
Offsets					
Number of services offset	73	50	34	23	16
Costs offset	$3,485	$2,366	$1,607	$1,091	$741
Net costs to patients	**$4,233**	**$7,444**	**$10,361**	**$13,099**	**$15,734**

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; PET = positron emission tomography

As seen in Table 31 and Table 32, ^{68}Ga-DOTA-peptide PET/CT listing may result in cost shifting from the state and territory government healthcare budgets to Medicare and patients.

E.6. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Sensitivity analyses around inputs to the financial model (incidence, diagnostic yield, benefit paid, number of cases eligible for surgery and uptake rates) are presented in Table 33. The costs to MBS are higher than the base-case analysis when the uptake rates are higher or diagnostic yield is lower. Other variables have a low to moderate impact on the estimated costs to the MBS.

Table 33 Sensitivity analysis of financial implications of listing ^{68}Ga-DOTA-peptide PET/CT

	2017–18	2018–19	2019–20	2020–21	2021–22
Base-case					
Net cost of ^{68}Ga-DOTA-peptide PET/CT to the MBS	**$438,794**	**$557,793**	**$680,469**	**$806,816**	**$936,765**
Net cost of ^{68}Ga-DOTA-peptide PET/CT to patients	**$7,717**	**$9,810**	**$11,968**	**$14,190**	**$16,475**
Incidence of GEP NET in Australia: 3.6 per 100,000 (base-case: 3 per 100,000) per year					
Net cost to the MBS	$485,529	$617,202	$752,944	$892,748	$1,036,538
Net cost to patients	$8,539	$10,855	$13,242	$15,701	$18,230

	2017–18	2018–19	2019–20	2020–21	2021–22
Base-case					
Net cost of ^{68}Ga-DOTA-peptide PET/CT to the MBS	**$438,794**	**$557,793**	**$680,469**	**$806,816**	**$936,765**
Net cost of ^{68}Ga-DOTA-peptide PET/CT to patients	**$7,717**	**$9,810**	**$11,968**	**$14,190**	**$16,475**
Diagnostic yield: 35% (base case: 59%)					
Net cost to the MBS	$609,075	$774,254	$944,536	$1,119,915	$1,300,292
Net cost to patients	$10,712	$13,617	$16,612	$19,697	$22,869
Diagnostic yield: 76% (base case: 59%)					
Net cost to the MBS	$383,247	$487,182	$594,328	$704,681	$818,180
Net cost to patients	$6,740	$8,568	$10,453	$12,394	$14,390
Benefit paid and the co-payments:85% and 15% of the schedule fee (base-case: average benefit paid and average co-payments based on MBS data)					
Net cost to the MBS	$433,192	$550,672	$671,781	$796,516	$924,805
Net cost to patients	$42,393	$53,890	$65,742	$77,948	$90,503
Incident cases eligible for repeat scan: 20% (base-case: 10%)					
Net cost to the MBS	$453,445	$576,417	$703,189	$833,755	$968,043
Net cost to patients	$7,975	$10,138	$12,367	$14,664	$17,025
Older cases amenable to surgery: 30% (base-case: 20%)					
Net cost to the MBS	$526,702	$669,541	$816,793	$968,453	$1,124,436
Net cost to patients	$9,263	$11,776	$14,365	$17,033	$19,776
Uptake rate: 30%–50% (base-case: 20%–40%)					
Net cost to the MBS	$658,191	$780,910	$907,292	$1,037,335	$1,170,956
Net cost to patients	$11,576	$13,734	$15,957	$18,244	$20,594

^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; GEP = gastroenteropancreatic; MBS = Medicare Benefits Schedule; NET = neuroendocrine tumour; PET = positron emission tomography; SPECT = single-photon emission computed tomography

SECTION F OTHER RELEVANT CONSIDERATIONS

None identified

Appendix A Clinical Experts and Assessment Group

CLINICAL EXPERTS WHO PROVIDED ADVICE

	Expertise or affiliation
A/Prof Paul Roach	nuclear medicine specialist
Dr David Wyld	medical oncologist
Prof Nick Pavlakis	medical oncologist

ASSESSMENT GROUP

AHTA, University of Adelaide, South Australia

	Position
Dr Judy Morona	Senior Research Officer
Dr Ruchi Mittal	Health Economist

Noted conflicts of interest

There were no conflicts of interest.

APPENDIX B STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Table 34 Characteristics of the evidence base included in the SRs for diagnostic accuracy

Study	Databases searched	Inclusion/exclusion criteria	Quality of included studies
Deppen et al. (2016b) USA	MEDLINE, EMBASE, Cochrane Reviews electronic databases, and grey literature from January 1999 to September 29, 2015.	**Inclusion criteria**: primary trials or studies with more than 10 human subjects conducted to investigate diagnosis for pulmonary or GEP NETs. **Exclusion criteria:** SRs, meta-analyses, or case reviews with 10 or fewer subjects; studies not reporting ^{68}Ga-DOTATATE compared with octreotide or conventional imaging; studies without pulmonary or GEP NET histology; studies reporting treatment, not diagnosis; and other reasons determined by reviewers making a study inapplicable.	k=10 studies for sensitivity Risk of bias: high in 1 study (5/13); moderate in 7 studies (7-9/13); low in 2 studies (11/13) k=5 studies for specificity Risk of bias: moderate in 4 studies (7-9/13); low in 1 study (11/13)
Geijer and Breimer (2013) Sweden	PubMed/MEDLINE, Embase, The Cochrane Library, Trip, International Network of Agencies for Health Technology Assessment and Centre for Reviews and Dissemination and ClinicalTrials.gov. from 1 November 2011 to 31 December 2012	**Inclusion criteria:** SMSR PET or PET/CT performed in a patient with NET in the thorax or abdomen; and sample size at least eight patients. **Exclusion criteria:** articles on another subject; reviews, editorials, comments or abstracts; case reports; studies including only patients with medullary thyroid cancer and/or paraganglioma or other tumours originating from the neural crest; insufficient data to calculate sensitivity and specificity at the patient level; duplicate publications of the same data.	k=22 studies for sensitivity 19 studies had a low risk of bias, 2 studies had an unclear risk of bias and 1 study had a high risk of bias k=11 studies for specificity All 11 studies had a low risk of bias
Mojtahedi et al. (2014) USA	PubMed and ovid MEDLINE databases ending 15 February 2014	**Inclusion criteria:** articles investigating the diagnostic and management role of ^{68}Ga-DOTATATE PET in patients with NETs comparing to ^{111}In-octreotide, MIBG scintigraphy or MRI. **Exclusion criteria:** review articles, case reports, editorial, letters, author reply, comments, duplicate data, studies using other radiopharmaceuticals, and articles that were not related to NETs.	k=5 studies for sensitivity Not appraised
Treglia et al. (2012) Italy	PubMed/MEDLINE, Scopus and Embase until 31 October 2011	**Inclusion criteria:** DOTA PET or PET/CT performed in patients with thoracic and/or GEP NETs; sample size of at least 8 patients with NET. **Exclusion criteria:** articles not within the field of interest of this review; review articles, editorials or letters, comments, conference proceedings; case reports or small case series (sample size of less than 8 patients with NET); articles including only patients with medullary thyroid carcinoma and/or paragangliomas and/or other neural crest derived tumours; insufficient data to reassess sensitivity (number of true positive and false negative) and specificity (number of true negative and false positive) on a per patient-based analysis, duplicate data	Overall medium-high quality indicating a low-moderate risk of bias.

Study	Databases searched	Inclusion/exclusion criteria	Quality of included studies
Yang et al. (2014) China	PubMed, Embase, and Scopus until 30 April 2013	**Inclusion criteria:** studies investigating the diagnostic role of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE PET in patients with NETs **Exclusion criteria:** case reports or very small case series; same patient data (such as duplicate publication); review articles, editorial, letters, author reply, comments, erratum, conference proceedings; insufficient data to reassess sensitivity or specificity from individual studies; articles not within the field of our study or using other radiopharmaceuticals	Overall, the quality of the included studies was medium–high with a low-moderate risk of bias. The studies scored a median of 11/13 (range 7–13).
Koopmans et al. (2009)	Medline and PubMed from 1995 to 2005 Non-systematic review	**Inclusion criteria:** papers with an English abstract, studies from which a clear description of sensitivity or specificity for individual tumour subgroups could be derived. **Exclusion criteria:** studies with fewer than 10 subjects except if a rare tumour type	k=18 studies for sensitivity Not appraised

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; DOTATOC = DOTA–D-Phe1-Tyr3-octreotide; GEP = gastroenteropancreatic; k = number of studies; NET = neuroendocrine tumour; PET = positron emission tomography; SR = systematic review

Table 35 Characteristics of the evidence base included in the SRs for change in management

Study	Databases searched	Inclusion/exclusion criteria	Quality of included studies
Barrio et al. (2017) USA	PubMed	**Inclusion criteria:** original research, cohort study, reported change in management after SRS imaging, number of patients >10. **Exclusion criteria:** not reported	k=14 studies for change in management after ^{68}Ga-DOTA-peptide PET/CT k=4 studies for change in management after both ^{68}Ga-DOTA-peptide PET/CT and ^{111}In-octreotide SPECT±CT Not appraised
Mojtahedi et al. (2014) USA	PubMed and ovid MEDLINE databases ending 15 February 2014	**Inclusion criteria:** articles investigating the diagnostic and management role of ^{68}Ga-DOTATATE PET in patients with NETs comparing to ^{111}In-octreotide, MIBG scintigraphy or MRI. **Exclusion criteria:** review articles, case reports, editorial, letters, author reply, comments, duplicate data, studies using other radiopharmaceuticals, and articles that were not related to NETs.	k=2 studies for change in management Not appraised

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; k = number of studies; NET = neuroendocrine tumour; PET = positron emission tomography; SRS = somatostatin receptor scintigraphy

Table 36 Study profiles of the studies reporting a change in management

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objective	Intervention / comparator	Outcomes assessed
Alonso et al.	Retrospective case series	N=29 patients with	**Inclusion criteria:** All patients had a biopsy-	^{68}Ga-DOTATATE PET/CT was performed on a dual-	Identification of

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objective	Intervention / comparator	Outcomes assessed
(2014) Uruguay	IHE moderate quality (8.5/13) Medium risk of bias	histopathologically proven metastatic NETs with unknown primary	proven NET and negative conventional imaging studies for primary tumour identification **Exclusion criteria:** Not reported	modality PET/CT tomography equipped with a 64-row spiral CT and time-of-flight correction (Discovery 690, GE Medical Systems, Waukesha, WI, USA).	primary tumour site Surgery resulting from PET/CT results
Deppen et al. (2016a) USA	Before and after case series IHE good quality (12.5/14) Low risk of bias	N=78 patients with ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans 58 GEP NET 5 pulmonary 1 other 14 unknown	**Inclusion criteria:** consecutively enrolled patients between March 2011 and November 2013, 90 having a proven diagnosis of NET **Exclusion criteria:** no prior ^{111}In-pentetreotide scan was available, no ^{111}In-pentetreotide scan was available after a major surgical intervention occurring between ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans, or if the time between ^{111}In-octreotide SPECT±CT and ^{68}Ga-DOTATATE PET/CT scans exceeded 3 years	The initial treatment plan was formulated using all available clinical, pathologic, and imaging information, including ^{111}In-octreotide SPECT±CT scans. This treatment plan was then reviewed after adding the information from the ^{68}Ga-DOTATATE scan. ^{68}Ga-DOTATATE PET/CT Imaging was performed with an 8-slice Discovery PET/CT full-ring integrated scanner (GE Healthcare), beginning 65 min (range, 55–93 min) after injection. Original clinical reports of ^{111}In-octreotide SPECT, CT, and MRI examinations were used for analysis of these examinations even if, in retrospect, additional sites of tumour were seen after comparison to ^{68}Ga-DOTATATE images.	Change in treatment plan
Hofman et al. (2012) Australia	Before and after case series IHE moderate quality (10.5/14) Medium risk of bias	N=40 patients with ^{111}In-pentetreotide and ^{68}Ga-DOTATATE scans Mostly GEP or bronchial NET	**Inclusion criteria:** recruited on the basis of clinical need targeting three specific patient groups: firstly, patients with potentially resectable primary or limited metastatic disease on anatomical and ^{111}In-octreotide SPECT/CT imaging; secondly, patients with biochemical, anatomical imaging, biopsy evidence of NET but negative ^{111}In-octreotide SPECT/CT; and thirdly, patients with clear evidence of somatostatin-receptor positive, metastatic disease on prior imaging but in whom no primary tumour had previously been identified. **Exclusion criteria:** not reported	The management impact associated with any incremental diagnostic information from ^{68}Ga-DOTATATE PET/CT compared with ^{111}In-octreotide SPECT±CT and conventional studies. A range of 165–243 MBq (mean 202 MBq) ^{68}Ga-DOTATATE was administered by intravenous injection followed by a 30-60-min uptake period. Imaging was performed, typically from vertex to upper thighs, using a PET/CT scanner incorporating contemporaneous PET and multislice CT (Discovery STE, General Electric Medical Systems, Milwaukee, WI, USA or Biograph 64, Siemen's, Knoxville, TN, USA). Prior ^{111}In-octreotide SPECT/CT scans were reviewed. This was used to determine incremental information provided by ^{68}Ga-DOTATATE PET/CT	High, moderate or low impact changes to treatment plan

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objective	Intervention / comparator	Outcomes assessed
				images	
Krausz et al.(2011) Israel	Before and after case series IHE moderate quality (10.5/14) Medium risk of bias	N=19 patients who underwent ^{68}Ga-DOTANOC PET/CT and Ostreoscan SPECT imaging. 17 GEP NETs 2 other	**Inclusion criteria:** Patients were referred for tumour staging, detection of somatostatin receptors prior to peptide receptor radionuclide therapy, and for evaluation of response to therapy. **Exclusion criteria:** Patients who were below 18 years of age, pregnant or nursing, or unwilling or unable to comply with the protocol	All patients underwent ^{68}Ga-DOTANOC PET/CT and ^{111}In-octreotide SPECT±CT imaging within 10–65 days of each other (median 24 days). PET/CT scans were acquired on a GE Discovery ST PET/CT scanner (GE Medical System, Waukesha, WI, USA). ^{68}Ga-DOTANOC 83.2–184.3 MBq (mean 144.7±23.8; median 146.5 MBq) was administered intravenously, with scan beginning 56–96 min (mean 77±13 min) after tracer injection. ^{111}In-octreotide SPECT±CT imaging was performed after intravenous administration of 222 MBq of ^{111}In-octreotide (MallinckrodtMedical, Petten, Holland). Images were acquired using a dual-head, large field-of-view gamma camera equipped with a medium-energy collimator. SPECT of the abdomen, pelvis, chest, neck, and head as required, with or without CT, was acquired in all patients at 24 h after tracer injection.	Changes to treatment plan
Prasad et al. (2010) Germany and Italy	Retrospective case series IHE moderate quality (9.5/13) Medium risk of bias	N=59 patients with histologically proven NET and unknown primary tumour	**Inclusion criteria:** Patients enrolled between July 2004 and February 2007 with (1) biopsy-proven NET and (2) an unidentified primary tumour (negative physical examination and conventional imaging) **Exclusion criteria:** Not reported	The patients fasted 6 h before the scans were carried out (intravenous injection of 185 MBq ^{68}Ga-DOTANOC, uptake time 60 min). PET scan emission images were recorded for 4 min per bed position; for non-uniform attenuation correction, CT images were used (acquisition parameters: 140 kV, 90 mA, 0.8 s, tube rotation, 5 mm thickness). PET images were acquired from the skull base to the middle part of the thigh.	Identification of primary tumour site Surgery resulting from PET/CT results
Sadowski et al. (2016) USA	Before and after case series IHE good quality (12/14) Low risk of bias	N=131 patients with suspected or known NETs 89 proven NETs 87 GEP NET 2 other	**Inclusion criteria:** Patients suspected or known to have GEP NETs on imaging (CT, MRI, FDG PET) and/or biochemical evidence of GEP NETs, and/or a familial predisposition to NET (multiple endocrine neoplasia type 1 or von Hippel-Lindau).	All patients underwent ^{68}Ga-DOTATATE PET/CT and ^{111}In-octreotide SPECT/CT imaging within 3 months of each other. For ^{68}Ga-DOTATATE PET/CT imaging, ^{68}Ga-DOTATATE 185 MBq (5 mCi) was administered through a peripheral vein. After approximately 60	Identification of unknown primary tumour Change in management plan

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objective	Intervention / comparator	Outcomes assessed
		14 unknown primary	**Exclusion criteria:** Patient unwilling to undergo serial non-invasive imaging; pregnant or lactating women; patient has recognized concurrent active infection; patient has had the use of any investigational product or device, excluding F-DOPA scans, within 30 days before dosing.	minutes, the patient was positioned supine in a PET/CT scanner, and images were obtained from the area of the upper thighs to midskull. A low-dose, noncontrast enhanced CT was used for attenuation correction and anatomic localization. An ^{111}In-octreotide SPECT scan was performed after intravenous administration of ^{111}In-octreotide 222 MBq (6 mCi) within 4weeks of ^{68}Ga-DOTATATE PET/CT. Planar whole body ^{111}In-octreotide SPECT scans of the chest (at 24 hours) and abdomen and pelvis (at 4 hours and repeated at 24 hours) were used for analyses. A low-dose, non-contrast enhanced CT was used for attenuation correction and anatomic localization.	
Srirajaskanthan et al. (2010) UK	Before and after case series IHE moderate quality (10.5/14) Medium risk of bias	N=51 patients who underwent ^{68}Ga-DOTATATE PET/CT and ^{111}In-octreotide SPECT scanning 37 GEP NET 2 bronchial NET 6 other 6 unknown	**Inclusion criteria:** patients who underwent ^{111}In-octreotide SPECT±CT with prospective follow-up between November 2006 and March 2008 **Exclusion criteria:** not reported	All patients underwent ^{68}Ga-DOTATATE PET/CT and ^{111}In-octreotide SPECT imaging within 4 months of each other. For ^{68}Ga-DOTATATE PET, images were acquired 1 h after injection of 120–200 MBq of ^{68}Ga-DOTATATE. Imaging was performed using a dedicated GE Discovery LS PET/CT unit. For ^{111}In-octreotide SPECT, patients were injected with 200 MBq of ^{111}In-octreotide IV (Covidien). Whole-body images were acquired at 24 h after injection on a dual-head g-camera (Picker Prism; Phillips Medical Technology). SPECT abdominal images were obtained from the dome of the liver downward	Change in clinical management

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTANOC = DOTA-Phe1-NaI3-octreotide; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; GEP = gastroenteropancreatic; IHE = Institute of Health Economics case series checklist; NET = neuroendocrine tumour; MBq = megabecquerel; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography

Table 37 Study profiles for the non-comparative studies reporting on the effectiveness of a change in management leading to either surgery or SSA therapy

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objective	Intervention	Outcomes assessed
Horsch et al. (2016) Germany	Retrospective non-comparative study IHE good quality (12/15) Low risk of bias	N=450 patients with progressive, locally advanced or metastatic low to intermediate grade GEP NET with overexpression of somatostatin receptors. 86 unknown primary	The registry was started in 2009 to document effectiveness and adverse events of PRRT by assessment of overall survival, progression-free survival, and side-effects from six centres in Germany. **Inclusion criteria:** patients registered between 2009 and 2012 **Exclusion criteria:** Not reported	The SSA/chelators DOTATATE and DOTATOC were applied in most therapy cycles, respectively. Between one and eight cycles were performed with a mean dose of 5.38 GBq at each cycle. ^{177}Lu was predominantly used as a radionuclide, either alone or in combination with ^{90}Y. Three patients were treated with ^{67}Ga.	Overall survival
Keck et al. (2017) USA	Prospective non-comparative study IHE moderate quality (10/15) Medium risk of bias	N=134 GEP NET patients who underwent an operation	Registry of patients presenting to the University of Iowa NET Clinic between 1999 and 2016 **Inclusion criteria:** Patients presenting with biopsy-proven or suspected GEP NET liver metastases (by virtue of increased biochemical markers and imaging characteristics) and a primary tumour still in place when evaluated by a single surgeon **Exclusion criteria:** Not reported	Surgery to resect primary tumour and/or de-bulk liver metastases	Median survival
Laskaratos et al. (2016) UK	Prospective non-comparative study IHE good quality (12.5/15) Low risk of bias	N=254 patients with SSA treatment-naïve NETs 233 GEP 14 lung 7 unknown	**Inclusion criteria:** Treatment-naïve patients with confirmed histopathological diagnosis of NET treated with octreotide LAR (as monotherapy) in our centre from 2001 to 2014. **Exclusion criteria:** Not reported but primary tumour resection before SSA therapy was permitted	All patients had an initial test dose of subcutaneous (s.c.) octreotide (50 mg). If no immediate adverse effect was noted, patients had either an initial 2-week course of s.c. octreotide (100/200 mg tds) and then were switched over to octreotide LAR or patients were given monthly octreotide LAR. The initial dose of octreotide LAR was 20 mg/28 days in 198 patients and 30 mg/28 days in 56 patients.	Time to radiological progression Partial response
Pasqual et al. (2016) Italy	Prospective non-comparative study IHE good quality (11/15) Low risk of bias	N= 26 patients, who underwent surgery for hepatic metastases from GEP NETs. 22 had hepatic resective surgery 4 had orthotopic liver	**Inclusion criteria:** Patients, who underwent surgery for hepatic metastases from NETs at the Departments of Surgery of 'Santa Maria della Misericordia' University Hospital (Udine, Italy) and 'Ospedali Riuniti Umberto I, G.M. Lancisi, G. Salesi' University Hospital (Ancona, Italy) between January 1990 and December 2012 **Inclusion criteria for liver transplantation:**	Hepatic resective surgery or orthotopic liver transplantation	Overall survival

Study Country	Study design Quality appraisal	Study population	Inclusion criteria / Exclusion criteria / Objective	Intervention	Outcomes assessed
		transplantation	Histological confirmation of NET; diffuse un-resectable hepatic disease; substitution of ≤50% hepatic parenchyma; stable disease during the preoperative period; absent or stable extra‑hepatic disease during the preoperative period; and hepatic insufficiency following the hepatic resection of stable disease. **Exclusion criteria:** Not reported		
Saglam et al. (2015) Turkey	Prospective non-comparative study IHE good quality (12/15) Low risk of bias	N=23 patients with locally inoperable or metastatic non-functional GEP NETs	**Inclusion criteria:** Unresectable, locally advanced or metastatic, non-functioning, somatostatin receptor-positive GEP NETs with grade 1 or 2 and Ki-67 proliferative index <10 that received first-line octreotide LAR treatment **Exclusion criteria:** Not reported	All patients had received octreotide LAR 30 mg for 4 weeks (Sandostatin LAR, Novartis) until progression	Progression-free survival Overall survival
Townsend et al. (2010) Australia	Retrospective non comparative study IHE moderate quality (10/15) Medium risk of bias	N= 92 patients diagnosed with carcinoid tumours 63 GEP 14 lung 5 other 10 unknown	**Inclusion criteria:** Patients diagnosed with carcinoid tumors in the North West Adelaide Health Service between January 1, 1985 andMarch 1, 2007 were identified from the South Australian Cancer Registry **Exclusion criteria:** not reported	SSA using octreotide (n=25) or octreotide LAR (n=24) Resection of primary tumour (n=71) versus intact primary tumour (n=11)	Median survival

^{67}Ga = ^{67}Gallium; ^{90}Y = ^{90}Yttrium; ^{177}Lu = ^{177}Lutetium; CT = computed tomography; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; DOTATOC = DOTA–D-Phe1-Tyr3-octreotide; GBq = gigabecquerel; GEP = gastroenteropancreatic; IHE = Institute of Health Economics case series checklist; LAR = long acting release; NET = neuroendocrine tumour; PRRT = peptide receptor radionuclide therapy; SIGN = Scottish Intercollegiate Guidelines Network; SSA = somatostatin analogue

APPENDIX C EXTRACTED DATA FROM INCLUDED STUDIES

Table 38 Sensitivity and specificity of ^{68}Ga-DOTA-peptide PET/CT compared with the reference standard

Included study	Population	Imaging method	Reference standard	Geijer and Breimer (2013) Sensitivity (95%CI) Specificity (95%CI)	Deppen et al. (2016b) Sensitivity (95%CI) Specificity (95%CI)
Alonso et al. (2014)	metastatic CUP NETs	^{68}Ga-DOTATATE PET/CT	Histopathology		79% (62, 90)
Ambrosini et al. (2012)	670 GEP, 158 lung, 81 CUP, 126 suspected, 204 other	^{68}Ga-DOTATOC PET/CT	Conventional imaging or follow-up	92% (90, 94) 98% (97, 99)	
Buchmann et al. (2007)	15 GEP, 8 CUP, 1 lung, 3 other	^{68}Ga-DOTATOC PET	Histopathology	100% (87, 100)	
Deppen et al. (2016a)	76 GEP, intestinal, or bronchial NETs	^{68}Ga-DOTATATE PET/CT	Histopathology and/or conventional imaging		96% (86, 100) 93% (77, 99)
Frilling et al. (2010)	49 GEP, 1 CUP, 2 lung	^{68}Ga-DOTATOC PET/CT	Histopathology and/or conventional imaging	100% (93, 100)	
Gabriel et al. (2007)	50 GEP, 9 CUP, 6 lung, 19 other	^{68}Ga-DOTATOC PET	Histopathology	97% (90, 100) 92% (64, 100)	
Haug et al. (2009)	14 GEP, 6 lung, 4 CUP, and 1 paranasal sinus	^{68}Ga-DOTATATE PET/CT	Histopathology	96% (80, 100)	96% (80, 100)
Haug et al. (2012)	Suspected: 20 GEP, 5 lung, 5 CUP, 6 other	^{68}Ga-DOTATATE PET/CT	Histopathology and/or conventional imaging	81% (64, 92) 90% (80, 96)	81% (64, 92) 90% (80, 96)
Haug et al. (2014)	48 GEP, 9 lung, 3 CUP, 10 other	^{68}Ga-DOTATATE PET/CT	Histopathology and/or follow-up	-	94% (73, 100) 89% (71, 98)
Hofman et al. (2001)	6 GEP, 2 lung	^{68}Ga-DOTATOC PET	Histopathology	100% (63, 100)	
Hofman et al. (2012)	26 GEP, 2 lung, 12 CUP, 8 other, 11 suspected	^{68}Ga-DOTATATE PET/CT	Histopathology	100% (93, 100) 86% (42, 100)	100% (93, 100) 86% (42, 100)
Jindal et al. (2010)	20 lung	^{68}Ga-DOTATOC PET/CT	Conventional imaging	95% (75, 100)	
Kabasakal et al. (2012)	6 GEP, 2 lung, 8 CUP, 3 other	^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC PET/CT	Histopathology	70% (46, 88)	
Kayani et al. (2008)	28 GEP, 6 lung, and 4 CUP	^{68}Ga-DOTATATE PET/CT	Histopathology	82% (66, 92)	82% (67, 91)

Included study	Population	Imaging method	Reference standard	Geijer and Breimer (2013) Sensitivity (95%CI) Specificity (95%CI)	Deppen et al. (2016b) Sensitivity (95%CI) Specificity (95%CI)
Kayani et al. (2009)	18 lung	^{68}Ga-DOTATATE PET/CT	Histopathology	72% (47, 90)	
Koukouraki et al. (2006)	9 GEP, 4 CUP, 2 lung, 2 thymus, 5 other	^{68}Ga-DOTATOC PET	Histopathology	95% (77, 100)	
Krausz et al. (2011)	15 GEP, 2 CUP, 1 lung, 1 other	^{68}Ga-DOTANOC PET/CT	Histopathology	100% (82, 100)	
Kumar et al. (2011)	20 pancreatic NET	^{68}Ga-DOTATOC PET/CT	Histopathology	100% (83, 100)	
Lastoria et al. (2016)	11 GEP NETs	^{68}Ga-DOTATATE PET/CT	Genetic diagnosis of MEN1		100% (82, 100)
Mayerhoefer et al. (2012)	49 GEP, 6 CUP	^{68}Ga-DOTATOC PET/CT	Histopathology	100% (89, 100) 95% (77, 100)	
Naswa et al. (2011)	109 GEP	^{68}Ga-DOTANOC PET/CT	Histopathology	97% (91, 100) 100% (89, 100)	
Pfeifer et al. (2012)	13 GEP, 1 lung	^{64}Cu-DOTATATE PET/CT	Histopathology	100% (74, 100) 100% (16, 100)	
Putzer et al. (2009)	Bone metastases from 35 GEP, 5 lung, 10 CUP, 1 other	^{68}Ga-DOTATOC PET	Histopathology	97% (86, 100) 92% (64, 100)	
Ruf et al. (2011)	33 GEP, 4 lung, 14 other	^{68}Ga-DOTATOC PET/CT	Histopathology and/or follow-up	82% (66, 92) 67% (35, 90)	
Srirajaskanthan et al. (2010)	37 GEP, 6 CUP, 2 lung, 2 thymus, 4 other	^{68}Ga-DOTATATE PET/CT	Histopathology and/or conventional imaging	87% (74, 95) 100% (40, 100)	87% (74, 95) 100% (40, 100)
Versari et al. (2010)	13 GEP, 6 other	^{68}Ga-DOTATOC PET/CT	Histopathology and/or conventional imaging	92% (64, 100) 83% (36, 100)	
Wild et al. (2013)	metastatic GEP NETs	^{68}Ga-DOTATATE PET/CT	Histopathology		94% (74, 99)

^{68}Ga = 68Gallium; CI = confidence interval; CT = computed tomography; CUP = carcinoma with unknown primary; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; DOTANOC = DOTA-Phe1-Nal3-octreotide; DOTATATE = DOTA–D-Phe1-Tyr3-Thr8-octreotate; DOTATOC = DOTA–D-Phe1-Tyr3-octreotide; GEP = gastroenteropancreatic; NET = neuroendocrine tumour; PET = positron emission tomography

Table 39 Studies included in the meta-analysis of ^{111}In-octreotide SPECT±CT compared with the reference standard

Included study	Population	Imaging method	Source
Briganti et al. (2001)	38 pancreatic NETs	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Chiti et al. (1998)	131 GEP NETs	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Corleto et al. (1996)	24 GEP NETs	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Koopmans et al. (2006)	53 NETs, 43 GEP, 5 lung, 16 CUP	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Koopmans et al. (2008)	44 GEP NETs	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Krausz et al. (1998)	41 GEP NETs	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Montravers et al. (2006)	33 GEP NETs	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Orlefors et al. (2005)	42 NETs 32 GEP, 6 lung, 4 other	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Raderer et al. (2000)	195 NETs 165 GEP, 20 lung, 10 CUP	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Rickes et al. (2003)	29 suspected pancreatic NETs	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Virgolini et al. (2001)	60 NETs	^{111}In-octreotide SPECT	Koopmans et al. (2009)
Binderup et al. (2010)	96 NETS 80 GEP, 7 lung, 9 other	^{111}In-octreotide SPECT/CT	Quick PubMed search
Deppen et al. (2016a)	78 NETs, 65 GEP, 5 lung, 7 CUP, 1 other	^{111}In-octreotide SPECT/CT	Quick PubMed search
Gabriel et al. (2007)	84 suspected NETs	^{111}In-octreotide SPECT/CT	Quick PubMed search
Jilesen et al. (2016)	62 pancreatic NETs	^{111}In-octreotide SPECT/CT	Quick PubMed search
Koopmans et al. (2006)	53 NETs, 43 GEP, 5 lung, 16 CUP	^{111}In-octreotide SPECT/CT	Koopmans et al. (2009)
Pfeifer et al. (2015)	112 NETs 80 GEP, 9 lung, 23 CUP	^{111}In-octreotide SPECT/CT	Quick PubMed search
Sainz-Esteban et al. (2015)	107 suspected NET, 51 GEP, 17 lung, 3 CUP, 36 other	^{111}In-octreotide SPECT/CT	Quick PubMed search
Squires et al. (2015)	131 GEP NETs	^{111}In-octreotide SPECT/CT	Quick PubMed search
Stokkel et al. (2011)	88 NETs, 64 GEP, 6 other, 18 CUP	^{111}In-octreotide SPECT/CT	Quick PubMed search

^{111}In = ^{111}Indium; CT = computed tomography; CUP = carcinoma with unknown primary; DTPA = diethylene-triamino-penta-acetic acid; GEP = gastroenteropancreatic; NET = neuroendocrine tumour; SPECT = single-photon emission computed tomography

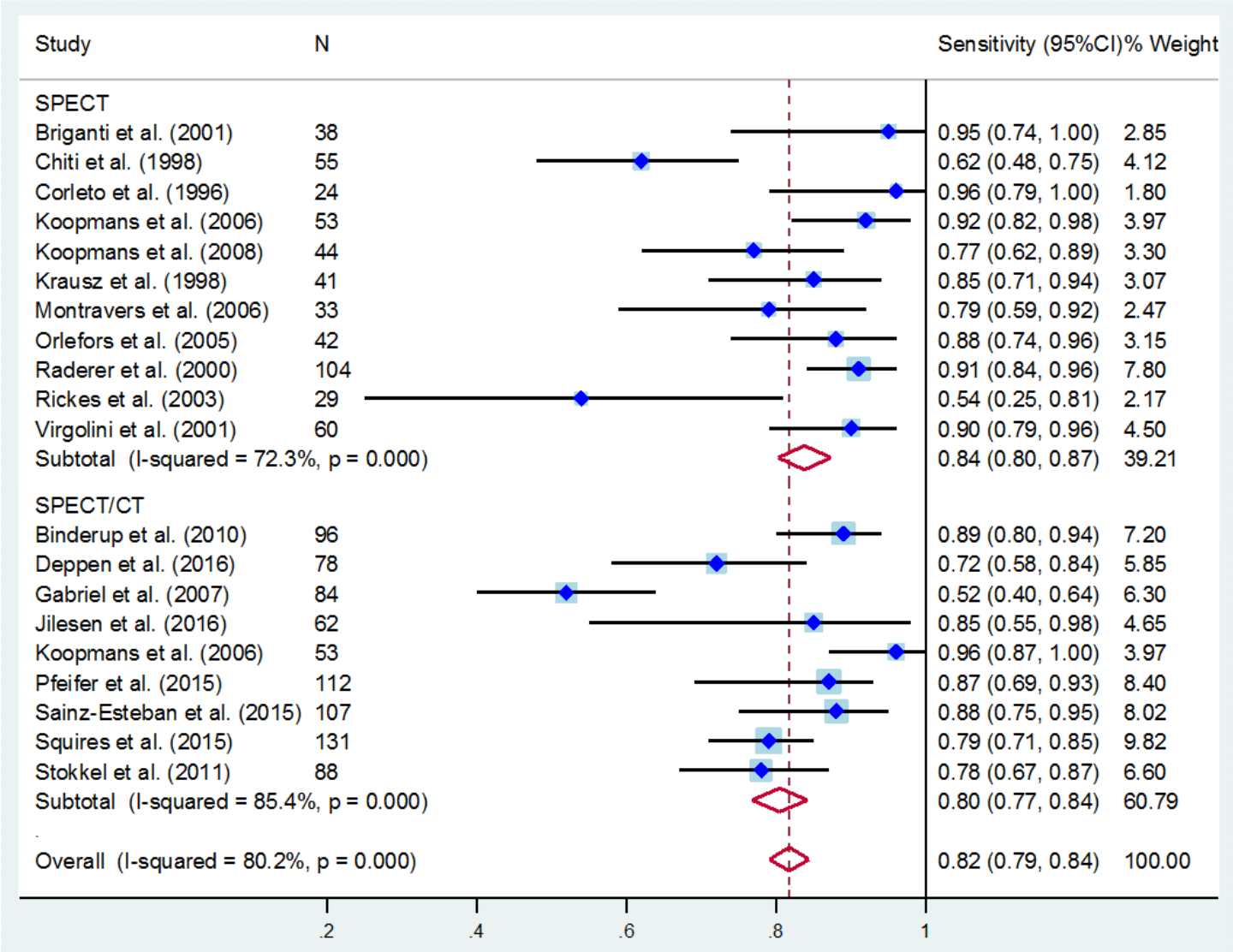

Figure 7 Forest plot showing the sensitivity of ^{111}In-octreotide SPECT and SPECT/CT compared with the composite reference standard

^{111}In = ^{111}Indium; CI = confidence interval; CT = computed tomography; N = number of patients; SPECT = single-photon emission computed tomography

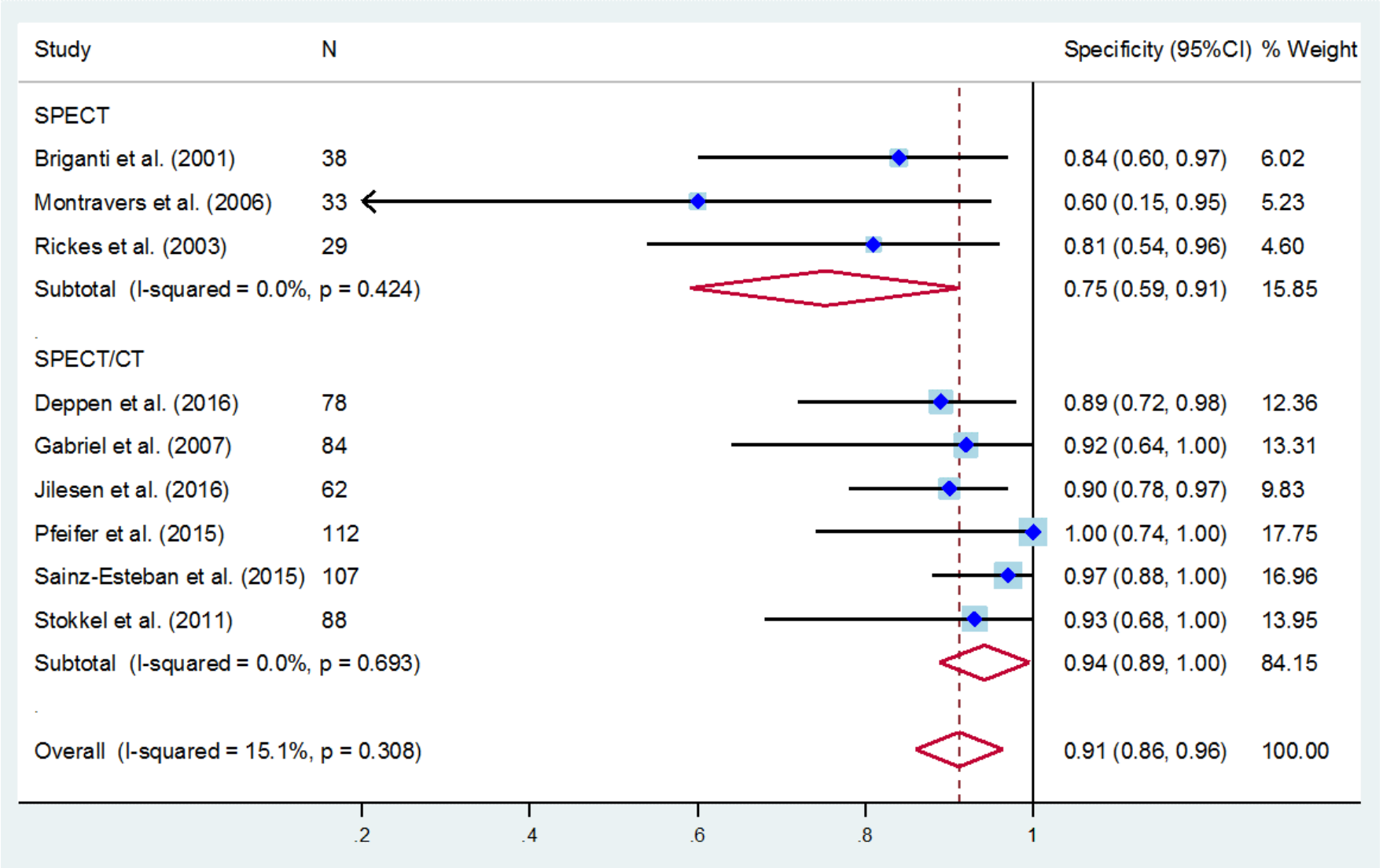

Figure 8 Forest plot showing the specificity of ^{111}In-octreotide SPECT and SPECT/CT compared with the composite reference standard

^{111}In = ^{111}Indium; CI = confidence interval; CT = computed tomography; N = number of patients; SPECT = single-photon emission computed tomography

APPENDIX D ADDITIONAL INFORMATION FOR FINANCIAL ANALYSIS

MBS utilisation for item 61369 since 2002–03.

Table 40 The MBS utilisation for item 61369 since 2002–03

Year	Number of services for MBS item 61369
2002/2003	251
2003/2004	237
2004/2005	273
2005/2006	354
2006/2007	436
2007/2008	542
2008/2009	712
2009/2010	802
2010/2011	693
2011/2012	484
2012/2013	419
2013/2014	236
2014/2015	146
2015/2016	106

Source: Medicare item reports; < http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp >, accessed on 2 February 2017.

MBS = Medicare Benefits Schedule

Projection of number of ^{111}In-octreotide SPECT services that would be MBS funded from 2017–22.

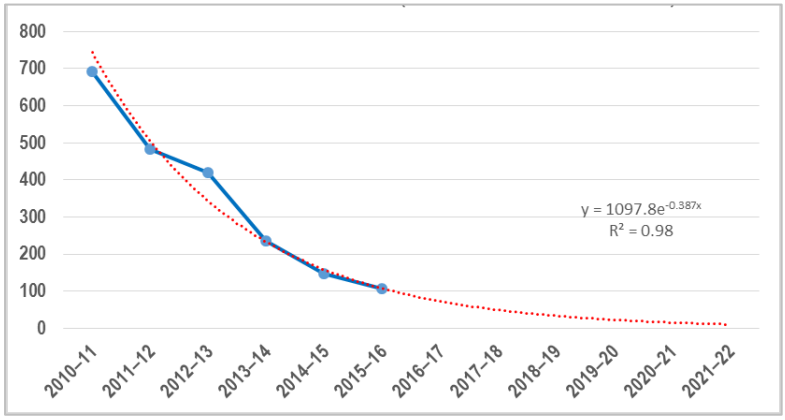

Figure 9 Projected number of ^{111}In-octreotide SPECT services that would be MBS funded (2017–18 to 2021–22) if not replaced by ^{68}Ga-DOTA-Peptide PET

^{111}In = ^{111}Indium; ^{68}Ga = ^{68}Gallium; DOTA = 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid; MBS = Medicare Benefits Schedule; PET = positron emission tomography; SPECT = single-photon emission computed tomography

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