Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Application Number: 2023-003

^{18}F-PSMA PET/CT in the staging of primary prostate cancer and the restaging of recurrent prostate cancer: Evidence synthesis to support a generic justification decision

Date of decision: 07 December 2023

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About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Foreword

The European Union Basic Safety Standards for the Protection Against Dangers from Medical Exposure to Ionising Radiation (Euratom) were initially transposed into Irish law under SI 256 in January 2019.(1) These Regulations named HIQA as the competent authority for medical exposure to ionising radiation. One requirement under the Regulations is that new practices involving medical exposures must be justified by HIQA before they are generally adopted – this is known as generic justification.

This report sets out an overview of reviews which provides the evidence base to inform HIQA's generic justification decision. The report also includes the consideration of this evidence by HIQA's multidisciplinary Medical Exposure to Ionising Radiation Expert Advisory Group which is formally reported using an evidence-to-decision framework. The review considers the net benefit for this patient population in the context of the medical exposure to ionising radiation; the potential for occupational and public exposure is also considered.

This review was undertaken by the Ionising Radiation Evidence Review Team from the HTA Directorate in HIQA and was supported by HIQA's Medical Exposure to Ionising Radiation Expert Advisory Group who advised on the preparation of this report and participated in the evidence-to-decision exercise. HIQA would like to thank the Evidence Review Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

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The findings of the evidence review prepared by HIQA informed the deliberations of the MEIR EAG in completing the evidence to decision framework. The output of the framework was reached through consensus.

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Conflicts of interest

None declared.

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List of abbreviations used in this report

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
ADT	androgen deprivation therapy
AUC	area under the curve
Bq	Becquerel
CAPRA	cancer of the prostate risk assessment
CASP	Critical Appraisal Skills Programme
CCA	corrected covered area
CI	confidence interval
CLR	correct localisation rate
CT	computed tomography
CT TAP	computed tomography of the thorax, abdomen and pelvis
$CTDI_{vol}$	computed tomography dose index volume
DLP	dose volume product
DR	detection rate
DRL	diagnostic reference level
DRR	detection rate ratio
EAG	expert advisory group
EMA	European Medicines Agency
EPA	Environmental Protection Agency
EPAR	European Public Assessment Report
^{18}F	Fluorine-18
FDA	Food and Drug Administration
^{68}Ga	Gallium-68

GRADE	Grading Of Recommendations, Assessment, Development And Evaluation
GROOVE	Graphical representation of overlap for overviews
HIQA	Heath Information and Quality Authority
HRQoL	health-related qualify of life
HSE	Health Service Executive
HTA	health technology assessment
IR-ERT	ionsing radiation evidence review team
ISUP	International Society for Urological Pathology
MEIR	medical exposure to ionising radiation
MRI	magnetic resonance imaging
mpMRI	multiparametric magnetic resonance imaging
NCCP	National Cancer Control Programme
NIH	National Institute of Health
NPV	negative predictive value
PET	positron emission tomography
PICOS	population, intervention, comparator, outcome, setting
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRIOR	Preferred Reporting Items For Overviews Of Reviews
PSA	prostatic specific antigen
PSMA	prostate specific membrane antigen
QUADAS	Quality Assessment Tool For Diagnostic Accuracy Studies
ROBIS	Risk Of Bias In Systematic Reviews

RCT	randomised controlled trial
RQ	research question
SAE	serious adverse event
SI	statutory instrument
SPECT	single positron emission computed tomography
SUV	standardised uptake value
Sv	sieverts
SWiM	synthesis without meta-analysis
TEAE	treatment emergent adverse events
TNM	tumour nodes metastasis
UK	United Kingdom
US	United States of America

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Plain Language summary

Prostate cancer is the most common cancer in men. As part of their care, patients diagnosed with prostate cancer can have different kinds of imaging (scans) to find out whether their cancer is confined to the prostate or whether it has spread to other parts of the body. These scans can include magnetic resonance imaging (MRI), bone scans and computed tomography (CT) scans.

There is a newer kind of scan which may be useful as part of the care of some men with prostate cancer. This scan works by detecting a protein called prostate specific membrane antigen (PSMA), which is found in large amounts on the surface of most prostate cancer cells. As part of this scan, the patient is injected with a diagnostic medicine. This medicine is made up of two parts: radioactive fluorine (^{18}F) and a substance which binds to PSMA. The medicine is taken up by prostate cancer cells and the radiation from the ^{18}F is detected during the positron emission tomography/computed tomography (PET/CT) scan. This makes it possible for doctors to see where in the body the cancer cells are.

^{18}F-PSMA PET/CT scans can be used for two reasons. Firstly, it is used before treatment starts to find out whether prostate cancer has spread to lymph nodes and other parts of the body. Secondly, it is used in men who have finished treatment whose prostate specific antigen (PSA) levels (a blood test) are rising, to find out if the prostate cancer has returned.

Under Irish law, any new practices which involve the exposure of patients to ionising radiation must be justified by the Health Information and Quality Authority (HIQA). Justification means making sure that the benefits of the practice outweigh the risks involved for the kind of patients undergoing this practice. To decide if this practice is justified, HIQA has reviewed the available evidence in the medical literature, and have sought input from a group of experts, including patient representatives. HIQA has also considered the occupational and public radiation safety issues in this review.

The available evidence indicates that ^{18}F-PSMA PET/CT scans are safe and effective imaging tools when used as part of the care of some patients with prostate cancer. No significant safety concerns were identified. Overall, the benefits of ^{18}F-PSMA PET/CT scans were considered to outweigh the risks.

After reviewing the risks and benefits of the practice, and considering the recommendation from its Medical Exposure to Ionising Radiation Expert Advisory Group, HIQA decided to justify this practice of ^{18}F-PSMA PET/CT for the staging of primary prostate cancer and the restaging of recurrent prostate cancer.

Key Points

Application

- This review was conducted in response to an application submitted by the Blackrock Clinic for the generic justification of fluorine-18 (^{18}F) labelled prostate specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) scans for the primary staging of prostate cancer and the re-staging of recurrent prostate cancer.
- Various ^{18}F-PSMA PET/CT radiotracers are available internationally, including ^{18}F-DCFPyL (Pylclari™) which has been approved by the European Medicines Agency. Other radiotracers include ^{18}F-PSMA-1007 and ^{18}F-rhPSMA-7.

Summary of evidence synthesis process

- In accordance with HIQA's Methods for generic justification of new practices in ionising radiation, an overview of reviews was conducted to establish the evidence base for this new type of practice.
- In total, 11 systematic reviews were identified.
- These systematic reviews were appraised using the ROBIS tool and were used to inform the GRADE table.
- From the included systematic reviews, 38 unique primary studies were identified
- In addition, seven records were identified as part of the targeted grey literature search – these records included international appraisals and clinical practice guidelines.

Clinical effectiveness evidence

- The primary outcomes assessed were measures of diagnostic accuracy, safety and radiation dose.
- Overall, the identified systematic reviews/primary studies had favourable conclusions in terms of the sensitivity, specificity and accuracy of ^{18}F-PSMA PET/CT relative to histopathology or clinical follow-up (which could include alternative imaging). Relevant comparators included ^{68}Ga-PSMA PET/CT and conventional imaging using bone scan, CT or MRI.
- Evidence for the primary staging of patients with high-risk prostate cancer was identified from 10 systematic reviews:
  - No review reported pooled estimates for per-patient, per-lesion or per-lymph node sensitivity, specificity or accuracy.
  - Reported per-patient sensitivity estimates ranged from 0.85 to 1.00; specificity estimates ranged from 0.88 to 1.00 and accuracy estimates ranged from 80% to 100%.

- Reported per-lymph node sensitivity estimates ranged from 0.40 to 0.72; specificity estimates ranged from 0.89 to 0.98; accuracy estimates ranged from 82.5% to 86.2%.
- Reported per-lesion sensitivity estimates ranged from 0.71 to 0.95; specificity estimates ranged from 0.81 to 1.00; accuracy estimates ranged from 93% to 100%.

- Evidence for the re-staging of patients with biochemically recurrent prostate cancer was identified from five systematic reviews with one review reporting pooled data based on a meta-analysis:
  - In terms of per-patient data, a pooled sensitivity estimate of 0.92 was reported in the meta-analysis with other reported estimates ranging from 0.60 to 1.00; specificity was estimated to be 0.83 in the meta-analysis with other reported estimates ranging from 0.70 to 0.89; there were no reported estimates of per-patient accuracy.
  - There were no reported estimates of per-lymph node sensitivity, specificity or accuracy.
  - In terms of per-lesion data, a pooled sensitivity estimate 0.91 was reported in the meta-analysis with an estimate of 0.47 reported in one study; specificity was estimated in the meta-analysis to be 0.91; accuracy was estimated to be 81.3% based on a single study.

Adverse events and safety evidence

- The overview of reviews did not highlight any significant safety concerns with ^{18}F-PSMA PET/CT.
- Three systematic reviews stated that no adverse events due to ^{18}F-PSMA PET/CT were reported in the primary studies; the other eight systematic reviews had no mention of possible adverse events.
- No safety alerts or variations to the marketing authorisation were identified.
- Three studies, incorporating a total of 797 patients, which informed the European Public Assessment report, reported a total of 108 treatment-emergent adverse events. These events were mainly mild and largely transient. The identified studies did not highlight any safety concerns for public and occupational exposure, and the risk is likely to be low, provided appropriate radiation protection safeguards are in place.

Certainty of the evidence

- For the primary staging of high-risk prostate cancer: the certainty of evidence for the per-patient data ranged from low (sensitivity, accuracy) to moderate (specificity); certainty for per-lymph node data ranged from low (sensitivity) to moderate (specificity).

- For the re-staging of recurrent and metastatic prostate cancer, the certainty of evidence for the per-patient data ranged from low (specificity) to moderate (sensitivity); for per lesion data ranged from very low (sensitivity) to low (specificity, accuracy).
- Most systematic reviews were found to be at unclear or high risk of bias.
- In general, the systematic reviews found low risk of bias in the primary studies. However, the review authors identified a high risk of bias in some of the studies due to issues with their reference standards, the index test, patient selection or because of flow and timing.

Clinical significance of reported change in ionising radiation dose

- The change in ionising radiation dose associated with this practice is likely to depend on whether ^{18}F-PSMA PET/CT is used in addition to, or as a replacement for conventional imaging (bone scan and CT of the thorax, abdomen and pelvis). This may depend on the clinical situation and the population involved.
- No national diagnostic reference level exists for ^{18}F-PSMA PET/CT. However, the estimated effective dose for ^{18}F-PSMA PET/CT is 5.68mSv for the PET component and 6.9mSv for the whole body CT component. This compares with 13.47mSv for a CT thorax, abdomen and pelvis and 3.07mSv for a bone scintigraphy scan.
- Accurate estimation of the clinical significance of increases or decreases in doses is challenging as there are many risk factors for cancer and the dose from medical imaging only forms part of a person's long-term risk of cancer. However, it is accepted that there is a clinical benefit in keeping dose as low as reasonably achievable.

Medical Exposure to Ionising Radiation Expert Advisory Group (MEIR EAG)

- Informed by the review of the above evidence, the MEIR EAG completed judgements under a modified evidence-to-decision making framework to arrive at a recommendation to HIQA on the generic justification of ^{18}F-PSMA PET/CT.
- While recognising that ^{18}F-PSMA PET/CT has high sensitivity, specificity and accuracy and that its use would enable improved equity of access to PSMA PET/CT, the MEIR EAG judged the benefit of this practice to be moderate given that the evidence is currently limited to diagnostic accuracy.
- The MEIR judged the overall potential for harm to be trivial. While the undesirable effects were not very well documented in the evidence identified, they appear to be mild and largely transient.

- When considering the balance between the desirable and undesirable effects, the MEIR EAG agreed that the practice was favoured over conventional imaging.
- The MEIR EAG recommended that ^{18}F-PSMA PET/CT should be generically justified for the primary staging of prostate cancer and the re-staging of recurrent prostate cancer.

Decision making

- Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.
- The practice of ^{18}F-PSMA PET/CT for the primary staging of prostate cancer and the re-staging of recurrent prostate cancer is generically justified under SI 256/2018.
- The generic justification of this practice is effective from 07 Dec 2023.

1 Introduction

1.2 Background to the application

Prostate specific membrane antigen (PSMA)-targeted diagnostic radiotracers are increasingly being applied in clinical practice worldwide for the diagnosis and or staging of prostate cancer. In May 2023, the European Medicines Agency's Committee for Medicinal Products for Human Use recommended the approval of piflufolastat (^{18}F) (formerly known as ^{18}F-DCFPyL) (Pylclari™), a fluorine-18 labelled small-molecule PSMA inhibitor for the primary staging of patients with high-risk prostate cancer and to localise the recurrence in those with suspected recurrence following initial treatment with curative intent.(2) Other available ^{18}F radiopharmaceuticals include ^{18}F-PSMA-1007 and ^{18}F-rhPSMA-7.

The Blackrock Clinic submitted an application for generic justification of this type of practice which they intend to generally adopt into clinical practice. Therefore, consistent with the requirements under the European Union Basic Safety Standards for the Protection Against Dangers from Medical Exposure to Ionising Radiation (Euratom), which were transposed into Irish law under Statutory Instrument (SI) 256 in January 2019, it requires generic justification before it can be generally adopted.(1)

In accordance with HIQA's Methods for generic justification of new practices in ionising radiation(3) an overview of reviews was undertaken.

1.2 Overall approach

A standing multidisciplinary MEIR expert advisory group (EAG) has been convened by HIQA comprising representation from key stakeholders. A full list of the membership of the MEIR EAG is available in the acknowledgements section of this report. The terms of reference for the MEIR EAG are published on the HIQA website.

Evidence synthesis was undertaken to inform the discussions of the MEIR EAG and its recommendation-making process as well as the subsequent decision-making by the Director of Health Technology Assessment (HTA). The following summarises the steps which were taken:

- An overview of reviews was performed by HIQA's Ionising Radiation Evidence Review Team (IR-ERT) to provide the evidence base for a generic justification decision.
- This overview of reviews systematically identified relevant evidence which related to the diagnostic accuracy and risk of adverse events of ^{18}F-PSMA

PET/CT.

- A draft report summarising the benefits and harms associated with this practice was produced and was circulated to the MEIR EAG for review.
- Following a meeting of the MEIR EAG, the draft of the report was amended as appropriate and was circulated to MEIR EAG for review.
- The final report was sent to the Director of HTA, along with a recommendation from the MEIR EAG regarding the generic justification of the practice.
- Following HIQA's decision, the final report and generic justification decision was published on the HIQA website.

2. Description of the technology

This technology is a type of positron emission tomography (PET) scan. PET scans produce detailed 3-dimensional images by analysing where an injected radiotracer accumulates and they are used to determine how certain body tissues are functioning. A PET scan, which is a type of functional imaging, is usually combined with computed tomography (CT) imaging; this is known as PET/CT.(4)

Each PET/CT scan relies on a radiotracer, which is typically composed of some substrate or antigen component labelled with a radioactive isotope. When the radioisotope decays it emits a positron. When a positron collides with an a electron, they undergo a process referred to as 'annihilation', where both the positron and electron are completely obliterated and all the energy is transferred into two gamma rays (photons) travelling in opposite directions.(5) When such a radioisotope is used to label a substrate or antigen preferentially taken up by cancer cells, the gamma rays can help determine if and where in the body disease is present.

PSMA PET/CT exploits the upregulation and overexpression of the PSMA protein on prostate cancer cells and tumour vascular cells, compared to the rare expression in normal prostate tissue.(6) By using an antigen specific to prostate cancer cells, PSMA PET/CT helps identify the presence of the disease, and aids staging and restaging of prostate cancer. The broad practice of PSMA PET/CT imaging can be further subdivided according to the radionuclide used.(7)

In Ireland, PSMA PET/CT using Gallium-68 (^{68}Ga) has been used in the diagnosis and restaging of prostate cancer. A new radiopharmaceutical, the fluorine-18 labelled PSMA inhibitor piflufolastat (previously known as ^{18}F-DCFPyL) has recently received marketing authorisation from the European Medicines Agency (EMA) under the trade name Pylclari™. Fluorine-18 (^{18}F) PSMA PET imaging has also been made available using the radiopharmaceutical ^{18}F-PSMA-1007. Other ^{18}F radiopharmaceuticals identified internationally include ^{18}F-rhPSMA-7. While these ^{18}F-PSMA radiopharmaceuticals may differ in terms of their underlying radiochemistry, pharmacokinetics and pharmacodynamics, it is suggested that the available agents have comparable diagnostic accuracy.(8)

3. Description of clinical condition and epidemiology

Prostate cancer is the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men worldwide.[9] In Ireland, for the period 2015 to 2017, there were, on average, 3,474 new cases of prostate cancer each year corresponding to an average annual incidence rate of 141 cases per 100,000 males. Prostate cancer accounts for, on average, 29.2% of all invasive cancers diagnosed in males and 11% of cancer deaths.[10]

The most appropriate treatment strategy for a given patient often depends on a number of disease-specific risk factors, including the stage of disease, the prostate specific antigen (PSA) level and the Gleason score.[11-13] These factors are also used to stratify patients into different risk categories. Although there is divergence between international bodies on how risk categories are defined, patients generally are risk-stratified as having low, intermediate, or high-risk (the latter of which is sometimes also further subdivided into 'very high-risk') prostate cancer. The National Cancer Control Programme (NCCP) guidelines provide guidance on how to assign risk categories in Ireland.[11] High-risk cancers are more likely to be aggressive and metastasise to lymph nodes and other parts of the body compared with non-high-risk cancers.[14] When the tumour is locally advanced or if factors such as PSA or Gleason score are high, evidence has shown that the risk of bone metastases and spread to lymph nodes also increases.[15] The risk of metastatic spread and cancer-specific death can also be estimated using tools such as the cancer of the prostate risk assessment (CAPRA) scoring tool. The Irish Prostate Cancer Outcomes Registry's (IPCOR's) 2019 annual report found that 19.3% of men with newly diagnosed prostate cancer are considered high-risk using the CAPRA tool.[16, 17]

After definitive treatment with some combination of radiotherapy, surgery, and androgen deprivation therapy (ADT), patients are followed up by physicians and their PSA closely monitored. If the PSA begins to rise again it is referred to as 'biochemical recurrence', 'biochemical relapse' or 'biochemical failure'.[18] Rising PSA levels may indicate that the cancer is still present in the prostate or prostate bed (part of the pelvis where the prostate was located before it was surgically removed), or alternatively has spread to other parts of the body. The incidence of biochemical recurrence varies according to the risk category to which the patient was originally assigned, with higher risk categories having a higher risk of biochemical recurrence compared with non-high-risk categories.[19]

Correct staging and risk stratification of patients is essential in ensuring the most appropriate treatment and the best possible patient outcomes are obtained.[20] Under-staging could result in a patient receiving a treatment regime that does not

confer the best possible benefits. Over-staging may also result in a patient receiving a less effective treatment, but may also result in unnecessary toxicity, morbidity and stress or upset to the patient and their families.

At present, prostate cancer may be detected by digital rectal examinations, PSA levels, and trans-rectal ultrasound (TRUS); histopathological confirmation is usually required to confirm a diagnosis as abnormal findings may be explained by other benign conditions.[13] However, histopathological confirmation is not always possible or appropriate especially in recurrent or metastatic disease, or populations such as the oldest old (≥85 years) and those with poor performance status. Metastatic spread to lymph nodes and distant organs is usually detected with 'conventional imaging' modalities, including a combination of computed tomography (CT), bone scintigraphy, and magnetic resonance imaging (MRI).[13]

There are a number of persisting limitations with the current reference standard of conventional imaging in the diagnosis and staging of prostate cancer. Despite improvements in the diagnosis and staging of disease with the addition of MRI, the false negative rate for MRI is estimated to be about 6.5% and sensitivity for lymph node imaging remains between 40-73%.[21, 22] Pooled data from a meta-analysis of patients imaged using MRI also showed a sensitivity of only 57%, 58% and 61% for extra-capsular extension, seminal vesicle involvement and overall stage T3 assessment (where the tumour has grown outside the prostate), respectively.[23] Similarly, MRI has poor sensitivity in detecting bone metastases. While bone scintigraphy performs better than MRI, it still has a low sensitivity of approximately 68% for bone metastases.[21] Hence, there has been a growing interest in radiotracers which may help improve the diagnosis and staging of prostate cancer.

As noted in Section 2, PSMA PET/CT exploits the upregulation and overexpression of the PSMA protein on prostate cancer cells and tumour vascular cells, compared with the rare expression on normal prostate tissue.[6] PSMA PET/CT is increasingly being used in clinical practice in an attempt to improve diagnostic accuracy and the sensitivity and specificity of staging. While some national and international guidelines have adopted and recommend the use of PSMA (PET/CT), others have not or have offered weak (as opposed to strong) recommendations.[24] A number of manufacturers offer similar PSMA radiotracers which differ slightly in terms of the radioligand attached, the exact antigen, and their pharmacokinetic properties.[25] In Ireland, ^{68}Ga-PSMA is already used in a number of centres as an alternative to conventional imaging. Most notably, the proPSMA trial found ^{68}Ga-PSMA PET/CT to be a suitable replacement for conventional imaging, providing superior accuracy to the combined findings of CT and bone scintigraphy in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy.[26] One meta-analysis found

^{68}Ga-PSMA PET/CT to have a higher sensitivity and a comparable specificity to MRI for staging pre-operative lymph node metastases in intermediate/high-risk prostate cancer.[27] Another meta-analysis reported on a per-patient basis, the sensitivity and specificity of ^{68}Ga-PSMA PET/CT were 77% and 97%, respectively, after lymph node dissection at the time of prostatectomy for patients with high-risk and metastatic prostate cancer.[28] Within the same meta-analysis, on a per-lesion basis, the sensitivity and specificity were 75% and 99%, respectively. Two retrospective studies also found that ^{68}Ga-PSMA PET/CT and PET-MRI demonstrated superiority to MRI alone in the staging of lymph nodes and other areas in cohorts of high-risk and intermediate/high-risk patients.[29, 30] However, the comparison of whole body MRI and PSMA PET/CT in detecting bone metastases has led to inconclusive and conflicting results in two small cohort studies.[27, 31]

4. Methods

This overview of reviews is reported in line with the Preferred Reporting Items for Overview of Reviews (PRIOR) statement.[32] A protocol for this overview was registered on the Open Science Framework (OSF)[33] and published on Health Research Board (HRB)-Open.[34] Meta-data, draft data extraction tables and other resources have been uploaded to the OSF registration and repository. In Ireland, public and occupational exposure is primarily the responsibility of the Environmental Protection Agency (EPA). However, the Regulations require HIQA to consider public and occupational exposure as part of the justification of medical exposures. The approach taken to this issue and the three research questions (RQs) are outlined in the following sections.

4.1 Research questions (RQs)

RQ 1 What is the diagnostic accuracy of ^{18}F-PSMA PET/CT in the primary staging of patients with high-risk prostate cancer?

RQ 2 What is the diagnostic accuracy of ^{18}F-PSMA PET/CT in the restaging of patients with biochemically recurrent prostate cancer?

RQ 3 What is the risk of adverse events (including those related to radiation dose) associated with receiving ^{18}F-PSMA PET/CT?

This review makes the key assumption that adequate diagnostic accuracy will result in better treatment allocation and improvements in patient related outcomes such as overall survival and health-related quality of life. If new or important information emerges regarding the effectiveness or harms associated with this practice, its generic justification may be re-assessed under Regulation 7(4).[35]

Table 1 outlines the Population, Intervention, Comparison, Outcomes, Setting (PICOS), as well as details of the eligible records and languages.

Table 1: PICOS table

PICOS	Description
Patient/Problem:	Adults aged 18 years and older with high-risk prostate cancer undergoing primary staging or adults with biochemically recurrent/persistent prostate cancer undergoing restaging.
Intervention:	^{18}F-PSMA PET/CT used to stage or re-stage prostate cancer
Comparison:	▪ Reference standards ○ Histopathology

	○ Clinical follow up - as defined by the study (including alternative imaging). ▪ Comparators ○ Conventional imaging using bone scan, CT or MRI ○ ^{68}Ga-PSMA PET/CT
Outcomes:	Any of the following as they relate to TNM staging for prostate cancer: ▪ sensitivity ▪ specificity ▪ accuracy* ▪ negative predictive value ▪ positive predictive value ▪ positive likelihood ratios ▪ negative likelihood ratios ▪ radiation dose ▪ adverse events (e.g., hypersensitivity, headache, fatigue, dysgeusia, paraesthesia).
Study Design:	▪ Only systematic reviews and meta-analyses were considered for inclusion within this overview of reviews. Cochrane defines a systematic review as one which attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question.[36] It uses explicit, systematic methods that are selected with a view to minimising bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.[37, 38] According to the Cochrane definition, the key characteristics of a systematic review are: ○ a clearly stated set of objectives with pre-defined eligibility criteria for studies ○ an explicit, reproducible methodology ○ a systematic search that attempts to identify all studies that would meet the eligibility criteria ○ an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias and ○ a systematic presentation, and synthesis, of the characteristics and findings of the included studies. ▪ Additionally, included reviews were required to have all of the following characteristics: ○ a systematic search of at least two databases

	○ a suitable analysis or subgroup analysis of risk groups or risk factors that allows reviewers to determine the effects on patients with high-risk (or intermediate/high-risk) prostate cancer or those with biochemically recurrent prostate cancer ○ a quality assessment was also accepted in lieu of an established risk of bias tool such as QUADAS-2.
Languages:	Only articles for which an adequate English translation could be obtained were included.

Key: ^{18}F - Fluorine-18; ^{68}Ga – Gallium-68; CT - computed tomography; MRI - magnetic resonance imaging; PET/CT - positron emission tomography/computed tomography; PSMA – prostate specific membrane antigen; TNM – tumour, nodes, metastasis; QUADAS – quality assessment of diagnostic accuracy studies.
*all measures of accuracy as defined by the review accepted

4.2 Search Strategy

Electronic searches were conducted in Medline (EBSCO), Embase (Ovid), Google Scholar and the Cochrane Database for Systematic Reviews. The full search strategy for the Medline (EBSCO) search is outlined in Table A.1 of Appendix 1. The full database search strategy can be found here: https://doi.org/10.5281/zenodo.8159119

A targeted search of the grey literature was also carried out - details of this search are outlined in Table A.2 of Appendix 1. This included a search of regulatory websites for any safety alerts or updates. European Public Assessment Reports (EPARs) for authorised forms of the radiotracer were also reviewed with a particular focus on identifying the evidence base supporting their application for marketing authorisation and possible adverse events not reported within the peer-reviewed literature.(2)

Reference lists from all included systematic reviews were searched for potentially relevant citations. Forward citation searching of included reviews was undertaken - searches were limited to systematic reviews; no language or date restrictions were applied to the eligibility criteria or the search strategy.

4.3 Record selection and data extraction

4.3.1 Record selection

Returned citations from the collective search were added to Endnote for reference management. Following de-duplication, the records were transferred to Covidence for screening. Title and abstract screening and full text screening were both piloted

on the first 20% of records to ensure a consistent application of the eligibility criteria. Thereafter, title and abstract screening and full text reviewing were performed independently by two reviewers, as per the pre-defined eligibility criteria. A small number of minor disagreements were resolved by discussion. Reasons for exclusion following full-text review were documented and summarised in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart (see Figure 1).[39] Where needed, corresponding and or senior authors of records were contacted to obtain additional information, for example to access the full risk of bias assessment for primary studies.

Outcomes were included regardless of whether they were analysed on a per-patient, per-lymph node, per-lesion, or per-segment basis. Similarly, no restriction was placed on outcomes if they were sub-analysed according to the effect of PSA levels, Gleason score, International Society for Urological Pathology (ISUP) grade, etc. No restrictions were placed on the method of image analysis - visual, semi-quantitative analysis using maximum standardised uptake value (SUV_{max}), etc. No restrictions were placed on definitions of biochemical recurrence, which may vary depending on the definitive treatment initially offered (i.e., radical prostatectomy versus definitive radiotherapy) or between professional bodies.[40, 41] Definitions of 'high-risk prostate cancer' may also vary between many organisations and institutions,[42-45] For the purposes of this review, whichever definition of high-risk that was used by the study authors was accepted. As study populations in this area often combine patient populations (e.g., both intermediate- and high-risk prostate cancer), these results were included for consideration compared with data from solely high-risk samples. No restrictions were placed on the reference standard, however pathological confirmation determined via prostatectomy, pelvic lymph node dissection or biopsy as appropriate to the population under consideration was used as the 'gold-standard'.[46]

4.3.2 Data extraction

A standard data extraction template was developed in Microsoft Excel and piloted by two independent reviewers on four records. Data extraction was performed by one reviewer, and a second reviewer checked 100% of variables. A few minor disagreements were resolved by discussion. DeepL Translate professional software was used to obtain translations of non-English language documents.[47] Data extracted on the primary studies from the systematic reviews was cross referenced for discrepant data. Where partial information on a given primary study was reported by more than one systematic review, the record for the primary study was generated by using the information provided across those overlapping systematic reviews. Where discrepant data were identified during cross-referencing of data

between systematic reviews, the reference in the bibliography, the calculations provided by the reviews, the primary study abstract and the primary study itself were checked to resolve the discrepancy in that order until the discrepancy was resolved.

4.3.3 Risk of bias assessment

Two reviewers independently appraised each selected systematic review using the risk of bias in systematic reviews (ROBIS) tool.[48]

As documented in the inclusion criteria for this overview, all reviews were required to have some form of risk of bias or quality assessment of their primary studies. The risk of bias assessment of the primary studies included within systematic reviews, as reported by the systematic review authors, was collected. Risk of bias was generally assessed at the study level, rather than at the level of the outcome for the primary studies. Where systematic reviews contained the same primary study, but concluded differing levels of bias, a conservative approach was taken in that the higher of the two biases was assumed.

4.4 Data synthesis

Results are synthesised narratively and reported in line with the Synthesis Without Meta-analysis (SWiM) reporting guidelines.[49] As the unit of analysis within this overview was the systematic review, it was not possible to conduct a bivariate meta-analysis on test accuracy because reviews did not typically present data on true or false positives and negatives. To structure our synthesis, findings have been synthesised by population (that is, high-risk prostate cancer and biochemically recurrent prostate cancer), and within those populations, findings have been reported on a patient basis and under the TNM staging system (that is, findings related to the staging of the tumour, lymph nodes and metastases).

The standardised metric for answering our research question was sensitivity, specificity and accuracy as reported in the review. If the requisite data on true and false positives or negatives were available at the review level, but not reported within the review, sensitivity and specificity were calculated. Separately, we also report on other data identified, for example, adverse events, dose, occupational and patient exposure as well as providing a summary of international practice and guidelines. Where available, relative measures against the comparators specified in our PICO were also synthesised in a separate section.

Other outcomes are also synthesised where reported or where the requisite data were available (for example, predictive values or accuracy estimates). Summary

characteristics of included systematic reviews and overall findings are presented in table format and graphically through the use of forest plots.

4.4.1 Grading of Recommendations Assessment, Development and Evaluation (GRADE)

A modified version of the grading of recommendations, assessment, development and evaluation (GRADE) was used to generate the summary of findings tables as there is currently no guidance on how to conduct GRADE within overviews of reviews. As none of the included reviews performed their own GRADE assessments, the principles of GRADE were applied to estimate the certainty of the evidence for each outcome considered important to this review, in keeping with JBI guidance.[50]

As per GRADE guidelines and in keeping with the assumptions of this review, cross-sectional or cohort studies in patients with diagnostic uncertainty and direct comparison of test results with an appropriate reference standard (which here, we considered to be histopathology or clinical follow up) started as high certainty, but could be rated down to moderate, low or very low certainty depending on other factors.[51-54] When downgrading the certainty of evidence, five domains were considered: risk of bias, indirectness, inconsistency, imprecision, and publication bias.[55] Judgements were made to classify the domains affecting the certainty of the evidence as either 'not serious', 'serious' or 'very serious'. Additionally, upgrading was considered based on two further domains: where there was large and consistent estimates of test accuracy, and where any residual plausible bias or confounding might further increase the confidence in these large estimates.

A global assessment was then made for each outcome, including how many levels the outcome should be downgraded by. The certainty of evidence was rated as either high (not downgraded), moderate (downgraded one level), low (downgraded two levels), or very low (downgraded by more than two levels). Three review authors discussed each judgment before deciding on any downgrades. Further details on the approach taken to upgrading and downgrading under the seven domains is given in Table A.3 in Appendix 2. As per GRADE guidelines, evidence was graded as high, moderate, low or very low certainty, the definitions of which are outlined in Table 2 below.

Table 2: GRADE working group definitions of the evidence grades

Certainty rating	Definition
High	'We are very confident that the true effect lies close to the estimate of the effect.'
Moderate	'We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.'
Low	'Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.'
Very low	'We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.'

The summary of findings table, including the certainty of the evidence for the most important outcomes, was produced using Microsoft Excel and GRADEpro.[54] This then helped populate the evidence-to-decision table for generic justification that is outlined in HIQA's methods document.[3]

4.4.2 Overlap within included reviews

Overlap of primary studies in each of the included systematic reviews were identified and handled in line with the Cochrane guidance.[36] Irrespective of the number of systematic reviews in which a primary study was reported, the data for that study were extracted and presented once.[56, 57]

A citation matrix was used to visualise the amount of overlap and the level of overlap was determined by calculating the corrected covered area (CCA), a measure of overlap calculated by dividing the frequency of repeat occurrences of the index publication in other reviews by the product of index publications and reviews, reduced by the number of index publications.[58] A CCA of 0-5 indicates slight overlap, 6-10 moderate overlap, 11-15 high overlap and >15 very high overlap. This assessment of overlap was limited to the primary studies included within the systematic reviews which contributed to the data collection, rather than all studies included within the systematic review.

Additionally, a pair-wise assessment of overlap between individual systematic reviews and a graphic representation of Overlap for OVErviews (GROOVE) was presented to better visualise discrete areas of overlap as opposed to global overlap.[58] This assessment of overlap was limited to the primary studies which contributed to the data extraction.

4.4.3 International practice and guidelines

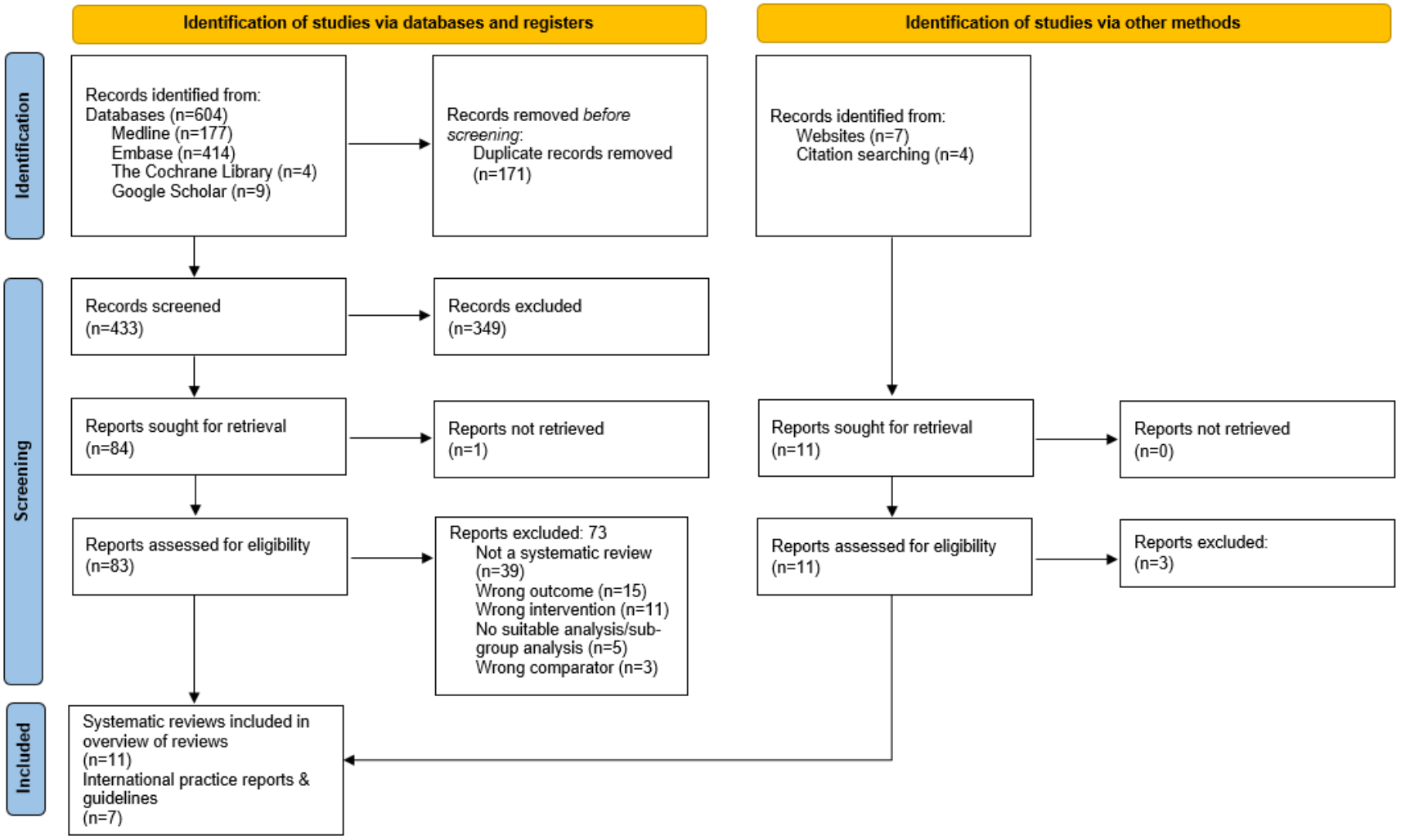
A high-level overview of relevant documents from international organisations identified during either the database or grey literature search was undertaken. The purpose of this overview was to provide an indication of international practice and clinical guidelines which may be relevant to this practice.

5. Results

5.1 Search results

After removal of duplicates, 433 title and abstracts were assessed for eligibility. 83 articles required full text review. An overview of the article selection process is presented in the PRISMA flowchart (Figure 1). After application of the inclusion and exclusion criteria, 11 systematic reviews and seven international practice reports and guidelines were identified for inclusion in this overview of reviews.[59-69] A full list of studies excluded during full text screening with the rationale for their exclusion are available from the OSF repository.[33]

Figure 1: PRISMA flow diagram



5.2 Review characteristics

A total of 11 systematic reviews were identified for inclusion in this overview of reviews.[59-69] The characteristics of the included systematic reviews are presented in Table 3. From the 11 included systematic reviews, there were 38 unique primary studies that contributed relevant data.[70-107] None of the reviews identified a randomised controlled trial (RCT) which met the inclusion criteria for this overview of reviews. A table summarising the key characteristics of the primary studies is included in Table A.4 in Appendix 2. The majority of studies used histopathology as their reference standard; however, other references standards were sometimes employed (particularly in the biochemical recurrence setting, likely due to issues accessing pathological samples for metastatic disease).

Three of the reviews only included evidence in relation to ^{18}F-DCFPyL,[64-66] four reviews only included evidence in relation to ^{18}F-PSMA-1007,[59, 61, 63, 69] three included evidence in relation to both ^{18}F-DCFPyL and ^{18}F-PSMA-1007,[60, 67, 68] while one review included evidence in relation to ^{18}F-DCFPyL, ^{18}F-PSMA-1007 and ^{18}F-rhPSMA-7.[62] All of the reviews were published between 2021 and 2023; the most recent specified search end date within these reviews was December 2022.[68] Six of the included reviews focused on primary staging,[59, 61, 64, 65, 67, 69] one on re-staging [68] and four considered both primary staging and restaging[60, 62, 63, 66] of patients with prostate cancer.

Estimates of diagnostic accuracy included in the systematic reviews included sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV). Unless otherwise specified, it appeared that the systematic review authors calculated accuracy estimates from primary studies as the proportion of all participants within a study that were correctly classified (see Appendix2, Table A.5).

Most systematic reviews[61-63, 65-69] used the QUADAS-2 tool[108] to assess the quality of primary studies; one review[64] used the original QUADAS tool;[109] one review[59] used the National Institute of Health (NIH) Quality Assessment tool;[110] and another review[60] used the Critical Appraisal Skills Programme (CASP) checklist for diagnostic test studies.[111]

Table 3: Summary of characteristics of included systematic reviews

Author (Year)	Indication	Review design	Search Date	Number of studies included* (number of participants**)	PET tracer	COIs Funding	Publication bias	Risk of bias for SR using ROBIS tool
Awenat [59] (2021)	Primary staging	SR	Dec 2020	6 (269)	^{18}F-PSMA-1007	No COIs declared No external funding declared	NR	High
Evangelista [60] (2022)	Primary staging + re-staging following biochemical recurrence	SR	NR but only studies published 2016-2021 included	1 (62)	^{18}F-DCFPyL ^{18}F-PSMA-1007	Grant support + consulting fees from Novartis/AAA, AstraZeneca, Janssen, Merck/MSD, Mundipharma, Point Biopharma	NR	High
Huang [61] (2022)	Primary staging	SR + MA	Sept 2021	6 (239)	^{18}F-PSMA-1007	No COIs declared No funding declared Primo Biotechnology Co. Ltd provided expert advice in idea creation & data management	Indicated publication bias	Unclear
Jeet [62] (2023)	Primary staging + re-staging following biochemical recurrence	SR + MA	Mar 2022	8 (676)	^{18}F-DCFPyL ^{18}F-PSMA-1007 ^{18}F-rhPSMA-7	No COIs declared No funding declared	Did not indicate publication bias	Low
Liu [63] (2022)	Primary staging + re-staging following biochemical	SR + MA	Feb 2021	11 (799)	^{18}F-PSMA-1007	No COIs declared No funding declared	Did not indicate publication bias	Unclear

	recurrence							
Pang[65] (2023)	Primary staging	SR + MA	Aug 2022	3 (151)	^{18}F-DCFPyL	No relevant COIs or funding	Did not indicate publication bias	High
Pan[64] (2021)	Primary staging + re-staging following biochemical recurrence	SR + MA	NR	9 (426)	^{18}F-DCFPyL	No relevant COIs or funding	Indicated publication bias	High
Sood[66] (2023)	Primary staging + re-staging following biochemical recurrence	SR	Aug 2022	3 (396)	^{18}F-DCFPyL	No COIs declared No funding declared	NR	High
Wang[67] (2023)	Primary staging	SR + MA	May 2022	5 (254)	^{18}F-DCFPyL ^{18}F-PSMA-1007	No COIs declared No funding declared Primo Biotechnology Co. Ltd provided expert advice in idea creation & data management	NR	Unclear
Yang [68] (2023)	Re-staging following biochemical recurrence	SR + MA	Dec 2022	16 (1162 patients)	^{18}F-DCFPyL ^{18}F-PSMA-1007	No COIs declared No funding declared	Did not indicate publication bias	Unclear
Zhao[69] (2022)	Primary staging	SR + MA	NR	1 (10)	^{18}F-PSMA-1007	Stock interests in Nuada Medical Ltd. Consultancy for Sonatherm Inc., Angiodynamics	NR	Unclear

Key: ^{18}F - Fluorine-18; COI – conflict of interest; MA – meta analysis; NR – not reported; PET – positron emission tomography; PSMA – prostate specific membrane antigen; ROBIS – risk of bias in systematic reviews; SR – systematic review.
Note: *refers to the number of primary studies which contributed relevant data; **refers to the total number of participants in the study who underwent an ^{18}F-PSMA PET/CT.
Numbers of participants may not be reflective of the number of events.

5.3 Risk of bias assessment

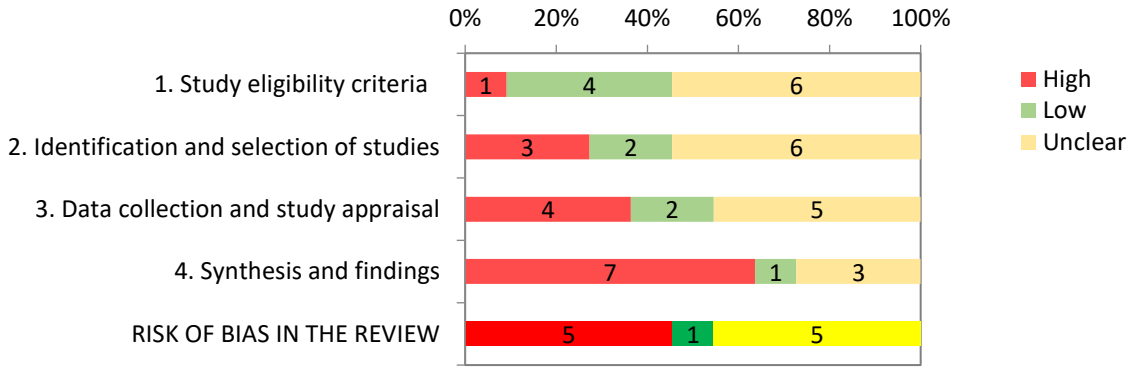
Systematic reviews

As assessed by the ROBIS tool, the majority of reviews had multiple methodological flaws, with five reviews deemed at 'high' risk of bias,[59, 60, 64-66] five at 'unclear' risk of bias[61, 63, 67, 69] and only one at 'low' risk of bias.[62]

The main issues of concern identified during the risk of bias assessment include not referencing a protocol or stating explicit aims; unclear inclusion/exclusion criteria; search strategies which were considered not comprehensive; not providing justification for foreign language exclusions; not describing their quality process for screening, data extraction and quality appraisal; not discussing the risk of bias or the effect of heterogeneity in the context of the results of the primary studies and inappropriate pooling of heterogeneous results.

Figure 2 provides a summary risk of bias plot. A table summarising the judgement for each ROBIS domain is included in Table A.6 of Appendix 1.

Figure 2: Summary risk of bias plot for included systematic reviews



Key: Numbers in bars represent the number of studies

Primary studies

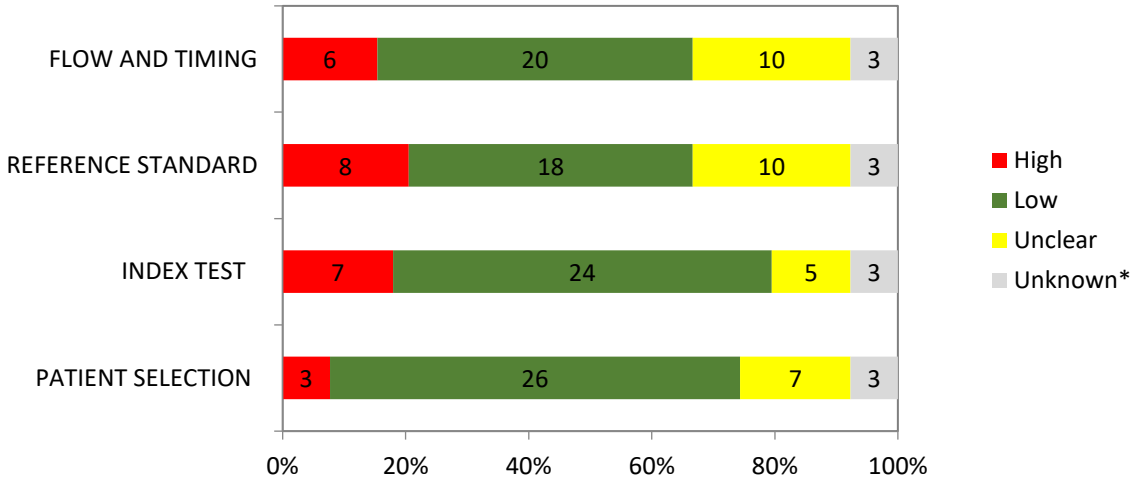
Across the 11 systematic reviews, 38 unique primary studies were identified that were of relevance to the research questions in this evidence summary. Eight of the 11 systematic reviews used the QUADAS-2 tool to assess risk of bias in the primary studies – Figure 3 summarises these assessments. One review used the CASP checklist to assess quality; however, the two studies which contributed data to this overview were also assessed using QUADAS-2 in another included systematic review. One review used a quality assessment tool from the National Institute of Health (NIH). Authors of this review were contacted for their detailed assessment of judgements made for each of their included studies, however no response was

received. A third review used the original QUADAS tool, which has been superseded by QUADAS-2.

In total, three of the 38 primary studies had no QUADAS-2 assessment. The use of an outdated risk of bias tool and issues with the approach to risk of bias were captured within the ROBIS assessment.

In general, the systematic reviews found low risk of bias in the primary studies that were assessed. However, high risk of bias was reported in eight studies due to issues with their reference standards, in seven studies due to issues with the index test and in six studies because of flow and timing. Only three studies were at high risk of bias due to patient selection.

Figure 3: QUADAS-2 assessment results for primary studies as reported by the included systematic reviews



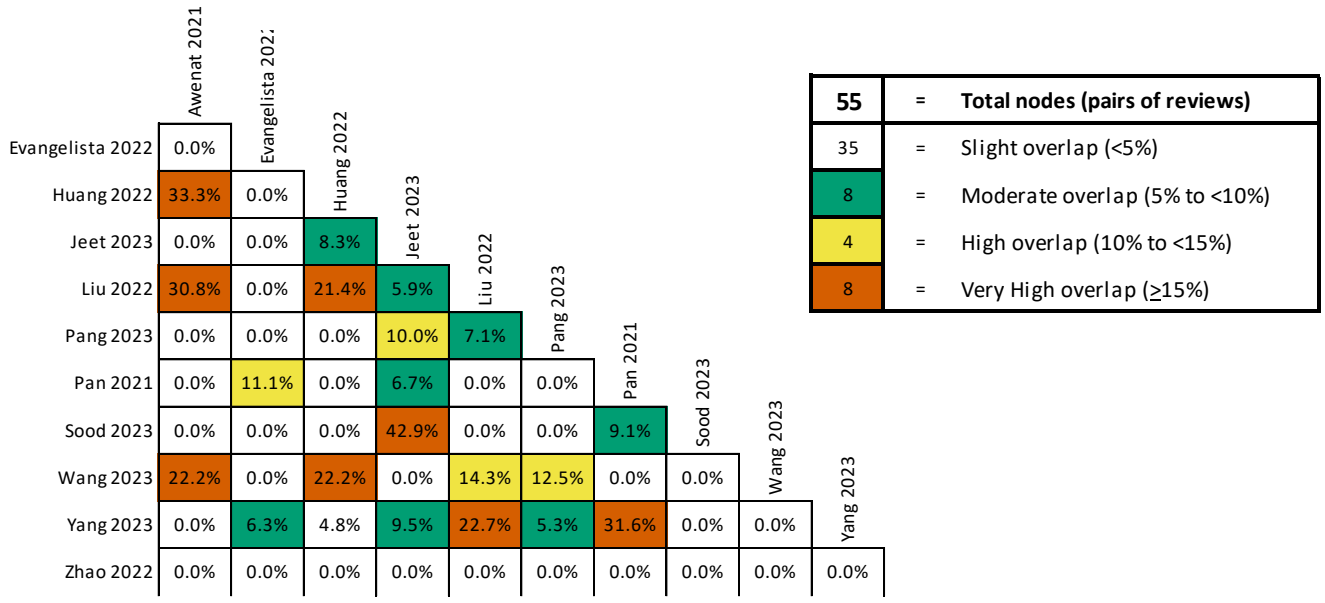
Key: Numbers in bars represent the number of studies. *QUADAS assessment available for three of the four primary studies with no QUADAS-2 assessment.

5.4 Overlap within included reviews

Graphical and quantitative investigations into the overlap between systematic reviews was conducted. The corrected covered area was 8.16%. This was considered to be moderate overlap.[58] A Graphical Representation of Overlap for OVErviews (GROOVE)[58] was generated to assess the corrected covered area between every possible pair of reviews (nodes), and produced a graphical representation of this assessment (Figure 4). A citation matrix is also provided in Appendix 2. The overlap between pairs of systematic reviews was very high, high, and moderate in eight, four and eight of the 55 nodes, respectively. A total of 35 of the 55 nodes had no overlap or slight overlap.

This information highlights that despite the fact that the reviews were published between 2021 and 2023, no single review captured all of the relevant evidence. The information was used to guide the narrative synthesis and ensure no findings were over-reported.

Figure 4: Graphical Representation of Overlap for OVErviews (GROOVE)



5.5 Primary staging for high-risk prostate cancer

Identified data related to the diagnostic accuracy of ^{18}F-PSMA PET/CT in the primary staging of patients with high-risk prostate cancer are detailed in the following sections. Forest plots relating to the extracted data are provided in Appendix 2 (Figure A.1). The GRADE certainty of evidence and summary of findings relating to

these data are presented in Tables 4 and 5, respectively. In reviewing the data in relation to primary staging, studies were also identified that presented data related to the diagnostic accuracy of ^{18}F-PSMA PET/CT for cohorts that comprised both those with intermediate-risk and those with high-risk prostate cancer, but which did not present disaggregated data for the high-risk cohort. For completeness, these data relating to those with intermediate/high-risk prostate cancer, where reported, are provided in the relevant sections below.

Per-patient data

No pooled estimates of per-patient sensitivity were identified for primary staging of patients with high-risk prostate cancer. Data from three systematic reviews [59, 63, 64] provided information on four primary studies with data in this area. Two of these were retrospective studies [77, 82] with only ten patients each and which estimated a sensitivity of 1.00 with no confidence intervals reported. Two prospective studies, one with 25 patients [79] and another with 79 patients [70] estimated per-patient sensitivity to be 0.90 (95% CI 0.82-0.96) and 0.85 (95% CI 0.62-0.97), respectively. The certainty of the evidence was considered to be low.

No pooled estimates of per-patient specificity were identified for high-risk prostate cancer. Data from the tables and supplementary materials of three systematic reviews [59, 63, 64] revealed three primary studies [70, 77, 79] with data in this area. One was a retrospective study [77] based on only ten patients which estimated a specificity of 1.00 with no confidence intervals reported. Two prospective studies,[70, 79] one with 25 patients and another with 79, estimated per-patient specificity to be 0.88 (95% CI 0.80-0.94) and 0.90 (95% CI 0.79-0.96), respectively. The certainty of the evidence was considered to be moderate.

Limited data were available for per-patient accuracy. Records for two primary studies identified from one systematic review [59] estimated the accuracy on a per-patient basis to be 80-89% (range was for four accuracy values from two readers that conducted a 'pessimistic' and 'optimistic' analysis) [70] or 100%.[77] The certainty of evidence for accuracy was considered to be low.

Separately, four studies [84, 91, 93, 107] were identified from two systematic reviews[59, 65] that provided evidence for sensitivity for a cohort of intermediate/high-risk patients. Three retrospective studies identified from these systematic reviews had modest sample sizes of 53,[93] 65[91] and 56[107] patients and estimated the sensitivity for this population to be 0.98 (no confidence intervals reported in the review), 0.97 (95% CI 0.89-1.00) and 0.90 (95% CI 0.78-0.97), respectively. One small prospective study of 16 patients reported a sensitivity of 1.00, but no confidence intervals were reported by the review.

Two further retrospective studies identified by two systematic reviews provided data on per-patient specificity in intermediate/high-risk patients. One with a sample of 65 patients was reported as having a specificity of 0.00 (95% CI 0.00-0.60). The other had a sample of 56 patients was reported as having a specificity of 1.00 (95% CI 0.54-1.00).

T-staging data

No information was identified on the use of ^{18}F-PSMA PET/CT tumour staging (T-staging) of cohorts with high-risk prostate cancer alone.

Three systematic reviews[63, 67] reported on the results from two studies comprising patients with intermediate/high-risk prostate cancer. One of the studies[72] reported a sensitivity of 0.95 (95% CI 0.88-0.99) and specificity of 0.32 (95% CI 0.15-0.54) for extracapsular extension, while the other[93] estimated a sensitivity of 0.41 (95% CI 0.18-0.67) and specificity of 0.83 (95% CI 0.36-1.00) based on 53 patients (23 of whom had extracapsular extension). Sood et el. also reported a sensitivity and specificity of 0.80 (95% CI 0.44-0.97) and 0.85 (95% CI 0.55-0.98) for seminal vesical involvement in a cohort with intermediate/high-risk prostate cancer; this estimate was based on this latter study of 53 patients (26 of whom had seminal vesicle involvement).[66]

Sood et al. presented data from one prospective study with 116 patients relevant to the initial T-staging of a cohort with intermediate/high-risk prostate cancer.[66] This study[81] estimated the sensitivity and specificity of ^{18}F-PSMA PET/CT for extracapsular extension in intermediate/high-risk prostate cancer were reported to be 0.18 and 0.97, respectively while the sensitivity and specificity for seminal vesicle involvement were reported to be 0.53 and 0.90, respectively. This study also provided an estimate for extracapsular extension positive predictive value (PPV) and negative predictive value (NPV) of 0.80 and 0.66, respectively. They estimated the PPV of seminal vesicle involvement to be 0.48 and the NPV to be 0.92. No confidence intervals were reported for any of these estimates.

Jeet et al. was the only review which contained relevant data on per-segment sensitivity and specificity, where each segment corresponds to an anatomic mapping model of the prostate.[62] A single study based on a cohort of 30 patients with intermediate/high-risk prostate cancer (and 420 segments) reported a per-segment sensitivity of 0.61 (95% CI 0.52-0.70) and a per-segment specificity of 0.88 (95% CI 0.84-0.94).[71]

Per lymph node data

No pooled estimates of per-lymph node sensitivity were identified for high-risk

prostate cancer. Data from the tables and supplementary materials of two systematic reviews[62, 66] provided information on three primary studies[79, 83, 92] with data in this area. One retrospective study of 58 patients reported a sensitivity of 0.72 (0.47-0.90).[83] Two prospective studies with 25 and 252 patients estimated sensitivity to be 0.71 (0.29-0.96) [79] and 0.40 (0.28-0.54), respectively.[79, 92] Sood et al. noted that in this later study (OSPREY trial) the sensitivity increased to 0.60 (no confidence interval given) in patients where lymph nodes were larger than 5mm.[92] The certainty of the evidence was considered to be low.

No pooled estimates of per-lymph node specificity were identified for high-risk prostate cancer. Data from the tables and supplementary materials of two systematic reviews provided information on three primary studies with data in this area.[62, 66] One retrospective study of 58 patients reported a specificity of 0.93 (95% CI 0.80-0.98).[83] Two prospective studies with 25 and 252 patients estimated specificity to be 0.89 (95% CI 0.65-0.99) [79] and 0.98 (95% CI 0.95-0.99),[92] respectively. The certainty of the evidence was considered to be moderate.

An additional four studies identified by three systematic reviews had data on sensitivity and specificity in a cohort with intermediate/ high-risk prostate cancer.[61, 62, 66] Two prospective studies with 117 patients[81] and 31 patients[89] estimated the sensitivity to be 0.41 (95% CI 0.18-0.67) and 0.83 (no confidence intervals reported), respectively. Two retrospective studies with 96 patients[102] and 10 patients[77] estimated the sensitivity to be 0.71 (95% CI 0.62-0.79) and 0.95 (no confidence intervals given), respectively. Two prospective studies with 117 patients [81] and 31 patients[89] estimated the specificity to be 0.94 (95% CI 0.87-0.98) and 0.99 (no confidence intervals reported), respectively. Two retrospective studies with 96 patients [112] and 10 [77] patients estimated the specificity to be 1.00 (95% CI 0.99-1.00) and 1.00 (no confidence intervals given), respectively.

Three studies identified from one review had estimates of accuracy in patients with high-risk prostate cancer.[62] Two prospective studies with 25[79] and 252 patients[92] estimated accuracy to be 84% and 82.5% respectively. One further retrospective study of 58 patients constructed a receiver operator characteristic (ROC) curve and estimated accuracy, based on the area under the curve (AUC) to be 86.2%.[83] The certainty of evidence was considered to be low.

Sood et al. identified two studies reporting per-lymph node PPV and NPV in high-risk prostate cancer.[66] These two prospective studies had 252 patients [92] and 28 patients,[79] respectively, and estimated the PPV to be 0.87 and 0.71 (no confidence interval reported for either estimate), respectively. The per-lymph node NPV was estimated to be 0.83 and 0.89, respectively (no confidence intervals provided for either estimate).

Huang et al.[61] and Sood et al.[66] provided estimates obtained from primary studies on per-lymph node PPV and NPV for patients with intermediate/high-risk prostate cancer. Huang et al.[61] identified two retrospective studies[77, 102] with samples of 96 and 10 patients which estimated the PPV and NPV to be 0.91 (95% CI 0.84-0.96) and 1.00 (95% CI 0.82-1.00), and 0.98 and 1.00 (no confidence intervals were provided for either NPV estimates) respectively. One prospective study had 31 patients and estimated the PPV and NPV to be 0.96 (95% CI 0.91-0.98) and 0.97 (no confidence intervals given).[89] Sood et al.[66] found one additional prospective study[81] with 116 patients which estimated the PPV and NPV to be 0.54 and 0.90, respectively (no confidence intervals given).

Per-lesion data

No pooled estimates of per-lesion sensitivity or specificity were identified for high-risk prostate cancer. Data from the tables and supplementary materials of three systematic reviews provided information on three primary studies with data in this area.[59, 63, 67] Data on the number of lesions were often not reported by reviews.

One retrospective study of ten patients estimated a sensitivity of 0.95.[77] A second retrospective study of ten patients (372 lesions) estimated this to be 0.71 (95% CI 0.65-0.77).[82] One prospective study with 79 patients (1581 lesions) estimated per-lesion sensitivity to be 0.86 (95% CI 0.81-0.91).[70] The certainty of the evidence was considered to be very low.

One retrospective study of 10 patients reported a specificity of 1.00, but no confidence intervals were reported.[77] A second retrospective study of ten patients (372 lesions) estimated this to be 0.81 (95% CI 0.74-0.86).[82] One prospective study with 79 patients (1581 lesions) estimated per-lesion specificity to be 0.98 (95% CI 0.98-0.99).[70] The certainty of the evidence was considered to be low.

The records for two retrospective studies,[8, 82] each with ten patients and, which were generated from the data from one systematic review [59] estimated the accuracy to be 93% and 100%. There were 212 lesions in one of these studies, and the number of lesions was not reported in the other. The certainty of the evidence was considered to be low.

Eight studies identified from six systematic reviews [59, 62, 63, 65, 67, 69] had per-lesion sensitivity data for intermediate/high-risk prostate cancer. Four prospective studies with 116 patients (number of lesions not reported),[81] 30 patients (number of lesions not reported),[71] 16 patients (145 lesions)[84] and 10 patients (14 lesions)[106] estimated per-lesion sensitivity to be 0.45 (95% CI 0.32-0.58), 0.84 (95% CI 0.77-0.90), 1.00 (95% CI 0.94-1.00) and 0.58 (95% CI 0.53-0.62) respectively. Four retrospective studies on intermediate/high-risk prostate cancer with 96 patients

(1,746 lesions),[102] 100 patients,[72] 65 patients (61 lesions),[91] and 53 patients (46 lesions)[93] estimated per-lesion sensitivity to be 0.71 (95% CI 0.62-0.79), 0.94 (no confidence interval reported), 0.97 (no confidence interval reported), and 0.56 (95% CI 0.35-0.75) respectively.

Eight studies identified from six systematic reviews[59, 62, 63, 65, 67, 69] had per-lesion specificity data for intermediate/high-risk prostate cancer. Four prospective studies with 116 patients,[81] 30 patients,[71] 16 patients (145 lesions)[84] and ten patients (14 lesions)[106] estimated per-lesion specificity to be 0.94 (95% CI 0.85-0.99), 0.97 (95% CI 0.94-0.99), 0.91 (95% CI 0.83-0.96) and 0.34 (95% CI 0.26-0.44) respectively. Four retrospective studies on intermediate/high-risk prostate cancer with 96 patients (1,746 lesions),[112] 100 patients,[72] 65 patients (61 lesions),[91] and 53 patients (46 lesions)[93] estimated per-lesion specificity to be 1.00 (0.99-1.00), 1.00 (no confidence interval reported), 1.00 (no confidence interval reported), and 0.84 (95% CI 0.60-0.97) respectively.

Table 4: GRADE certainty assessment for high-risk prostate cancer

Outcomes	No. Primary Studies	No. Systematic Reviews*	Risk of Bias		Inconsistency	Indirectness	Imprecision	Publication Bias	Grading		
			QUADAS-2	ROBIS					Initial GRADE	No. of Downgrades	Final GRADE
Per-patient level											
Sensitivity	4	6	Not Serious	Serious[b]	Not Serious	Not Serious	Serious[e]	Not Serious	High	2	Low
Specificity	3	4	Not Serious	Serious[b]	Not Serious	Not Serious	Not Serious	Not Serious	High	1	Moderate
Accuracy	2	3	Not Serious	Serious[b]	Not Serious	Not Serious	Very Serious[f]	Serious[g]	High	2	Low
Per-lymph node (N-stage)											
Sensitivity	3	3	Not Serious	Serious[b]	Serious[d]	Not Serious	Serious[e]	Not Serious	High	2	Low
Specificity	3	3	Not Serious	Serious[b]	Not Serious	Not Serious	Not Serious	Not Serious	High	1	Moderate
Accuracy	3	2	Not Serious	Serious[b]	Not Serious	Not Serious	Very Serious[f]	Not Serious	High	2	Low
Per-Lesion (M-stage)											
Sensitivity	3	4	Not Serious	Serious[b]	Serious[d]	Not Serious	Serious[e]	Serious[g]	High	3	Very Low
Specificity	3	4	Not Serious	Serious[b]	Not Serious	Not Serious	Serious[e]	Serious[g]	High	2	Low
Accuracy	2	4	Serious[a]	Very Serious[c]	Not Serious	Not Serious	Very Serious[f]	Serious[g]	High	2	Low
Other Outcomes											

Dose	0	0	-	-	-	-	-	-	-	-	-
Adverse Events	0	0	-	-	-	-	-	-	-	-	-

*Some of these reviews did not include the specified outcome in their review, however data from all possible reviews were used to gather detail on the primary study and its risk of bias. Hence, the number of reviews cited here may differ from the number of reviews referred to in Section 5.

Explanations

a. Some of the QUADAS-2 domains within these primary studies were at an unclear to high-risk, but many were still low risk.
b. Many reviews had an overall unclear or high-risk of bias. Many of the domains within these reviews were at an unclear to high-risk.
c. Most reviews studies had a high-risk of bias. Most of the domains within these reviews were at an unclear or high-risk of bias
d. Variation in point estimates across studies
e. Large confidence intervals, too few events, or suspected too few events where the number of events was not reported within the systematic review.
f. No confidence intervals, far too few events or suspected far too few events where the number of events was not reported within the systematic review.
g. The rationale for a serious or very serious judgement on the ROBIS was considered, however it was felt that there were still residual issues with the comprehensiveness of the search, search strategy, or inclusion and exclusion criteria.

Table 5: Summary of findings table for high-risk prostate cancer

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants or lesions (studies)	Certainty of the evidence (GRADE)
Per-patient sensitivity	0.85 (0.62-0.97) 0.90 (0.82-0.96) 1.00 (No CI) 1.00 (No CI)	Not reported§	124 patients (4 studies)	⨁⨁◯◯ LOW [a,b]
Per-patient specificity	0.90 (0.79-0.96) 0.88 (0.80-0.94) 1.00 (No CI)	Not reported§	114 patients (3 studies)	⨁⨁⨁◯ MODERATE [a]
Per-patient accuracy	100.0% (No CI) 80-89% (No CI)	Not reported§	89 patients (2 studies)	⨁⨁◯◯ LOW [a,b,c]
Per-lymph node sensitivity	0.40 (0.28-0.54) 0.72 (0.47-0.90) 0.71 (0.29-0.96)	Not reported§	335 patients (3 studies)	⨁⨁◯◯ LOW [a,b,d]
Per-lymph node specificity	0.98 (0.95-0.99) 0.93 (0.80-0.98) 0.89 (0.65-0.99)	Not reported§	335 patients (3 studies)	⨁⨁⨁◯ MODERATE [a]
Per-lymph node Accuracy	82.5% (No CI) 86.2% (No CI) 84.0% (No CI)	Not reported§	335 patients (3 studies)	⨁⨁◯◯ LOW [a,b]
Per-lesion sensitivity	0.86 (0.81-0.91) 0.71 (0.65-0.77) 0.95 (No CI)	Not reported§	461 lesions (3 studies)	⨁◯◯◯ VERY LOW [a,b,c,d]
Per-lesion specificity	0.98 (0.98-0.99) 0.81 (0.74-0.86) 1.00 (No CI)	Not reported§	461 lesions (3 studies)	⨁⨁◯◯ LOW [a,b,c]
Per-lesion accuracy	100.0% (No CI) 93.0% (No CI)	Not reported§	372† lesions (2 studies)	⨁⨁◯◯ LOW [a,b,c,e]

Dose	Not reported§	Not reported§	-	-
Adverse events	Not reported§	Not reported§	-	-

*Figures are presented for each of the primary studies reported in the reviews (unless otherwise specified) and are presented in descending order from the largest study to the smallest.
†372 lesions reported for one study of 10 patients, the number of lesions was not reported on the second study of 10 patients.
§ Not reported by the *systematic reviews*
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias in the reviews
b. Imprecision in the results, wide confidence intervals (or no confidence intervals) or too few events.
c. Concerns regarding the search strategy or inclusion and exclusion criteria.
d. Inconsistency of estimates across studies.
e. Risk of bias in the primary studies (as determined from QUADAS-2 assessments in the systematic reviews)

5.6 Re-staging after biochemical recurrence

Identified per-patient, per-lymph node and per-lesion data related to the diagnostic accuracy of ^{18}F-PSMA PET/CT in the re-staging of patients with prostate cancer following biochemical recurrence are detailed in the following sections. Forest plots relating to the extracted data are provided in Appendix 2 (Figure A.3). The GRADE certainty of evidence and summary of findings relating to these data are presented in Tables 6 and 7, respectively. Where identified within the included studies, the diagnostic accuracy stratified by PSA level for those with biochemical recurrence are also reported for completeness.

Per-patient data

One systematic review by Yang et al. included a meta-analysis that provided a pooled estimate for sensitivity based on five studies. The estimated sensitivity was 0.92 (95% CI 0.86-0.96), with no evidence of heterogeneity (I^2=0.0%; p = 0.727).[68] However, possible discrepancies within the conduct of the meta-analysis identified during this review suggest that this reported pooled result may be an underestimate. Authors were contacted for further detail on these analyses however no response was received. Sensitivity data from five other primary studies were identified from the tables and supplementary materials of three other systematic reviews.[60, 63, 64] Two prospective studies with 130 patients[96] and 40 patients[104] estimated per-patient sensitivity to be 0.90 (95% CI 0.82-0.95) and 0.88 (95% CI 0.73-0.96), respectively. Three retrospective studies with 102,[95] 100,[94] and 25[99] patients estimated per-patient sensitivity to be 0.86 (95% CI 0.78-0.92), 0.95 (95% CI 0.89-0.98), and 0.60 (95% CI 0.39-0.79), respectively. The certainty of evidence for sensitivity was considered to be moderate.

Based on a meta-analysis of five studies, Yang et al. estimated the pooled per-patient specificity for patients with biochemical recurrence to be 0.83 (95% CI 0.41-0.97).[68] Possible errors within the conduct of the meta-analysis identified during this review suggest that this may be an underestimate. Specificity data from one other primary studies were identified from the tables and supplementary materials of two other systematic reviews.[64] One prospective study with 130 patients estimated the per-patient specificity to be 0.89 (95% CI 0.81-0.94).[96] The certainty of the evidence for per-patient specificity was considered to be low.

No other per-patient accuracy estimates were found for patients with biochemical recurrence.

Per-patient sensitivity was also analysed and presented according to PSA level by some reviews and primary studies. Pooled results were often not specific to the

research questions in the current overview and therefore were not used, however three studies identified by one review[63] had subgroup analysis and data related to PSA that were considered relevant to this overview of reviews. One retrospective study of 251 patients stratified patients according to a PSA>2ng/mL and a PSA ≤2ng/mL. No statistically significant difference in sensitivity was observed (0.94 (95% CI 0.87-0.98) versus 0.91 (95% CI 0.80-0.97).[78] A second retrospective study of 100 patients which reported data at a per-patient level also did not find a significant difference in sensitivity when stratified by PSA values (>2ng/mL vs. ≤2ng/mL: 0.95 (95% CI 0.89-0.98) vs. 0.92 (95% CI 0.84-0.96).[94] One further prospective study estimated per-patient sensitivity for patients with a PSA ≤2ng/mL to be 0.49 (95% CI 0.31-0.66).[104]

Data according to PSA levels was also available for specificity. One retrospective study of 251 patients did not find a significant difference in specificity when they compared those with a PSA>2ng/mL and PSA ≤2ng/mL: 0.28 (95% CI 0.21-0.36), vs. 0.24 (95% CI 0.18-0.31).[78] A second study retrospective study of 100 patients could not estimate specificity for patients with a PSA of >2ng/mL, however they estimated the specificity for patients with a PSA of ≤2ng/mL to be 1.00 (95% CI 0.48-1.00).[94] One further prospective study estimated that per-patient specificity for patients with a PSA ≤2ng/mL was 1.00 (95% CI 0.48-1.00).[104]

Per-lymph node data

No data were reported on per-lymph node sensitivity, specificity, or accuracy in patients with biochemical recurrence in the five systematic reviews identified.

Per-lesion data

The systematic review by Yang et al. included a meta-analysis that provided a pooled estimate for sensitivity on a per-lesion basis. Their pooled estimate, based on 11 studies, was 0.91 (95% CI 0.86-0.94); however, significant heterogeneity was observed I^2=70.06% (p <0.01).[68] One other study was identified by Liu et al.[63] reported data from a large prospective study of 251 patients which estimated the sensitivity to be 0.47 (95% CI 0.41-0.53).[78] While this study was included by Yang et al. in their systematic review, this estimate was not included in their per-lesion analysis. The certainty of the evidence was considered to be very low.

Yang et al. estimated the pooled per-lesion specificity for patients with biochemical recurrence to be 0.91 (95% CI 0.86-0.94). No additional primary studies or data were identified by the other five systematic reviews for this outcome. The certainty of the evidence was considered to be low.

One study identified by one systematic review[62] estimated the per-lesion accuracy

to be 81.3% (no confidence interval given).[86] The certainty of the evidence for this outcome was considered to be low.

Table 6: GRADE certainty assessment for biochemically recurrent prostate cancer

Outcomes	No. Primary Studies	No. Systematic Reviews*	Risk of Bias		Inconsistency	Indirectness	Imprecision	Publication Bias	Grading		
			QUADAS-2	ROBIS					Initial GRADE	No. of Downgrades	Final GRADES
Per-Patient Level											
Sensitivity	10	4	Serious[a]	Very Serious[b]	Not Serious	Not Serious	Not Serious	Serious[i]	High	1	Moderate
Specificity	7	4	Serious[a]	Very Serious[b]	Serious[d]	Not Serious	Serious[g]	Serious[i]	High	2	Low
Accuracy	0	0	-	-	-	-	-	-	N/A	-	N/A
Per-lymph node (N-stage)											
Sensitivity	0	0	-	-	-	-	-	-	N/A	-	N/A
Specificity	0	0	-	-	-	-	-	-	N/A	-	N/A
Accuracy	0	0	-	-	-	-	-	-	N/A	-	N/A
Per-lesion (M-stage)											
Sensitivity	6	3	Serious[a]	Serious[c]	Very Serious[e]	Not Serious	Serious[g]	Serious[i]	High	3	Very Low
Specificity	5	3	Serious[a]	Serious[c]	Serious[f]	Not Serious	Not Serious	Serious[i]	High	2	Low
Accuracy	1	2	Not Serious	Serious[c]	Not Serious	Serious[j]	Very Serious[h]	Not Serious	High	2	Low
Other outcomes											
Dose	0	0	-	-	-	-	-	-	N/A	-	N/A

Adverse Events	0	0	-	-	-	-	-	-	N/A	-	N/A

*Some of these reviews did not include the specified outcome in their review, however data from all possible reviews were used to gather detail on the primary study and its risk of bias. Hence, the number of reviews cited here may differ from the number of reviews referred to in Section 5.

Explanations

a. Some of the QUADAS-2 domains within these primary studies were at an unclear to high-risk, but many were still low risk.
b. Most reviews studies had a high-risk of bias. Most of the domains within these reviews were at an unclear or high-risk of bias.
c. Many reviews had an overall unclear or high-risk of bias. Many of the domains within these reviews were at an unclear to high-risk.
d. Variation in point estimates across studies, particularly within the meta-analysis performed by Yang et al.[68]
e. Highly inconsistency results and point estimates. We also considered the statistical heterogeneity to be serious.
f. Variation in point estimates across studies and some statistical heterogeneity of concern.
g. Large confidence intervals of primary studies and (or) the overall pooled estimate provided by Yang et al.[68]
h. No confidence intervals, far too few events or suspected far too few events where the number of events was not reported within the systematic review.
i. The rationale for a serious or very serious judgement on the ROBIS was considered, however it was felt that there were still residual issues with the comprehensiveness of the search, search strategy, or inclusion and exclusion criteria. Additionally, there was evidence of publication bias in one or more of the reviews which was felt to be of relevance.
j. Only study with a moderate sample size.

Table 7: Summary of findings table for biochemically recurrent prostate cancer

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	Nº of participants or lesions (studies)	Certainty of the evidence (GRADE)
Per-patient sensitivity	0.92 (0.86-0.96)† 0.90 (0.82-0.95) 0.86 (0.78-0.92) 0.95 (0.89-0.98) 0.88 (0.73-0.96) 0.60 (0.39-0.79)	Not reported§	791 patients (10 studies)	⊕⊕⊕◯ MODERATE [a,b,c]
Per-patient specificity	0.83 (0.41-0.97)† 0.89 (0.81-0.94) 0.70 (0.35-0.93)	Not reported§	524 patients (7 studies)	⊕⊕◯◯ LOW [a,b,c,d,e]
Per-patient accuracy	Not reported§	Not reported§	-	-
Per-lymph node sensitivity	Not reported§	Not reported§	-	-
Per-lymph node specificity	Not reported§	Not reported§	-	-
Per-lymph node accuracy	Not reported§	Not reported§	-	-
Per-lesion sensitivity	0.91 (0.86-0.94)‡ 0.47 (0.41-0.53)	Not reported§	1874 lesions (12 studies)	⊕◯◯◯ VERY LOW [a,b,c,d,e]
Per-lesion Specificity	0.91 (0.86-0.94)‡	Not reported§	1874 lesions (11 studies)	⊕⊕◯◯ LOW [a,b,c,d]

Per-lesion Accuracy	81.3% (No CI)	Not reported§	36 lesions (1 Study)	⊕⊕◯◯ LOW [b,e,f]
Dose	Not reported§	Not reported§	-	-
Adverse Events	Not reported§	Not reported§	-	-

*Figures are presented for each of the primary studies reported in the reviews (unless otherwise specified) and are presented in descending order from the largest study to the smallest.
§ Not reported by the *systematic reviews*
†Figures are from the meta-analysed results of 367 patients from 5 studies.
‡Figures are from the meta-analysed results of 1874 lesions from 11 studies.
CI: Confidence interval;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias in the reviews
b. Risk of bias in the primary studies (as determined from QUADAS-2 assessments in the systematic reviews)
c. Concerns regarding the search strategy or inclusion and exclusion criteria.
d. Inconsistency of estimates across studies.
e. Imprecision in the results, wide confidence intervals (or no confidence intervals) or too few events.
f. Inconsistency was considered serious as there was just one study.

5.7 Comparative data

Differences between ^{18}F-PSMA radiopharmaceuticals

One meta-analysis of 16 studies on patients with biochemically recurrent prostate cancer was identified which compared ^{18}F-PSMA-DCFPyL with ^{18}F-PSMA-1007.[68] The review authors combined per-patient and per-lesion outcomes to generate the pooled estimates for these radiopharmaceuticals. Sensitivity and specificity were estimated to be 0.90 (95% CI 0.85–0.94) and 0.89 (95% CI 0.85–0.93) for ^{18}F-PSMA-DCFPyL, and 0.93 (95% CI 0.86–0.96) and 0.93 (95% CI 0.70–0.99) for ^{18}F-PSMA-1007, respectively. Of note, substantial heterogeneity was observed for ^{18}F-PSMA-DCFPyL (I^2 = 68.91%, p=0.002); lower heterogeneity was noted for ^{18}F-PSMA-1007 (I^2 = 40.99%, p<0.105).

Differences between ^{18}F-PSMA and ^{68}Ga-PSMA radiopharmaceuticals

Evangelista et al.[60] reported on one study[74] which made an iterative match-paired analysis of 191 retrospectively enrolled patients with biochemical recurrence. They observed that at low PSA concentrations, the PSA stratified sensitivity curve was more robust and superior for ^{18}F-DCFPyL than for ^{68}Ga-PSMA-11. The average sensitivity was 0.80 for ^{18}F-DCFPyL and 0.68 for ^{68}Ga-PSMA-11 in patients with PSA levels ranging between 0.5 and 3.5ng/ml.

Differences between ^{18}F-PSMA and MRI

On a per-patient level, limited comparative evidence with multiparametric MRI (mpMRI) was identified from the reviews for high-risk or biochemically recurrent patients. Wang et al.[67] reported on one prospective study of 26 high-risk patients with a PSA >10ng/ml which found a non-statistically significant per-patient sensitivity ratio of 1.04 (95% CI 0.96-1.12) in favour of ^{18}F-PSMA PET/CT.[76]

Two systematic reviews [61, 63] reported on a single primary retrospective study of 53 patients which reported comparative data for T-staging .[93] This study found that ^{18}F-PSMA PET/CT correctly staged seminal vesicle invasion (pT3b) more often than mpMRI (that is, the accuracy was 90% vs. 76%), whereas mpMRI detected extracapsular extension (pT3a) more often than ^{18}F-PSMA PET/CT (that is, the accuracy was 90% vs. 57%).

On a per-lesion level, relatively more data were available. Liu et al.[63] identified three studies that compared MRI and ^{18}F-PSMA PET/CT, in patients with a PSA greater than 2ng/ml. One prospective study including 79 patients with high-risk prostate cancer (1,581 lesions) estimated the per-lesion sensitivity for MRI to be 0.37 (95% CI 0.30-0.44) compared with 0.86 (95% 0.81-0.91) for ^{18}F-PSMA PET/CT.[70] A retrospective study comprising 10 patients with high-risk prostate

cancer (372 lesions) estimated the per-lesion sensitivity for MRI and [18]F-PSMA PET/CT to be 0.86 (95% CI 0.79-0.92) and 0.71 (95% CI 0.65-0.77), respectively.(82) A second study comprising 53 patients with intermediate/high-risk prostate cancer (46 lesions) reported per-lesion sensitivity estimates of 0.74 (95% CI 0.54-0.89) and 0.56 (95% CI 0.35-0.75) for MRI and [18]F-PSMA PET/CT, respectively.(93) The same two studies estimated the per-lesion specificity of MRI compared to [18]F-PSMA PET/CT to be 0.64 (95% CI 0.57-0.70) versus 0.81 (95% CI 0.74-0.86) and 0.79 (95% CI 0.54-0.94) versus 0.84 (95% CI 0.60-0.97), respectively. Partial information on these studies was obtained from several reviews. Zhao et al.(69) reported on one prospective study of 10 intermediate/high-risk patients (14 lesions) with a per-lesion sensitivity and specificity for MRI compared to [18]F-PSMA PET/CT of 0.53 (95% CI 0.48-0.57) versus 0.58 (95% CI 0.53-0.62) and 0.91 (95% CI 0.84-0.96) versus 0.34 (95% CI 0.26-0.44), respectively.(106)

Systematic reviews by Wang et al.(67) and Huang et al.(61) reported further on Kesch et al.'s(82) study of 10 patients (212 lesions) with high-risk prostate cancer, which estimated the per-lesion sensitivity ratio to be 0.83 (95% CI 0.74-0.92) for patients with a PSA of ≥10ng/mL in favour of mpMRI. Conversely, the same study estimated the per-lesion specificity ratio to be 1.27 (95% CI 1.12-1.44) in favour of [18]F-PSMA PET/CT.(67) The total agreement sensitivity of [18]F-PSMA PET/CT was found to be lower than that of mpMRI for localising the primary prostate tumour (71% vs. 86%), but the total agreement PPV was higher ([18]F-PSMA PET/CT vs mpMRI 83%, 95% CI 77%-88%, vs. 60%, no CI reported) with fewer false positives.(82) This study found the per-lesion near total agreement (defined as allowing a discrepancy of up to 1 region in any direction) PPV for [18]F-PSMA PET/CT and mpMRI was similar (91% vs 91%) while the accuracy was greater for [18]F-PSMA PET/CT compared with mpMRI (93% vs. 87%).

Data on per-lesion sensitivity ratio was also reported by Wang et al. for two studies which looked at patients with intermediate/high-risk prostate cancer. One study of 100 patients (72) estimated the per-lesion sensitivity ratio to be 1.11 (95% CI 1.00-1.22) for intermediate/high-risk patients with a PSA <10ng/mL, and another with 65 patients estimated a per-lesion sensitivity ratio for patients with a PSA >10ng/ml of 1.04 (95% CI 0.95-1.12) in favour of [18]F-PSMA PET/CT.(91) One of these studies also estimated the per-lesion specificity ratio to be 1.00 (95% CI 0.80-1.25).(72)

When [18]F-PSMA PET/CT was combined with mpMRI the per-lesion sensitivity and specificity were estimated to be 0.81 (no confidence intervals provided) and 0.81 (no confidence intervals provided), respectively for patients with high-risk prostate cancer.(82) Another study with 100 intermediate/high-risk patients estimated the combined per-lesion sensitivity of [18]F-PSMA PET/CT and mpMRI to be 0.82 (no

confidence intervals) and the combined per-lesion specificity to be 0.67 (no confidence intervals provided).[72]

Differences between ^{18}F-PSMA PET/CT and conventional imaging

No evidence was found comparing ^{18}F-PSMA PET/CT with the combined findings from bone scintigraphy and CT of the thorax, abdomen and pelvis (CT TAP), or with either of these modalities individually. As outlined Section 3, the proPSMA trial demonstrated that ^{68}Ga-PSMA PET/CT is superior to conventional imaging in the staging of patients with high-risk prostate cancer. Evidence from this overview suggests that ^{18}F-PSMA PET/CT may have comparable diagnostic accuracy to ^{68}Ga-PSMA PET/CT. While evidence identified in this overview suggests that ^{18}F-PSMA PET/CT may have comparable diagnostic accuracy to ^{68}Ga-PSMA PET/CT, the findings are limited by a lack of directly applicable data.

5.8 Adverse events

Three systematic reviews stated that no adverse events due to ^{18}F-PSMA were reported in the included primary studies.[59, 61, 113] The other eight systematic reviews had no mention of possible adverse events. None of the 11 systematic reviews were designed to explicitly seek outcome data on adverse events. No safety alerts or variations to the marketing authorisation were identified during the targeted search of the grey literature (see Table 2 in Appendix 1).

The EPAR for one marketed form of this drug did detail adverse events from three trials.[92, 114, 115]Among the 797 patients in the three studies, a total of 108 treatment-emergent adverse events (TEAEs) were reported in 69 (8.6 %) patients, with headache (1.4%), dysgeusia (loss of taste) (1.0%), and fatigue (0.5%) being the most frequent. Three serious TEAEs (hypersensitivity, headache, and paraesthesia) were reported, all experienced by one patient who had a significant history of allergic reactions; only hypersensitivity was assessed as drug-related; all three serious TEAEs were resolved. In total, eight patients (1%) reported serious adverse events (SAEs); seven with recurrent or metastatic prostate cancer and one with high-risk prostate cancer.

5.9 Radiation dose to patients

The change in ionising radiation dose associated with this practice is likely to depend on whether ^{18}F-PSMA PET/CT is used in addition to, or as a replacement for conventional imaging. This decision and what constitutes conventional imaging will depend on the clinical context. However, in general, it is anticipated that PSMA PET/CT will replace conventional imaging.

Accurate estimation of the clinical significance of dose reduction is challenging as there are many risk factors for cancer and the dose from medical imaging only forms part of a person's long-term risk of cancer. However, it is accepted that there is a benefit in keeping dose, even for low dose medical exposures, as low as reasonably achievable.

[18]F-PSMA PET/CT

A large range of activities was reported by systematic reviews. Seven of the 11 systematic reviews provided estimates of injection activity, however none of the reviews provide any estimates of patient dose in milli-Gray (mGy) or milli-Sieverts (mSv).

Huang et al.[61] calculated the mean of means from 12 studies, and estimated an injection activity of 277.3MBq with a range of 111MBq to 458MBq. The injection activity was greater than 240MBq in nine of their 12 included studies. Estimates from additional individual studies included by the other six systematic reviews were included within this range. Three individual studies identified from the tables of Awenat et al.[59] reported weight-based estimates of injection activity. Two of these three studies reported an estimate of 4MBq/kg,[80, 84] while 4.44MBq/kg was reported in the other study.[116] The EPAR for one marketed form of ^{18}F-PSMA PET/CT notes an effective dose of 4.2mSv when the maximal recommended activity of 360MBq is administered in a 70 kg-weighted patient.[2]

Diagnostic reference level (DRL) data collected by HIQA for ^{18}F-PSMA PET imaging indicate that the radiation dose used is broadly comparable with the above ranges. However, this is based on a limited number of procedures carried out to date, with only three centres reporting local DRLs (201MBq, 222MBq and 347MBq). For a mean injection activity of 257MBq, a mean effective dose of 5.68mSv is estimated using a conversion factor of 0.0221.[117, 118] An additional 6.9mSv must be taken into account arising from the whole body CT component of these scans, which was estimated from a mean dose length product of 452 mGy.cm using a conversion factor of 0.0154.[119] At present, there is no national DRL for ^{18}F-PSMA PET.

[68]Ga-PSMA PET/CT

DRL data were also collected by HIQA for ^{68}Ga-PSMA PET; however, as limited data were received during the last national survey it was not possible to calculate a national DRL for ^{68}Ga-PSMA PET. However, two institutions reported a median injection activity of 364MBq and 182MBq with approximately 317 procedures occurring annually. For a mean injection activity of 273MBq, the mean effective dose is estimated to be 6.28 based on a conversion factor of 0.023. Mean effective dose

for the CT component of PET/CT as outlined above should be considered in addition to the doses specified here for the ^{68}Ga-PSMA PET.(117)

Bone scintigraphy

National DRL data on bone scintigraphy estimates the dose to be approximately 613MBq for planar imaging, 680 MBq for single positron emission CT (SPECT), and 658MBq for planar and SPECT combined. For a combined mean injection activity of 626MBq, a mean effective dose of 3.07mSv was estimated using a conversion factor of 0.0049.

CT of thorax, abdomen and pelvis

The HIQA DRL guidance (updated July 2021)(120) reported a DLP for CTs of the thorax, abdomen and pelvis (CT TAP) of 635mGy.cm in adults undergoing oncological follow up. Work by the former Medical Exposure Radiation Unit (MERU) of the Health Service Executive (HSE) in 2017 estimated the mean effective dose to male patients from CT TAP to be 13.47mSv.(121)

Summary of radiation dose to patients

No national diagnostic reference level exists for ^{18}F-PSMA PET/CT. However, the estimated effective dose for ^{18}F-PSMA PET/CT is 5.68mSv for the PET component and 6.9mSv for the whole body CT component. This compares with 13.47mSv for a CT thorax, abdomen and pelvis and 3.07mSv for a bone scintigraphy scan.

5.10 Public and occupational exposure

In accordance with Regulation 12(5) of S.I. No. 30 of 2019, all practices involving the use of ionising radiation must be authorised in advance by the Environmental Protection Agency (EPA).(122) All undertakings carrying out a radiological practice must fully comply with the relevant provisions of the S.I. No. 30 of 2019 and any conditions attached to an authorisation.

In the context of Ireland, exposure to staff, the public, carers and comforters can be minimised through a carefully considered prospective risk assessment and use of a well-developed quality management system. The design stage of the risk assessment must be completed prior to the installation and commissioning of all sources of ionising radiation.

Local policies, procedures and guidelines must be in place to protect staff and members of the public. Procedures to be followed in the event of an incident liable to have radiation safety implications for workers and members of the public must be developed. It must be ensured that dose constraints and limits for occupational and

public exposure as set out in Part 3, Sections 1 and 2 of SI 30 of 2019 are adhered to.(122) In assessing compliance with the dose constraints for medical applications, account should be taken of the principles and approach set out in the EPA's guidance document "The Design of Diagnostic Medical Facilities Where Ionising Radiation Is Used" (2009).(123)

Further information on the EPA requirements is provided in their guidance for undertakings on the application of the IRR19.(124) Information on the dose constraints for carers and comforters, and individuals participating in medical or biomedical research is also available in guidance issued by HIQA.

The identified studies did not highlight any safety concerns for public and occupational exposure, and the risk is likely to be low, provided appropriate radiation protection safeguards are in place.

5.11 International guidelines and reports

Primary studies identified from the 11 systematic reviews included in this overview of reviews originated from a range of countries including Australia, Austria, Belgium, Canada, Chile, China, Finland, Germany, India, Israel, Italy, Japan, the Netherlands, Norway, Poland, South Africa, Spain, Sweden, Switzerland, Turkey, United Kingdom (UK), and United States (US).

In terms of international guidelines and reports, seven relevant records were identified as part of the targeted grey literature search. These included:

- An appraisal of ^{18}F-PSMA and ^{68}Ga-PSMA PET/CT radiotracers by Health Technology Wales published in 2019.(125) This appraisal supported the use of ^{68}Ga-PSMA PET/CT only if it was not more expensive that current standard of care, but indicated that there was insufficient evidence at that time to support the use of ^{18}F-PSMA.

- A rapid response report on PET/CT PSMA diagnostic imaging for prostate cancer by Canada's Drug and Health Technology Agency published in 2020.(126) This report indicated that although there was heterogeneity in the primary studies and a lack of diagnostic accuracy data, it appeared that PSMA PET was a useful tool in the care of patients with advanced prostate cancer.

- Clinical practice guidelines for the diagnosis and staging of patients with prostate cancer by the Irish National Cancer Control Programme updated in 2022.(127) These guidelines recommend that the use of PSMA PET/CT should be considered for the primary staging of patients with high-risk prostate cancer who are deemed suitable for definitive treatment, providing this

imaging is available within four weeks. The guidelines note that PSMA PET/CT should also be considered for patients with biochemical recurrence in cases where the imaging will influence patient management, providing it is available within the timeframe recommended by the multidisciplinary team.

- Imaging guidelines for newly diagnosed and biochemical recurrent prostate cancer by the European Society of Radiology accessed in August 2023.[24] These guidelines do not include a final recommendation for the use of PSMA PET/CT in primary staging, but indicate that the use of ^{68}Ga-PSMA PET/CT should be considered in the recurrent setting, if available.

- Evidence-based indications for the use of PET/CT in the UK by the Royal College of Radiologists published in 2022.[128] This report indicates that PSMA tracers are the first-line PET tracers for prostate cancer, but notes that their availability may be limited at some sites. The report highlights that PSMA PET/CT is recommended in patients with biochemical relapse post prostatectomy or radical radiotherapy if their PSA is ≥2ng/ml; in the metastatic setting, if patients are being considered for ^{177}Lutetium radioligand therapy; and for primary staging of high-risk prostate cancer if there are equivocal lesions or if there is a discordant biopsy or a contraindication to biopsy.

- Joint procedure guidelines by the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging on PSMA PET/CT published in 2023.[129] These guidelines provide support to physicians on acquiring, interpreting and reporting the results of PSMA PET/CT imaging.

- A rapid response report published in 2022 by the Institute for Clinical Effectiveness in Argentina. This report supported the use of ^{18}F-PSMA PET/CT given the higher diagnostic yield and higher detection rate compared to conventional imaging, despite the quality of evidence being judged as low.[130]

- A European Public Assessment Report (EPAR) for Pylcari™ (^{18}F-DCFPyL).[2] This report is a set of documents describing the evaluation of a medicine authorised via the centralised procedure and including the product information, published on the their website. The EPAR detailed three key studies for this particular ^{18}F-PSMA drug, which included the OSPREY study,[92] the PYTHON study,[114] and the CONDOR study.[115]

6. Discussion

This report summarises the existing evidence syntheses on the diagnostic accuracy of [18]F-PSMA PET/CT in the staging of primary prostate cancer and the restaging of recurrent and metastatic prostate cancer. These data are supplemented with additional data from the EPAR of one marketed form of the drug and the available DRL data in Ireland.

Considering the existing evidence syntheses, it is noted that the evidence on diagnostic accuracy related mainly to [18]F-DCFPyL PET/CT and [18]F-1007 PET/CT.

Summary of RQ1 findings

RQ1 focused on the diagnostic accuracy of PET/CT in the staging of patients with high-risk prostate cancer and identified 10 relevant systematic reviews. No pooled estimates were available for per-patient, per-lesion or per-lymph node sensitivity, specificity or accuracy.

For patients with high-risk prostate cancer, per-patient sensitivity estimates reported in systematic reviews ranged from 0.85 to 1.00, per-patient specificity estimates ranged from 0.88 to 1.00, while reported per-patient accuracy estimates ranged from 80 to 89% (two readers) to 100% (one reader). Considering per-lymph node data in this cohort, sensitivity estimates reported in systematic reviews ranged from 0.40 to 0.72, specificity estimates ranged from 0.89 to 0.98 and accuracy estimates ranged from 82.5 to 86.2%. Considering per-lesion estimates in this cohort, sensitivity estimates reported in systematic reviews ranged from 0.86 to 0.95 while specificity estimates ranged from 0.81 and 1.00; no accuracy estimates were identified.

Risk of bias in the systematic reviews, wide confidence intervals (or non-reporting of confidence intervals), too few events, and inconsistency of findings were the general contributors to the downgrading of the certainty of the evidence. The evidence appeared relatively more consistent and precise when considered from a per-patient level compared to a per-lesion level. In a number of reviews, only aggregated data were presented for a population with intermediate/high-risk prostate cancer.[59, 61-63, 65-67, 69] These aggregate data were not considered directly relevant to the overview of reviews regarding diagnostic accuracy in a population with high-risk prostate cancer, and therefore were not used to inform the GRADE assessment.

Summary of RQ2 findings

RQ2 focused on the diagnostic accuracy of PET/CT in the restaging of patients with biochemically recurrent prostate cancer. There was no clear synthesis of evidence

specific to local recurrence in the prostate bed in the reviews identified. On a per-patient basis, sensitivity was estimated to be 0.92 in one meta-analysis based on pooled data from 11 studies;(68) other estimates reported by systematic reviews ranged from 0.60 to 1.00.(60, 63, 64) Per-patient specificity was estimated to be 0.83 in one meta-analysis based on pooled data from seven studies;(68) other estimates ranged from 0.70 to 0.89.(60, 63, 64) There were no estimates of per-patient accuracy. No estimates of per-lymph node sensitivity, specificity or accuracy were identified in the included systematic reviews for patients with biochemical recurrence. Considering per-lesion estimates, pooled data were identified from a published meta-analysis along with estimates from two single additional studies. Sensitivity was estimated to be 0.91 in the meta-analysis based on pooled data from 11 studies(68) and 0.47 in the single study.(78) Per-lesion specificity was estimated in the meta-analysis to be 0.91. Per lesion accuracy was estimated to be 81.3% based on a single study.(86)

In terms of the certainty of the evidence, considering per-patient level data, the evidence for sensitivity, specificity and accuracy were found to be of low to moderate certainty. On a per-lesion level, based on evidence from three reviews, the data for sensitivity, specificity and accuracy were relatively less consistent and precise and were deemed to be of very low to low certainty. In terms of the certainty of the evidence, the possibilities of biases in the primary studies and systematic reviews were contributing factors, as were the imprecision and inconsistency of results observed.

Summary of RQ3 findings

No systematic review identified for inclusion in this report was explicitly designed to address research questions related to adverse events or dose. Although three of the identified reviews concluded no adverse events were identified from the available literature they synthesised,(59, 61, 113) the EPAR for one marketed form of ^{18}F-PSMA did contain evidence on mainly mild and largely transient adverse events from three studies. The possibility for a change in the radiation dose to which patients are exposed is dependent on the extent to which the practice replaces or is used in addition to existing imaging in the staging and re-staging of patients with high-risk and biochemically recurrent prostate cancer.

Considerations

A previous overview of meta-analyses published in 2020 aimed to consolidate evidence from published meta-analyses.(131) However, this review's scope was much broader, aiming to summarise information on the diagnostic accuracy and detection rate of PSMA PET/CT imaging in prostate cancer more generally using a number of

different radiotracers. Only one of the meta-analyses included looked at ^{18}F-PSMA PET/CT, and its results were limited to detection rates. The current report which focusses on ^{18}F-PSMA PET/CT, includes more recent systematic reviews, a risk of bias assessment of the included reviews and use of GRADE principles to assess the certainty of the evidence.

Sensitivity, specificity and accuracy were the main outcomes found in published systematic reviews. Other outcomes such as predictive values, while usual in interpreting test results for a given individual, were not typically reported in the systematic reviews identified in this current overview.

A number of systematic reviews were identified that reported detection rates[132, 133] (also sometimes called 'detection performance', 'diagnostic performance' or 'positivity rate'). While commonly reported, detection rates do not provide any insight into false positives (which may arise from benign ganglia, tumours, bone lesions, inflammation or non-specific lymph nodes) or false negatives. Detection rates are also expected to vary depending on the population included in the primary studies and the prevalence of metastatic disease in that population. Systematic reviews (or studies within systematic reviews) that only reported detection rates were therefore not included within this overview of reviews. However, it is likely that the findings of the systematic reviews that focused exclusively on detection rates were not inconsistent with those of this overview. Authors of one review[133] concluded that ^{18}F-PSMA PET/CT has advantages over other radiotracers, particularly at low PSA levels while in another review,[132] it was noted that standardisation of PSMA PET was required for it to be adopted in the diagnosis of prostate cancer, given potential issues with the homogeny of studies. It is for this reason that the PYTHON study[114] which was reported in the EPAR was not included in the current review; their use of a choline radiotracer as a comparator also made this study less applicable to the Irish setting.

Similarly, a previous network meta-analysis which found ^{18}F-PSMA-1007 PET/CT to be superior to other radiotracers typically used in prostate cancer, including ^{68}Ga-PSMA PET/CT, was not included in the current review as it only focused on detection rates.[134] However, authors of this network meta-analysis also acknowledged that there was insufficient evidence to recommend any one of the four ^{18}F- or ^{68}Ga-PSMA radiotracers over one another due to a limited evidence basis and the risk of publication bias. They also acknowledged the lack of evidence on diagnostic accuracy, which might favour radiotracers with low specificity (that is, one that tends to be poor at correctly identifying those that do not have the disease) in an analysis restricted to only detection rate. This hypothesis is supported by the observation that the differences in detection rate between ^{18}F-PSMA PET/CT and ^{68}Ga PSMA

PET/CT appear to get larger as PSA levels rise as PSA itself is associated with the incidence of metastatic disease.[135, 136]

Where histopathological confirmation is not possible, alternative reference standards likely introduce error and bias. However, this is likely reflective of real world clinical practice as at times, histopathological confirmation is not appropriate in these patients. A general consideration in this area of research is that the "truth" in men with negative ^{18}F-PSMA PET/CT results is often unknown because verification results are usually not required in clinical practice. However, confirmation of true negatives in a number of studies could have been improved with follow-up. False negatives may be attributed to inexperienced readers of these scans, small-volume disease, the obscuration of lesions in or adjacent to organs with high ^{18}F-PSMA uptake (for example, the liver) or excretory organs (for example, bladder, urethra, ureters) where signal is high due to the concentration of metabolised ^{18}F-PSMA.

While there are conflicting conclusions between reviews as to whether one radiotracer can be recommended over another, there are differences in their pharmacokinetic and pharmacodynamics properties [(8)]. Total equivalence between ^{68}Ga-PSMA PET/CT and ^{18}F-PSMA PET/CT should not be assumed and the individual justification of the available radiotracers for a given patient should be considered.

One primary study of particular relevance to this area was not included as its outcomes were not in keeping with that of the systematic reviews identified. The CONDOR study by Morris et al. assessed the correct localisation rate (CLR) in patients with biochemical recurrence, defined as the percentage of patients with a one-to-one correspondence between at least one lesion identified on ^{18}F-PSMA PET/CT by the readers of the scan and the composite standard of truth (consisting of histology where available, subsequent correlative imaging findings and post-radiation PSA response in descending priority). As CLR was defined as "at least one lesion", this study does not provide insight as to whether additional lesions or all lesions are correctly identified. Patients in this study also required negative or equivocal (indeterminate) findings on standing imaging, but because of the unstandardised imaging work up of these patients (which may have included CT, MRI, bone scan, ^{18}F-fluciclovine or ^{11}C-Choline PET) the comparative findings were difficult to definitively interpret. They did, however, conclude a favourable CLR of 84.8% -87.0%, and the lower bound of the 95% CI ranged from 77.8% to 80.4% which was superior to that of their unstandardised imaging work up. Although this study was excluded within the body of evidence synthesised, its findings are not contrary to the findings of this report.

While limited comparative data were found in the systematic reviews, there was evidence that different ^{18}F-PSMA radiopharmaceuticals used in PET/CT were broadly

comparable to the diagnostic accuracy of [68]Ga-PSMA PET/CT. Previously, the proPSMA RCT which focused on patients with nodal and metastatic spread demonstrated that [68]Ga-PSMA PET/CT had superior diagnostic accuracy over CT and bone scintigraphy.(137) Non-specific bone uptake with [18]F-PSMA-1007 has been highlighted anecdotally as a possible concern, however this finding was not identified in the systematic reviews included in this overview. It is likely that the evidence basis for the role of PSMA PET/CT in T-staging and primary diagnosis to avoid biopsies will continue to evolve with studies such as PRIMARY2.(138)

Strengths and limitations

The quality of reviews included in this overview of reviews were largely deemed to be at 'high' or 'unclear' risk of bias. A particular challenge of this overview was the lack of definitions provided by systematic reviews, or at times the lack of consistent definitions across systematic reviews. For example, it is known that definitions of high-risk prostate cancer or biochemical recurrence can vary. This overview accepted the definitions of high-risk or biochemical recurrence as provided by the review authors. Inconsistencies in definitions were unlikely to be an issue within the primary studies as it is assumed that the same definition would have applied to all patients included within the study; however, there is potential for bias when comparing between studies and limits the potential to pool data. Some authors also did not specify the exact nature of their 'per-patient' analysis. The approach taken was to assume that in the high-risk setting, 'per-patient' analysis referred to 'any findings of regional or distant nodal disease or metastatic disease' and in the biochemical recurrence setting it referred to 'any finding of prostate cancer'.

Similarly, the definition of 'per-lesion' was often unclear and was at times incorrectly reported as per-patient. Therefore, where the denominator and calculations were available, attempts were made to confirm whether the figures were per patient or per lesion. Similarly, there was some data on characteristics of primary studies which were misreported by systematic reviews. Discrepant data were resolved where possible through thorough cross-referencing as outlined in Section 4, however it is possible that residual misreporting and data extraction errors remain. Confidence intervals were often not reported for primary studies, however where a bivariate meta-analysis was planned a priori, these did not necessarily need to be extracted by the systematic review.

Reviews in this area often combined per-patient and per-lesion data to provide pooled estimates for sensitivity, specificity, accuracy and other outcomes. While these aggregate outcomes were data extracted and will be included in the OSF repository, they were not reported in the results section as it was thought that the pooling of this data may not be appropriate, and likely produces estimates that are

not reflective of the diagnostic accuracy of the test on either a per-patient or per-lesion level. This is supported by the observation that in Yang et al.'s meta-analysis heterogeneity significantly increased when per-patient data was pooled with per-lesion data. One exception to this approach was made when we reported on subgroup analyses comparing ^{18}F-PSMA-DCFPyL to ^{18}F-PSMA-1007, where pooled per-patient and per-lesion data was reported as no other estimates were available. Caution is urged when attempting to interpret such pooled data. Some systematic review authors also pooled data from biochemically recurrent patients and data from primary staging of patients with low, intermediate, and high-risk prostate cancer in varying proportions. An attempt was made to overcome such limitations by referring to individual primary study results rather than the pooled results in the meta-analyses, aided by the use of a structured narrative synthesis which was reported in line with SWiM reporting guidelines.

Finally, it must be acknowledged that no patient relevant outcome data (for example, survival data) were identified as part of this overview which instead focused on diagnostic test accuracy. As noted in Section 4, correct staging and risk stratification of patients is essential in ensuring the most appropriate treatment and the best possible patient outcomes are obtained.[20] There is an assumption that improvements in diagnostic test accuracy will result in improved staging and risk stratification thereby optimising the potential to improve patient relevant outcomes (for example, survival). While some evidence has emerged which demonstrates the use of ^{18}F-PSMA PET/CT does result in changes in patient management,[62, 66] long-term follow-up studies are required to determine the extent to which this has a positive impact on patient outcomes.

Conclusion

Overall, while significant gaps and uncertainty in the evidence remain, research to date is broadly supportive of ^{18}F-PSMA PET/CT imaging in the staging and restaging of patients with high-risk prostate cancer and biochemical recurrence. Although evidence may continue to accumulate to optimise the exact application of this technology, it is not likely that such evidence would come from RCTs of 'test-and-treat' strategies nor would it overcome some of the limitations that are inherent to research in this area. The change in radiation dose will depend on the extent to which ^{18}F-PSMA PET/CT replaces or is used in addition to existing imaging.

7. Evidence to decision

A draft of this report was submitted to the MEIR EAG for their consideration and feedback. Following this, a discussion was held on 19 October 2023, in which the evidence summary and additional contextual factors were considered. As per the

HIQA Methods for generic justification of new practices in ionising radiation, a modified version of the GRADE evidence-to-decision (EtD) framework was used to support the MEIR EAG in coming to a recommendation regarding the generic justification of [18]F-PSMA PET/CT imaging in the staging and restaging of patients with high-risk prostate cancer and biochemical recurrence.(3)

7.1 Overview of MEIR EAG GRADE EtD discussion

Informed by the review of the above evidence, the MEIR EAG completed judgments under a modified evidence-to-decision (EtD) framework to arrive at a recommendation to HIQA on the generic justification of [18]F-PSMA PET/CT in the staging and restaging of patients with high-risk prostate cancer and biochemical recurrence. The full EtD framework including a summary of the panel discussion and the final judgements can be found in Appendix 3 and Table 8, respectively. In terms of benefits and harms, the MEIR EAG considered the evidence for the outcomes listed in terms of both the magnitude of the effect and the certainty of the evidence. In accordance with the available GRADE guidance, the certainty of evidence was considered to be 'very low'.

The MEIR EAG acknowledged that the benefits of [18]F PSMA PET/CT may be large given the sensitivity, specificity and accuracy of the test, and recognised that its use would enable improved equity of access to PSMA PET/CT. However, they agreed that a judgement of moderate was appropriate given that the evidence is currently limited to diagnostic accuracy. There was agreement among the EAG that potential undesirable effects appeared to be trivial while acknowledging that they did not appear to be well documented in the evidence identified. The MEIR EAG agreed that for the majority of patients [18]F-PSMA PET/CT is intended to replace conventional imaging and therefore use of this practice is not likely to result in an increase in radiation dose to patients.

When considering the balance between the desirable and undesirable effects, the MEIR EAG judged that [18]F-PSMA PET/CT was favoured over conventional imaging. The MEIR EAG recommended to HIQA that [18]F-PSMA PET/CT in the staging of primary prostate cancer and the restaging of recurrent prostate cancer should be generically justified.

Table 8: [18]F PSMA PET/CT imaging in the staging and restaging of patients with high-risk prostate cancer and biochemical recurrence

	Summary of judgements					
Desirable Effects	Trivial	Small	**Moderate**	Large	Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**	Varies	Don't know
Certainty Of Evidence	**Very low**	Low	Moderate	High	No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability		
Balance Of Effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know

7.2 HIQA Decision

Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.

The practice ^{18}F-PSMA PET/CT for the primary staging of prostate cancer and the re-staging of recurrent prostate cancer is generically justified under SI 256/2018.

The generic justification of this practice is effective from 07 Dec 2023. Under the Regulations, HIQA may review the generic justification of this practice if new and important evidence about the practice emerges. HIQA may also review this practice if new and important evidence about alternative techniques and technologies (including non-ionising practices) emerges.

References

1. European Union (Basic Safety Standards for Protection Against Dangers Arising from Medical Exposure to Ionising Radiation) Regulations 2018 as amended. Dublin: The Stationary Office, (2019).
2. European Medicines Agency (EMA). Pylclari - piflufolastat (18F) 2023 [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/pylclari.
3. Health Information & Quality Authority (HIQA). Methods for Generic Justification of New Practices in Ionising Radiation. 2022.
4. Blodgett TM, Meltzer CC, Townsend DW. PET/CT: form and function. Radiology. 2007;242(2):360-85.
5. Martínez MJ, Ziegler SI, Beyer T. PET and PET/CT: Basic Principles and Instrumentation. In: Dresel S, editor. PET in Oncology. Berlin, Heidelberg: Springer Berlin Heidelberg; 2008. p. 1-23.
6. Sheehan B, Guo C, Neeb A, Paschalis A, Sandhu S, de Bono JS. Prostate-specific Membrane Antigen Biology in Lethal Prostate Cancer and its Therapeutic Implications. Eur Urol Focus. 2022;8(5):1157-68.
7. Simon H, Henkel D, Chiron P, Helissey C. New perspectives on metabolic imaging in the management of prostate cancer in 2022: A focus on radiolabeled PSMA-PET/CT (Review). Mol Clin Oncol. 2023;19(1):51.
8. Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging. 2017;44(4):678-88.
9. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
10. National Cancer Registry Ireland (NCRI). Cancer Factsheet: Prostate (Incidence: 2015-2017 estimated averages and mortality: 2012-2014 averages). Cork, Ireland: 2018.
11. National Cancer Control Programme (NCCP). National Clinical Guideline – Diagnosis and staging of patients with prostate cancer Version 2.0. 2022.
12. European Society of Radiology (ESR). Imaging guidelines in newly diagnosed prostate cancer: 2023 [16/08/23]. Available from: https://www.myesr.org/research/biomarkers-inventory/biomarkers-prostate.
13. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. (1873-7560 (Electronic)).
14. Yossepowitch O, Eggener SE, Bianco FJ, Carver BS, Serio A, Scardino PT, et al. Radical Prostatectomy for Clinically Localized, High Risk Prostate Cancer: Critical Analysis of Risk Assessment Methods. Journal of Urology.

2007;178(2):493-9.
15. Abuzallouf S, Dayes IAN, Lukka H. Baseline staging of newly diagnosed prostate cancer: a summary of the literature. The Journal of Urology. 2004;171(6, Part 1):2122-7.
16. Irish prostate cancer outcomes research: annual report: 2018 [cited 14/11/2023 14/11/2023]. Available from: https://www.ipcor.ie/wp-content/uploads/2019/01/IPCOR_Annual-Report2018_Digital_NEW.pdf.
17. Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. J Natl Cancer Inst. 2009;101(12):878-87.
18. Simon NI, Parker C, Hope TA, Paller CJ. Best Approaches and Updates for Prostate Cancer Biochemical Recurrence. Am Soc Clin Oncol Educ Book. 2022;42:1-8.
19. Shore ND, Moul JW, Pienta KJ, Czernin J, King MT, Freedland SJ. Biochemical recurrence in patients with prostate cancer after primary definitive therapy: treatment based on risk stratification. Prostate Cancer and Prostatic Diseases. 2023.
20. James N, Graham J, Maurer T, Eiber M, Gschwend JE. Diagnosis and Treatment of Prostate Cancer: What Americans Can Learn From International Oncologists. American Society of Clinical Oncology Educational Book. 2017(37):344-57.
21. Eyrich NW, Tosoian JJ, Drobish J, Montie JE, Qi J, Kim T, et al. Do patients who undergo multiparametric MRI for prostate cancer benefit from additional staging imaging? Results from a statewide collaborative. Urologic Oncology: Seminars and Original Investigations. 2020;38(7):636.e13-.e19.
22. Harisinghani MG, Barentsz J Fau - Hahn PF, Hahn Pf Fau - Deserno WM, Deserno Wm Fau - Tabatabaei S, Tabatabaei S Fau - van de Kaa CH, van de Kaa Ch Fau - de la Rosette J, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. (1533-4406 (Electronic)).
23. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. (1873-7560 (Electronic)).
24. European Society of Radiology. Imaging guidelines in newly diagnosed prostate cancer: [Available from: https://www.myesr.org/research/biomarkers-inventory/biomarkers-prostate/.
25. Dias AH, Jochumsen MR, Zacho HD, Munk OL, Gormsen LC. Multiparametric dynamic whole-body PSMA PET/CT using [(68)Ga]Ga-PSMA-11 and [(18)F]PSMA-1007. EJNMMI Res. 2023;13(1):31.
26. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. (1474-547X (Electronic)).
27. Van Damme JA-O, Tombal BA-O, Collette L, Van Nieuwenhove S, Pasoglou V, Gérard TA-O, et al. Comparison of (68)Ga-Prostate Specific Membrane Antigen (PSMA) Positron Emission Tomography Computed Tomography (PET-CT) and Whole-Body Magnetic Resonance Imaging (WB-MRI) with Diffusion

Sequences (DWI) in the Staging of Advanced Prostate Cancer. LID - 10.3390/cancers13215286 [doi] LID - 5286. (2072-6694 (Print)).
28. Perera M, Papa N, Roberts M, Williams M, Udovicich C, Vela I, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. (1873-7560 (Electronic)).
29. Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M, Haller B, Weirich G, et al. Diagnostic Efficacy of (68)Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. (1527-3792 (Electronic)).
30. Herlemann A, Wenter V, Kretschmer A, Thierfelder KM, Bartenstein P, Faber C, et al. (68)Ga-PSMA Positron Emission Tomography/Computed Tomography Provides Accurate Staging of Lymph Node Regions Prior to Lymph Node Dissection in Patients with Prostate Cancer. (1873-7560 (Electronic)).
31. Anttinen M, Ettala O, Malaspina S, Jambor I, Sandell M, Kajander S, et al. A Prospective Comparison of (18)F-prostate-specific Membrane Antigen-1007 Positron Emission Tomography Computed Tomography, Whole-body 1.5 T Magnetic Resonance Imaging with Diffusion-weighted Imaging, and Single-photon Emission Computed Tomography/Computed Tomography with Traditional Imaging in Primary Distant Metastasis Staging of Prostate Cancer (PROSTAGE). (2588-9311 (Electronic)).
32. Gates M, Gates A, Pieper D, Fernandes RM, Tricco AC, Moher D, et al. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. BMJ. 2022;378:e070849.
33. Dullea A. Diagnostic Accuracy of 18F Prostate Specific Membrane Antigen (PSMA) PET-CT radiotracers in staging and restaging of high- risk prostate cancer patients and patients with biochemical failure: Protocol for an Overview of Reviews. : 2023 [Oct 2023]. Available from: https://osf.io/fpzxd/.
34. Dullea A, O'Sullivan L, Carrigan M, Ahern S, McGarry M, O'Brien K, et al. Diagnostic accuracy of 18F Prostate Specific Membrane Antigen (PSMA) PET-CT radiotracers in staging and restaging of high-risk prostate cancer patients and patients with biochemical recurrence: protocol for an overview of reviews [version 1; peer review: awaiting peer review]. HRB Open Research. 2023;6(57).
35. European Union (Basic Safety Standards for Protection Against Dangers Arising from Medical Exposure to Ionising Radiation) Regulations 2018 as amended. Dublin: The Stationary Office (2019). .
36. Pollock M FR, Becker LA, Pieper D, Hartling L. . Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). . Cochrane: 2022.
37. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. Jama. 1992;268(2):240-8.

38. Oxman AD, Guyatt GH. The science of reviewing research. Ann N Y Acad Sci. 1993;703:125-33; discussion 33-4.
39. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9.
40. Stephenson AJ, Kattan MW, Eastham JA, Dotan ZA, Bianco FJ, Lilja H, et al. Defining Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy: A Proposal for a Standardized Definition. Journal of Clinical Oncology. 2006;24(24):3973-8.
41. Tourinho-Barbosa R, Srougi V, Nunes-Silva I, Baghdadi M, Rembeyo G, Eiffel SS, et al. Biochemical recurrence after radical prostatectomy: what does it mean? Int Braz J Urol. 2018;44(1):14-21.
42. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. Jama. 1998;280(11):969-74.
43. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer—2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. European Urology. 2021;79(2):243-62.
44. National Comprehensive Cancer Network® (NCCN®). Prostate Cancer V.3.2022. 2022.
45. National Institute for Health and Care Excellence. NICE guideline [NG131]: Prostate cancer: diagnosis and management. . May 2019.
46. Magi-Galluzzi C. Prostate cancer: diagnostic criteria and role of immunohistochemistry. Modern Pathology. 2018;31(1):12-21.
47. DeepL Translator. Germany: [Available from: www.deepl.com.
48. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225-34.
49. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020;368:l6890.
50. Aromataris E MZ. JBI Manual for Evidence Synthesis. 2020.
51. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology. 2011;64(4):401-6.
52. Schünemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. Journal of Clinical Epidemiology. 2016;76:89-98.
53. Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336(7653):1106-10.
54. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. : [Available from: https://gradepro.org.

55. Schünemann HJ, Mustafa RA, Brozek J, Steingart KR, Leeflang M, Murad MH, et al. GRADE guidelines: 21 part 2. Test accuracy: inconsistency, imprecision, publication bias, and other domains for rating the certainty of evidence and presenting it in evidence profiles and summary of findings tables. J Clin Epidemiol. 2020;122:142-52.
56. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016;353:i2016.
57. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
58. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-75.
59. Awenat S, Piccardo A, Carvoeiras P, Signore G, Giovanella L, Prior JO, et al. Diagnostic role of18f-psma-1007 pet/ct in prostate cancer staging: A systematic review. Diagnostics. 2021;11(3):552.
60. Evangelista L, Maurer T, van der Poel H, Alongi F, Kunikowska J, Laudicella R, et al. [68Ga]Ga-PSMA Versus [18F]PSMA Positron Emission Tomography/Computed Tomography in the Staging of Primary and Recurrent Prostate Cancer. A Systematic Review of the Literature. European Urology Oncology. 2022;5(3):273-82.
61. Huang Y-T, Tseng N-C, Chen Y-K, Huang K-H, Lin H-Y, Huang Y-Y, et al. The Detection Performance of 18 F-Prostate-Specific Membrane Antigen-1007 PET/CT in Primary Prostate Cancer : A Systemic Review and Meta-analysis. Clinical nuclear medicine. 2022;47(9):755-62.
62. Jeet V, Parkinson B, Song R, Sharma R, Hoyle M. Histopathologically Validated Diagnostic Accuracy of PSMA-PET/CT in the Primary and Secondary Staging of Prostate Cancer and the Impact of PSMA-PET/CT on Clinical Management: A Systematic Review and Meta-analysis. Seminars in Nuclear Medicine. 2023.
63. Liu X, Wang Q, Zhang B, Jiang T, Zeng W. Diagnostic accuracy of 18 F-PSMA-1007 PET/CT for prostate cancer in primary staging and biochemical recurrence with different serum PSA levels: A systematic review and meta-analysis. Hellenic journal of nuclear medicine. 2022;25(1):88-102.
64. Pan K-H, Wang J-F, Wang C-Y, Nikzad AA, Kong FQ, Jian L, et al. Evaluation of 18F-DCFPyL PSMA PET/CT for Prostate Cancer: A Meta-Analysis. Frontiers in oncology. 2021;10:597422.
65. Pang W, Cheng S, Du Z, Du S. The diagnostic performance of 18 F-DCFPyL PET in patients with suspected prostate cancer: A systemic review and meta-analysis. Frontiers in oncology. 2023;13:1145759.
66. Sood A, Kishan AU, Evans CP, Feng FY, Morgan TM, Murphy DG, et al. The Impact of Positron Emission Tomography Imaging and Tumor Molecular Profiling on Risk Stratification, Treatment Choice, and Oncological Outcomes of Patients with Primary or Relapsed Prostate Cancer: An International Collaborative Review of the Existing Literature. European urology oncology.

2023.
67. Wang Y-F, Lo C-Y, Chen L-Y, Chang C-W, Huang Y-T, Huang Y-Y, et al. Comparing the Detection Performance Between Multiparametric Magnetic Resonance Imaging and Prostate-Specific Membrane Antigen PET/CT in Patients With Localized Prostate Cancer: A Systematic Review and Meta-analysis. Clinical nuclear medicine. 2023;48(7):e321-e31.
68. Yang YY, Liu ZM, Peng RC. Diagnostic performance of 18F-labeled PSMA PET/CT in patients with biochemical recurrence of prostate cancer: a systematic review and meta-analysis. Acta Radiol. 2023:2841851231184210.
69. Zhao Y, Simpson BS, Morka N, Freeman A, Kirkham A, Kelly D, et al. Comparison of Multiparametric Magnetic Resonance Imaging with Prostate-Specific Membrane Antigen Positron-Emission Tomography Imaging in Primary Prostate Cancer Diagnosis: A Systematic Review and Meta-Analysis. Cancers. 2022;14(14).
70. Anttinen M, Ettala O, Malaspina S, Jambor I, Sandell M, Kajander S, et al. A Prospective Comparison of 18F-prostate-specific Membrane Antigen-1007 Positron Emission Tomography Computed Tomography, Whole-body 1.5 T Magnetic Resonance Imaging with Diffusion-weighted Imaging, and Single-photon Emission Computed Tomography/Computed Tomography with Traditional Imaging in Primary Distant Metastasis Staging of Prostate Cancer (PROSTAGE). European Urology Oncology. 2021;4(4):635-44.
71. Bodar YJL, Jansen BHE, van der Voorn JP, Zwezerijnen GJC, Meijer D, Nieuwenhuijzen JA, et al. Detection of prostate cancer with (18)F-DCFPyL PET/CT compared to final histopathology of radical prostatectomy specimens: is PSMA-targeted biopsy feasible? The DeTeCT trial. World J Urol. 2021;39(7):2439-46.
72. Brauchli D, Singh D, Chabert C, Somasundaram A, Collie L. Tumour-capsule interface measured on 18F-DCFPyL PSMA positron emission tomography/CT imaging comparable to multi-parametric MRI in predicting extra-prostatic extension of prostate cancer at initial staging. J Med Imaging Radiat Oncol. 2020;64(6):829-38.
73. Dietlein F, Kobe C, Hohberg M, Zlatopolskiy BD, Krapf P, Endepols H, et al. Intraindividual Comparison of (18)F-PSMA-1007 with Renally Excreted PSMA Ligands for PSMA PET Imaging in Patients with Relapsed Prostate Cancer. J Nucl Med. 2020;61(5):729-34.
74. Dietlein F, Kobe C, Neubauer S, Schmidt M, Stockter S, Fischer T, et al. PSA-Stratified Performance of (18)F- and (68)Ga-PSMA PET in Patients with Biochemical Recurrence of Prostate Cancer. J Nucl Med. 2017;58(6):947-52.
75. Dietlein M, Kobe C, Kuhnert G, Stockter S, Fischer T, Schomäcker K, et al. Comparison of [(18)F]DCFPyL and [(68)Ga]Ga-PSMA-HBED-CC for PSMA-PET Imaging in Patients with Relapsed Prostate Cancer. Mol Imaging Biol. 2015;17(4):575-84.
76. Gaur S, Mena E, Harmon SA, Lindenberg ML, Adler S, Ton AT, et al. Prospective Evaluation of (18)F-DCFPyL PET/CT in Detection of High-Risk Localized Prostate Cancer: Comparison With mpMRI. AJR Am J Roentgenol. 2020;215(3):652-9.

77. Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. European Journal of Nuclear Medicine and Molecular Imaging. 2017;44(4):678-88.
78. Giesel FL, Knorr K, Spohn F, Will L, Maurer T, Flechsig P, et al. Detection Efficacy of (18)F-PSMA-1007 PET/CT in 251 Patients with Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy. J Nucl Med. 2019;60(3):362-8.
79. Gorin MA, Rowe SP, Patel HD, Vidal I, Mana-Ay M, Javadi MS, et al. Prostate Specific Membrane Antigen Targeted (18)F-DCFPyL Positron Emission Tomography/Computerized Tomography for the Preoperative Staging of High Risk Prostate Cancer: Results of a Prospective, Phase II, Single Center Study. J Urol. 2018;199(1):126-32.
80. Hong JJ, Liu BL, Wang ZQ, Tang K, Ji XW, Yin WW, et al. The value of (18)F-PSMA-1007 PET/CT in identifying non-metastatic high-risk prostate cancer. EJNMMI Res. 2020;10(1):138.
81. Jansen BHE, Bodar YJL, Zwezerijnen GJC, Meijer D, van der Voorn JP, Nieuwenhuijzen JA, et al. Pelvic lymph-node staging with (18)F-DCFPyL PET/CT prior to extended pelvic lymph-node dissection in primary prostate cancer - the SALT trial. Eur J Nucl Med Mol Imaging. 2021;48(2):509-20.
82. Kesch C, Vinsensia M, Radtke JP, Schlemmer HP, Heller M, Ellert E, et al. Intraindividual Comparison of (18)F-PSMA-1007 PET/CT, Multiparametric MRI, and Radical Prostatectomy Specimens in Patients with Primary Prostate Cancer: A Retrospective, Proof-of-Concept Study. J Nucl Med. 2017;58(11):1805-10.
83. Kroenke M, Wurzer A, Schwamborn K, Ulbrich L, Jooß L, Maurer T, et al. Histologically Confirmed Diagnostic Efficacy of (18)F-rhPSMA-7 PET for N-Staging of Patients with Primary High-Risk Prostate Cancer. J Nucl Med. 2020;61(5):710-5.
84. Kuten J, Fahoum I, Savin Z, Shamni O, Gitstein G, Hershkovitz D, et al. Head-to-Head Comparison of ⁶⁸Ga-PSMA-11 with ¹⁸F-PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as a Reference Standard. Journal of Nuclear Medicine. 2020;61(4):527.
85. Lengana T, Lawal IO, Rensburg CV, Mokoala KMG, Moshokoa E, Ridgard T, et al. A comparison of the diagnostic performance of (18)F-PSMA-1007 and (68)GA-PSMA-11 in the same patients presenting with early biochemical recurrence. Hell J Nucl Med. 2021;24(3):178-85.
86. Lindenberg L, Mena E, Turkbey B, Shih JH, Reese SE, Harmon SA, et al. Evaluating Biochemically Recurrent Prostate Cancer: Histologic Validation of (18)F-DCFPyL PET/CT with Comparison to Multiparametric MRI. Radiology. 2020;296(3):564-72.
87. Liu W, Zukotynski K, Emmett L, Chung HT, Chung P, Wolfson R, et al. Utilization of Salvage and Systemic Therapies for Recurrent Prostate Cancer as a Result of (18)F-DCFPyL PET/CT Restaging. Adv Radiat Oncol.

2021;6(1):100553.
88. Liu Y, Liu J, Zhang Z, Wang M, Dong Y, Yin X. 18F-DCFPyL PET/CT in pre-operative diagnosis of regional lymph node metastasis from prostate cancer. Chin J Med Imaging Technol. 2020;36(6).
89. Malaspina S, Anttinen M, Taimen P, Jambor I, Sandell M, Rinta-Kiikka I, et al. Prospective comparison of (18)F-PSMA-1007 PET/CT, whole-body MRI and CT in primary nodal staging of unfavourable intermediate- and high-risk prostate cancer. Eur J Nucl Med Mol Imaging. 2021;48(9):2951-9.
90. Mingels C, Bohn KP, Rominger A, Afshar-Oromieh A, Alberts I. Diagnostic accuracy of [(18)F]PSMA-1007 PET/CT in biochemical recurrence of prostate cancer. Eur J Nucl Med Mol Imaging. 2022;49(7):2436-44.
91. Parathithasan N, Perry E, Taubman K, Hegarty J, Talwar A, Wong LM, et al. Combination of MRI prostate and 18F-DCFPyl PSMA PET/CT detects all clinically significant prostate cancers in treatment-naive patients: An international multicentre retrospective study. J Med Imaging Radiat Oncol. 2022;66(7):927-35.
92. Pienta KJ, Gorin MA, Rowe SP, Carroll PR, Pouliot F, Probst S, et al. A Phase 2/3 Prospective Multicenter Study of the Diagnostic Accuracy of Prostate Specific Membrane Antigen PET/CT with (18)F-DCFPyL in Prostate Cancer Patients (OSPREY). J Urol. 2021;206(1):52-61.
93. Privé BM, Israël B, Schilham MGM, Muselaers CHJ, Zámecnik P, Mulders PFA, et al. Evaluating F-18-PSMA-1007-PET in primary prostate cancer and comparing it to multi-parametric MRI and histopathology. Prostate Cancer and Prostatic Diseases. 2021;24(2):423-30.
94. Rahbar K, Weckesser M, Ahmadzadehfar H, Schäfers M, Stegger L, Bögemann M. Advantage of (18)F-PSMA-1007 over (68)Ga-PSMA-11 PET imaging for differentiation of local recurrence vs. urinary tracer excretion. Eur J Nucl Med Mol Imaging. 2018;45(6):1076-7.
95. Rauscher I, Markus K, Michael K, Andrei G, Tobias M, Thomas H, et al. Matched-Pair Comparison of ⁶⁸Ga-PSMA-11 PET/CT and ¹⁸F-PSMA-1007 PET/CT: Frequency of Pitfalls and Detection Efficacy in Biochemical Recurrence After Radical Prostatectomy. Journal of Nuclear Medicine. 2020;61(1):51.
96. Rousseau E, Wilson D, Lacroix-Poisson F, Krauze A, Chi K, Gleave M, et al. A Prospective Study on (18)F-DCFPyL PSMA PET/CT Imaging in Biochemical Recurrence of Prostate Cancer. J Nucl Med. 2019;60(11):1587-93.
97. Rowe SP, Campbell SP, Mana-Ay M, Szabo Z, Allaf ME, Pienta KJ, et al. Prospective Evaluation of PSMA-Targeted (18)F-DCFPyL PET/CT in Men with Biochemical Failure After Radical Prostatectomy for Prostate Cancer. J Nucl Med. 2020;61(1):58-61.
98. Rowe SP, Macura KJ, Mena E, Blackford AL, Nadal R, Antonarakis ES, et al. PSMA-Based [(18)F]DCFPyL PET/CT Is Superior to Conventional Imaging for Lesion Detection in Patients with Metastatic Prostate Cancer. Mol Imaging Biol. 2016;18(3):411-9.
99. Sachpekidis C, Afshar-Oromieh A, Kopka K, Strauss DS, Pan L, Haberkorn U, et al. (18)F-PSMA-1007 multiparametric, dynamic PET/CT in biochemical

relapse and progression of prostate cancer. Eur J Nucl Med Mol Imaging. 2020;47(3):592-602.
100. Saule L, Radzina M, Liepa M, Roznere L, Kalnina M, Lioznovs A, et al. Diagnostic scope of (18)F-PSMA-1007 PET/CT: comparison with multiparametric MRI and bone scintigraphy for the assessment of early prostate cancer recurrence. Am J Nucl Med Mol Imaging. 2021;11(5):395-405.
101. Song H, Harrison C, Duan H, Guja K, Hatami N, Franc BL, et al. Prospective Evaluation of (18)F-DCFPyL PET/CT in Biochemically Recurrent Prostate Cancer in an Academic Center: A Focus on Disease Localization and Changes in Management. J Nucl Med. 2020;61(4):546-51.
102. Sprute K, Kramer V, Koerber SA, Meneses M, Fernandez R, Soza-Ried C, et al. Diagnostic Accuracy of (18)F-PSMA-1007 PET/CT Imaging for Lymph Node Staging of Prostate Carcinoma in Primary and Biochemical Recurrence. J Nucl Med. 2021;62(2):208-13.
103. Tragardh E, Simoulis A, Bjartell A, Jogi J. Tumor detection of (18)F-PSMA-1007 in the prostate gland in patients with prostate cancer using prostatectomy specimens as reference method. J Nucl Med. 2021;62(12):1735-40.
104. Witkowska-Patena E, Giżewska A, Dziuk M, Miśko J, Budzyńska A, Walęcka-Mazur A. Diagnostic performance of 18F-PSMA-1007 PET/CT in biochemically relapsed patients with prostate cancer with PSA levels ≤ 2.0 ng/ml. Prostate Cancer Prostatic Dis. 2020;23(2):343-8.
105. Wondergem M, M. van der Zant F, J. J. Knol R, Sergiy VL, Jan P, Igle JdJ. 18F-DCFPyL PET/CT in the Detection of Prostate Cancer at 60 and 120 Minutes: Detection Rate, Image Quality, Activity Kinetics, and Biodistribution. Journal of Nuclear Medicine. 2017;58(11):1797.
106. Zamboglou C, Kramer M, Kiefer S, Bronsert P, Ceci L, Sigle A, et al. The impact of the co-registration technique and analysis methodology in comparison studies between advanced imaging modalities and whole-mount-histology reference in primary prostate cancer. Scientific Reports. 2021;11(1):5836.
107. Zhang T, Yang S, Lin L, Wang S, Xia D, Chen D, et al. Role of (18)F-DCFPyL PET/CT in patients with suspected prostate cancer. Hell J Nucl Med. 2022;25(1):11-8.
108. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
109. Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology. 2003;3(1):25.
110. National Institute of Health Quality Assessment Tool: [Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
111. Critical Appraisal Skills Programme (CASP). Checklist for diagnostic test studies: 2022 [Available from: https://casp-

uk.net/images/checklist/documents/CASP-Diagnostic-Study-Checklist/CASP-Diagnostic-Checklist-2018_fillable_form.pdf.
112. Katharina S, Vasko K, Stefan AK, Manuel M, Rene F, Cristian S-R, et al. Diagnostic Accuracy of ¹⁸F-PSMA-1007 PET/CT Imaging for Lymph Node Staging of Prostate Carcinoma in Primary and Biochemical Recurrence. Journal of Nuclear Medicine. 2021;62(2):208.
113. Ferrari M, Treglia G. 18 F-PSMA-1007 PET in Biochemical Recurrent Prostate Cancer: An Updated Meta-Analysis. Contrast media & molecular imaging. 2021;2021:3502389.
114. Oprea-Lager D-E, Gontier E, García-Cañamaque L, Gauthé M, Olivier P, Mitjavila M, et al. [18F]DCFPyL PET/CT versus [18F]fluoromethylcholine PET/CT in Biochemical Recurrence of Prostate Cancer (PYTHON): a prospective, open label, cross-over, comparative study. European Journal of Nuclear Medicine and Molecular Imaging. 2023;50(11):3439-51.
115. Morris MJ, Rowe SP, Gorin MA, Saperstein L, Pouliot F, Josephson D, et al. Diagnostic Performance of (18)F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study. Clin Cancer Res. 2021;27(13):3674-82.
116. Chen M, Zhang Q, Zhang C, Zhou YH, Zhao X, Fu Y, et al. Comparison of (68)Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) and multi-parametric magnetic resonance imaging (MRI) in the evaluation of tumor extension of primary prostate cancer. Transl Androl Urol. 2020;9(2):382-90.
117. International Commission on Radiological Protection. Radiation dose to patients from radiopharmaceuticals: a compendium of current information related to frequently used substances. 2015 Contract No.: Publication 128. Ann. ICRP 44(2S).
118. Administration of Radioactive Substances Advisory Committee. Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources. London: 2023.
119. Huda W, Magill D, He W. CT effective dose per dose length product using ICRP 103 weighting factors. Med Phys. 2011;38(3):1261-5.
120. Health Information & Quality Authority (HIQA). Guidance on the establishment, use and review of diagnostic reference levels for medical exposure to ionising radiation. Updated 2021.
121. Medical Exposure Radiation Unit. National Survey on Population Dose from Computed Tomography. 2017.
122. Radiological Protection Act 1991 (Ionising Radiation) Regulations 2019 as amended. Dublin: The Stationary Office (2019). .
123. Environmental Protection Agency. The Design of Diagnostic Medical Facilities where Ionising Radiation is used. 2009.
124. Environmental Protection Agency. Guidance for undertakings on the application of the ionising radiation regulations (IRR19): 2022 [Available from: https://www.epa.ie/publications/licensing--permitting/radiation/EPA_IRR19_Guidance_2022.pdf.
125. Health Technology Wales. Fluorine- or gallium- prostate-specific membrane

antigen positron emission tomography radiotracers: 2021 [Available from: https://healthtechnology.wales/reports-guidance/fluorine-or-gallium-prostate-specific-membrane-antigen-positron-emission-tomography-radiotracers/
126. Canadian Agency for Drugs and Technologies in Health. PET Diagnostic Imaging with Prostate-Specific Membrane Antigen for Prostate Cancer: A Review of Clinical Utility, Cost-Effectiveness, Diagnostic Accuracy, and Guidelines: [Available from: https://www.cadth.ca/sites/default/files/pdf/htis/2020/RC1321%20PSMA%20for%20Prostate%20Cancer%20Final.pdf.
127. National Cancer Control Programme. Diagnosis and staging of patients with prostate cancer: 2022 [Available from: https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/updated-diagnosis-and-staging-of-prostate-cancer-guideline.pdf.
128. The Royal College of Radiologists. Evidence-based indications for the use of PET-CT in the United Kingdom 2022 [Available from: https://www.rcr.ac.uk/system/files/publication/field_publication_files/evidence-based_indications_for_the_use_of_pet-ct_in_the_united_kingdom_2022.pdf.
129. Fendler WP, Eiber M, Beheshti M, Bomanji J, Calais J, Ceci F, et al. PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0. European Journal of Nuclear Medicine and Molecular Imaging. 2023;50(5):1466-86.
130. Institute for Clinical Effectiveness A. PSMA radiopharmaceuticals versus other radiopharmaceuticals in positron emmission tomography/computed tomoraphy for staging biochemical recurrence: Rapid Response Report No.859. 2022.
131. Annunziata S, Pizzuto DA, Treglia G. Diagnostic Performance of PET Imaging Using Different Radiopharmaceuticals in Prostate Cancer According to Published Meta-Analyses. Cancers [Internet]. 2020; 12(8).
132. Ptasznik G, Moon D, Buteau J, Kelly BD, Ong S, Murphy DG, et al. A Systematic Review of the Variability in Performing and Reporting Intraprostatic Prostate-specific Membrane Antigen Positron Emission Tomography in Primary Staging Studies. European urology open science. 2023;50:91-105.
133. Wang R, Shen G, Huang M, Tian R. The Diagnostic Role of 18 F-Choline, 18 F-Fluciclovine and 18 F-PSMA PET/CT in the Detection of Prostate Cancer With Biochemical Recurrence: A Meta-Analysis. Frontiers in oncology. 2021;11:684629.
134. Alberts IL, Seide SE, Mingels C, Bohn KP, Shi K, Zacho HD, et al. Comparing the diagnostic performance of radiotracers in recurrent prostate cancer: a systematic review and network meta-analysis. Eur J Nucl Med Mol Imaging. 2021;48(9):2978-89.
135. Reina Y, Villaquirán C, García-Perdomo HA. Advances in high-risk localized prostate cancer: Staging and management. Current Problems in Cancer. 2023;47(4):100993.
136. Ho TY. A systematic review: head-to-head comparison study on the biochemical recurrence of prostate cancer using [^{18}F] F-PSMA-1007 and

[68Ga] PSMA-11. HKU Theses Online (HKUTO). 2022.
137. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. The Lancet. 2020;395(10231):1208-16.
138. Buteau JP, Moon D, Fahey MT, Roberts M, Thompson J, Murphy DG, et al. PRIMARY2: A phase III, multi-centre, randomised controlled trial investigating the additive diagnostic value of [68Ga]Ga-PSMA-11 PET/CT in men with negative/equivocal MRI in the diagnosis of clinically significant prostate cancer. Journal of Clinical Oncology. 2023;41(6_suppl):TPS397-TPS.
139. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Annals of Internal Medicine. 2011;155(8):529-36.
140. Whiting P, Harbord R, Kleijnen J. No role for quality scores in systematic reviews of diagnostic accuracy studies. BMC Med Res Methodol. 2005;5:19.
141. Jüni P, Witschi A, Bloch R, Egger M. The Hazards of Scoring the Quality of Clinical Trials for Meta-analysis. JAMA. 1999;282(11):1054-60.
142. Deeks JJ, Higgins JP, Altman DG. Analysing Data and Undertaking Meta-Analyses. Cochrane Handbook for Systematic Reviews of Interventions2008. p. 243-96.
143. Guyatt G, Zhao Y, Mayer M, Briel M, Mustafa R, Izcovich A, et al. GRADE guidance 36: updates to GRADE's approach to addressing inconsistency. Journal of Clinical Epidemiology. 2023;158:70-83.
144. Schünemann HB, Jan; Guyatt, Gordon; Oxman, Andrew. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Handbook2013.
145. Schünemann HJ, Mustafa RA, Brozek J, Steingart KR, Leeflang M, Murad MH, et al. GRADE guidelines: 21 part 1. Study design, risk of bias, and indirectness in rating the certainty across a body of evidence for test accuracy. Journal of Clinical Epidemiology. 2020;122:129-41.
146. Schünemann HJ, Mustafa RA, Brozek J, Steingart KR, Leeflang M, Murad MH, et al. GRADE guidelines: 21 part 2. Test accuracy: inconsistency, imprecision, publication bias, and other domains for rating the certainty of evidence and presenting it in evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2020;122:142-52.
147. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews. J Clin Epidemiol. 2016;70:106-10.
148. Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. Systematic Reviews. 2014;3(1):82.
149. Li CR, Liao CT, Liu JP. A non-inferiority test for diagnostic accuracy based on the paired partial areas under ROC curves. Stat Med. 2008;27(10):1762-76.

Appendix 1

Table A.1 Full search strategy – Medline (EBSCO)

Database name			**Medline Complete via Ebscohost**	
Date search was run			**18/07/2023**	
#	***Query***	***Limiters/Expanders***	***Last Run Via***	***Results***
S10	S3 AND S8 AND S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	177
Concept 3: Study design filter for systematic reviews designed by Health Library Ireland (HSE) librarians				
S9	MH "Systematic Review" OR MH "Meta Analysis" OR PT "Systematic Review" OR PT "Meta-Analysis" OR TI systematic* N1 (review* OR overview*) OR AB systematic* N1 (review* OR overview*) OR TI "meta analys*" OR TI "meta analyz*" OR AB "meta analys*" OR AB "meta analyz* OR TI literature N2 (review* OR overview*) OR AB literature N2 (review* OR overview*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	785,971
Concept 2: F18 PSMA PET				
S8	S4 OR S5 OR S6 OR S7	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	24,338

S7	TI PSMA N1 PET OR AB PSMA N1 PET	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	1,830
S6	AB ("F-PSMA" OR "PSMA-1007" OR "18FPSMA-1007" OR "F-PSMA-1007") OR TI ("F-PSMA" OR "PSMA-1007" OR "18FPSMA-1007" OR "F-PSMA-1007")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	226
S5	AB ((18-F OR 18F OR F18 OR "F 18" OR F-18 OR 18F-DCFPyL OR fluorine-18) N3 ("prostate specific membrane antigen" OR "positron emission tomography computed tomography" OR PSMA OR PET-CT OR PET/CT)) OR TI ((18-F OR 18F OR F18 OR "F 18" OR F-18 OR 18F-DCFPyL OR fluorine-18) N3 ("prostate specific membrane antigen" OR "positron emission tomography computed tomography" OR PSMA OR PET-CT OR PET/CT))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	7,307
S4	(MH "Positron Emission Tomography Computed Tomography")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	19,148
Concept 1: Prostate Cancer				
S3	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	202,418
S2	AB (prostat* N4 (neoplas* or cancer* or carcinoma* or malignan* or tumour* or tumor* or metasta* or adenocarcinoma* or angiosarcoma* or sarcoma*)) OR TI (	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	179,776

	prostat* N4 (neoplas* or cancer* or carcinoma* or malignan* or tumour* or tumor* or metasta* or adenocarcinoma* or angiosarcoma* or sarcoma*))			
S1	(MH "Prostatic Neoplasms+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	148,703

Table A.2 Details of grey literature search

Organisation, country	Description	URL link
General grey literature sources		
Google and Google Scholar	The first five pages of each were checked. Keywords: PSMA AND (PET or PET-CT)	https://scholar.google.com/, https://www.google.ie
International or regional organisations		
World Health Organization		www.who.int/en
European Network for Health Technology Assessment (EUnetHTA)		https://www.eunethta.eu/
International HTA database (INAHTA)		https://database.inahta.org/
Guidelines International Network (G-I-N)		https://g-i-n.net/international-guidelines-library
Agence Fédérale de Contrôle Nucléaire		https://afcn.fgov.be/
European Society for Radiotherapy and Oncology (ESTRO)		https://www.estro.org/Science/Guidelines
European Society for Medical Oncology (ESMO)		https://www.esmo.org/guidelines
European Society for Radiology (ESR)		https://www.myesr.org/publications/guidelines-and-recommendations
American Society for Clinical Oncology (ASCO)		https://old-prod.asco.org/practice-patients/guidelines
European Association of Nuclear Medicine (EANM)		https://www.eanm.org/publications/guidelines/
Country specific organisations		

Canada	
Canadian Agency for Drugs and Technology in Health (CADTH)	http://www.cadth.ca
Health Quality Canada	https://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment/Reviews-And-Recommendations
France	
Autorité de Sûreté Nucléaire	https://www.asn.fr/
Ireland	
National Cancer Control Programme HSE	https://www.hse.ie/eng/services/list/5/cancer/
Health Products Regulatory Authority	https://www.hpra.ie/
Norway	
Norwegian Institute of Public Health (NIPH)	https://www.fhi.no/en/qk/HTA/
Sweden	
Swedish Agency for Health Technology Assessment and Assessment of Social Services	https://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health	https://www.bag.admin.ch/bag/de/home/das-bag/organisation/ausserparlamentarische-kommissionen/eidgenoessische-kommission-fuer-strahlenschutz-ksr/expertengruppe-MEG.html
United Kingdom	
The Royal College of Radiologists	https://www.rcr.ac.uk

National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/
National Institute for Health and Social Care Research Health Technology Assessment Programme	https://www.nihr.ac.uk/explore-nihr/funding-programmes/health-technology-assessment.htm
Health Technology Wales	https://healthtechnology.wales/
SHTG, Scotland	https://shtg.scot/about-us/
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/

Appendix 2

Table A.3 Further guidance on how GRADE assessments were performed

General Approach to Downgrading	
Risk of Bias	Similar to Pollock et al.'s algorithm, we downgraded for the risk of bias in the primary studies and separately for the risk of bias in the reviews. For the primary studies, we downgraded by one where the risk of bias was thought to be serious, and by two where risk of bias was thought to be very serious. Judgements were informed by the QUADAS-2 findings collected from the systematic reviews and the ROBIS assessment. In deciding to downgrade for risk of bias in the primary studies and systematic reviews, we looked for issues across the QUADAS-2 and ROBIS domains with unclear or high biases, or systematic issues across one or more particular domains where across studies a particular domain is found to be at unclear or high-risk of bias. For ROBIS, the overall risk of bias for the review was also considered, however this summary "quality score" was not used for QUADAS-2, because of the well-known problems associated with such scores highlighted by the tool developers.[139-141]
Inconsistency	Similar to Pollock et al., we also assessed statistical heterogeneity; however, rather than just downgrading by one for an I^2 of <75%, we considered downgrading by one where the I^2 was substantial (50-90%) and by two if considerable (75-100%) as these are the categories of heterogeneity specified by Deeks, section 9.5.2 of the Cochrane Handbook and section 3.3.10.2 of the JBI Manual for Evidence Synthesis.[36, 50, 142] As pooled results from meta-analyses were not readily available for the specific research questions posed in this overview, we often judged inconsistency on the variability in the study results as suggested in GRADE guidance 36[143] and the GRADE handbook.[144] Similar to judgements on I^2, there should be an explanation for the observed heterogeneity and if no plausible explanation is present downgrading is recommended. The decision to treat inconsistency as 'serious' or 'very serious' depended on the extent of the heterogeneity observed.

Indirectness	For indirectness we referred to the GRADE guidelines for test accuracy.[144-146] No 'test-and-treat' randomised control trials related to our research question on 18F-PSMA PET/CT were identified. Test accuracy studies were considered high quality, and an underlying assumption of this overview is that a change in staging or diagnosis would lead to a change in management or meaningful changes to patient important outcomes. Indirect comparisons or tests are avoided in the generation of evidence profiles and summary of findings tables, and hence these factors were not considered in downgrading. However, when moving from evidence to decision making, the two-step process of linking evidence between different studies (e.g., evidence on MRI and evidence on 18F-PSMA) was considered in the judgements made. Similarly, in keeping with GRADE guidance although the review question focuses on test accuracy rather than patient important outcomes, the indirectness related to patient important outcomes was not considered in grading the certainty of the evidence but was considered when making judgements and moving from evidence to decision making. Although we include 'high-risk patients' and 'biochemically recurrent patients' under any definition, we did not downgrade for indirectness where definitions may vary from the one given in national guidelines for prostate cancer.[11] We considered rating down in situations where outcomes may not be generalisable to all patients with either high-risk prostate cancer or biochemical recurrent. For example, where outcome data was only available for patients with certain PSA levels (e.g. >10ng/ml) which may not represent all those with high-risk prostate cancer or biochemical recurrence, or where results for high-risk patients could not be disaggregated from those with intermediate risk, we considered downgrading.
Imprecision	Pollock et al. assess imprecision by using sample size and patient numbers as a proxy, however it was feasible for us to take an approach more consistent with the original GRADE guidelines in our overview.[145-147] We assessed imprecision by looking at the number of events AND the width and overlap of confidence intervals as suggested by the GRADE guidance for test accuracy.

Publication Bias	Our approach to assessing publication bias was largely based on the comprehensiveness and quality of the search, the inclusion of grey literature or trial registry data, the presence of only studies that produce precise estimates of high accuracy despite small sample size, and the influence of industry funding. The decision to assess publication bias under these factors was influenced by GRADE guidance, and the GRADE checklist.[148] Additionally, but to a lesser extent, the results of Deeks tests or Trim and Fill methods had some influence on our decision making where the review question was similar or identical to the overview question. Results from funnel plots (e.g., Egger's or Begg's tests) in test accuracy systematic reviews are likely to result in rating down for publication bias more frequently than appropriate, and hence these were not considered.[146] Although non inferiority test accuracy studies may suffer from a unique publication bias situation due to their ability to assess statistical significance with Bayesian methods, it was not possible to assess this phenomenon in the grading of the certainty of the evidence within this overview.[149] As many of these factors are also included in the ROBIS assessment, care was taken to not inadvertently 'double penalise' reviews under risk of bias and publication bias. Where an outcome was already downgraded due to risk of bias in the systematic reviews' search methods, our judgement were largely limited to whether there was a presence of only small studies that produce precise estimates for high accuracy despite the small sample size, and the possible role of industry funding.
General Approach to Upgrading	
Test Outcome Relations & Large Effect Estimates	As noted in the GRADE guidelines, the certainty in test accuracy may increase if summary ROC curves show a clear and consistent sensitivity-specificity relationship (which GRADE authors consider the equivalent of a dose-effect relationship).[146] As did not produce pooled meta-analysed results ourselves, we looked for large and consistent effect sizes across the body of evidence.
Residual Plausible Bias or Confounding	Very high accuracy of a test and the presence of minimal opposing residual confounding might also increase one's confidence in the usefulness of the test.

Table A.4 Summary of key characteristics of primary studies identified by systematic reviews included in this overview of reviews

Author (Year)	Population/Indication	Number of participants (lesion number)	Study design	PET tracer
Anttinen[70] (2021)	High-risk	79 (1581)	Prospective	^{18}F-PSMA-1007
Bodar[71] (2020)	Intermediate/high-risk	30 (420 segments)	Prospective	^{18}F-DCFPyL
Brauchli[72] (2020)	Intermediate/high-risk	100 (100)	Retrospective	^{18}F-DCFPyL
Dietlein[75] (2015)	Biochemical recurrence	14 (98)	Retrospective	^{18}F-PSMA-1007
Dietlein[74] (2017)	Biochemical recurrence	62 (100)	Retrospective	^{18}F-PSMA-1007
Dietlein[73] (2020)	Biochemical recurrence	27 (not reported)	Retrospective	^{18}F-PSMA-1007
Gaur[76] (2020)	High-risk	26 (not reported)	Prospective	^{18}F-DCFPyL
Giesel[77] (2017)	High-risk	10 (not reported)	Retrospective	^{18}F-PSMA-1007
Giesel[78] (2019)	Biochemical recurrence	251 (not reported)	Retrospective	^{18}F-PSMA-1007
Gorin[79] (2018)	High-risk/very high-risk	25 (not reported)	Prospective	^{18}F-DCFPyL
Hong[80] (2020)	Intermediate/high-risk	101 (not reported)	Retrospective	^{18}F-PSMA-1007
Jansen[81] (2021)	Intermediate/high-risk	116 (not reported)	Prospective	^{18}F-DCFPyL
Kesch[82] (2017)	High-risk	10 (372)	Retrospective	^{18}F-PSMA-1007
Kroenke[83] (2020)	High-risk	58 (not reported)	Retrospective	^{18}F-rhPSMA-7
Kuten[84] (2019)	Intermediate/high-risk	16 (145)	Prospective	^{18}F-PSMA-1007
Lengana[85] (2021)	Biochemical recurrence	21 (not reported)	Prospective	^{18}F-PSMA-1007

Lindenburg [86] (2020)	Biochemical recurrence	80 (36)	Prospective	^{18}F-DCFPyL
Liu[87] (2020)	Biochemical recurrence	79 (14)	Retrospective	^{18}F-DCFPyL
Liu Yachao[88] (2020)	Primary staging	49 (not reported)	Retrospective	^{18}F-DCFPyL
Malaspina[89] (2021)	Intermediate/high-risk	31 (not reported)	Prospective	^{18}F-PSMA-1007
Mingels[90] (2022)	Biochemical recurrence	177 (40)	Retrospective	^{18}F-PSMA-1007
Parathithisan[91] (2022)	Intermediate/high-risk	65 (61)	Retrospective	^{18}F-DCFPyL
Pienta[92] (2021)	High-risk	252 (not reported)	Prospective	^{18}F-DCFPyL
Privé[93] (2021)	Intermediate/high-risk	53 (46)	Retrospective	^{18}F-PSMA-1007
Rahbar[94] (2018)	Biochemical recurrence	100 (not reported)	Retrospective	^{18}F-PSMA-1007
Rauscher[95] (2020)	Biochemical recurrence	102 (371)	Retrospective	^{18}F-PSMA-1007
Rousseau[96] (2019)	Biochemical recurrence	100 (130)	Prospective	^{18}F-PSMA-1007
Rowe[98] (2016)	Known metastatic disease	71 (not reported)	Prospective	^{18}F-DCFPyL
Rowe[97] (2020)	Biochemical recurrence	31 (100)	Prospective	^{18}F-DCFPyL
Sachpekidis[99] (2020)	Biochemical recurrence	25 (not reported)	Retrospective	^{18}F-PSMA-1007
Saule[100] (2021)	Biochemical recurrence	28 (not reported)	Prospective	^{18}F-PSMA-1007
Song[101] (2020)	Biochemical recurrence	72 (100)	Prospective	^{18}F-DCFPyL
Sprute[102] (2021)	Biochemical recurrence	96 (1746)	Prospective	^{18}F-PSMA-1007
Tragaradh[103] (2021)	Intermediate/high-risk	39 (not reported)	Retrospective	^{18}F-PSMA-1007
Witkowska-Patena[104] (2019)	Biochemical recurrence, pre-operative	40 (not reported)	Prospective	^{18}F-PSMA-1007

	diagnosis, metastatic disease			
Wondergem[105] (2017)	Biochemical recurrence	34 (100)	Retrospective	^{18}F-DCFPyL
Zamboglou[106] (2021)	Intermediate/high-risk	10 (14; 601 segments)	Prospective	^{18}F-PSMA-1007
Zhang[107] (2022)	Intermediate/high-risk	56 (not reported)	Retrospective	^{18}F-DCFPyL

Table A.5: Formulae

Equation 1: Detection Rate
$Detection\ Rate = \frac{True\ Postives + False\ Positives}{All\ Those\ Tested}$
Equation 2: Sensitivity
$Sensitivity = \frac{True\ Positives}{Total\ Number\ of\ People\ with\ Metastatic\ Disease}$
Equation 3: Specificity
$\boldsymbol{Specificity = \frac{True\ Negatives}{Total\ Number\ of\ People\ Without\ Metastatic\ Disease}}$
Equation 4: Diagnostic effectiveness (accuracy)
$\boldsymbol{Accuracy = \frac{True\ Positives + True\ Negatives}{All\ Those\ Tested}}$

Table A.6 Risk of bias in systematic reviews (ROBIS): summary of judgments

	Phase 2				Phase 3
SR First author (Year)	***1. Study eligibility criteria***	***2. Identification & selection of studies***	***3. Data collection & study appraisal***	***4. Synthesis & findings***	***Risk of bias in the review***
Awenat (2021)[59]	Low	Unclear	High	High	High
Evangelista (2022)[60]	High	High	High	High	High
Huang (2022)[61]	Unclear	Unclear	High	High	Unclear
Jeet (2023)[62]	Low	Low	Unclear	Low	Low
Liu (2022)[63]	Unclear	Unclear	Unclear	High	Unclear
Pang (2023)[65]	Unclear	High	Unclear	Unclear	High
Pan (2021)[64]	Unclear	Unclear	High	High	High
Sood (2023)[66]	Low	High	Unclear	High	High
Wang (2023)[67]	Low	Unclear	Low	Unclear	Unclear
Yang (2023)[68]	Unclear	Unclear	Unclear	Unclear	Unclear
Zhao (2022)[69]	Unclear	Low	Low	High	Unclear

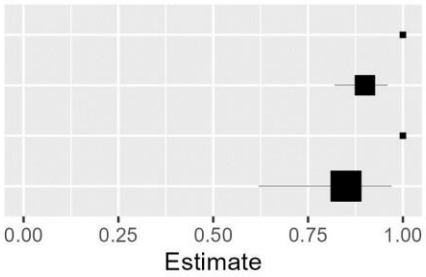
Table A.7: Citation matrix

Study ID	Reference	Awenat 2021	Evangelista 2022	Huang 2022	Jeet 2023	Liu 2022	Pang 2023	Pan 2021	Sood 2023	Wang 2023	Yang 2023	Zhao 2022
1	Anttinen 2020	1				1						
2	Bodar 2020				1		1					
3	Brauchli 2020									1		
4	Dietlein 2015							1			1	
5	Dietlein 2017		1					1			1	
6	Dietlein 2020					1					1	
7	Gaur 2020									1		
8	Giesel 2017	1		1								
9	Giesel 2019					1					1	
10	Gorin 2018				1			1	1			
11	Hong 2020	1										
12	Jansen 2021				1				1			
13	Kesch 2017	1		1		1				1		
14	Kroenke 2020				1							
15	Kuten 2020	1				1						
16	Lengana 2021										1	
17	Lidenburg 2020				1						1	
18	Liu 2020										1	
19	Liu Yachao 2020							1				
20	Malaspina 2021			1								
21	Mingels 2022										1	
22	Parathithasan 2022						1			1		
23	Pienta 2021				1				1			
24	Privé 2020	1		1		1				1		
25	Rahbar 2018					1						
26	Rauscher 2020					1					1	
27	Rousseau 2019							1			1	
28	Rowe 2016							1				
29	Rowe 2020							1			1	
30	Sachpekidis 2020					1						
31	Saule 2021										1	
32	Song 2020							1			1	
33	Sprute 2021			1	1	1					1	
34	Tragardh 2021			1								
35	Witkowska-Patena 2019					1	1				1	
36	Wondergem 2017							1			1	
37	Zamboglou 2021											1
38	Zhang 2022						1					

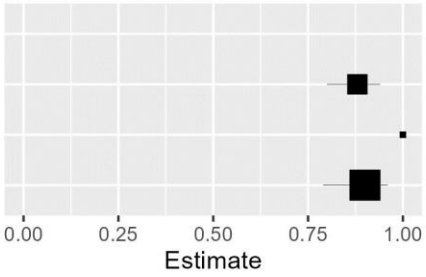
Figure A.1: Forest plots of sensitivity and specificity data from primary studies on a per-patient, per lymph node and per-lesion basis for patients with high-risk prostate cancer

Per-Patient Data

Study (No. Patients)	Sensitivity (95% CI)
Kesch 2017 (10)	1.00 (No CI)
Gorin 2018 (25)	0.90 (95%CI 0.82-0.96)
Giesel 2017 (10)	1.00 (No CI)
Anttinen 2020 (79)	0.85 (95%CI 0.62-0.97)

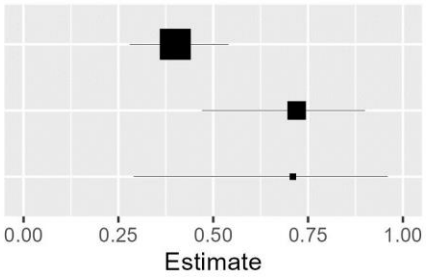


Study (No. Patients)	Specificity (95% CI)
Kesch 2017 (10)	No Estimate Reported
Gorin 2018 (25)	0.88 (95%CI 0.80-0.94)
Giesel 2017 (10)	1.00 (No CI)
Anttinen 2020 (79)	0.90 (95%CI 0.79-0.96)

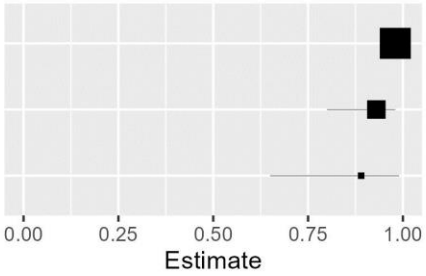


Per-Lymph Node Data

Study (No. Patients)	Sensitivity (95% CI)
Pienta 2021 (252)	0.40 (95%CI 0.28-0.54)
Kroenke 2020 (58)	0.72 (95%CI 0.47-0.90)
Gorin 2018 (25)	0.71 (95%CI 0.29-0.96)

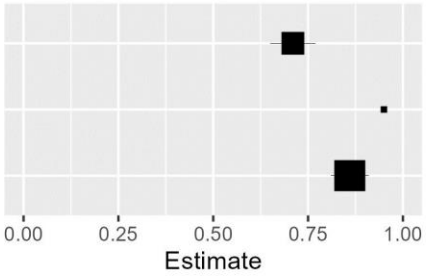


Study (No. Patients)	Specificity (95% CI)
Pienta 2021 (252)	0.98 (95%CI 0.95-0.99)
Kroenke 2020 (58)	0.93 (95%CI 0.80-0.98)
Gorin 2018 (25)	0.89 (95%CI 0.65-0.99)

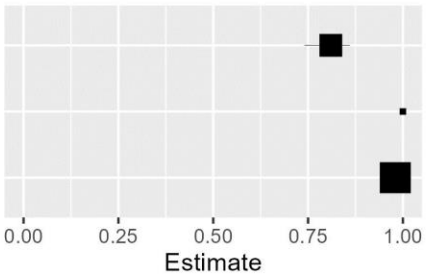


Per-Lesion Data

Study (No. Lesions)	Sensitivity (95% CI)
Kesch 2017 (372)	0.71 (95%CI 0.65-0.77)
Giesel 2017 (NR)*	0.95 (No CI)
Anttinen 2020 (1581)	0.86 (95%CI 0.81-0.91)

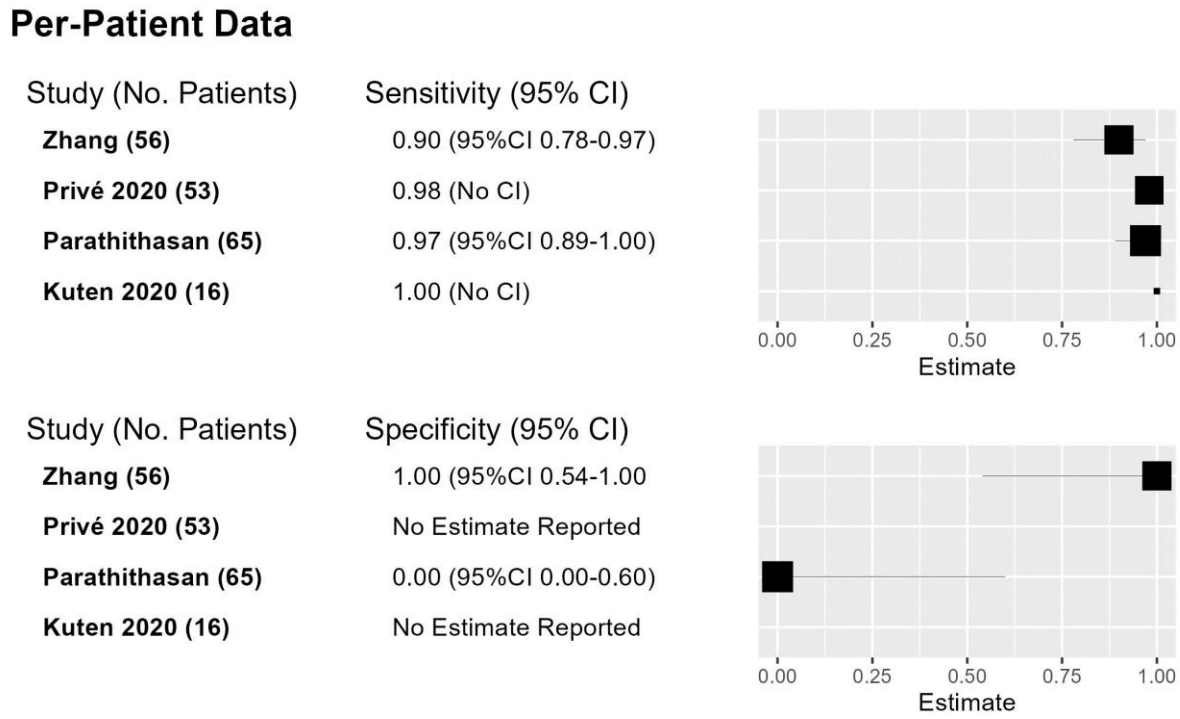


Study (No. Lesions)	Specificity (95% CI)
Kesch 2017 (372)	0.81 (95%CI 0.74-0.86)
Giesel 2017 (NR)*	1.00 (No CI)
Anttinen 2020 (1581)	0.98 (95%CI 0.98-0.99)



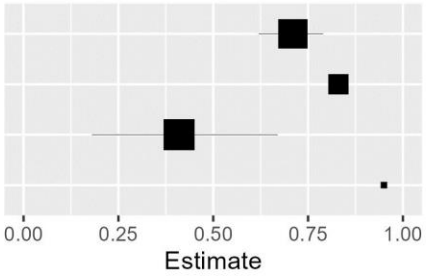
Key: NR = Number of lesions not reported by the systematic review.
Note: All estimates extracted as reported by the included systematic reviews.

Figure A.2: Forest plots of sensitivity and specificity data from primary studies on a per-patient, per lymph node and per-lesion basis for patients with intermediate/high-risk prostate cancer.

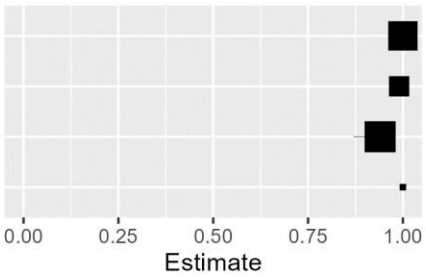


Per-Lymph Node Data

Study (No. Patients)	Sensitivity (95% CI)
Sprute 2021 (96)	0.71 (95%CI 0.62-0.79)
Malaspina 2021 (31)	0.83 (No CI)
Jansen 2021 (117)	0.41 (95%CI 0.18-0.67)
Giesel 2017 (10)	0.95 (No CI)

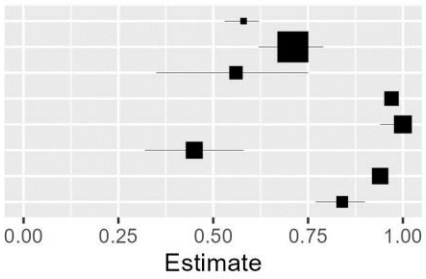


Study (No. Patients)	Specificity (95% CI)
Sprute 2021 (96)	1.00 (95%CI 0.99-1.00)
Malaspina 2021 (31)	0.99 (No CI)
Jansen 2021 (117)	0.94 (95%CI 0.87-0.98)
Giesel 2017 (10)	1.00 (No CI)

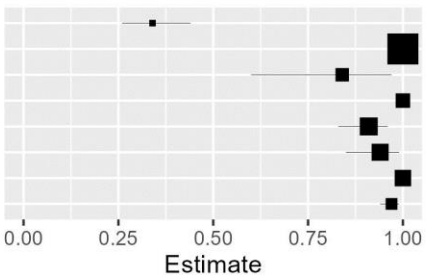


Per-Lesion Data

Study (No. Lesions)	Sensitivity (95% CI)
Zamboglou 2021 (14)	0.58 (95%CI 0.53-0.62)
Sprute 2021 (1746)	0.71 (95%CI 0.62-0.79)
Privé 2020 (46)	0.56 (95%CI 0.35-0.75)
Parathithasan 2022 (61)	0.97 (No CI)
Kuten 2019 (145)	1.00 (95%CI 0.94-1.00)
Jansen 2021 (NR)*	0.45 (95%CI 0.32-0.58)
Brauchli 2020 (100)	0.94 (No CI)
Bodar 2020 (NR)*	0.84 (95%CI 0.77-0.90)



Study (No. Lesions)	Specificity (95% CI)
Zamboglou 2021 (14)	0.34 (95%CI 0.26-0.44)
Sprute 2021 (1746)	1.00 (95%CI 0.99-1.00)
Privé 2020 (46)	0.84 (95%CI 0.60-0.97)
Parathithasan 2022 (61)	1.00 (No CI)
Kuten 2019 (145)	0.91 (95%CI 0.83-0.96)
Jansen 2021 (NR)*	0.94 (95%CI 0.85-0.99)
Brauchli 2020 (100)	1.00 (No CI)
Bodar 2020 (NR)*	0.97 (95%CI 0.94-0.99)

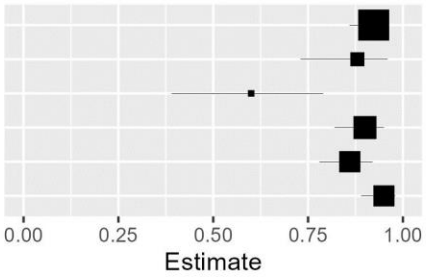


Key: NR = Number of lesions not reported by the systematic review.
Note: All estimates extracted as reported by the included systematic reviews.

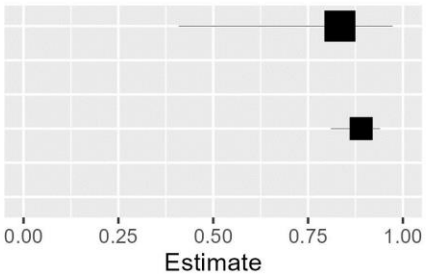
Figure A.3: Forest plots of sensitivity and specificity data from primary studies on a per-patient and per-lesion basis for patients with biochemically recurrent prostate cancer

Per Patient Data

Study (No. Patients)	Sensitivity (95% CI)
Yang 2023 (367)†	0.92 (95%CI 0.86-0.96)
Witkowska-Patena 2019 (40)	0.88 (95%CI 0.73-0.96)
Sachpekidis 2020 (25)	0.60 (95%CI 0.39-0.79)
Rousseau 2019 (130)	0.90 (95%CI 0.82-0.95)
Rauscher 2020 (102)	0.86 (95%CI 0.78-0.92)
Rahbar 2018 (100)	0.95 (95%CI 0.89-0.98)

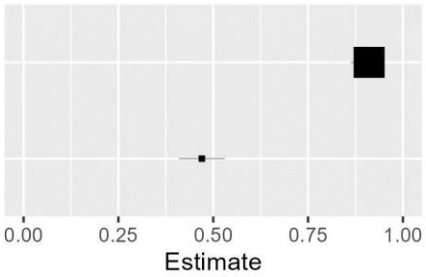


Study (No. Patients)	Specificity (95% CI)
Yang 2023 (367)†	0.83 (95%CI 0.41-0.97)
Witkowska-Patena 2019 (40)	No Estimate Reported
Sachpekidis 2020 (25)	No Estimate Reported
Rousseau (2019) (130)	0.89 (95%CI 0.81-0.94)
Rauscher 2020 (102)	No Estimate Reported
Rahbar 2018 (100)	No Estimate Reported

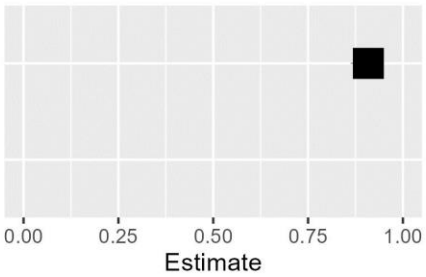


Per-Lesion Data

Study (No. Lesions)	Sensitivity (95% CI)
Yang 2023 (1,874)†	0.91 (95%CI 0.86-0.94)
Giesel 2019 (251)‡	0.47 (95%CI 0.41-0.53)



Study (No. Lesions)	Specificity (95% CI)
Yang 2023 (1,874)†	0.91 (95%CI 0.86-0.94)
Giesel 2019 (251)‡	No Estimate Reported



Notes: † results from meta-analysis. ‡Although Yang et al. included a per-patient estimate from this primary study, they did not capture a per-lesion estimate which was identified from other systematic reviews.

Table A.8: Synthesis Without Meta-analysis (SWiM) reporting items

SWiM is intended to complement and be used as an extension to PRISMA			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
Methods			
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design)	Section 4.4 Data Synthesis	
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	Section 4.4 Data Synthesis	
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	Section 4.4 Data Synthesis	
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	Section 4.4 Data Synthesis	
4 Criteria used to prioritise results for summary and	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	Section 4.4 Data Synthesis	

synthesis			
SWiM reporting item	***Item description***	***Page in manuscript where item is reported***	***Other****
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	Appendix 2 Table A.4	
6 Certainty of evidence	Describe the methods used to assess certainty of the synthesis findings	Section 4.4.1 Grading of Recommendations Assessment, Development and Evaluation (GRADE)	
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots). Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included.	Section 4.4 Data Synthesis	
Results			
8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	Section 5.5 and Section 5.6	

Discussion			
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question	Section 6 Discussion (Limitations)	

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
*If the information is not provided in the systematic review, give details of where this information is available (e.g., protocol, other published papers (provide citation details), or website (provide the URL)).

Table A.9: Preferred reporting items for overviews of review (PRIOR) reporting items

Section Topic	#	Item	Location reported
Title			
Title	1	Identify the report as an overview of reviews.	Section 1.1
Abstract			
Abstract	2	Provide a comprehensive and accurate summary of the purpose, methods, and results of theoverview of reviews.	Key Points
Introduction			
Rationale	3	Describe the rationale for conducting the overview of reviews in the context of existingknowledge.	Section 2 & 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) addressed by the overview ofreviews.	Section 4.1
Methods			
Eligibility criteria	5a 5b	Specify the inclusion and exclusion criteria for the overview of reviews. If supplemental primary studies were included, this should be stated, with a rationale. Specify the definition of 'systematic review' as used in the inclusion criteria for the overview of reviews.	Section 4.1 Section 4.1
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searchedor consulted to identify systematic reviews and supplemental primary studies (if included). Specify the date when each source was last searched or consulted.	Section 4.2
Search strategy	7	Present the full search strategies for all databases, registers and websites, such that they could bereproduced. Describe any search filters and limits applied.	Section 4.2, Zenodo and Appendix 1
Selection process	8a 8b	Describe the methods used to decide whether a systematic review or supplemental primary study(if included) met the inclusion criteria of the overview of reviews. Describe how overlap in the populations, interventions, comparators, and/or outcomes of systematic reviews was identified and managed during study selection.	Section 4.3 Section 4.4.2
Data collection process	9a 9b	Describe the methods used to collect data from reports. If applicable, describe the methods used to identify and manage primary study overlap at the level of the comparison and outcome during data collection. For each outcome, specify the	Section 4.3.2 N/A

		method used to illustrate and/or quantify the degree of primary study overlap across systematic reviews.	
	9c	If applicable, specify the methods used to manage discrepant data across systematic reviews during data collection.	Section 4.3.2
Data items	10	List and define all variables and outcomes for which data were sought. Describe any assumptions made and/or measures taken to identify and clarify missing or unclear information.	Section 4.1, 4.3.1 and 4.3.2
Risk of bias assessment	11a	Describe the methods used to *assess* risk of bias or methodological quality of the included systematic reviews.	Section 4.3.3
	11b	Describe the methods used to *collect* data on (from the systematic reviews) and/or *assess* the risk of bias of the primary studies included in the systematic reviews. Provide a justification for instances where flawed, incomplete, or missing assessments are identified but not re-assessed.	Section 4.3.2
	11c	Describe the methods used to *assess* the risk of bias of supplemental primary studies (if included).	N/A
Synthesis methods	12a	Describe the methods used to summarize or synthesize results and provide a rationale for the choice(s).	Section 4.4
	12b	Describe any methods used to explore possible causes of heterogeneity among results.	N/A
	12c	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting bias assessment	13	Describe the methods used to *collect* data on (from the systematic reviews) and/or *assess* the risk of bias due to missing results in a summary or synthesis (arising from reporting biases at the levels of the systematic reviews, primary studies, and supplemental primary studies, if included).	Section 4.3.2
Certainty assessment	14	Describe the methods used to *collect* data on (from the systematic reviews) and/or *assess* certainty (or confidence) in the body of evidence for an outcome.	Section 4.4.1
Results			
Systematic review and supplemental primary study selection	15a	Describe the results of the search and selection process, including the number of records screened, assessed for eligibility, and included in the overview of reviews, ideally with a flow diagram.	Section 5.1
	15b	Provide a list of studies that might appear to meet the inclusion criteria, but were excluded, with the main reason for exclusion.	OSF Repository

Characteristics of systematic reviews and supplemental primary studies	16	Cite each included systematic review and supplemental primary study (if included) and present itscharacteristics.	Section 5.2 and Appendix 1
Primary study overlap	17	Describe the extent of primary study overlap across the included systematic reviews.	Section 5.4
Risk of bias in systematic reviews, primary studies, and supplemental primary studies	18a	Present assessments of risk of bias or methodological quality for each included systematic review.	Section 5.3, 5.5 and 5.6
	18b	Present assessments (*collected* from systematic reviews or *assessed* anew) of the risk of bias of the primary studies included in the systematic reviews.	Section 5.3
	18c	Present assessments of the risk of bias of supplemental primary studies (if included).	N/A
Summary or synthesis of results	19a	For all outcomes, summarize the evidence from the systematic reviews and supplemental primary studies (if included). If meta-analyses were done, present for each the summary estimate and its precision and measures of statistical heterogeneity. If comparing groups, describe the direction ofthe effect.	Section 5.5 and 5.6
	19b	If meta-analyses were done, present results of all investigations of possible causes of heterogeneity.	N/A
	19c	If meta-analyses were done, present results of all sensitivity analyses conducted to assess the robustness of synthesized results.	N/A
Reporting biases	20	Present assessments (*collected* from systematic reviews and/or *assessed* anew) of the risk of bias due to missing primary studies, analyses, or results in a summary or synthesis (arising from reporting biases at the levels of the systematic reviews, primary studies, and supplemental primary studies, if included) for each summary or synthesis assessed.	Section 5.2, 5.5 and 5.6
Certainty of evidence	21	Present assessments (*collected* or *assessed* anew) of certainty (or confidence) in the body of evidence for each outcome.	Section 5.5 and 5.6
Discussion			
Discussion	22a	Summarize the main findings, including any discrepancies in findings across the included systematic reviews and supplemental primary studies (if included).	Section 6
	22b	Provide a general interpretation of the results in the context of other evidence.	Section 6 and 7

	22c	Discuss any limitations of the evidence from systematic reviews, their primary studies, and supplemental primary studies (if included) included in the overview of reviews.	Section 6
	22d	Discuss implications for practice, policy, and future research (both systematic reviews and primary research). Consider the relevance of the findings to the end users of the overview of reviews, e.g., healthcare providers, policymakers, patients, among others.	Section 6 and 7
Other information			
Registration and protocol	23a	Provide registration information for the overview of reviews, including register name and registration number, or state that the overview of reviews was not registered.	Section 4
	23b	Indicate where the overview of reviews protocol can be accessed, or state that a protocol was not prepared.	Section 4
	23c	Describe and explain any amendments to information provided at registration or in the protocol. Indicate the stage of the overview of reviews at which amendments were made.	N/A
Support	24	Describe sources of financial or non-financial support for the overview of reviews, and the role of the funders or sponsors in the overview of reviews.	N/A
Competing interests	25	Declare any competing interests of the overview of reviews' authors.	Conflicts of Interest
Author information	26a	Provide contact information for the corresponding author.	Final Page
	26b	Describe the contributions of individual authors and identify the guarantor of the overview of reviews.	N/A
Availability of data and other materials	27	Report which of the following are available, where they can be found, and under which conditions they may be accessed: template data collection forms; data collected from included systematic reviews and supplemental primary studies; analytic code; any other materials used in the overview of reviews.	Section 4

Appendix 3

Evidence-to-Decision Framework Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Overall, the identified systematic reviews/primary studies had favourable conclusions in terms of the sensitivity, specificity and accuracy of ^{18}F-PSMA PET/CT relative to histopathology or clinical follow-up (which could include alternative imaging). Relevant comparators included ^{68}Ga-PSMA PET/CT and conventional imaging using bone scan, CT or MRI. **<u>Primary staging of high-risk prostate cancer</u>** Evidence from 10 systematic reviews: • No pooled estimates were available for per-patient, per-lesion or per-lymph node sensitivity, specificity or accuracy. • Per-patient sensitivity estimates ranged from 0.85 to 1.00; specificity estimates ranged from 0.88 to 1.00 and accuracy estimates ranged from 80 to 100%. • Per-lymph node sensitivity estimates ranged from 0.40 to 0.72; specificity estimates ranged from 0.89 to 0.98; accuracy estimates ranged from 82.5 to 86.2%. • Per-lesion sensitivity estimates ranged from 0.86 to 0.95; specificity estimates ranged from 0.81 to 1.00; accuracy estimates ranged from 93% to 100%. **<u>Re-staging of recurrent prostate cancer</u>**	It was noted that ^{68}Gallium involves a significant investment in terms of set-up of the service and is limited to centres who have a generator. In contrast, ^{18}F PSMA can be made in a cyclotron and shipped throughout the country with the potential therefore to increase access to PSMA PET/CT.

	Evidence from five systematic reviews with one review reporting pooled databased on a meta-analysis: • In terms of per-patient data, sensitivity was estimated to be 0.92 in the meta-analysis with other estimates ranging from 0.60 to 1.00; specificity was estimated to be 0.83 in the meta-analysis with other estimates ranging from 0.70 to 1.00; there were no estimates of per-patient accuracy. • There were no estimates of per-lymph node sensitivity, specificity or accuracy. • In terms of per-lesion data, sensitivity was estimated to be 0.91 in the meta-analysis with an estimate of 0.47 reported in a single study; specificity was estimated in the meta-analysis to be 0.91; accuracy was estimated to be 81.3% based on a single study.	
Panel discussion: The MEIR EAG considered the evidence for the outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence. It was recognised that the benefits of ^{18}F PSMA PET/CT may be 'large' given the sensitivity, specificity and accuracy of the test. A judgement of 'moderate' was however considered appropriate, given the available evidence, and recognising that data relating to the impact on clinical outcomes are not yet available. It was noted that there would be potential to improve equity of access to PSMA PET/CT with the introduction of ^{18}F-PSMA PET/CT, given the improved logistics, compared with ^{68}Ga. A judgement of 'moderate' was recorded by the MEIR EAG for this criterion.		
Undesirable Effects **How substantial are the undesirable anticipated effects?**		
Judgement	Research evidence	Additional considerations

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	• The overview of reviews did not highlight any significant safety concerns with [18]F-PSMA PET/CT. • 3 systematic reviews: no adverse events due to [18]F-PSMA PET/CT reported in the primary studies; the other 8 systematic reviews had no mention of possible adverse events. • No safety alerts or variations to the marketing authorisation were identified. • 3 studies (n=797 patients), which informed the European Public Assessment report, reported a total of 108 treatment-emergent adverse events (TMAE). These events were mainly mild and largely transient. The identified studies did not highlight any safety concerns for public and occupational exposure, and the risk is likely to be low, provided appropriate radiation protection safeguards are in place. • The change in ionising radiation dose associated with this practice is likely to depend on whether [18]F-PSMA PET/CT is used in addition to, or as a replacement for conventional imaging. This may depend on the clinical situation and the population involved. • No national diagnostic reference level exists for [18]F-PSMA PET/CT. However, the estimated effective dose for [18]F-PSMA PET/CT is 5.68mSv for the PET component and 6.9mSv for the whole body CT component. This compares with 13.47mSv for a CT thorax, abdomen and pelvis and 3.07mSv for a bone scintigraphy scan.	

Panel discussion:

The MEIR EAG considered the evidence for the outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence. It was noted that while the undesirable effects were not very well documented in the evidence identified in this overview of reviews, they appear to be mild and largely transient. It was agreed that for the majority of patients [18]F PSMA PET/CT would likely replace conventional imaging. However it was highlighted that this decision and what constitutes conventional imaging depends on the clinical context. The MEIR EAG noted that the CT component of the [18]F PSMA PET/CT is a low-dose CT and that the DRL doses identified in the HIQA report were in accordance with those seen clinically. Considering the implications of this in terms of the radiation dose, it was agreed that replacing conventional imaging with [18]F PSMA PET/CT is not likely to result in a dose increase.

Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Primary staging of high-risk prostate cancer:** the certainty of evidence for the per-patient data ranged from low (sensitivity, accuracy) to moderate (specificity); certainty for per-lymph node data ranged from low (sensitivity) to moderate (specificity). **Re-staging of recurrent prostate cancer:** the certainty of evidence for the per-patient data ranged from low (specificity) to moderate (sensitivity); for per lesion data ranged from very low (sensitivity) to low (specificity, accuracy). Overall, the certainty of the evidence is **Very Low.**	
Panel discussion: The finding for this criterion was noted to be based on the standard GRADE methodology, so no panel discussion around this criterion was required. The certainty of the evidence ranged from 'low' to 'very low'; therefore the overall certainty is 'very low'.		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important		

uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		
Panel discussion: The MEIR EAG considered the main outcomes, which are the sensitivity, specificity and accuracy of ^{18}F PSMA PET/CT. It was noted that there is a clear link between accurate staging and adequate treatment and that additional treatment benefits are likely if it is possible to target treatment more closely to the area(s) of disease. A judgement of 'probably no important uncertainty or variability' was recorded by the MEIR EAG for this criterion.		
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations

○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	**<u>Primary staging of high-risk prostate cancer</u>** See Table 4 (Summary of Findings Table), Page 47-48 **<u>Re-staging of recurrent prostate cancer</u>** See Table 5 (Summary of Findings Table), Page 54-55	

Panel discussion:

After considering the balance between the desirable and undesirable effects, it was agreed that the balance favoured the use of ^{18}F PSMA PET/CT.

A judgement of 'favours the intervention' was recorded by the MEIR EAG for this criteria.

Recommendation

On consideration of the balance between the benefits and harms, the MEIR EAG found that this favoured the use of ^{18}F-PSMA PET/CT. The MEIR EAG have recommended to HIQA that ^{18}F PSMA PET/CT should be generically justified for the staging of high-risk prostate cancer and re-staging of recurrent prostate cancer.

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