EVIDENCE APPRAISAL
REPORT

Technoleg Iechyd Cymru
Health Technology Wales

The clinical and cost effectiveness of fluorine- or gallium- prostate-specific membrane antigen (PSMA) positron emission tomography (PET) radiotracers in the investigation of recurrent prostate cancer

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1. Purpose of the Evidence Appraisal Report

The Evidence Appraisal Report is a rapid systematic literature search of published evidence and websites to identify the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Prostate cancer is the most common cancer in males in the UK, accounting for 26% of all new cancer cases in males(Cancer Research UK). In 2015, there were 2,552 new cases of prostate cancer in Wales. Prostate cancer incidence is strongly associated with age; over a third (35%) of new cases between 2013 and 2015 were in males aged 75 and over (Cancer Research UK). Although the incidence rate of prostate cancer in Wales has remained stable, the number of cases are increasing due to an aging population and changes in diagnosis (Welsh Cancer Intelligence and Surveillance Unit 2016).

The diagnosis of localised prostate cancer involves the detection of abnormal prostate specific antigen (PSA) level and/or digital rectal examination, and confirmation by prostate biopsy (Mottet et al. 2018). Staging of prostate cancer guides appropriate treatment and is driven by the results of imaging including positron emission tomography/computed tomography (PET/CT). Following diagnosis, treatment can be deferred and the disease is monitored by 'watchful waiting' or active surveillance. Active treatment can comprise radical prostatectomy, radiotherapy (which can be delivered externally (for example external beam radiotherapy) or internally (for example brachytherapy), or pelvic lymph node dissection plus radiotherapy (Mottet et al. 2018).

Between 27-53% of all men with prostate cancer develop recurrent disease following radical prostatectomy or radiotherapy (Mottet et al. 2018). Recurrence is initially demonstrated by a rise in total serum PSA; this is known as a biochemical relapse or recurrence. There is no specific PSA threshold for clinically relevant recurrence as it depends on the primary treatment that the person received. European Association of Urology guidelines on prostate cancer state:

- After radical prostatectomy, a PSA threshold of > 0.4 ng/ml defines relapse. However, a lower PSA level would be a concern with ultra-sensitive PSA testing.
- After radiotherapy, with or without short-term hormonal manipulation, relapse is any PSA increase ≥ 2 ng/ml higher than the PSA nadir value, regardless of the serum concentration of the nadir.

- After high-intensity focused ultrasound or cryotherapy, an acceptable PSA threshold has not been recommended as no endpoints have been validated against clinical progression or survival in these treatments (Mottet et al. 2018).

Early detection and precise localisation of the site of recurrence is critical and provides a basis for further therapeutic decisions.

3. Health technology and Welsh context

Positron emission tomography (PET) is a non-invasive imaging technique used to detect metabolic activity or cell surface molecules that are usually associated with cancer (Bednarova et al. 2017, Shen et al. 2014). The procedure usually involves injecting a radiolabelled tracer into the body, but some tracers can be ingested or inhaled. The radiolabelled tracer can be a sugar (glucose), an amino acid, or a vitamin which is taken up and accumulates in metabolically active cells (such as malignant cells). It emits gamma rays detected by the PET scanner to produce colour-coded images of the body, showing the cellular activity of both normal and malignant tissue. The radiolabelled tracers are then excreted through urine or bowel movement. PET is commonly used in conjunction with CT; this gives a precise anatomical localisation of tracer uptake. Images from both PET and CT devices can be combined into a single superimposed image and provide important diagnostic information as well as assessing the effectiveness of treatment in cancer.

The most well-known PET tracer used with PET/CT is ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG); however, FDG PET has low specificity in prostate cancer. This is mainly due to the low metabolism of glucose in prostate cancer but also the rapid dephosphorylating and excretion into the urinary system (Bednarova et al. 2017).

Several non-FDG tracers have been developed and used with PET in cancers where glucose metabolism is low, such as prostate cancer. Prostate specific membrane antigen (PSMA) is a membrane protein that is highly expressed by prostate cancer cells. Small-molecule PSMA inhibitors labelled with radionuclides have been developed with the aim of producing tracers that localise to prostate cancer sites. The focus of this appraisal is on PET using tracers labelled with ^{68}Gallium or ^{18}Fluorine, commonly known as ^{68}Ga-PSMA PET and ^{18}F-PSMA PET (Eissa et al. 2018).

Other non-FDG tracers include:

- ^{18}F-fluoroethylcholine (^{18}F-FEC)
- ^{18}F-fluoromethylcholine (^{18}F-FCH)
- ^{11}C-choline
- anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (anti-^{18}F-FACBC, also known as ^{18}F-fluciclovine)
- 2-(3-(1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid (^{18}F-DCFPyl).

Expert opinion sought during the production of this report suggests that choline-based PET (using either ^{18}fluorine or ^{11}carbon radiotracers) represents current standard of care. The Welsh Health Specialised Services Committee (WHSCC) approves funding for ^{18}F-choline-based PET/CT in the assessment of suspected recurrence in patients with a rapidly rising prostate-specific antigen (PSA) and negative or equivocal conventional imaging where the results would directly influence patient management.

Guideline recommendations vary on the use of non-FDG PET tracers in the investigation of suspected recurrent prostate cancer (see Appendix 2 for details). The European Association of Urology guidelines recommend use of PSMA-based PET/CT imaging for PSA recurrence; for recurrence after radical prostatectomy, use of PSMA tracers is only recommended if the PSA level is ≥ 1 ng/ml (Mottet et al. 2018). Otherwise, choline-based tracers are recommended. Joint UK guidance from the Royal Colleges of Physicians, the Royal College of Radiologists and the British Nuclear Medicine Society supports the use of

choline tracers and ^{68}Ga-PSMA in patients with suspected recurrent prostate cancer (The Royal College of Radiologists et al. 2016). Similarly, joint guidance from the European Association of Nuclear Medicine/Society of Nuclear Medicine and Molecular Imaging guidance recommends ^{68}Ga-PSMA in patients with suspected recurrent prostate cancer, particularly in patients with low PSA values (Fendler et al. 2017). Cancer Care Ontario does not routinely recommend choline PET/CT in this patient population and its use is considered investigational (Matthew et al. 2015).

4. Evidence search methods

Selection criteria used to identify evidence for appraisal are detailed in Appendix 3. Selection criteria were originally adapted from those used in the Scottish Health Technologies Group (SHTG) Evidence Note 67 (SHTG 2017). Changes were made to the protocol following comments from the Health Technology Wales (HTW) Assessment Group and topic experts, primarily to focus on PSMA-based tracers as the intervention of interest (see Appendix 4 for details).

We aimed to identify the following types of evidence:

(i) systematic reviews of diagnostic accuracy studies, comparative trials of any design, or cost effectiveness studies, published after July 2016 (any evidence published prior to this date was included in SHTG Evidence Note 67)
(ii) ongoing clinical trials.

Background studies and other papers identified at the topic exploration stage were also assessed for relevance.

A systematic literature search was first undertaken on 9 August 2018 and an updated search was done on 23 October 2018. The search strategy and list of sources searched is available on request. Appendix 4 and Section 5 summarise the selection of studies for inclusion in the review.

Patient safety and organisational issues were identified from the papers included in the clinical effectiveness section, and expert advice; no specific searches were undertaken.

5. Clinical effectiveness

Searches identified two systematic reviews that summarised evidence on the diagnostic accuracy, disease detection rates or clinical utility of ^{68}Ga PSMA PET (Eissa et al. 2018, Sathianathen et al. 2018). Both reviews also included some evidence on outcomes with other PET tracers or other imaging modalities. A third systematic review (Sandgren et al. 2017) assessed the use of PET imaging in recurrent prostate cancer without focussing on any particular tracer. This review did not include any studies of ^{68}Ga-PSMA PET, but is included as it reports diagnostic accuracy of several potential comparators.

Because the systematic reviews did not include any evidence on the effectiveness of ^{18}F-PSMA PET, we also considered primary studies that provided this evidence. Three studies of ^{18}F-PSMA tracers were included (all of which reported detection rates as their sole outcome). We also included any primary studies on ^{68}Ga-PSMA PET that (i) were published subsequent to the searches detailed in the relevant systematic reviews, or (ii) met the inclusion criteria for HTW's evidence review (Appendix 3), but were not included in any systematic review (for example, some reviews did not include clinical utility outcomes, or data from comparative studies). This identified a further 14 relevant studies.

5.1. Systematic reviews

Evidence on the diagnostic accuracy of ^{68}Ga-PSMA PET and several comparators is available from three recent good quality systematic reviews. Two reviews included ^{68}Ga-PSMA PET, either alone or compared to other tracers (Eissa et al. 2018, Sathianathen et al. 2018); a third review (Sandgren et al. 2017) did not include any studies of ^{68}Ga-PSMA PET, but is included as it reports diagnostic accuracy of several potential comparators. Tables 1 to 3 summarise the characteristics and findings of each of the three reviews included.

All three reviews appear to have been well-conducted. In all relevant reviews, concerns about the high likelihood of bias in included studies was noted. The majority of studies were retrospective, and the nature of prostate cancer means that unequivocal verification of test results using a suitable reference standard (such as pathological verification of disease at each lesion site) is not always practical or ethical. For negative test results, few studies included a standardised follow-up protocol to confirm the absence of disease.

In the two systematic reviews that included data on the diagnostic accuracy of ^{68}Ga-PSMA PET, five relevant studies were identified. Estimates of sensitivity ranged from 76% to 93% and estimates of specificity ranged from 50% to 100%. No attempts were made by the authors to conduct pooled analysis; given the differences in study design and population, pooled analysis is unlikely to have been appropriate.

One systematic review (Eissa et al. 2018) included evidence on the influence of ^{68}Ga PSMA PET on subsequent patient management. All included studies used ^{68}Ga PSMA PET/CT. The proportion of patients in whom ^{68}Ga PSMA PET/CT had a moderate or major impact on management plans ranged from 13.6% to 75.6% (ten studies).

Table 1. Systematic review: Eissa et al. (2018)

Included studies	Design	Quality	Observations/notes
Total number of included studies: 37 Search period: up to September 2017.	**Research objective:** to review systematically the available literature data to identify the role of ^{68}Ga-PSMA PET/CT in cases of biochemical recurrence (BCR) after prostate cancer (PCa), analyse the imaging technique, compare ^{68}Ga with other radiotracers, study its effect on the management strategy and analyse the site of detected recurrence. **Population:** people with recurrent PCa. **Intervention:** ^{68}Ga-PSMA PET/CT **Reference standard:** any or no reference standard permitted **Study design:** clinical trials, prospective studies, retrospective studies and comparative series. **Excluded:** studies assessing only specific visceral metastatic recurrences (such as lung or brain); studies of primary PCa or mixed primary and recurrent PCa populations. **Outcomes measured:** "evaluation of ^{68}Ga-PSMA PET/CT in recurrent Pca and its effect on treatment plans"	**Study design:** Systematic review **Risk of bias:** assessed using QUADAS-2. Patients selection was judged to be a risk of bias in 17/37 studies (some studies did not report a precise inclusion criterion and some studies included mixed patients). Histological correlation was included as a reference standard in 16/37 studies. References standard was not used, or was unclear, in the remainder of studies. Four studies were prospective and the remainder were retrospective.	• The authors have used QUADAS-2 to assess study quality. However, this tool is designed to assess studies of diagnostic accuracy (the assumption being that these would include a reference standard, and measures of sensitivity and specificity). The review inclusion criteria are somewhat broader than this, permitting the inclusion of studies reporting other outcomes (such as detection rates and changes in patient management) from studies that did not include a reference standard. • Some review inclusion/exclusion criteria are unclear. Outcomes considered relevant are not clearly reported in the selection criteria.

Results

Diagnostic accuracy of ^{68}Ga PSMA PET/CT (five studies; one study reported results for each lymph node region and also for each patient)

	Sensitivity, %	Specificity, %
Lesion-based analysis, two studies	76.6 and 86.9	100 and 91.9
Lymph node field/region-base analysis, two studies	93.2 and 77.9	100 and 97.3
Patient-based analysis, two studies	76.5 and 100	50 and 91.7

Detection rate (25 studies) ranged from 47% to 96.6%.

The proportion of patients in whom ^{68}Ga PSMA PET/CT had a moderate or major impact on management plans ranged from 13.6% to 75.6% (ten studies)

Table 2. Systematic review: Sathianathen et al. (2018)

Included studies	Design	Quality	Observations/notes
Total number of included studies: 21. 1 study of ^{68}Ga-PSMA 5 studies of ^{18}F-FACBC 16 studies of ^{11}C-choline Search period: up to April 2018.	**Research objective:** to assess the diagnostic ability of ^{11}C-choline, ^{18}F-FACBC, and ^{68}Ga-PSMA PET/CT in detecting local recurrent and metastatic prostate cancer in men with BCR. **Population**: prostate cancer patients with evidence of BCR (PSA > 0.2 ng/ml after radical prostatectomy or a rise by at least 2 ng/ml above the PSA nadir after radiotherapy), undergoing PET-based imaging. **Intervention:** PET using one of the following tracers: ^{68}Ga-PSMA ^{18}F-FACBC ^{11}C-choline **Reference standard:** results of imaging were validated using a combination of histology, further imaging and/or clinical follow-up with PSA results or response to treatment based on the results of PET imaging **Excluded:** patients undergoing primary staging; studies in which only positive PET/CT scans were included and followed-up; studies in which only the outcomes of a single type or site of metastasis were included (e.g., bone, local recurrence, or nodal) **Outcomes measured:** diagnostic accuracy; detection rate	**Study design:** Systematic review with meta-analysis. **Risk of bias:** assessed using QUADAS-2. All studies were judged as at high risk of bias.	• ^{11}C choline PET/CT was not specified as a test of interest in the HTW review, but is reported by the authors of this review and therefore included here for transparency • Number of included studies is smaller than some other reviews, as authors only included studies where diagnostic accuracy was reported or could be calculated.

Results	Authors' observations
Diagnostic accuracy **Tracer** / **Sensitivity, % (95% CI)** / **Specificity, % (95% CI)** ^{68}Ga-PSMA (per-lesion basis; one study) / 76.4 (68.3 to 82.9) / 99.8 (97.5 to 100) ^{18}F-FACBC (per-patient basis; four studies) / 79.7 (51.9 to 93.4) / 61.9 (41.1 to 79.0) ^{18}F-FACBC (per-lesion basis; one study) / 62.7 (56.4 to 68.5) / 69.8 (64.5 to 74.7) ^{11}C-choline (per-patient basis; 16 studies) / 80.9 (70.4 to 88.3) / 84.1 (70.2 to 92.2) Detection rate for recurrence (pooled analysis) **Detection rate, % (95% CI)** ^{68}Ga-PSMA (one study) / 82.8 (78.2 to 86.5) ^{18}F-FACBC (five studies) / 58.6 (41.1 to 87.5) ^{11}C-choline (16 studies) / 62.2 (48.9 to 74.4)	"PET-based imaging with ^{11}C-choline, ^{18}F-FACBC, and ^{68}Ga-PSMA demonstrates the potential to detect disease in the early BCR setting, where conventional modalities are less useful. There are some concerns regarding false-positive findings especially with ^{18}F-FACBC that should be considered before initiating salvage therapy. Moreover, there is a lack of high-quality studies which validate the findings from PET/CT against a reliable reference standard, and therefore, it is challenging to accurately characterize the diagnostic performance of these tests." "Early data suggest that ^{68}Ga-PSMA may be the most accurate [of the tracers studied here], but high-quality comparative studies are required to provide clarity to this space."

Table 3. Systematic review: Sandgren et al. (2018)

<table>
<tr><th>Included studies</th><th>Design</th><th>Quality</th><th>Observations/notes</th></tr>
<tr>
<td>Total number of included studies: 15.

1 study of ^{18}F-flouroethylcholine

5 studies of ^{18}F-choline

7 studies of ^{11}C-choline

2 studies of ^{11}C-acetate

Search period: up to December 2015.</td>
<td>Research objective: to summarise the diagnostic accuracy of PET imaging techniques in the detection of local and/or regional recurrent disease post-RP when used in SRT planning.

Population: prostate cancer patients with local and/or regional recurrence identified by BCR

Intervention: PET or PET/CT; any tracer.

Reference standard: biopsy or SRT follow-up (by PSA follow-up or radiological follow-up)

Excluded: studies that did not report sensitivity and specificity as part of the primary end point.

Outcomes measured: diagnostic accuracy.</td>
<td>Study design: Systematic review with meta-analysis.

Risk of bias: assessed using QUADAS-2.

All studies were judged as at high or unclear risk of bias regarding the conduct or interpretation of the reference standard. In 11/14 studies, patient flow was judged to be at high risk of bias.

Risk of bias was not reported for 1/15 studies (the reason for this omission is unclear).</td>
<td>• The population studied is prostate cancer patients who have undergone RP and are being considered for SRT following disease recurrence: it is not clear if this treatment pathway is representative of usual care in Wales.
• ^{11}C choline and ^{11}C-acetate PET/CT were not specified as tests of interest in the HTW review, but are reported by the authors of this review and therefore included here for transparency.
• Authors of this review also studied the specified population using MRI; these studies (n = 15) are outside the scope of this review and are therefore not included here.</td>
</tr>
<tr><th colspan="3">Results</th><th>Authors' observations</th></tr>
<tr>
<td colspan="3">Diagnostic accuracy
<table>
<tr><th>Tracer</th><th>Sensitivity, % (95% CI)</th><th>Specificity, % (95% CI)</th></tr>
<tr><td>^{18}F-flouroethylcholine
• Detection of lymph node metastases
• Correct detection of site of lymph node metastases</td><td>
40 (NR)
69 (NR)</td><td>
96 (NR)
73 (NR)</td></tr>
<tr><td>^{18}F-choline</td><td>83.6 (71.1 to 96.0)</td><td>74.6 (50.8 to 98.4)</td></tr>
<tr><td>^{11}C-choline</td><td>70.9 (50.6 to 91.2)</td><td>86.3 (62.3 to 110.2)</td></tr>
<tr><td>^{11}C-acetate</td><td>92.0 (75.6 to 108.3)</td><td>79.9 (40.7 to 119.1)</td></tr>
</table>
</td>
<td>"PET has reasonable sensitivity and specificity for the detection of [prostate cancer] LR and RR post-RP."

"Choline appears to be the most reliable PET tracer, although no PSMA data were currently of sufficient quality to be included in the analysis."</td>
</tr>
<tr><td colspan="4">BCR: biochemical recurrence; RP: radical prostatectomy; SRT: salvage radiotherapy</td></tr>
</table>

5.2. Additional studies

Fourteen studies of ^{68}Ga-PSMA tracers were included. Of these, four compared ^{68}Ga-PSMA PET to PET using other tracers, or to conventional imaging (usually defined by the study authors as CT or MRI ± bone scan). A further two studies comparing ^{68}Ga-PSMA PET to ^{18}F-choline-based PET were included in the systematic review by Eissa (2018). Outcomes from these comparative studies are summarised in Table 4.

Of the remaining ten non-comparative studies. one study (Hamed et al. 2018), published since the last search date of the most recent systematic review, reported estimates of the diagnostic accuracy of ^{68}Ga-PSMA PET. Sensitivity and specificity were estimated as 98.8% (95% CI 95.7 to 99.8%) and 100.0% (95% CI 83.4 to 100.0%) respectively. The remaining studies reported detection rates and/or measures of clinical utility for ^{68}Ga-PSMA PET only; none reported results from a reference standard to verify the results of imaging, or compared ^{68}Ga-PSMA PET to other tracers or imaging modalities. All measured clinical outcomes for ^{68}Ga-PSMA PET are reported in Table 5 (lesion detection outcomes) and Table 6 (clinical utility outcomes). Full details of study design and outcomes are reported in Appendix 1, Tables 1 to 14.

Nine studies (919 patients in total) reported the effect of ^{68}Ga-PSMA PET on subsequent patient management, or other clinical utility outcomes. Four of these studies reported actual changes in patient management (as opposed to intended changes) following imaging: changes in implemented patients management after imaging ranged from 39% to 70% of patients. In the remaining studies, changes in intended management were reported for 22% to 61% of patients. Two studies reported changes in staging/prognosis as a result of ^{68}Ga-PSMA PET imaging; changes were made in 51% to 63% of patients.

Three studies of ^{18}F-PSMA tracers were included: one case-series study (Giesel et al. 2018a) and two cross-sectional studies (Giesel et al. 2018b, Rahbar et al. 2018). All three studies assessed detection rates of ^{18}F-PSMA-1007 in patients referred for suspected recurrence of prostate cancer. Reported detection rates ranged from 75 to 95%. None reported diagnostic accuracy, or included results from a reference standard to verify the results of imaging. Results are summarised in Table 7. Full details of study design and outcomes are reported in Appendix 1, Tables 15 to 17.

5.3. Ongoing trials

The literature search identified three ongoing trials of the effectiveness of PSMA PET, and other tracers, in the investigation of recurrent prostate cancer. Table 8 summarises details of these ongoing studies.

Table 4. Outcomes from studies directly comparing PSMA-based tracers to other imaging modalities

Study	Number of patients	Design	Population	Outcome	Results
Afshar-Oromieh, 2014*	37	Retrospective	Biochemical recurrence	Proportion of patients with lesions detected	^{68}Ga-PSMA PET/CT: 32/37 (86.5%) ^{18}F-fluoromethyl-choline PET/CT: 26/37 (70.3%)
Alonso, 2018	36	Prospective	Biochemical recurrence, median PSA level 3.3 ng/mL	Proportion of patients with lesions detected	^{68}Ga-PSMA PET/CT: 27/36 (75%) ^{11}C-choline PET/CT: 19/36 (53%)
				Total number of lesions detected	^{68}Ga-PSMA PET/CT: 183 ^{11}C-choline PET/CT: 98
Calais, 2018a	10	Retrospective	Any recurrence, PSA levels not reported	Proportion of patients with lesions detected	^{68}Ga-PSMA PET/CT: 7/10 (70%) 18F-fluciclovine PET/CT: 2/10 (20%)
Koerber, 2018	71	Retrospective	Biochemical recurrence or PSA persistence after primary treatment. Median PSA level 1.2 ng/ml	Proportion of patients with lymph node metastasis detected	^{68}Ga-PSMA PET/CT: 31/71 (43.7%) Conventional imaging (CT or MRI ± bone scan): 10/71 (13.2%)
				Proportion of patients with distant metastasis detected	^{68}Ga-PSMA PET/CT: 36/71 (50.7%) Conventional imaging (CT or MRI ± bone scan): 23/71 (32.4%)
Morigi, 2015*	38	Prospective	Biochemical recurrence	Proportion of patients with lesions detected	^{68}Ga-PSMA PET/CT: 25/38 (66%) ^{18}F-fluoromethyl-choline PET/CT: 12/38 (31.6%)
Kranzbuhler, 2018	56	Retrospective	Biochemical recurrence after prostatectomy. Median PSA level: 0.99 ng/mL	Proportion of patients with lesions detected	^{68}Ga-PSMA PET/MRI: 44/56 (78.6%) MRI only: 13/54 (24%)
*Outcomes as reported in systematic review by Eissa et al. 2018					

Table 5. All lesion detection outcomes from primary studies of ^{68}Ga-PSMA PET

Outcome	Study	Number of Patients	Design	Population	Result
Proportion of patients with lesions detected	Alonso, 2018	36	Prospective	Biochemical recurrence, median PSA level 3.3 ng/mL	27/36 (75%)
	Zacho, 2018	70	Prospective	Biochemical recurrence, median PSA level 0.55 ng/mL	37/70 (53%)
	Calais, 2018a	10	Retrospective	Any recurrence, PSA levels not reported	7/10 (70%)
	De Bari, 2018	40	Retrospective	Biochemical recurrence, median PSA level 0.51 ng/mL	31/40 (77%)
	Farolfi, 2018	119	Retrospective	Biochemical recurrence, median PSA level 0.34 ng/mL	41/119 (34%)
	Afaq, 2018	100	Retrospective	Biochemical recurrence, PSA levels not reported	47/100 (47%)
	Grubmuller, 2018	117	Retrospective	Biochemical recurrence, median PSA level 1.04 ng/mL	100/117 (85.5%)
	Hamed, 2018	188	Prospective	Biochemical recurrence, median PSA level 2.2 ng/mL	165/188 (87.8%)
	Kranzbuhler, 2018	56	Retrospective	Biochemical recurrence, median PSA level 0.99 ng/mL	44/56 (78.6%)
	Mattiolli, 2018	125	Retrospective	Biochemical recurrence, median PSA level 1.8 ng/mL	80/125 (64%)
Proportion of patients with lymph node metastasis detected	Koerber, 2018	71	Retrospective	Biochemical recurrence or PSA persistence after primary treatment. Median PSA level 1.2 ng/ml	31/71 (44%)
Proportion of patients with distant metastasis detected	Koerber, 2018	71	Retrospective	Biochemical recurrence or PSA persistence after primary treatment. Median PSA level 1.2 ng/ml	36/71 (51%)

Table 6. All clinical utility outcomes from primary studies of ^{68}Ga-PSMA PET

Outcome	Study	Number of Patients	Design	Population	Result
Implemented changes in patient management, proportion of patients	Calais, 2018c	101	Prospective	Any recurrence, PSA levels not reported	54/101 (53%)
	De Bari, 2018	40	Retrospective	Biochemical recurrence, median PSA level 0.51 ng/mL	28/40 (70%)
	Afaq, 2018	100	Retrospective	Biochemical recurrence, PSA not reported	39/100 (39%)
	Mattiolli, 2018	125	Retrospective	Biochemical recurrence, median PSA level 1.8 ng/mL	66/104 (63.4%)
Intended changes in patient management, proportion of patients	Calais, 2018c	101	Prospective	Any recurrence, PSA levels not reported	62/101 (61%)
	Zacho, 2018	70	Prospective	Biochemical recurrence, median PSA level 0.55 ng/mL	15/69 (21.7%)
	Roach, 2018	312	Prospective	Biochemical recurrence, median PSA level 1.1 ng/ml	192/312 (62%)
	Farolfi, 2018	119	Retrospective	Biochemical recurrence, median PSA level 0.34 ng/mL	36/119 (30%)
	Koerber, 2018	71	Retrospective	Biochemical recurrence or PSA persistence after primary treatment. Median PSA level 1.2 ng/ml	40/71 (56%)
	Grubmuller, 2018	117	Retrospective	Biochemical recurrence, median PSA level 1.04 ng/mL	50/67 (74.6%)
Change in staging/prognosis, proportion of patients	Roach, 2018	312	Prospective	Biochemical recurrence, median PSA level 1.1 ng/ml	198/312 (63%)
	Koerber, 2018	71	Retrospective	Biochemical recurrence or PSA persistence after primary treatment. Median PSA level 1.2 ng/ml	36/71 (51%)

Table 7. All lesion detection outcomes with ^{18}F-PSMA PET reported in primary studies

Outcome	Study	Number of Patients	Design	Population	Result
Proportion of patients with lesions detected	Giesel, 2018a	12	Retrospective	Biochemical recurrence, median PSA level 0.6 ng/ml	9/12 (75%)
	Rahbar, 2018	100	Retrospective	Any recurrence, median PSA level 1.34 ng/ml	95/100 (95%)
	Giesel, 2018b	251	Retrospective	Biochemical recurrence, median PSA level 1.2 ng/ml	204/251 (81%)

Table 8. Ongoing trials of PET/CT

Study name, ID	Design and setting	Eligibility criteria	Interventions	Outcomes	Expected completion
^{68}Ga-THP-PSMA PET/CT Imaging in High Risk Primary Prostate Cancer or Biochemical Recurrence of Prostate Cancer (THERAG0001) NCT03617588	Open-label, single group assessment. Two centres, UK	Prostate cancer patients who are either: newly diagnosed with primary high risk prostate cancer and are scheduled for radical prostatectomy diagnosed with BCR with previous radical prostatectomy, and being considered for radical salvage therapy diagnosed with BCR with previous radical radiotherapy (but no surgery), and are being considered for radical salvage therapy Planned enrolment: 20 patients per group.	All subjects will undergo a Gallium-68 THP-PSMA scan in addition to standard of care monitoring.	Primary outcome: Change in patient management as a result of ^{68}Ga-PSMA PET documented after scan, compared with pre-scan management plan. Secondary outcome: Treatment Emergent Adverse Events Other outcome: Positive histopathological staining for PSMA as per standard of care where histology is available	December 31, 2018
PET/MRI for Men Being Considered for Radiotherapy for Suspected Prostate Cancer Recurrence Post-Prostatectomy (PROPS) NCT02131649	Open-label, single group assessment. Multicentre, Australia, Canada, UK	Men with suspected local recurrence of prostate cancer post-prostatectomy. Enrolment: 99 patients.	PET/MRI scan using ^{18}F-FCH as the radiolabelled tracer. If prostate cancer is detected outside the prostate, patients may undergo a biopsy or follow-up ^{18}F-FCH PET/MRI to confirm the results.	Primary outcome: Proportion of men with negative or equivocal conventional restaging imaging (bone scan + CT scan of abdomen and pelvis) with uptake identified outside of the prostate bed on ^{18}F-FCH PET Secondary outcome: Biochemical disease free survival at 3 years post-treatment	January 2020
Investigation of Therapy Response With Amino Acid Analogue Transport PET Imaging, NCT02830880	Open-label, single group assessment. Single centre, US.	Male adults aged 18 years and older with primary or recurrent castration-resistant prostate cancer with skeletal and/or nodal involvement not currently undergoing systemic chemotherapy who are about to commence therapy with docetaxel/prednisone.	Patients will receive ^{18}-F-FACBC PET/CT, and also conventional imaging (bone scanning CT or MRI of the abdomen)	Primary outcomes: Change in clinical response assessed by: FACBC PET/CT scan, PSA, MRI, CT scan, and bone scan.	Estimated completion date December 2021.

Study name, ID	Design and setting	Eligibility criteria	Interventions	Outcomes	Expected completion
A Phase 3, Open-label Study to Assess the Clinical Utility of Fluciclovine (^{18}F) PET/CT in Patients With Prostate Cancer With Biochemical Recurrence After Radical Treatment, NCT02578940	Open-label, single arm trial. Multicentre, UK.	Male adults aged 18 years and older, who have had original diagnoses of prostate cancer and underwent radical curative therapy (at least 3 months before enrolment), and have been diagnosed with biochemical recurrence.	Patients receive ^{18}F-FACBC PET/CT.	Primary outcome: Impact on patient treatment/management (compared to pre-scan management plan). Secondary outcomes: Response rate to salvage therapy; diagnostic performance of the PET/CT scan; effect of PSA levels on detection of recurrent cancer by the PET/CT scan; safety and tolerability; detection rates for ^{18}F-FACBC PET/CT and choline PET/CT (in subgroup who receive choline as standard care).	Estimated completion date August 2018.
CT: computed tomography; PET: positron emission tomography; PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiotherapy.					

6. Safety

None of the systematic reviews or primary studies identified by this appraisal reported evidence on the safety of ^{18}F-Choline or ^{68}Ga-PSMA ligand PET/CT. SHTG Evidence Note 67 included two primary studies that assessed adverse effects (Afshar-Oromieh et al. 2014, Nanni et al. 2015). Afshar-Oromieh (2014) and Nanni et al (2015) reported that there were no adverse effects with ^{68}Ga-PSMA or ^{18}F-choline PET/CT, and anti-^{18}F-FACBC or ^{11}C-choline PET/CT respectively.

7. Cost effectiveness

No primary or secondary evidence was identified which assessed the cost effectiveness of ^{18}F-Choline or ^{68}Ga-PSMA ligand PET/CT in the investigation of recurrent prostate cancer

Procurement of ^{11}C-choline based PET-CT scans within Wales currently cost £1,285 each according to commissioning figures. Scans are undertaken at Wales Research and Diagnostic PET Imaging Centre for patients in South Wales and in Wrexham for North Wales patients. ^{68}Ga-PSMA based PET-CT scans are commissioned from University College London Hospitals for £1,658 each. Patients residing in North Wales may have ^{68}Ga-PSMA commissioned from the Christie Hospital, Manchester. The additional scan specific cost of £373 for ^{68}Ga-PSMA compared to ^{11}C-choline may underestimate the full scan cost impact due to the disparity in organisational considerations.

8. Organisational issues

No specific organisational issues were identified from the evidence searched. The topic referrer highlighted that there are currently two PET centres in Wales: 1 fixed site in Cardiff and 1 mobile site in Wrexham. Provision of non-FDG PET/CT, such as the ^{18}F-choline tracer approved by WHSSC, would impact on the limited PET capacity in Wales. Expert reviewers also highlighted that introduction of ^{68}Ga-based tracers could result in differences in production capacity and availability of the technology across Wales.

The topic referrer also highlighted that the Wales Research and Diagnostic PET Imaging Centre (PETIC) is currently one of the few centres worldwide that can produce 68-Gallium. PETIC is in discussion with industrial partners to act as a pilot centre for the manufacture of ^{68}Ga-PSMA.

9. Patient issues

The evidence searched did not identify any research on patients' experiences or perspectives relating to imaging during the investigation of prostate cancer recurrence.

10. Conclusions

Evidence on the clinical effectiveness of PET using ^{68}Ga-PSMA and other PET tracers is available from two systematic reviews and a large number of primary studies. Although the most recent review searched for articles published up to 2017, we have identified a notable number of relevant articles published subsequent to this, suggesting that this is an area of active research.

In the two systematic reviews that studied ^{68}Ga-PSMA PET, this imaging modality was noted by the systematic reviews authors to have consistently high specificity and reported detection rates suggest this tracer can detect disease even at low PSA levels. The evidence identified from two systematic reviews also reports that ^{68}Ga PSMA PET has generally higher sensitivity and specificity than other imaging modalities. However, the small study populations, identified risks of bias, and lack of studies comparing tracers directly to each other render head-to-head comparisons of their effectiveness difficult, and no formal statistical comparison of diagnostic accuracy is possible.

One prospective study published subsequent to the systematic reviews (Hamed et al. 2018) reports very high sensitivity and specificity for ^{68}Ga-PSMA PET in identifying prostate cancer recurrence. Although no studies exist of head-to-head comparisons of the diagnostic accuracy of ^{68}Ga-PSMA PET to other imaging techniques, several studies have compared detection rates of ^{68}Ga-PSMA PET to other non-FDG PET tracers (four studies), or to conventional imaging (two studies). Results of these consistently showed higher detection rates with ^{68}Ga-PSMA PET than with any of the comparators investigated.

Clinical utility outcomes for PSMA-based PET were reported by one systematic review (ten relevant studies included) and nine studies (919 patients in total) published subsequent to the systematic review, all using ^{68}Ga-PSMA. All these demonstrated that the findings of ^{68}Ga-PSMA PET can influence subsequent treatment planning, although the percentage of patients affected varied widely between studies.

Data on the effectiveness of ^{18}F-PSMA PET/CT is available from three retrospective case series. These only reported detection rates for positive lesions, and did not include any data on verification of test results. Reported detection rates ranged from 75 to 95%.

No published primary or secondary research on the cost effectiveness of PSMA-based PET for the investigation of recurrent prostate cancer were identified.

11. Further research

Large, prospective, comparative multicentre studies are recommended to evaluate the cost effectiveness, diagnostic performance, and impact on patient management of PSMA-based PET tracers compared to currently-used imaging modalities in the assessment of patients with suspected prostate cancer recurrence.

12. Contributors

The HTW staff and contract researchers involved in writing this report were:

- L Elston – wrote first draft of EAR, quality assurance of evidence review
- D Jarrom – carried out evidence review; revised EAR post-consultation
- J Washington – carried out literature searches; completed quality assurance of finalised EAR
- T Winfield – provided health economics support

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

This report was in part adapted from SHTG Evidence Note 67. HTW gratefully acknowledge SHTG's input and support.

A range of experts from the UK provided material and commented on drafts of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

Experts who contributed to this appraisal:

- A Afaq, Consultant Radiologist (PET imaging), Institute of Nuclear Medicine, University College Hospital London
- C Marshall, Director, PET Imaging Centre, University Hospital of Wales
- G Flux, Head of Radioisotope Physics, Royal Marsden Hospital
- J Harbour, Health Services Researcher, Scottish Health Technologies Group
- J Staffurth, Consultant Clinical Oncologist, School of Medicine, Cardiff University and Velindre Cancer Centre
- K Collins, Knowledge Officer, Prostate Cancer UK
- N Hartman, Head of Nuclear Medicine, Singleton Hospital, Swansea

Review period

Two years after the date of publication, a high-level literature search will be undertaken to determine if there is new evidence that could alter the conclusions of this report. If so, the appraisal will be updated.

13. Glossary

BCR	Biochemical recurrence
CT	Computed tomography
DCFPyl	2-(3-(1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid
FACBC	1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid
FCH	Fluoromethylcholine
FDG	2-fluoro-2-deoxy-D-glucose
FEC	Fluoroethylcholine
HTW	Health Technology Wales
QUADAS-2	A tool used to evaluate the risk of bias and applicability of diagnostic accuracy studies
LR	Local recurrence
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PCa	Prostate cancer
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
RP	Radical prostatectomy
RR	Regional recurrence
SHTG	Scottish
SRT	Scottish Health Technologies Group
WHSCC	Welsh Health Specialised Services Committee

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Appendix 1. Data tables for primary studies

Appendix Table 1. Study details: Alonso et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Single centre, Uruguay. n = 36 Mean age 67.4 years (range 45 to 77 years) Median PSA level 3.3 ng/mL (range 0.2 to 138 ng/mL) Recruitment period August 2015 to March 2016	**Population:** prostate cancer patients with biochemical recurrence (defined as PSA > 0.2 ng/ mL, PSA doubling time less than 6 months or PSA increase above 2 ng/ml per year). **Intervention:** PET/CT scans with and ^{68}Ga PSMA, performed in random order within 1 to 2 weeks of each other. Images were acquired from skull to mid-thigh. MRI images of the pelvis were also acquired **Comparison:** ^{11}C choline PET/CT. MRI images of the pelvis were also acquired **Outcomes measured:** lesion detection rates.	**Study design:** prospective. Unclear how patients were recruited to the study, and therefore whether recruitment could have introduced bias. PET/CT scans with ^{11}C choline and ^{68}Ga PSMA, performed in random order within 1 to 2 weeks of each other.	• Reference standard/conventional imaging was not included for comparison. • Study reported detection rates and did not report on diagnostic accuracy. • There was no follow-up/further diagnostics/histopathological confirmation reported to confirm accuracy of the detection rates.

Results	Authors' observations
Detection rate **Numbers of patients with positive scan results, n (%)** / **Total number of lesions detected, n** / **Median number of lesions detected per patient, n (range)** ^{68}Ga-PSMA: 27/36 (75%) / 183 / 2 (0 to 93) ^{11}C-choline: 19/36 (53%) / 98 / 1 (0 to 57) Pelvic evaluation **Number of patients with metastatic lesions found, n (%)** ^{68}Ga-PSMA: 25 (69%) ^{11}C-choline: 18 (50%) MRI: 21 (58%)	"In patients with prostate cancer with biochemical recurrence ^{68}Ga-PSMA detected more lesions than ^{11}C-Choline regardless of PSA levels."

Appendix Table 2. Study details: Calais et al. (2018a)

Descriptive details	PICO	Quality of study	Observations/notes
United States; number of centres not reported. n = 10 Mean age: 71 years Recruitment period: October 2016 to November 2017.	**Population:** patients with prostate cancer recurrence, recruited to undergo ^{68}Ga-PSMA PET/CT who had undergone ^{18}F-fluciclovine PET/CT in the previous 4 months. **Intervention:** ^{68}Ga-PSMA PET/CT. **Comparison:** ^{18}F-fluciclovine PET/CT. **Outcomes measured:** detection rate.	**Study design:** subgroup analysis of an ongoing (currently unpublished) prospective study of ^{68}Ga-PSMA PET/CT. Patients were selected on the basis of whether they had received ^{18}F-fluciclovine PET/CT prior to ^{68}Ga-PSMA PET/CT. This may have introduced selection bias, as an initial negative test for the first scan may have increased the likelihood of selection to undergo a second scan. Patients received ^{18}F-fluciclovine PET/CT prior to ^{68}Ga-PSMA PET/CT by a median of 2.2 months; tumour growth in the intervening period may have increased the likelihood of lesion detection at a later date and could have biased the results towards ^{68}Ga-PSMA PET/CT.	• Patients were identified retrospectively from a cohort (n = 288) recruited as part of a larger trial of ^{68}PSMA PET/CT imaging for recurrent disease localisation. • No reference standard/conventional imaging was included for comparison. • Study reported detection rates and did not report on diagnostic accuracy.

Results	Authors' observations
Detection rate **Numbers of patients with recurrence site detected, n (%)** ^{68}Ga-PSMA: 7 (70%) ^{18}F-fluciclovine: 2 (20%)	• Three patients had concordantly negative findings on ^{68}Ga-PSMA-11 PET/CT and ^{18}F-fluciclovine PET/CT. • Disease extent was underestimated in both of the patients in which ^{18}F-fluciclovine PET/CT detected recurrence.

Appendix Table 3. Study details: Calais et al. (2018b)

Descriptive details	PICO	Quality of study	Observations/notes
United States and Germany; four centres. n = 270 Mean age: 68 year, (range 43 to 90 years) Recruitment period: August 2013 to May 2017.	**Population:** prostate cancer patients with biochemical recurrence after prior treatment (radical prostatectomy) and had not undergone prior radiotherapy. Serum PSA level of less than 1 mg/ml at the time of ^{68}Ga-PSMA PET/CT. **Intervention:** ^{68}Ga-PSMA PET/CT used to inform radiotherapy planning. **Comparison:** simulated radiotherapy planning based on consensus clinical target volumes. **Outcomes measured:** impact on salvage radiotherapy planning.	**Study design:** retrospective post-hoc analysis of patient databases. Radiotherapy planning using clinical target volumes was carried out by personnel masked to PET findings.	• Patients were identified retrospectively from databases established at each participating institution. Forty-seven patients from one institution were included in NCT02940262, from which Calais 2018a and Calais 2018c also recruited patients. • No reference standard was included to verify imaging findings.

Results	Authors' observations
Potential impact of ^{68}Ga-PSMA PET/CT on SRT planning	• ^{68}Ga-PSMA-11 PET/CT would have had a major impact on 19% of patients imaged (39% of PSMA-11–positive patients) and a minor impact on 30% (61%). Overall, the addition of ^{68}Ga-PSMA-11 PET/CT may affect SRT planning in half the patients with a PSA level of less than 1 ng/ml. • This finding justifies a randomized prospective trial to determine whether ^{68}Ga-PSMA PET/CT can improve outcomes in prostate cancer patients with early biochemical recurrence after radical prostatectomy.

Impact	n (%)
Major impact on SRT planning—outside RTOG CTV recurrence	52 (19%)
Minor impact on SRT planning—covered by planning based on consensus CTVs; dose escalation to gross disease (^{68}Ga-PSMA-11–positive disease)	80 (29.5%)
No impact on SRT planning—negative ^{68}Ga-PSMA-11 PET/CT results	138 (51%)

Appendix Table 4. Study details: Calais et al. (2018c)

<table>
<tr><th>Descriptive details</th><th>PICO</th><th>Quality of study</th><th>Observations/notes</th></tr>
<tr>
<td>United States; number of centres not reported.

n = 101

Median age: 69 years (range 43 to 88 years)

Recruitment period: October 2016 to June 2017.</td>
<td>Population: patients with prostate cancer recurrence.

Intervention: ^{68}Ga-PSMA PET/CT.

Comparison: none.

Outcomes measured: changes in patient management (planned and/or implemented).</td>
<td>Study design: prospective survey carried out as part of an ongoing (currently unpublished) prospective study of ^{68}Ga-PSMA PET/CT.

161 consecutively recruited patients were identified as eligible, but completed surveys were only returned for 101 patients.</td>
<td>• Subgroup analysis of a larger cohort (n = 288) recruited as part of a trial of ^{68}Ga PSMA PET/CT imaging for recurrent disease localisation.

• No reference standard was included to verify imaging findings.</td>
</tr>
<tr><th colspan="2">Results</th><th colspan="2">Authors' observations</th></tr>
<tr>
<td colspan="2">Changes to patient management following ^{68}Ga-PSMA PET/CT
<table>
<tr><th></th><th>n (%)</th></tr>
<tr><td>Intended changes</td><td>62 (61%)</td></tr>
<tr><td>Implemented changes</td><td>54 (53%)</td></tr>
</table>
</td>
<td colspan="2">• Following ^{68}Ga-PSMA PET/CT, changes to management were implemented in 54/101 (53%) of patients.</td>
</tr>
</table>

Appendix Table 5. Study details: De Bari et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Single centre, Italy. n = 40 Median age: 69.5 years (range 51 to 83 years) Median PSA level at time of imaging: 0.51 ng/ml (range 0.1 to 1.62 ng/ml) Recruitment period: June 2016 to April 2017	**Population:** prostate cancer patients presenting with biochemical recurrence. **Intervention:** ^{68}Ga-PSMA PET/CT. **Comparison:** none (before-after study). **Outcomes measured:** detection rate; changes in therapeutic approach based on ^{68}Ga-PSMA PET/CT imaging.	**Study design:** retrospective analysis of a patient database. Unclear whether patients were all eligible/consecutive patients were included in the study.	• Intended management of patients was based on standard departmental protocol, and reviewed by the institution's multidisciplinary tumour board following ^{68}Ga-PSMA PET/CT imaging, who then decided whether to confirm or alter the initial treatment.

Results	Authors' observations
Detection rate: 31/40 patients showed positive findings on ^{68}Ga PSMA PET/CT. After ^{68}Ga PSMA PET/CT imaging, the therapeutic approach was changed in 28/40 patients.	• Noted the substantial number of patients who changed from palliative to curative treatment after imaging: whether this resulted in improved patient outcomes is not clear. • Prospective, larger series are needed to establish the correct role of this very promising tool in the staging and therapeutic approach of PC patients.

Therapeutic approach	Before imaging	After imaging
Watch and wait	6	3
Curative treatment	12	31
Palliative treatment	22	6

Appendix Table 6. Study details: Grubmuller et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Single centre, Austria. n = 117 Mean age: 74 years (IQR 68-76 years) Median PSA level: 1.04 ng/ml (IQR 0.58-1.87) Recruitment period: May 2014 to January 2017.	**Population:** prostate cancer patients with BCR after treatment with radical prostatectomy. **Intervention:** ^{68}Ga-PSMA PET/CT (n = 68) or ^{68}Ga-PSMA PET/MRI (n = 77) **Comparison/reference standard:** none. **Outcomes measured:** detection rate, impact of imaging on further treatment decisions.	**Study design:** retrospective case series. Patient selection criteria for the study are not clearly described, it is unclear whether methods of recruitment could have introduced bias. Authors made no distinction between PET/CT and PET/MRI when reporting outcomes.	• Reference standard/conventional imaging was not included for comparison. There was no follow-up/further diagnostics/histopathological confirmation reported to confirm accuracy of the detection rates. • Initially, all patients were intended to undergo PET/MRI, but patients with metal implants in the pelvic region, any other implants not suitable for the PET/MRI system used, claustrophobia and/or pain were shifted to PET/CT. • Impact on treatment decision making was measured based on the decisions of a multidisciplinary tumour board who reviewed patients retrospectively and were blinded to the actual therapy patients received. • Impact on treatment decision is only reported for a subgroup of patients who had had negative findings on conventional imaging, but positive findings on ^{68}Ga-PSMA PET/CT or ^{68}Ga-PSMA PET/MRI (n = 67)

Results

Detection rate (proportion of patients with at least one PSMA-avid lesion): 100/117 (85.5%).

Number of patients with a recommended change in therapeutic strategy following positive PSMA PET imaging: 50/67 (74.6%) (see observations/notes)

Treatment decision based on standard imaging		Treatment decision based on PSMA PET	
Therapy	**Number of patients**	**Therapy**	**Number of patients**
Radiotherapy	3/50	Wait and see	1/3
		Salvage surgery	1/3
		Radiotherapy	1/3
Androgen deprivation therapy	29/50	Wait and see	1/29
		Salvage surgery	10/29
		Radiotherapy	13/29
		Multiple therapies	5/29
Wait and see	18/50	Salvage surgery	2/18
		Radiotherapy	16/18

Appendix Table 7. Study details: Zacho et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Two centres, Denmark. n = 70 Mean age: 67.5 years Median PSA level at time of PET imaging: 0.55 ng/ml (range 0.2 to 11.3 ng/ml) Recruitment period: July 2015 to April 2016	**Population:** prostate cancer patients diagnosed with biochemical recurrence after primary curative treatment. **Intervention:** ^{68}Ga PSMA PET/CT. **Comparison:** none. **Outcomes measured:** detection rate; impact of imaging results on patient management in terms of changes in treatment.	**Study design:** prospective case series Unclear how patients were chosen for the study/whether they were a consecutive or random sample. PET/CT images were independently read by two nuclear medicine physicians. Equivocal lesions (which could not be definitely categorized as benign or malignant) were considered as positive findings for the purposes of measuring detection rates. Change in patient management was not evaluated in one patient.	• No reference standard was included to verify imaging results. • To assess changes in patient management, physicians were asked to consider the optimal treatment for each patient before the results of imaging were available. Subsequently, the same physician was asked to fill out the same form after having the results of the ^{68}Ga-PSMA PET/CT. • 17 patients (24.3%) underwent salvage radiotherapy after first biochemical relapse and before study recruitment.

Results	Authors' observations
Detection rate (per-patient basis): 37/70 (53%) Definite change of patient management after PET/CT imaging: 15/69 (21.7%) PET/CT used to guide the choice of treatment: 15/69 (21.7%)	The proportion of patients in whom lesions were detected was greater in patients with higher PSA levels.

Appendix Table 8. Study details: Farolfi et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Single centre, Italy. n = 119 Median age: 66 years (range 44 to 78 years) Mean PSA level before imaging: 0.34 ng/ml (range 0.2 to 0.5 ng/ml) Recruitment period: March 2016 to July 2017	**Population:** prostate cancer patients with biochemical recurrence and PSA levels in the range 0.2-0.5 ng/ml. Only patients who had radical prostatectomy as primary therapy were included; patients who had already received salvage radiotherapy after recurrence were excluded. **Intervention:** ^{68}Ga PSMA PET/CT. **Comparison:** none. **Outcomes measured:** detection rate; influence of imaging treatment planning.	**Study design**: retrospective case series Unclear how patients were chosen for the study/whether they were a consecutive or random sample. Treatment planning was assessed by a radiation oncologist and a urologist who were initially blinded to the PET/CT results.	• No reference standard was included to verify imaging results. Of the 41 patients with positive scan results, 23 were followed up and none were considered to be false positive. • Patients were enrolled prospectively as part of an investigational new drug trial, but data was analysed retrospectively. The inclusion/exclusion criteria for the prospective trial are not defined here.

Results	Authors' observations
Detection rate: 41/119 (34.4%) Change in treatment strategy following imaging: 36/119 (30.2%). All 36 patients had positive PET/CT results; i.e. treatment strategy was changed in 36/41 (87.8%) of patients with positive PET/CT results.	"These results support the hypothesis that ^{68}Ga-PSMA-11 PET/CT is a valid procedure in the management of patients with recurrent prostate cancer with low PSA levels after radical surgery, and support the implementation of this imaging procedure in routine clinical practice."

Appendix Table 9. Study details: Koerber et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Single centre, Germany. n = 71 (121 recruited; see observations/notes) Median age: 71 years (range 50 to 84 years) Median PSA level before imaging: 1.2 ng/ml (range 0.03 to 41.24 ng/ml) Recruitment period: July 2011 to August 2017.	**Population:** patients with prostate carcinoma who had ^{68}Ga PSMA PET/CT at initial diagnosis or with PSA persistence/recurrence after primary treatment, and for whom conventional imaging (carried out a maximum four months before/after PET/CT) results were also available. **Intervention:** ^{68}Ga PSMA PET/CT. **Comparison:** Conventional imaging (CT or MRI ± bone scan). **Outcomes measured:** detection rate; influence of imaging on staging and treatment planning.	**Study design:** retrospective case series PET/CT and conventional imaging were evaluated retrospectively. Conventional imaging was evaluated without knowledge of PSMA PET/CT results; unclear whether evaluation of PSMA PET/CT was done by personnel blinded to other imaging results.	• The study included patients who received PET/CT newly diagnosed prostate cancer (n = 50), PSA persistence after surgery (n =11), or recurrent disease after initial definitive therapy (n = 60). Results for the former group are outside the scope of this review and therefore not reported here. The study authors did not report separate results for the PSA persistence and PSA recurrence groups and therefore both groups have been included.

Results	Authors' observations
Detection rate: **^{68}Ga PSMA PET/CT, n (%)** / **Conventional imaging, n (%)** Patients with lymph node metastasis detected, n (%): 31/71 (43.7%) / 10/71 (13.2%) Patients with distant metastasis detected, n (%): 36/71 (50.7%) / 23/71 (32.4%) Change in TNM staging following ^{68}Ga PSMA PET/CT imaging: 36/71 (50.7%) (all patients were upstaged) Change in treatment planning following ^{68}Ga PSMA PET/CT imaging: 40/71 (56.3%)	"^{68}Ga-PSMA PET/CT is well suited to detect intra- and extraprostatic prostate cancer in men with high risk disease. "^{68}Ga-PSMA PET/CT frequently results in a change in TNM staging and therefore, radiotherapeutic management."

Appendix Table 10. Study details: Afaq et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Single centre, UK. n = 100 Median age: 68 years (range 47 to 89 years) PSA level not reported. Recruitment period: June 2015 to February 2017.	**Population:** prostate cancer patients with biochemical recurrence and a recordable management plan. **Intervention:** ^{68}Ga PSMA PET/CT. **Comparison:** none. **Outcomes measured:** influence of imaging on patient management.	**Study design:** retrospective case series All eligible patients were included consecutively. Intended management plan before ^{68}Ga-PSMA PET/CT and the actual management plan after ^{68}Ga-PSMA PET/CT were recorded from electronic medical records.	• No reference standard was included to verify imaging results. Pathologic validation of positive findings was available in 11 cases. Ten of these were concordant with ^{68}Ga PSMA PET/CT findings.

Results	Authors' observations
Positive ^{68}Ga PSMA PET/CT findings in 47/100 patients (47%) Change in patient management following imaging: 39/100 (39%)	Authors state that management changed occurred more often in patients with higher PSA levels. However, baseline PSA levels were not reported.

Appendix Table 11. Study details: Roach et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Four centres, Australia. n = 312 relevant patients, 420 total (see observations/notes) Median age: 68.9 years (SD ± 7.5 years) Median PSA level before imaging: 1.1 ng/ml (range 0.01 to 75 ng/ml) Recruitment period: January 2015 to June 2016	**Population:** prostate cancer patients with biochemical failure, with detectable PSA but negative, or equivocal, conventional imaging. **Intervention:** ^{68}Ga PSMA PET/CT. **Comparison:** none. **Outcomes measured:** influence of imaging on treatment planning and assessment of disease.	**Study design:** prospective case series. Unclear how patients were chosen for the study/whether they were a consecutive or random sample.	• The study also included ^{68}Ga PSMA PET/CT indicated for primary staging (108 patients), but as these results are outside the scope of this review they are not reported here. • Change in intended management was assessed using a management questionnaire completed by clinicians before ^{68}Ga PSMA PET/CT and 4 to 5 weeks later, once clinicians were aware of ^{68}Ga PSMA PET/CT results.

Results	Authors' observations
Change in intended clinical management following imaging: 192/312 (62%) Disease considered to be more extensive following imaging: 158/312 (51%) Disease considered to be less extensive following imaging: 30/312 (10%)	The authors noted that ^{68}Ga PSMA PET/CT resulted in a planned management change in 51% of patients, and a higher proportion (62%) of patients who had biochemical failure. The authors also noted that ^{68}Ga -PSMA PET/CT has the potential to reduce the need for other imaging/biopsies in the assessment of prostate cancer.

Appendix Table 12. Study details: Hamed et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Multicentre study (number of centres not reported), Egypt. n = 188 Mean age: 67.4 years (range 56 to 79 years) Median PSA level: 2.2 ng/mL (range 0.01 to 70 ng/mL) Recruitment period: October 2016 to December 2017	**Population:** patients with rising PSA after primary definitive prostate cancer treatment. **Intervention:** ^{68}Ga-PSMA PET/CT. **Reference standard:** histopathology (n = 151) or clinical and imaging follow up (n = 37) **Outcomes measured:** detection rates and diagnostic accuracy	**Study design:** prospective study of diagnostic accuracy. Patients' recruitment described as consecutive; some excluded from the study but according to clear exclusion criteria.	• All patients with positive PSMA PET findings were considered 'true positive based on the reference standard (histopathology in 151 patients; clinical and imaging follow up in 14 patients) • 21/23 patients with negative PSMA PET findings were considered 'true negative' based on being alive and disease-free after at least one year of follow up.
Results			
Detection rate: positive PSMA PET findings in 165/188 patients (87.8%) Sensitivity: 98.8% (95% CI 95.7 to 99.8%) Specificity: 100.0% (95% CI 83.4 to 100.0%)			

Appendix Table 13. Study details: Kranzbuhler et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Single centre, Switzerland. n = 56 Median age: 69 years (IQR 11 years) Median PSA level: 0.99 ng/mL (IQR 3.1 ng/mL) Recruitment period: April 2016 to December 2016.	**Population**: prostate cancer patients with biochemical recurrence after prostatectomy. **Intervention**: ^{68}Ga-PSMA-11 PET/MRI. **Comparison**: MRI only. **Outcomes measured:** detection rates	**Study design:** retrospective case series. Patients are described as a consecutive sample of all who met the inclusion criteria.	• Study reported detection rates and did not report on diagnostic accuracy. There was no follow-up/further diagnostics/histopathological confirmation reported to confirm accuracy of the detection rates.

Results

Detection rate

	Patients with lesions detected, n (%)
^{68}Ga-PSMA PET/MRI	44/56 (78.6%)
^{68}Ga-PSMA PET only	43/56 (76%)
MRI only*	13/54 (24%)
*two patients could not be evaluated by MRI as the protocol was not complete	

Appendix Table 14. Study details: Mattiolli et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Multicentre study (number of centres not reported), Brazil. n = 125 Median age: 68 years (range 43 to 89 years) Median PSA level: 1.8 ng/mL (range 0.003 to 395 ng/mL) Recruitment period: November 2015 to July 2016.	**Population**: patients with biochemical recurrence following an initial diagnosis of adenocarcinoma of the prostate and negative findings on conventional imaging (pelvic ultrasound, bone scintigraphy, pelvic MR and CT of the abdomen). **Intervention**: ^{68}Ga-PSMA PET/CT. **Comparison/reference standard**: none. **Outcomes measured:** lesion detection rates, impact of imaging on treatment planning.	**Study design:** retrospective case series. Unclear whether a consecutive/random sample of patients was included in the study, and therefore unclear whether recruitment could have introduced bias. Change in management could only be evaluated in 104/125 patients as the remainder were lost to follow up.	• Study reported detection rates and did not report on diagnostic accuracy. There was no follow-up/further diagnostics/histopathological confirmation reported to confirm accuracy of the detection rates. • Change in treatment planning was based on actual recorded changes to the treatment received.

Results

Proportion of patients with lesions detected by ^{68}Ga-PSMA-PET/CT: 80/125 (64%)

Change in patient management after ^{68}Ga-PSMA-PET/CT imaging:

	Number of patients who underwent a change of management, n (%)
All patients (n = 104)	66 (63.4%)
Positive imaging findings (n = 69)	59 (85.5%)
Negative imaging findings (n = 35)	7 (20%)

Appendix Table 15. Study details: Giesel et al. (2018a)

Descriptive details	PICO	Quality of study	Observations/notes
Single centre, Germany. n = 12 Mean age 68 years (range 54 to 79 years) Median PSA-level: 0.6 ng/ml (range: 0.2-228 ng/mL) Recruitment period May 2016 – July 2017	**Population**: prostate cancer patients with a rising serum PSA level after previous local treatment (prostatectomy, radiotherapy or both). **Intervention**: ^{18}F-PSMA-1007 tracer followed by PET/CT 1 and 3 hours after tracer injection. **Reference standard**: none. **Outcomes measured:** detection rate of ^{18}F-PSMA-1007-positive lesions; ^{18}F-PSMA-1007 uptake at 1 and 3 hours.	**Study design:** retrospective single-arm case-series study.	• Reference standard/conventional imaging was not included for comparison. • Study reported detection rates and did not report on diagnostic accuracy. • There was no follow-up/further diagnostics/histopathological confirmation reported to confirm accuracy of the detection.

Results	Authors' observations
• ^{18}F-PSMA-1007-positive lesions were detected in 9 (75%) of the 12 patients.	"All 3 patients with negative PET findings had PSA values of 0.5 ng/ml or less. However, 1 patient with positive PET findings had a PSA level of 0.08 ng/ml. These results suggest that ^{18}F-PSMA-1007 has a limited sensitivity below a PSA level of 0.5 ng/ml"

Appendix Table 16. Study details: Rahbar et al. (2018)

Descriptive details	PICO	Quality of study	Observations/notes
Number of centres not reported; Germany, Switzerland. n = 100 Mean age 68.75 years (±7.6 years) Median PSA level: 1.34 ng/ml (range 0,04–41.3 ng/ml) Recruitment period October 2017 – May 2018	**Population**: prostate cancer patients who were referred for the detection of recurrent disease. **Excluded**: patients with no primary therapy with curative intent, or patients referred for PSMA radioligand therapy. **Intervention**: ^{18}F-PSMA-1007 tracer followed by PET/CT 2 hours after injection. **Reference standard**: none. **Primary outcome measure:** detection rate of ^{18}F-PSMA-1007-positive lesions.	**Study design:** retrospective single-arm subgroup analysis.	• Reference standard/conventional imaging was not included for comparison. • Study reported detection rates and did not report on diagnostic accuracy. • The parameters used to define biochemical relapse in this group of patients was not reported. • There was no follow-up/further diagnostics/histopathological confirmation reported to confirm the accuracy of the diagnostics.

Results	Authors' observations
• ^{18}F-PSMA-1007-positive lesions were detected in 95 (95%) of the 100 patients.	"Of all the patients included in this analysis, 95% showed at least one lesion with characteristics suggestive of [prostate cancer] on ^{18}F-PSMA-1007 PET/CT." "^{18}F-PSMA-1007 PET/CT can detect recurrent [prostate cancer] in a high percentage of patients with biochemical relapse. The probability of a pathological ^{18}F-PSMA-1007 PET/CT seems to be high even in patients with a low PSA level of ≤0.5 ng/ml, which may have a significant impact in the further clinical management of patients. Prospective controlled trials are mandatory to validate these data."

Appendix Table 17. Study details: Giesel et al. (2018b)

Descriptive details	PICO	Quality of study	Observations/notes
Multicentre, 2 centres in Germany and 1 in Chile. n = 251 Median age 70 years (range 48-86) Median PSA-level: 1.2 ng/ml (range: 0.2-228 ng/mL) Recruitment period February 2017 – January 2018	**Population**: prostate cancer patients who received primary RP with or without salvage radiation, who had PSA levels ≥ 0.2 ng/ml. Excluded: patients with advanced castration-resistant prostate cancer who underwent second-line ADT, chemotherapy, or radionuclide therapy. **Intervention**: ^{18}F-PSMA-1007 PET/CT. **Reference standard**: none. **Primary outcome measure:** detection rate of ^{18}F-PSMA-1007-positive lesions.	**Study design:** retrospective single-arm analysis.	• Reference standard/conventional imaging was not included for comparison. • Study reported detection rates and did not report on diagnostic accuracy. • There was no follow-up/further diagnostics/histopathological confirmation reported to confirm the accuracy of the diagnostics.

Results	Authors' observations
• ^{18}F-PSMA-1007-positive lesions were detected in 204 (81.3%) of the 251 patients.	"[18F]PSMA-1007 PET/CT demonstrates a high detection rate for patients with biochemical recurrence after radical prostatectomy. [18F]PSMA-1007 PET/CT could improve patient management by correctly identifying sites of recurrence early in the course of the disease. [18F]PSMA-1007, perhaps due to its alternate route of excretion, that bypasses the urinary tract, shows specific advantages for detecting local recurrence and loco-regional nodes which are generally more prevalent at very low PSA levels."

Appendix 2. Guideline recommendations on the use of non-FDG PET/CT in patients with biochemical recurrent prostate cancer

Guideline	Tracers	Recommendations
European Association of Urology (2015)	Choline (type not specified)	Choline PET/CT scan is not recommended in patients with biochemical recurrence and a PSA-level < 1 ng/ml.
Cancer Care Ontario (2015)	Choline (^{18}F and ^{11}C-choline)	Use of choline PET is not usually appropriate, and should be considered experimental when: • salvage radiotherapy is planned after radical prostatectomy • local salvage therapy is planned after radiotherapy.
UK guidance from the Royal Colleges of Physicians, the Royal College of Radiologists and the British Nuclear Medicine Society (2016)	^{11}C-choline, ^{18}F-fluorocholine (both F-FEC and F-FCH) or ^{68}Ga-PSMA	PET/CT is recommended in suspected recurrence in patients with a rapidly rising PSA and negative or equivocal conventional imaging where the results would directly influence patient management.
European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI).	^{68}Ga-PSMA	In the setting of biochemical recurrence, use of ^{68}Ga-PSMA is especially recommended in patients with low PSA values between 0.2 and 10 ng/ml to identify the site of recurrence and to potentially guide salvage therapy.
PSA: prostate-specific antigen.		

Appendix 3. Study selection criteria*

Population	Patients with known or suspected relapsed or recurrent prostate cancer (after treatment with curative intent)
Intervention	Positron emission tomography (PET) using the following radiotracers: • 68-gallium prostate-specific membrane antigen (PSMA) • ^{18}F PSMA
Comparison/ comparators	Tracers will be compared to each other, or to other radiotracers such as (but limited to): • ^{18}F-fluorocholine (FCH) • ^{18}F-ethylcholine (FEC) • anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (anti-^{18}F-FACBC, ^{18}-f fluciclovine) • FDG • ^{11}C choline • ^{11}C acetate • ^{18}F DCFPyl or to current prostate imaging techniques such as: • magnetic resonance imaging (MRI) – for assessment of lymph node invasion • computed tomography (CT) – for staging • isotope bone scan/bone scintigraphy - for assessment of bone metastases
Outcomes	Diagnostic accuracy (sensitivity and specificity) Detection rates (proportion of patients with recurrence detected; proportion of lesions detected) Clinical utility (changes in patient management, staging or prognosis, following imaging or in comparison to decisions made using other imaging techniques)
Study design	SHTG Evidence Note 67 summarises all published secondary evidence published up to August 2016, and assessed primary evidence for outcomes and interventions for which no secondary evidence was available. We will conduct a separate search for secondary evidence published since the date of last search by SHTG (August 2016). If no new secondary evidence is found on the interventions listed above, or where the secondary evidence does not address all outcomes of interest, primary studies will also be considered.

* This is a modified version of the original protocol for this review. The original protocol was an adaptation of that used for SHTG Evidence Note 67, and was used to produce the first draft of HTW's Evidence Appraisal Report in August 2018. This report was sent to expert reviewers for comment and discussed with Assessment Group on 4 September 2018. In both cases, it was noted that a more targeted focus on assessing the effectiveness of specific classes of PET radiotracer would be beneficial. Therefore, HTW revised the protocol of the appraisal to take account of these comments and ensure the scope answers the question of most relevance to NHS Wales. A copy of the original protocol is available on request.

Appendix 4 - PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness