Clinical priorities advisory group
4 December 2024

Agenda Item No	2.3
National Programme	Cancer Programme of Care
Clinical Reference Group	Nuclear Medicine Respond and Advise
URN	2307

Title
Prostate-Specific Membrane Antigen (PSMA) radiotracers in Positron Emission Tomography – Computed Tomography (PET-CT) Imaging for individuals with high-risk primary or recurrent prostate cancer

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
PSMA PET-CT is recommended to be available as a routine commissioning imaging option for high-risk primary or recurrent prostate cancer within the criteria set out in this document. For the purposes of this document, PSMA PET-CT refers to PET-CT imaging using either Ga68-PSMA or F18-PSMA radiotracers. Delegation status – service retained.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the policy proposition has completed the appropriate sequence of governance steps and includes an: Evidence Summaries; Clinical Panel Report.
2.	The Deputy Director of Cancer Programme confirms the policy proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.

3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy
2.	Engagement Report
3.	Evidence Summaries and a Public Health Evidence Report
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

<table>
<tr><th>Outcome</th><th>Evidence statement</th></tr>
<tr><td colspan="2">Clinical effectiveness</td></tr>
<tr><td>Accuracy of imaging

Certainty of evidence:
Not assessed for 3 paper summaries</td><td>Accuracy of imaging was reported in all 3 of the papers included in the summary.

Hofman et al 2020 reported accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease[1] at six-month follow-up in men with prostate cancer and high-risk features.

Data were available for 295 (of 302) men. ^{68}Ga-PSMA-11 PET-CT (n=150) had an absolute greater area under the curve (AUC) for accuracy than conventional imaging (n=145), reflecting the lower sensitivity and specificity for conventional imaging (Table 1). The difference of 27% (95% CI 23 to 31) was statistically significant (p<0.0001).

Table 1: Imaging accuracy results reported by Hofman et al 2020
<table>
<tr><th></th><th>^{68}Ga-PSMA-11 PET-CT</th><th>Conventional imaging</th></tr>
<tr><td>Area under the curve</td><td>92% (95% CI 88 to 95)</td><td>65% (95% CI 60 to 69)).</td></tr>
<tr><td>Sensitivity</td><td>85% (95% CI 74 to 96)</td><td>38% (95% CI 24 to 52)</td></tr>
<tr><td>Specificity</td><td>98% (95% CI 95 to 100)</td><td>91% (95% CI 85 to 97)</td></tr>
</table>
^{68}Ga-PSMA-11 PET-CT remained superior to conventional imaging in sensitivity analysis where lesions rated as equivocal were considered positive rather than negative (absolute greater AUC 28% [95%CI 23 to 33]).

The superiority of 68Ga-PSMA-11 PET-CT was demonstrated for subgroups of patients with pelvic nodal (absolute greater AUC 32% [95%CI 28 to 35])</td></tr>
</table>

and distant metastasis (absolute greater AUC 22% [95%CI 18 to 26]). The authors reported that ^{68}Ga-PSMA-11 PET-CT was also superior in subgroup analysis of men with Gleason grade group 4 disease of higher, grade group 3 or lower and PSA concentration of ≥20 ng/mL.

Hofman et al 2020 also reported AUC for men who crossed-over to second-line imaging (n=291). The AUC of accuracy was 17% higher (95%%CI 13 to 22) for ^{68}Ga-PSMA-11 PET-CT (84% [95%CI80 to 88]) than conventional imaging (67% [95%CI 62 to 71]). No statistical comparison was reported.

Hope et al 2021 reported the accuracy of ^{68}Ga-PSMA-11 PET for the detection of regional nodal metastasis on a per-patient basis using nodal regional correlation in men with intermediate to high-risk prostate cancer (n=277). Patients received either ^{68}Ga-PSMA- 11 PET-CT (n=214) or ^{68}Ga-PSMA-11 PET-MRI (n=63) (outcomes for each scan type not separately reported). Imaging results[2] were compared to a reference standard of pathology at radical prostatectomy.

Table 2: Imaging accuracy results reported by Hope et al 2021

	^{68}Ga-PSMA-11 PET
Sensitivity	0.40 (95% CI 0.30 to 0.51)
Specificity	0.95 (95% CI 91 to 97)
Positive predictive value	0.75 (95% CI 0.60 to 0.86)
Negative predictive value	0.81 (95% CI 0.76 to 0.85)

Post-hoc analysis found that larger pelvic nymph node metastasis size (>10mm) was associated with higher sensitivity for the detection of pelvic nodal metastasis. The authors reported that there was insufficient evidence to conclude that Gleason score, PSA level category or D'Amico risk were associated with sensitivity.

Ferraro et al 2020 reported that ^{68}Ga-PSMA-11 PET detected the primary tumour in 113 of 116 patients (97%) with intermediate or high-risk prostate cancer. One false positive ^{68}Ga-PSMA-11 PET finding of a single pelvic positive node was proven with histopathology. The patients were imaged using either ^{68}Ga-PSMA- 11 PET-CT or ^{68}Ga-PSMA-11 PET- MRI (proportion of patients receiving each scan type not reported; outcomes for each scan type not separately reported).

One of the included papers reported statistically significantly higher accuracy with ^{68}Ga-PSMA-11 PET-CT (n=150) compared to conventional imaging (n=145) in men with prostate cancer and high-risk features. Sensitivity was 85% vs 38% and specificity 98% vs 91% respectively. A second included paper (n=277) reported a sensitivity of 0.40 and specificity of 0.95 for men with intermediate to high-risk prostate cancer receiving ^{68}Ga-PSMA-11 PET-CT (n=214) or ^{68}Ga-PSMA-11 PET-MRI (n=63). A third included paper (n=116) reported that ^{68}Ga- PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI detected the primary tumour in 97% of patients with intermediate or high-risk prostate cancer. In the third

	paper the proportion of patients receiving PET-CT or PET-MRI was not reported.
Reporter Agreement **Certainty of evidence:** Not assessed for 3 paper summaries	Reporter agreement was reported in 2 of the 3 papers included in the summary. Hofman et al 2020 reported that reporter agreement was high with ^{68}Ga-PSMA-11 PET-CT (n=148) for nodal (pairwise kappa value (κ) =0.87 (95% CI 0.81 to 0.94)) and distant (κ =0.88 (95% CI 0.84 to 0.82)) disease in men with prostate cancer and high-risk features. Hope et al 2021 reported inter-reader agreement for ^{68}Ga-PSMA- 11 PET for men with intermediate to high-risk prostate cancer (n=277). This was reported as substantial for right-sided nodes (κ =0.61 (95%CI 0.55 to 0.67)) and left-sided nodes (κ =0.66 (95% CI0.60 to 0.71) and moderate for other nodes (κ =0.52 (95% CI 0.46 to 0.58)). Patients received either ^{68}Ga-PSMA-11 PET-CT (n=214) or ^{68}Ga-PSMA-11 PET-MRI (n=63) (outcomes for each scan type not separately reported). **One of the included papers (n=148) reported high agreement between readers with ^{68}Ga-PSMA-11 PET-CT for nodal and distant disease in men with prostate cancer and high-risk features. A second included paper (n=277) reported substantial to moderate inter-reader agreement for nodal disease with ^{68}Ga-PSMA-11 PET-CT (n=214) or ^{68}Ga-PSMA-11 PET-MRI (n=63) in men with intermediate to high-risk prostate cancer.**
Equivocal findings **Certainty of evidence:** Not assessed for 3 paper summaries	Equivocal findings were reported in 1 of the 3 papers included in the summary. Hofman et al 2020 reported statistically significantly fewer equivocal findings with ^{68}Ga-PSMA-11 PET-CT (11/148; 7% [95% CI 4 to 13]) compared to conventional imaging (35/152; 23% [95% CI 17 to 31]), p<0.001 in men with prostate cancer and high-risk features. The authors reported similar results for subgroups of men with pelvic nodal and distant metastasis. **One of the included papers reported statistically significantly fewer equivocal findings with ^{68}Ga-PSMA-11 PET-CT (n=148) (7%) compared to conventional imaging (n=152) (23%).**
Change in Staging **Certainty of evidence:** Not assessed for 3 paper summaries	Change in staging was reported in 2 of the 3 papers included in the summary. Hofman et al 2020 reported a change of stage or nodal or distant metastasis for men with prostate cancer and high-risk features who crossed-over to second-line imaging (n=291). Stage was changed for more men following second-line imaging with ^{68}Ga-PSMA-11 PET-CT (33/146; 22% [95% CI 16 to 30]) than after second-line conventional imaging (20/135; 14% [95% CI 9 to 22]). Change in stage was compared to the reference standard. The change in stage was judged correct more often with ^{68}Ga-PSMA-11 PET-CT (26 men) than conventional imaging (3 men). No statistical comparisons were reported.

	Ferraro et al 2020 reported that ^{68}Ga-PSMA-11 PET brought new information in 42 of 116 men with intermediate or high-risk prostate cancer. The most frequent new findings were lymph node metastasis (n=20) and suspected bone metastasis (n=11). Patients were imaged using either ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA11 PET- MRI (proportion of patients receiving each scan type not reported; outcomes for each scan type not separately reported). **One of the included papers (n=291) reported a change of stage for 22% of patients after ^{68}Ga-PSMA-11 PET-CT and 14% of patients after conventional imaging. The change of stage was judged correct more often with ^{68}Ga-PSMA-11 PET-CT. No statistical comparison was reported. A second included paper reported that ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI brought new information in 42 of 116 men with intermediate or high-risk prostate cancer (proportion of patients receiving PET-CT or PET-MRI not reported).**
Change in patient management **Certainty of evidence:** Not assessed for 3 paper summaries	Change in patient management was reported in 2 of the 3 papers included in the summary. Hofman et al 2020 reported that a statistically significantly greater number of men with prostate cancer and high-risk features had a change in their management with high or medium effect[3] with first line ^{68}Ga-PSMA-11 PET-CT (41/148; 28% [95% CI 21 to 36]) compared to conventional imaging (23/152; 15% [95% CI 10 to 22]), p=0.008. Following first line ^{68}Ga-PSMA-11 PET-CT, 20 (14%) of 148 patients were directed from curative to palliative-intent treatment, 11 patients (7%) had a change in radiotherapy technique and 11 patients (7%) had a change in surgical technique. Hofman et al 2020 also reported changes in patient management for men who crossed-over to second-line imaging (n=291). The number of men who had a change in their management with high or medium effect was higher with second-line ^{68}Ga-PSMA-11 PETCT (39/146; 27% [95% CI 20 to 35]) compared to conventional imaging (7/135; 5% [95% CI 2 to 10]). Ferraro et al 2020 reported that for 32 of 116 men (27%) with intermediate or high-risk prostate cancer, the new information gained from ^{68}Ga-PSMA-11 PET staging had an impact on disease management. The patients were imaged using either ^{68}Ga-PSMA11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI (proportion of patients receiving each scan type not reported; outcomes for each scan type not separately reported). The new information led to a modification of some detail within the same therapy modality in 17 of these patients (14%). For the remaining 15 patients (13%), the previously intended therapy was not considered the best treatment option anymore. The changes in disease management are summarised in Tables 3 and 4. **Table 3: Change in intended therapy reported by Ferraro et al 2020**

Change made with ^{68}Ga-PSMA-11 PET	Patients (n=15)
Change from local therapy to local treatment plus additional or metastases-targeted treatment due to new bone metastasis	6 (40%)
Change from local therapy plus androgen deprivation therapy (ADT) to systemic treatment only or additional chemotherapy due to more extensive disease	3 (20%)
Change from local therapy plus ADT to local therapy alone due to ruling out bone metastasis or showing oligometastatic disease	4 (27%)
Change from active surveillance to local therapy due to location of the prostatic lesion for targeted biopsy	1 (7%)
Change from focal therapy to surgery due to more extensive tumour	1 (7%)

Table 4: Change in therapy modality reported by Ferraro et al 2020

Change made with ^{68}Ga-PSMA-11 PET	Patients (n=17)
Change in radiation field due to previously undetected nodal metastasis	7 (41%)
Change in whether radiation of the lymphatic drainage was included or excluded	3 (18%)
Change to additional stereotactic body radiotherapy for bone metastasis	3 (18%)
Change in modality detail in surgical approach due to extracapsular extension or additional common nodes included in lymphadenectomy	4 (24%)

The new information gained from ^{68}Ga-PSMA-11 PET was not relevant to management for 10 patients (of 42 with new information). For example, because the additional bone metastasis or lymph node metastasis within the surgical/radiotherapy field. In subgroup analysis, Ferraro et al 2020 found a statistically significant association between PSA and clinical TNM stage and therapy change (Table 5).

Table 5: Patients with a change in their management by subgroup reported by Ferraro et al 2020

	Patients with change in management
PSA level ≤5 ng/mL	1/21 (4%)
PSA level between >5 and <10 ng/mL	5/26 (19%)
PSA level between ≥10 and ≤20 ng/mL	13/39 (33%)
PSA level of >20 ng/mL	13/30 (43%)
Tumour, node and metastasis (TNM) staging group II	5/42 (12%)
TNM staging group III	16/54 (30%)
TNM staging group IV	8/15 (53%)

D'Amico and Gleason score risk groups did not show a statistically significant correlation with a change in management.

One of the included papers reported that a statistically significantly greater number of men with prostate cancer and

	high-risk features had a change in their management with first-line ^{68}Ga-PSMA-11 PET-CT (n=148) compared to conventional imaging (n=152) (28% vs 15%). A greater proportion of men also had a change in management after cross-over to second-line ^{68}Ga-PSMA-11 PET-CT (27%) compared to conventional 5%). A second included paper (n=116) reported that the new information gained from ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI staging had an impact on disease management for 27% of men with intermediate or high-risk prostate cancer (proportion of patients receiving PET-CT or PET-MRI not reported).
Radiation Exposure **Certainty of evidence:** Not assessed for 3 paper summaries	Radiation exposure was reported in 1 of the 3 papers included in the summary. Hofman et al 2020 reported that radiation exposure from first line diagnostic imaging was lower with ^{68}Ga-PSMA-11 PET-CT (n=148) (8.4 millisieverts (mSv) (95%CI 8.1 to 8.7)) compared to conventional imaging (n=152) (19.2 mSv (95%CI 18.2 to 20.3)). The difference of 10.9 mSv (95%CI 9.8 to 12.0) was statistically significant (p<0.001). **One of the included papers reported statistically significantly lower radiation exposure with ^{68}Ga-PSMA-11 PET-CT (n=148) (8.4mSv) compared to conventional imaging (n=152) (19.2mSv).**
Biochemical recurrence **Certainty of evidence:** Not assessed for 3 paper summaries	Biochemical recurrence was reported in 1 of the 3 papers included in the summary. Ferraro et al 2020 reported that 11 of 58 men (19%) men with intermediate or high-risk prostate cancer selected for radical prostatectomy based on ^{68}Ga-PSMA-11 PET had biochemical recurrence after a mean (standard deviation) follow-up of 12 months (± 2.4). The patients were imaged using either ^{68}Ga-PSMA11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI (proportion of patients receiving each scan type not reported; outcomes for each scan type not separately reported). **One of the included papers reported biochemical recurrence after a mean follow-up of 12 months in 19% of 58 men with intermediate or high-risk prostate cancer selected for radical prostatectomy based on ^{68}Ga-PSMA-11 PET. Patients were imaged using either ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET- MRI (proportion of patients receiving PET-CT or PET-MRI not reported).**
Safety	
Safety **Certainty of evidence:** Not assessed for 3 paper summaries	Safety was reported in 2 of the 3 of the papers included in the summary. Hofman et al 2020 stated that no adverse events were reported with ^{68}Ga-PSMA-11 PET-CT for 150 men with prostate cancer and high-risk features. No statement was made regarding adverse events with conventional imaging.

	Hope et al 2021 reported no Grade 2 or higher adverse events for men with intermediate to high-risk prostate cancer with ^{68}Ga PSMA-11 PET. Grade 1 adverse events were reported in 44 of 764 patients (6%), none of which required intervention. The most common adverse events were diarrhoea (n=16), fatigue (n=6), rash (n=4) and nausea (n=4). The authors reported that these events were possibly related to contrast administration. Of the 764 patients, 612 received ^{68}Ga-PSMA-11 PET-CT and 152 ^{68}Ga PSMA-11 PET-MRI (outcomes for each scan type not separately reported). **One of the included papers (n=150) reported no adverse events with ^{68}Ga-PSMA-11 PET-CT. A second included paper (n=764) reported no adverse events with ^{68}Ga-PSMA-11 PET that were Grade 2 or higher and Grade 1 adverse events in 6% of patients. Of the 764 patients, 612 received ^{68}Ga-PSMA-11 PET-CT and 152 ^{68}Ga-PSMA-11 PET-MRI.**
Outcome	**Evidence statement**
Clinical effectiveness	
Detection rates **Certainty of evidence:** Not assessed for 3 paper summaries	Detection rates were reported in all 3 of the papers included in the summary. Calais et al 2019 reported greater overall detection rates for biochemical recurrence of prostate cancer with ^{68}Ga-PSMA-11 PET-CT (28 of 50 patients; 56% [95% confidence interval (CI) 41% to 70%]) compared to ^{18}F-fluciclovine PET-CT (13 of 50 patients; 26% [95% CI 15% to 40%]) at the patient level. The difference was statistically significant (odds ratio (OR) 4.8 [95% CI 1.6 to 19.2], p=0.0026). Calais et al 2019 also reported subgroup analyses for detection rates for biochemical recurrence of prostate cancer by anatomical region. Statistically significantly greater detection rates were reported for ^{68}Ga-PSMA-11 PET-CT compared with ^{18}F-fluciclovine PET-CT in the pelvic nodes region (15 of 50 patients; 30% [95% CI 18% to 45%]) versus 4 of 50 patients; 8% [95% CI 2% to 19%], respectively); OR 12·0 (95% CI 1·8 to 513·0^{4}], p=0·0034); and in the subgroup analysis of any extrapelvic lesions (8 of 50 patients; 16% [95% CI 7% to 29%) versus 0 of 50 patients; 0% [95% CI 0% to 6%]; OR non-estimable [95% CI non-estimable], p=0·0078). No statistically significant differences in detection rates were reported between ^{68}Ga-PSMA-11 PET-CT and ^{18}F-fluciclovine PET-CT for individual extrapelvic lesion locations: extrapelvic nodes (M1a) (6% versus 0%, respectively), bone (M1b) (8% versus 0%, respectively), and other organ (M1c) (4% versus 0%, respectively). Detection rates for prostate bed recurrence were slightly higher by ^{18}F-fluciclovine PET-CT compared with ^{68}Ga-PSMA-11 PET-CT, but the difference was not statistically significant (9 of 50 patients; 18% [95% CI 9% to 31%] versus 7 of 50 patients; 14% [95% CI 6% to 27%], respectively). The OR was 0.6 (95% CI 0.1 to 3.1) p=0·73. Calais et al 2019 also reported subgroup analyses for detection rates based on PSA concentration levels. There were no statistically significant differences in detection rates between ^{68}Ga-PSMA-11 PET-CT and ^{18}F-fluciclovine PET-CT for patients with PSA 0.2 to 0.5 ng/mL (12 of 26 patients;

46% [95% CI 27% to 67%] versus 7 of 26 patients; 27% [95% CI 12% to 48%] respectively; p=0.227), or PSA 1.01 to 2.00 ng/mL (4 of 6 patients; 67% [95% CI 22% to 96%] versus 1 of 6 patients; 17% [95% CI 0% to 64%] respectively; p=0.250). There was a statistically significant difference in detection rates in patients with PSA 0.51 to 1.00 ng/mL, with greater detection rates reported for ^{68}Ga-PSMA-11 PET-CT compared with ^{18}F-fluciclovine PET-CT (12 of 18 patients; 67% [95% CI 41% to 87%] versus 5 of 18 patients; 28% [95% CI 10% to 53%] respectively; p=0.039). No statistically significant differences were reported for PSA subgroups by patient or disease location.

Olivier et al 2022 reported the overall proportion of patients with correct detection rates for recurrence at the patient level and by anatomical region. They reported higher rates for overall correct detection of positive recurrence by ^{18}F-PSMA-1007 PET-CT (0.82 [95% CI 0.78 to 0.86]) compared to ^{18}F-fluorocholine PET-CT (0.65 [95% CI 0.60 to 0.71]). The difference of 0.16 (95% CI 0.11 to 0.22) was statistically significant (p<0.0001); the OR was 2.40 (95% CI 1.79 to 3.21; p<0.0001). There were no statistically significant differences in positive predictive values between the ^{18}F-PSMA-1007 PET-CT and ^{18}F-fluorocholine PET-CT scans: OR 0.95 (95% CI 0.42 to 2.15; p=0.90). The difference in overall correct detection rates in determining negative recurrence was greater with ^{18}F-PSMA-1007 PET-CT (0.77 [95% CI 0.72 to 0.82]) compared to ^{18}F-fluorocholine PET-CT (0.57 [95% CI 0.51 to 0.62]). The difference of 0.21 (95% CI 0.15 to 0.26) was statistically significant (p<0.0001); the OR was 2.61 (95% CI 1.97 to 3.46; p<0.0001). Positive predictive values were not statistically significantly different between the ^{18}F-PSMA-1007 PET-CT and ^{18}F-fluorocholine PET-CT scans (OR 0.58 [95% CI 0.22 to 1.55]; p=0.27).

Olivier et al 2022 also reported sub-group analyses on detection rates for prostate cancer recurrence based on PSA levels. They reported that detection rates for recurrence were greater in patients with higher PSA levels (Table 1). Detection rates were statistically significantly greater with ^{18}F-PSMA-1007 PET-CT compared to ^{18}F-fluorocholine PET-CT for all PSA levels (Table 1).

Table 1: Patient level proportion of patients with correct detection rates for prostate cancer lesions by PSA level at baseline reported by Olivier et al 2022

PSA level*	^{18}F-PSMA-1007	^{18}F-fluorocholine	Odds ratio	p-value
<0.5 ng/mL (n=43)	0.57 (95% CI 0.45 to 0.68)	0.39 (95% CI 0.28 to 0.50)	2.10 (95% CI 1.13 to 3.89)	0.002
≤0.5 ng/mL to <1.0 ng/mL (n=25)	0.83 (95% CI 0.72 to 0.93)	0.43 (95% CI 0.28 to 0.58)	6.88 (95% CI 3.3 to 14.13)	<0.0001
≤1.0 ng/mL to <2.0 ng/mL (n=33)	0.81 (95% CI 0.72 to 0.89)	0.50 (95% CI 0.37 to 0.62)	4.31 (95% CI 2.26 to 8.24)	<0.0001
≥2.0 ng/mL (n=78)	0.85 (95% CI 0.79 to 0.91)	0.74 (95% CI 0.66 to 0.82)	2.01 (95% CI 1.27 to 3.19)	0.003

	*Number of patients with recurrence detected by standard of truth (i.e. recurrence, no recurrence, or undetermined based on all available clinical patient data from pre-inclusion to end of follow-up) Olivier et al 2022 also reported patient level correct detection rates based on clinical investigators' overall findings which demonstrated statistically significantly greater detection rates with ^{18}F-PSMA-1007 PET-CT (0.80 [95% CI 0.74 to 0.86]) compared to ^{18}F-fluorocholine PET-CT (0.50 [95% CI 0.42 to 0.57]), p<0.0001. The same paper also reported correct detection rates by anatomical region based on masked readers' findings. Seventy two patients had 78 anatomical regions with confirmed prostate cancer, with more lesions detected with ^{18}F-PSMA-1007 PET-CT compared with ^{18}F-fluorocholine PET-CT. The superiority of ^{18}F-PSMA-1007 PET-CT was demonstrated for overall composite anatomical region sensitivities (0.77 [95% CI 0.69 to 0.84]) compared to ^{18}F-fluorocholine PET-CT (0.57 [95% CI 0.48 to 0.67]). The difference was statistically significant (p<0.0001). Fendler et al 2020 reported differences in pre- and post-^{68}Ga-PSMA-11 PET-CT referring physician indications for site of recurrence and detection rates based on location of disease post-^{68}Ga-PSMA-11 PET-CT. No lesion localisation was reported in 27% (103 of 382) patients by ^{68}Ga-PSMA-11 PET (reported difference -19% post-^{68}Ga-PSMA-11 PET-CT compared to pre-^{68}Ga-PSMA-11 PET-CT by referring physician indication), locoregional disease in 33% (126 of 382) patients by ^{68}Ga-PSMA-11 PET (reported difference +51% post-^{68}Ga-PSMA-11 PET-CT compared to pre-^{68}Ga-PSMA-11 PET-CT by referring physician indication), extrapelvic nodal metastatic disease (M1a) in 17% (64 of 382) patients by ^{68}Ga-PSMA-11 PET-CT (reported difference +41% post-^{68}Ga-PSMA-11 PET-CT compared to pre-^{68}Ga-PSMA-11 PET-CT by referring physician), and osseous (M1b) or visceral (M1b) metastatic disease detected in 85 and four patients, respectively, by ^{68}Ga-PSMA-11 PET-CT (reported difference +37% post-^{68}Ga-PSMA-11 PET-CT compared to pre-^{68}Ga-PSMA-11 PET-CT by referring physician). **One of the included papers (n=50) reported a statistically significant difference in detection rates for biochemical recurrence of prostate cancer at the patient level and by anatomical region, with greater rates reported by ^{68}Ga-PSMA-11 PET-CT compared to ^{18}F-fluciclovine PET-CT. The same paper also reported statistically significantly greater detection rates in patients with PSA 0.51 to 1.00 ng/mL with ^{68}Ga-PSMA-11 PET-CT compared to ^{18}F-fluciclovine PET-CT, no significant differences were reported between ^{68}Ga-PSMA-11 PET-CT and ^{18}F-fluciclovine PET-CT scans for other PSA levels. The second paper (n=195) reported statistically significantly greater detection rates for correctly determining positive or negative recurrence of prostate cancer by ^{18}F-PSMA-1007 PET-CT compared to ^{18}F-fluorocholine PET-CT. The paper also demonstrated that positive predictive values were equivocal for ^{18}F-PSMA-1007 PET-CT and ^{18}F-fluorocholine PET-CT scans. The third paper (n=382) reported that referring physicians often**

	accepted the reported location of disease by ^{68}Ga-PSMA-11 PET-CT, and this impacted on subsequent patient management.
Validation of PET-CT findings **Certainty of evidence:** Not assessed for 3 paper summaries	Validation of PET-CT findings was reported in 1 of the 3 papers included in the summary. Calais et al 2019 reported that ^{68}Ga-PSMA-11 PET-CT and ^{18}F-fluciclovine PET-CT findings were validated in 15 of 50 patients (30%) using reference standards including histopathology, follow-up imaging, and PSA decreases after focal treatment without androgen deprivation treatment: 5 of 13 (38%) patients with ^{18}F-fluciclovine PET-CT positive findings and 10 of 28 (36%) patients with ^{68}Ga-PSMA-11 PET-CT positive findings. Five patients had MRI or CT follow-up imaging but lesion validation was not confirmed because follow-up scans were negative. Neither PET-CT scans showed false-positive findings in the 15 patients in whom lesions were verified (both ^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT findings had 100% positive predictive values). There was no statistically significant difference in per-patient sensitivity between ^{18}F-fluciclovine PET-CT (33% [95% CI 15% to 58%]; five true positives and ten false negatives) and ^{68}Ga-PSMA-11 PET-CT (66% [95% CI 42% to 85%]; ten true positive and five false negative). The OR was 3·5 (95% CI 0·67 to 34·5); p=0·18. The specificity and negative predictive values of ^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT scans could not be established. **One of the included papers (n=50) reported validation of findings with ^{68}Ga-PSMA-11 PET-CT and ^{18}F-fluciclovine PET-CT in 15 patients using reference standards.**
Patient management **Certainty of evidence:** Not assessed for 3 paper summaries	Patient management was reported in all 3 of the papers included in the summary. Calais et al 2019 reported patient management following ^{18}F-fluciclovine PET-CT or ^{68}Ga-PSMA-11 PET-CT scans. They reported that 11 of 50 patients (22%)[5] received focal treatment (e.g. metastasis surgery and metastasis stereotactic body radiation treatment), 30 of 50 patients (60%) underwent androgen deprivation treatment, and nine of 50 patients (18%) were managed with active surveillance. However, the authors reported that their study was not designed to assess the effect of ^{18}F-fluciclovine PET-CT or ^{68}Ga-PSMA-11 PET-CT on patient management and no statistical comparisons were reported. Olivier et al 2022 reported changes in patient treatment plans before and after ^{18}F-PSMA-1007 PET-CT and ^{18}F-fluorocholine PET-CT scans in 187 patients; data were missing for three patients. Treatment decisions were changed in 100 patients, with 89 decisions considered major changes. No statistical comparisons were reported. **Table 2: Major and minor changes in patient management before and after ^{18}F-PSMA-1007 PET-CT and ^{18}F-fluorocholine PET-CT scans reported by Olivier et al 2011**

Before PET-CT	**After PET-CT**						
		ADT only	**Radiation treatment only**	**Radiation treatment + ADT**	**No treatment**	**Other**	**Surgery**
	No treatment	**16**	**13**	**9**		**3**	**1**
	ADT only		**7**	**5**	**2**	**2**	0
	Radiation treatment only	**6**		4	**1**	0	**1**
	Radiation treatment + ADT	**6**	7		**1**	**2**	0
	Other	**5**	**4**	**3**	**1**		0
	Chemotherapy	0	**1**	0	0	0	0

Major changes – figures in bold. ADT – androgen deprivation treatment.

Fendler et al 2020 reported intended management implementation at 3- to 6-month follow-up in 206 patients after ^{68}Ga-PSMA-11 PET-CT. They reported that the intended management was implemented in 160 of 206 (78%) patients. A change in management was intended in 136 of the 206 patients, of whom 98 (72%) patients received the intended management change after ^{68}Ga-PSMA-11 PET-CT, whilst 38 (28%) patients did not. The intended pre-^{68}Ga-PSMA-11 PET management plan was implemented in 62 of 70 (89%) patients at 3- to 6-month follow-up. Minor changes in management were implemented in 31 of 40 (78%) patients, while major changes in different types of treatment ranged from 66% (major change to systemic treatment in 19 of 29 patients) to 76% (major change to local treatment in 26 of 34 patients).

Fendler et al 2020 reported changes in intended management strategies after ^{68}Ga-PSMA-11 PET-CT by location of disease. Major changes were reported in the subgroup of patients with no lesion localisation by ^{68}Ga-PSMA-11 PET-CT (38 of 103 patients; 37%), with the greatest change towards active surveillance (18 of 38 patients; 47%). Major changes were reported in the subgroup of patients with locoregional disease by ^{68}Ga-PSMA-11 PET-CT (61 of 126 patients; 48%), with the greatest change towards local treatment (34 of 61 patients; 56%). In the subgroup of patients with extrapelvic nodal metastatic disease (M1a) according to ^{68}Ga-PSMA-11 PET-CT, major changes were implemented in 31 of 64 (48%) patients, with the largest group changing to systemic treatment (20 of 31 patients; 65%). In the subgroup of patients with osseous or visceral metastatic disease (M1b/c), major changes were implemented after ^{68}Ga-PSMA-11 PET-CT in 52% (46 of 89) patients, with the largest group intended for local or systemic treatment after ^{68}Ga-PSMA-11 PET-CT; 15 of 46 (33%) patients and 20 of 46 (43%) patients, respectively.

Fendler et al 2020 also reported changes in intended management after ^{68}Ga-PSMA-11 PET-CT based on PSA levels. Major changes were implemented in 39% of patients with PSA <0.5 ng/mL (n=85), 58% of

	patients with PSA 0.5 to <1.0 ng/mL (n=57), 53% of patients with PSA 1.0 to < 2.0 ng/mL (n=90), 45% of patients with PSA 2.0 to < 5.0 ng/mL (n=96), and 35% of patients with PSA ≥5.0 ng/mL (n=54). Minor changes were implemented in 26% of patients with PSA <0.5 ng/mL (n=85), 25% of patients with PSA 0.5 to <1.0 ng/mL (n=57), 22% of patients with PSA 1.0 to < 2.0 ng/mL (n=90), 17% of patients with PSA 2.0 to < 5.0 ng/mL (n=96), and 22% of patients with PSA ≥5.0 ng/mL (n=54). **One of the included papers (n=50) reported patient management after ^{68}Ga-PSMA-11 PET-CT and ^{18}F-fluciclovine PET-CT, with the majority of patients receiving androgen deprivation treatment (60%), but no statistical comparisons were reported. The second paper (n=195) reported changes to patient management in 53% of patients after ^{18}F-PSMA-1007 PET-CT and ^{18}F-fluorocholine PET-CT, with the majority considered major changes, but no statistical comparisons were reported. The third paper (n=382) reported that patient management decisions changed in over half the patients after ^{68}Ga-PSMA-11 PET-CT.**
Impact of PET-CT scans on diagnostic tests **Certainty of evidence:** Not assessed for 3 paper summaries	The impact of PET-CT scans on diagnostic tests was reported in 2 of the 3 papers included in the summary. Olivier et al 2022 reported changes in diagnostic thinking for 149 patients, with a greater proportion of changes due to ^{18}F-PSMA-1007 PET-CT which contributed more to changes in 93 patients (62%) compared to ^{18}F-fluorocholine PET-CT which contributed more to changes in four patients (3%). The paper also reported a more accurate diagnosis and changes in treatment that were more beneficial to patients after PET-CT scans (122 patients), with benefit reported more in 88 (46.3%) patients by ^{18}F-PSMA-1007 PET-CT compared to ^{18}F-fluorocholine PET-CT which contributed more benefit in only 6 patients (3.2%). No statistical comparisons were reported. Fendler et al 2020 reported on the diagnostic tests planned before ^{68}Ga-PSMA-11 PET-CT and tests prevented or implemented after ^{68}Ga-PSMA-11 PET-CT according to the referring physicians. Before ^{68}Ga-PSMA-11 PET-CT, referring physicians intended to perform 443 tests on 382 patients. After ^{68}Ga-PSMA-11 PET-CT, 150 tests were prevented, mostly bone scans or ^{18}F-NaF PET (52 of 150 tests, 35%) and CT scans (43 of 150 tests, 29%). After ^{68}Ga-PSMA-11 PET-CT, 73 diagnostic tests were implemented in 70 patients, mainly biopsies to confirm ^{68}Ga-PSMA-11 PET-CT–positive sites of disease (44 of 73 tests, 60%). **One of the included papers (n=195) reported a greater proportion of changes in diagnostic thinking and more accurate diagnosis with ^{18}F-PSMA-1007 PET-CT compared to ^{18}F-fluorocholine PET-CT, but no statistical comparisons were reported. A second paper (n=382) reported that more diagnostic tests were prevented than implemented after ^{68}Ga-PSMA-11 PET-CT.**

Reporter agreement **Certainty of evidence:** Not assessed for 3 paper summaries	Reporter agreement was reported in 2 of the 3 papers included in the summary. Calais et al 2019 reported statistically significantly lower inter-reader agreement in detection rates for ^{18}F-fluciclovine (pairwise kappa value (κ) ≤0·20) compared to ^{68}Ga-PSMA-11 PET-CT (κ values ≥0·60) at the patient level (p=0.0020) and by disease location (p ≤0·016), with the exception of prostate bed recurrence (p=0.046). Olivier et al 2022 reported intra- and inter-reader kappa agreements for the detection of metastases at the patient level which ranged between 0.24 to 0.73 and 0.30 to 0.36 for ^{18}F-PSMA-1007 PET-CT, respectively, and between 0.48 to 0.72 and 0.34 to 0.40 for ^{18}F-flourocholine PET-CT, respectively. The same paper also reported intra- and inter-reader kappa agreements for the detection of metastases at the anatomical region level which ranged between 0.62 to 0.72 and 0.70 to 0.75 for ^{18}F-PSMA-1007 PET-CT, respectively, and between 0.68 to 0.76 and 0.61 to 0.64 for ^{18}F-flourocholine PET-CT, respectively. No statistical comparisons were reported. **One of the included papers (n=50) reported significantly higher agreement between readers in interpreting detection rates by ^{68}Ga-PSMA-11 PET-CT compared to ^{18}F-fluciclovine PET-CT, with the exception of prostate bed recurrence. The second paper (n=195) reported reader agreements for the detection of metastases at the patient and anatomical region level, but no statistical comparisons were reported.**
Safety	
Safety **Certainty of evidence:** Not assessed for 3 paper summaries	Safety was reported in 1 of the 3 papers included in the summary. Olivier et al 2022 reported that four patients who underwent ^{18}F-PSMA-1007 PET-CT had four adverse events (i.e. toothache, diarrhoea, chest discomfort, and arterial hypertension) and one patient had one adverse event (i.e. shoulder pain) after the administration of ^{18}F-fluorocholine PET-CT. None of the adverse events were considered to be related to the two PET-CT scans. They reported no serious adverse events and no patient discontinued participation in the study due to an adverse event. **One of the included papers (n=195) reported that five patients experienced an adverse event not related to PET-CT scans (4 patients with ^{18}F-PSMA-1007 PET-CT and one patient with ^{18}F-fluorocholine PET-CT). No serious adverse events occurred.**

Footnotes:
1 Assessed by the area under the curve (AUC) of the receiver-operating curve using a predefined reference standard including histopathology, imaging and biochemistry. The AUC was calculated as the mean of the estimated sensitivity and specificity
2 Based on the majority read of the three blinded independent central readers

3 A change in treatment intent (e.g. curative to palliative), addition or removal of a treatment modality or change in surgery or radiotherapy technique

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility**: Patients can have significant fatigue or weakness and dizziness which affects mobility • **ability to provide self-care**: Patients can have moderate problems in washing or dressing • **undertaking usual activities**: Patients can have moderate problems in doing their usual activities with shortness of breath when exercising or being active. • **experience of pain/discomfort**: Patients can have moderate pain or discomfort • **experience of anxiety/depression**: Patients can be moderately anxious or depressed
Further details of impact upon patients: People with prostate cancer commonly experience urinary symptoms, fatigue and pain. These symptoms may limit their exercise tolerance and, as a result, patients are unable to fully participate in their daily activities including self-care and physical exercise. These consequences have the potential to significantly decrease quality of life. With progressive disease patients may experience worsening symptoms, in addition to symptoms related to metastatic spread, causing more difficulties in participating in their daily activities and may require additional support from carers. Many people suffer with anxiety as a result of their diagnosis. In addition, following treatment people may experience anxiety due to the risk of recurrence. Some people experience severe anxiety and depression which has the potential to significantly decrease their quality of life and ability to do normal tasks. **Further details of impact upon carers:** Prostate cancer can lead to a moderate burden on carers, who may need to assist the individual with self-care tasks and daily activities. Mental health problems as a consequence of their diagnosis may also affect the relationship between the patient and their family/carers.

Considerations from review by Rare Disease Advisory Group
Not Applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
The PoC was supportive of the policy proposition however, note that practice has moved on since the 2019 interim commissioning position (which this policy proposition seeks to regularise) and that a new policy is required to move the intervention earlier in the prostate cancer pathway.