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SYSTEMATIC REVIEW

HTA in nuclear medicine: [^{68}Ga]PSMA PET/CT for patients with prostate cancer

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Abstract

The [^{68}Ga]PSMA PET/CT has been an option on clinical research tools to stage and to restage prostate cancer patients, although, with promising results, this radiopharmaceutical cannot be commercialized yet. Hence, up to date, [^{68}Ga]PSMA has been used in a clinical research context. Once regulatory body approved it for marketing, health systems are responsible for the reimbursement decision. Health Technology Assessments (HTA) tools should be considered to base and to help decision-makers to spread or not this new technology. Regarding [^{68}Ga]PSMA, under HTA framework, the present study searched for secondary studies and hence assessed three systematic reviews with meta-analyses published considering prostate cancer patients in different scenarios, same imaging technology but different comparators and outputs. The secondary studies considered outputs such as accuracy, detectability, positivity and change of management. Using AMSTAR-2, the meta-analysis methods and results were evaluated with 16 questions able to identify critical weaknesses, such as risk of bias, publication bias, true effect, and study heterogeneity. To increase the observational number of patients, to register positive and negative findings, and consolidate regional and multi-center clinical data which were suggestions on study design, structure and statistics made to improve the quality in future primary and secondary studies.

Keywords Meta-analysis · HTA · [^{68}Ga]PSMA

Abbreviations

[^{18}F]FDG	^{18}F-fluorodeoxyglucose
AMSTAR	A measurement tool to assess systematic reviews
BS	Bone scan
BCR	Biochemical recurrence
EANM	European association of nuclear medicine
EAU	European association of urology
[^{18}F]FACB	^{18}F-fluorocyclobutane-1-carboxylic acid
FDA	Food and drug administration
GRADE	Grading of recommendations assessment, development and evaluation
HTA	Health technology assessment
MRI	Magnetic resonance imaging
PRISMA	Preferred reporting items for systematic review and meta-analysis
PICO	Population, intervention, comparator, outcome
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
QUADAS-2	Quality assessment of diagnostic accuracy studies
RoB	Risk of bias
SNMMI	Society of nuclear medicine and molecular imaging
SR/MA	Systematic review and meta-analysis

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Introduction

Health Technology Assessment (HTA) [1–3] is a systematic and structured analysis performed to provide an input in policy decision of some new procedure, device, medicine, vaccine, or systems developed to solve a health problem and improve quality of lives. HTA main concerns are related to whether the technology works, for whom, at what cost, how to compare on new procedure with the current standard intervention, which works best.

As addressed by HTA, contextual factors include economic, organizational, social, and ethical impacts. The scope and methods of HTA may be adapted may be directed to respond to the policy needs of a particular health system (private or public, local or regional). The use of scientific method provides transparency on discussions and decisions. HTA tools are based on scientific evidences which are considered relevant according to a quality graduation (Fig. 1). The highest level of confidence to evidence is attributed to Systematic reviews and Meta-analysis (SR/MA) and the lowest one to Background information and expert opinion [4]. HTA embraces a diverse group of methods to be applied to nine different domains [1] (Fig. 2).

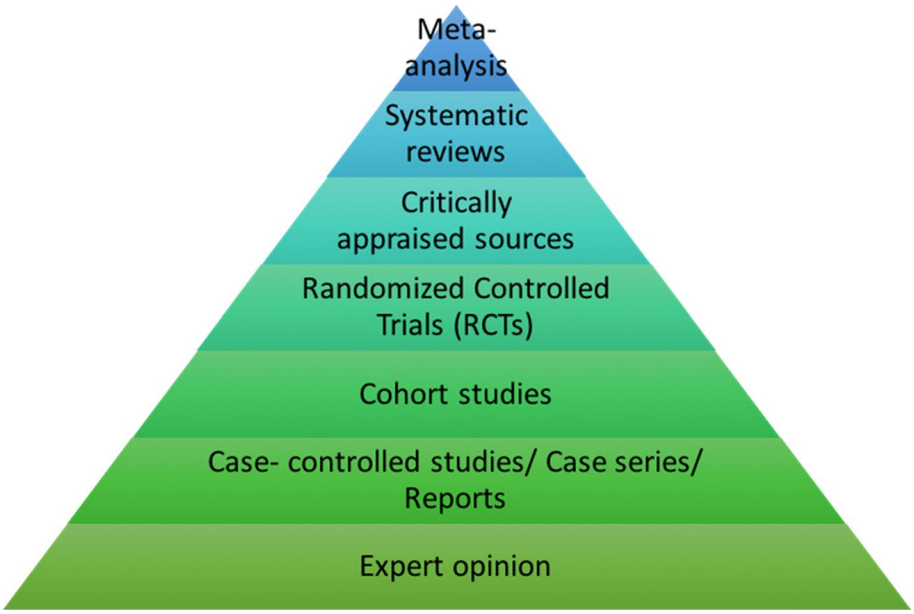

Fig. 1 Adapted from The Evidence Hierarchy, In Ebling Library 2015, from http://researchguides.ebling.library.wisc.edu/EBM/acquire

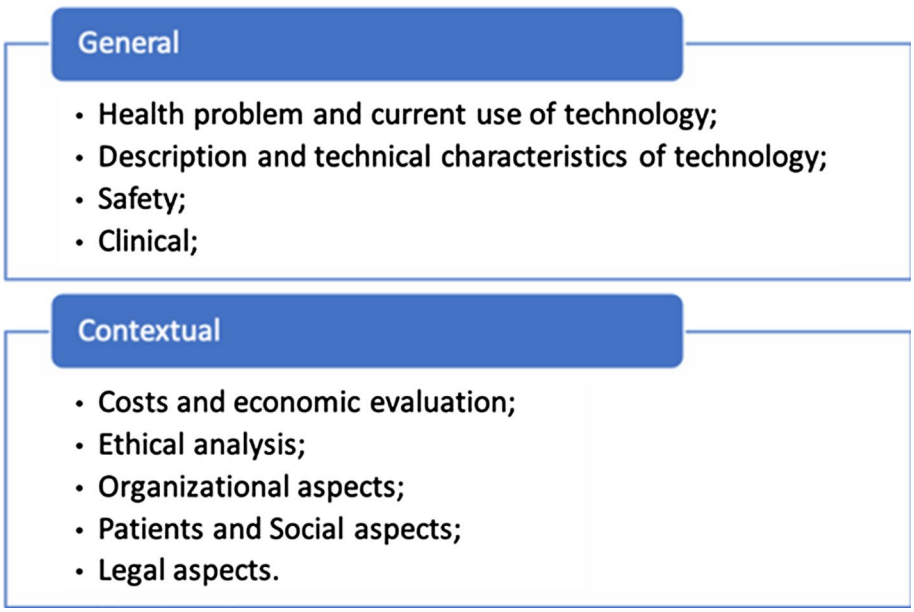

Fig. 2 The nine domains of HTA

Primary data collection methods and secondary or integrative methods are necessary steps. The first one involves collection of original data, such as clinical trials and observational studies. Integrative methods, secondary or synthesis methods, involve combining data or information from the existing sources, including primary studies. Economic analysis methods can involve one or both of them.

In nuclear medicine, after market authorization for radiopharmaceuticals and equipment, the reimbursement of the possible new procedures is necessary. Public and private health systems need evidence-based information, such as proof of security and efficacy in real conditions, and after it, effectiveness, costs optimization, and cost-effectiveness, especially comparing the new procedure with the current practice considered as reference. Only after this assessment, it would be possible to decide how to invest the finite financial resources. However, in nuclear medicine diagnostics, there are some difficulties to produce typical evidence used in these decision discussions, like randomized clinical trials, for example.

Due to its particular conditions, randomized studies are scarce. Clinical research studies are frequent and SR/MA are an alternative to evaluate larger data groups looking for useful clinical information that could help on decision-making. However, statistical controversies are often reported in clinical research [5, 6]. Ioannidis [6] lists several of the most common reasons why clinical studies are weakened to provide robust evidence, and suggestions on how to improve the situation.

The present paper intends to discuss HTA secondary studies on [^{68}Ga]PSMA PET/CT for patients with prostate cancer. Considering the HTA framework, this work discusses the quality of the evidence presented so far and proposes improvements and more robust scientific evidence to future primary and secondary studies.

[^{68}Ga]PSMA PET/CT

According to the GLOBOCAN 2012, prostate cancer is the second most commonly diagnosed worldwide cancer in men, with an estimated 1.1 million diagnoses, accounting for 15% of all cancers diagnosed [7]. Positron emission tomography/computed tomography (PET/CT) has been used to (re) staging different cancer types specially using [^{18}F]FDG. However, this procedure has low specificity although high sensitivity when applied to patients with prostate cancer. Then, other molecules were developed, like [^{11}C]Choline, [^{18}F]FACBC (fluciclovine), approved by US Food and Drug Administration (FDA) on 2012 and 2016, respectively [8].

Most prostate cancer cells express prostate-specific membrane antigen (PSMA) and is significantly over-expressed in prostate cancer cells compared to other PSMA-expressing tissues such as kidney, proximal small intestine, and salivary glands [9]. In 2012, Afshar-Oromieh et al. [10] developed a PSMA inhibitor labeled with ^{68}Ga, a positron emitter. [^{68}Ga]PSMA-11, as it is known, has been the main molecule used to imaging prostate cancer [11], although there are other PSMA molecules, labeled with ^{68}Ga and ^{18}F [11–13]. PSMA has the great advantage that it can be labeled with a beta emitter and then can be used to treat metastatic prostate cancer in the exact local as viewed on images. This is a great possibility towards the concept of theranostics in a context of an individualized medicine.

In its more recent guideline [14], European Association of Urology (EAU) recommends at least a cross-sectional abdominopelvic imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] and a bone-scan (BS) for metastasis screening in intermediate–high-risk primary prostate cancer. For biochemical recurrence (BCR), EAU weakly recommends a prostate-specific membrane antigen positron emission tomography–computed tomography ([^{68}Ga]PSMA PET/CT), if available, or a choline PET/CT imaging otherwise if PSA level is $\geq$1 ng/mL after radical prostatectomy.

EAU strongly recommends prostate multiparametric MRI to localize abnormal areas and guide biopsies in patients who are considered candidates for local salvage therapy and [^{68}Ga]PSMA PET/CT (if available) or choline PET/CT imaging to rule out positive lymph nodes or distant metastases in patients fit for curative salvage treatment after radiotherapy. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) [15] provided standards for the recommendation, performance, interpretation, and reporting on [^{68}Ga]PSMA PET/CT for prostate cancer imaging.

As an option of imaging modalities in the early diagnosis, the [^{68}Ga]PSMA PET/CT is just one in many options of management on advanced prostate cancer that would require multi-centric studies to confirm the ability to do better than bone scintigraphy in terms of disease detection, prove of recurrence, and to provide an earlier optimal timing to change treatment [16].

Method

The population studied was the prostate cancer patient, treated or not treated, submitted to the index text [^{68}Ga]PSMA PET/CT. All comparators, such as other imaging tests or physiopathology were considered, once in those studies prostate cancer patients are included in different clinical conditions, using the same methodology under analysis but with different comparators. Usually, diagnostic tests evaluate accuracy, sensitivity, and sensibility as outcomes. However, this study is opened to other possibilities.

The search was performed using PubMed, EMBASE, and Cochrane databases until August 30th, 2018. We used Mesh terms and free text words to be more inclusive. The following keywords and expressions were used, modifying its structure according the used database: ((“positron emission tomography”[Mesh] OR (PET[All Fields] OR PET/CT[All Fields] OR (“positron emission tomography computed tomography”[MeSH Terms] OR (“positron”[All Fields] AND “emission”[All Fields] AND “tomography”[All Fields] AND “computed”[All Fields] AND “tomography”[All Fields]) OR “positron emission tomography computed tomography”[All Fields] OR (“pet”[All Fields] AND “ct”[All Fields]) OR “pet ct”[All Fields])))) AND ((((“prostatic neoplasms” [Mesh] OR (“prostate”[MeSH Terms] OR “prostate”[All Fields])) OR (“prostatic neoplasms”[MeSH Terms] OR (“prostatic”[All Fields] AND “neoplasms”[All Fields]) OR “prostatic neoplasms”[All Fields] OR (“prostate”[All Fields] AND “cancer”[All Fields]) OR “prostate cancer”[All Fields])) OR ((“prostate”[MeSH Terms] OR “prostate”[All Fields]) AND (“neoplasms”[MeSH Terms] OR “neoplasms”[All Fields] OR “malignancy”[All Fields])))) AND (PSMA[All Fields] OR ((“prostate”[MeSH Terms] OR “prostate”[All Fields] OR “prostatic”[All Fields]) AND specific[All Fields] AND (“membranes”[MeSH Terms] OR “membranes”[All Fields] OR “membrane”[All Fields]) AND (“antigens”[MeSH Terms] OR “antigens”[All Fields] OR “antigen”[All Fields]))).

We used A MeaSurement Tool to Assess systematic Reviews (AMSTAR2) [17] to appraisal the remained systematic reviews [18–20, 22–25]. The original AMSTAR had been designed as a practical critical appraisal tool for use by health professionals and policymakers to carry out rapid and reproducible assessments of the quality of conduct of systematic reviews especially of randomized-controlled trials of interventions. Nuclear medicine studies, as other diagnostic studies, almost never use this kind of model due to many factors, including ethical questions mainly about the use of ionizing radiation in health patients or without disease indication.

The spread use of non-randomized studies obligated the inclusion of an assessment of the risk of bias inherent on them in AMSTAR tool. It is a key issue given the diversity of designs that such studies may use and the biases that may affect them. In this way, AMSTAR2 proposes to align the definition of research questions with the PICO (Population, Intervention, Comparator, Outcome) framework, seek justification for the review authors’ selection of different study designs (randomized and non-randomized) for inclusion in systematic reviews, seek more details on reasons for exclusion of studies from the review, determine whether the review authors had made a sufficiently detailed assessment of risk of bias for the included studies, determine whether risk of bias with included studies was considered adequately during statistical pooling of results (if this was performed), and determine whether risk of bias with included studies was considered adequately when interpreting and discussing the review findings. Among these issues,some are considered “critical” and a weakness in one of those lower the confidence of a study’s result to a “low” level.

Results

As shown in Fig. 3, from the 1062 articles found, just those categorized as systematic reviews by the databases used were selected for screening. We excluded trials, editorials, letters, comments, congress, case reports, books and documents, electronic supplementary materials, only abstracts, preclinical studies, and other Cochrane reviews and protocols and duplicates studies. We considered only studies in English and Latin languages. Then, 65 articles were eligible for full-text lecture. From those, authors LP and ET excluded narrative reviews, clinical trial, no PSMA study, no prostate study, one paper in German, and another one in Chinese. From the remaining 16 studies, read integrally, one was a case series and was excluded [21]. One was a translation in Spanish [22] of an original in English and was excluded. The original study [23] mixed results from [^{18}F]PSMA and [^{68}Ga]PSMA and was also excluded. One was a search about the nature of clinical trials using PET/CT on prostate cancer [24] and was excluded. Most of the remained studies demonstrated the complexity of the disease management and of the diagnostic area exposed before in the difficulty to choose a specific outcome and then a comparator. Some of them consider the different radiopharmaceuticals in use but used less than ten references for [^{68}Ga]PSMA PET/CT and were excluded [25–29].

From the seven systematic reviews selected, four did not present meta-analyses [22–25]. For these, we applied AMSTAR 2, but they showed more than three Critical flaws and then were excluded for deep analysis. The remained three SR/MA considered primary staging and restaging after BCR. Each one included approximately 15 studies. Most of these were retrospective studies. The two oldest studies [19, 20] applied the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) statement [30]. Han et al. [18] used Grading of Recommendations Assessment, Development and Evaluation (GRADE) [31] to assess quality of evidence (Table 1). The studies differed on the chosen outcome. Perera et al. [19] and von Eyben et al. [20] considered as outcome the detectability of the lesion and (predictors of) positivity of PET/CT. Perera et al. [19] considered also sensitivity and specificity of [^{68}Ga]PSMA imaging, and Han et al. [18] considered the change of management as outcome (Table 2).

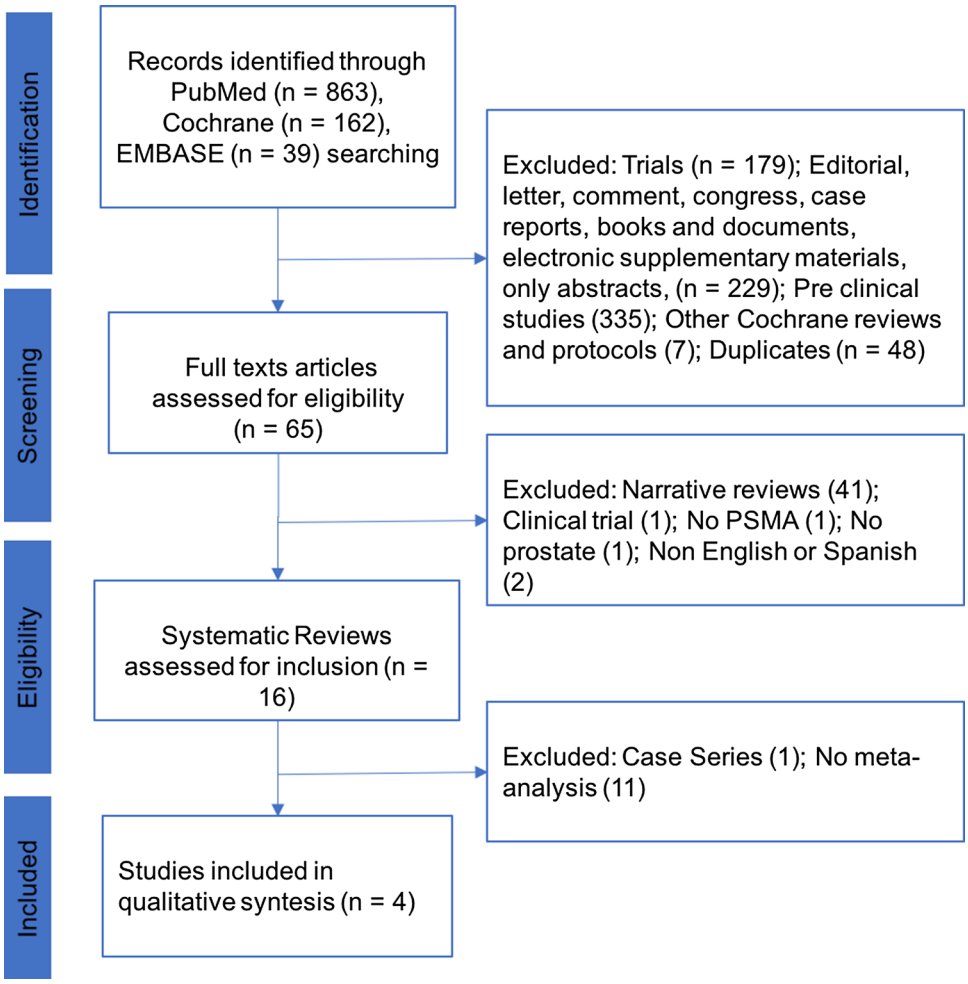

Fig. 3 Flowchart representing the search algorithm used. Mesh and no mesh terms for positron emission tomography, prostatic neoplasms, and prostatic-specific membrane antigen

Table 1 Characteristics of selected articles: number of studies used, if retrospectives or prospectives, primary staging or BCR, outcomes, and method used to assess quality

Study	# Included articles (retrospective/prospective)	Primary staging/BCR	Outcome	Quality method for individual studies
VonEyben [20]	15 (12/3)	8/9	Detectability of lesions and positivity of PET/CT Sensitivity and specificity of 68 Ga-PSMA imaging	QUADAS 2
Perera [19]	16 (15/1)	7/10	Positivity of PET/CT Sensitivity and specificity of ^{68}Ga-PSMA imaging	QUADAS 2
Han [18]	15 (10/5)	4/14	Change of management	GRADE

AMSTAR-2

As required, PICO proposed question was formulated before beginning the reviews. This is an important point, once questions formulated after the beginning of the study are more susceptible to bias than those formulated before. The selected reviews considered almost the same patient (with diagnosed prostate cancer) and Intervention or Index Test ([^{68}Ga]PSMA PET/CT), as described in our inclusion criteria. Thus, amid the selected meta-analysis, there were different Outcome and Comparators in their main analyses. Detection of lesions/positivity and accuracy/sensitivity/specificity was outcomes considered by [19] and [20]. Han et al. [18] considered just the change in management as a well-defined outcome. The detection of lesions/positivity of [^{68}Ga]PSMA PET/CT was compared to the SUV max and PSA values at the moment of the index test. Accuracy/sensitivity/specificity was compared to histopathology after biopsy or surgery by [20], while [19] just the histopathology after surgery once the biopsy made

Table 2 AMSTAR2 assessment

	VonEyben [20]	Perera [19]	Han [18]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? #	Partial yes	Partial yes	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy? #	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions? #	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Partial yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? #	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? #	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Yes	Yes
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? #	No	Yes	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? #	No	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding that they received for conducting the review?	Yes	Yes	Yes
Critical weakness	3	1	2
Non-critical weakness	3	1	0
Quality of evidence of systematic review	Critically low	Low	Critically low

Questions 2, 4, 7, 9, 11, 13, 15 are "critical"

for restaging usually does not consider negative lymph nodes. Finally, Han et al. [18] considered as comparators the other conventional imaging modalities suggested by international guidelines for prostate cancer treatment and follow-up. The meta-analysis authors stated that followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [32]. The search flowcharts were presented.

The best practice requires two review authors, to determine eligibility of studies for inclusion in systematic reviews and to extract datawhich will be analyzed. Considering nuclear medicine practice, data extraction is a very sensitive and difficult part, because this step requires measures of treatment or intervention effects extraction, that have been adjusted for potential confounding. Perera et al. [19] did not evidence clearly in the methodology if the data extraction was made by more than one person (but, in the authors´ contribution section, this review mentions four authors as responsible for acquisition data). The summary on how the studies were graded regarding the HTA is presented in Table 2, which corresponds to the AMSTAR2 check list.

Questions 2, 4, 7, 9, 11, 13, 15 in Table 2 are considered "critical" points for a systematic review. In AMSTAR2 framework, it is possible to have a weakness on a non-critical question and still obtain a "high" confidence classification. More than one weakness on a non-critical question results in a "moderate" classification. However, just one weakness in a critical question lowers the confidentiality to "low". More than one critical flaw is sufficient to classify the systematic review as "critically low" evidence level.

All assessed SR/MA contain an explicit statement that the review methods were established prior to the conduct of the review and justified any significant deviations from the protocol (question 2 on Table 2), and two of them adequately included their protocol in the PROSPERO register platform [33, 34]. This and a clear plan for investigating causes of heterogeneity are necessary conditions to assign a good quality to this item according to the AMSTAR2 scores. All of them

used a comprehensive literature search strategy. In this way, these three studies were transparent and were easily been reproducible. All the three searches were conducted at least in two databases, provided keywords and search strategies, as well as justified criteria restrictions. Importantly, every effort towards search strategies completeness was made, e.g., they documented searches into the reference lists of included studies, clinical trials, and registries. As usual, however, a list of all potentially relevant studies that were read in full text but excluded from the review was not provided. AMSTAR-2 states that there is a risk that they remain invisible and the impact of their exclusion from the review would be unknown. This is a methodological issue on reporting an SR/MA. The full text of most Cochrane systematic reviews includes an annotated list of excluded studies. Because of its big impact on quality if not documented, AMSTAR2 consider it as a critical domain.

The applied exclusion criteria were clearly presented in all meta-analysis papers. von Eyben et al. [20] excluded studies which would have increased pooled detection rates like those that only reported patients with a positive [^{68}Ga] PSMA PET/CT and studies that only undertook [^{68}Ga] PSMA PET/CT for patients with a negative [^{18}F]Choline PET/CT. Studies with staging and restaging data combined were excluded as well as studies with $N < 20$ patients. These important exclusion criteria were adopted to reduce possible selection, publication bias, and imprecision. Perera et al. [19] excluded studies when [^{68}Ga]PSMA PET was used in assessing primary (prostatic) disease only or a specific visceral metastatic deposit (e.g., pulmonary or cerebral metastases). Studies using different radiolabels bounded to PSMA other than ^{68}Ga were also excluded. Considering the risk of bias, one exclusion criterion was linked to patient flow and timing. Particularly the timing when the biopsy was planned was considered sensitive to influence imaging interpretation, such as if the biopsy occurred before or after the [^{68}Ga] PSMA PET/CT, because, when only suspicious lesions were targeted to biopsy, false-negative data may not be accurate.

However, no limitation on the number of patients was set, but effect of the sample size was adjusted in the data analysis performed.

As Han et al. [18] considered a different outcome, the exclusion criteria were simpler. Like Perera et al. [19], papers using [^{18}F]PSMA were excluded, as the molecule biodistribution can be altered when tracer is changed. A minimal number of patients were set ($N > 10$) as an inclusion criterion and only one report was included when study populations overlapped among the published studies.

The [^{68}Ga]PSMA PET/CT is a complex procedure involving the radiopharmaceutical manipulation and labeling, up to the diagnostic performed by one experienced physician or a team. Therefore, each component is susceptible to alter the test sensitivity/specificity or detectability study, which could consequently have an impact in the clinical procedure. Then, a good description was considered regarding:

1. the study design (retrospective/prospective; staging or restaging; multi-center or not; consecutive enrollment or not),
2. the study acquisition (uptake time; CT technique; administrated activity; acquisition and processing parameters; PET model; use of furosemide), and
3. patient characteristics (median age; median PSA; risk stratification and description of previous imaging tests and treatments).

Accordingly, two of the selected papers had insufficient information regarding the studies included in the meta-analysis, possibly due to the lack of data in original primary studies.

The results adopted in each of the selected meta-analysis regarding the methods used by the authors to evaluate the primary studies quality follow hereafter with its results by outcomes.

How SR/MA assessed primary studies?

QUADAS-2

As clear aspects of diagnostic tests were evaluated, Perera et al. [19] and von Eyben et al. [20] used QUADAS-2 approach to assess primary studies. In QUADAS-2, quality is understood as both the risk of bias (RoB) and the applicability of a study [31]. For the quality assessment, four domains for appraisal of RoB are considered (Patient selection, Index test—[^{68}Ga]PSMA PET/CT, Reference standard—SUV_{max}, histopathology/Biopsy, and Patient flow).

Under these four aspects, the study quality is classified as “high”, “low”, and “unclear”. Applicability concerns are scrutinized under each domain less patient flow as preconized. Perera et al. [19] have made both analyses but opted using just “high” and “low” classes for individual studies presented as a summary. The used classification criteria were clearly explained. The patient selection was reported with a high risk of bias for 55% of studies, but the clinical applicability for the study question was of 39%. An equal level of uncertainty was reported for the reference standard used as control, with the correspondent concerns on RoB and on the applicability to the review question in 39% and 55% of studies, respectively. Finally, according to the authors, patient’s flow and biopsy-imaging time schedules also presented high risk of bias in 72% of the primary studies. This item describes patients who received no index test or reference standard as well as describes the interval or any interventions between index tests and the reference standard.

von Eyben et al. [20] used all tree class levels, reported as aggregated summary result, and no explicit criteria classification was presented. High risk of bias for the patient selection of ~ 50% was estimated. High concerns about applicability of the selected patients to the review question corresponded to ~ 40%. Moreover, for ~ 30% of the studies, the risk of bias domain was unclear, and for ~ 40%, there were concerns about its applicability to the reviewed question. For the reference standard domain, authors considered a high risk of bias of ~ 30% of the studies (more ~ 10% classified as unclear) and ~ 50% of high concerns about applicability, in accordance with Perera et al. [19]. The patient flow showed ~ 90% of high or unclear RoB.

In both analyses, the index test appeared with low risk of bias and in accordance with the study question. Mainly because primary studies showed good description according the authors. However, large variation in parameters like uptake time (45–85 min [20] and 45–180 min [19]), CT technique (low dose, contrast-enhanced or non-enhanced), or administered activity (showed in von Eyben's study only) was observed. Therefore, the large heterogeneity on results could be attributed to these variations. Nowadays, there are guidelines available to uniform acquisition and processing-parameters [15]. But even so some heterogeneity is expected.

GRADE

This method was used by Han et al. [18]. In this approach to grade the global quality of evidence (not only the RoB), randomized-controlled trials start as high-quality evidence in a ranking of four levels (high, moderate, low, and very low). As frequently observed in Nuclear Medicine, observational studies are graded as low-quality evidence. However, Han et al. [18] graded the quality of studies as high from the beginning, as hypothetically, the change in the management of patients who did not undergo [^{68}Ga]PSMA PET/CT would be null. According to the authors, this would be indicated by GRADE guidelines 4 [31]. After this, five factors may lead to rating down the quality of evidence (Risk of Bias, Inconsistency, Indirectness, Imprecision, and Publication Bias) and four factors may lead to rating up (Large effect, Dose–response for interventions, All plausible confounding, and Suggestion of a spurious effect when results show no effect). GRADE's approach considers each outcome and grading could be different amid the various outcomes of the same study.

All studies were rated down in RoB domain by Han et al. [18] mainly because to perform blind studies considering management decisions with and without [^{68}Ga]PSMA PET/CT would be virtually impossible. One study was rated down due to potential industry influence, which demonstrates a critical concern about funding of studies. The indirectness domain considered lower grades for studies that reported "intended" management changes but not actually "implemented". The effect magnitude (50%) upgraded all except four studies. The study design, the imprecision, the dose–response relationship, and the consideration of all plausible residual confounders, as the remaining GRADE domains were not rated up or down in the studies, but no further explanation was provided. Although the analysis of the remaining GRADE domains was proposed, no evidence profile (EP) nor summary of findings (SoF) was showed as suggested by GRADE approach [31]. A final graduation was provided considering nine studies with high quality, five moderate, and one low.

Outcomes

Detectability of lesions/and (Predictors of) Positivity of [^{68}Ga]PET/CT

Perera et al. [19] and von Eyben et al. [20] considered basically the same output with some differences in deep regarding staging and restaging. The first SR/MA performed by Perera et al. [19] covered 18 studies (1309 patients) with overall [^{68}Ga]PSMA PET positivity of 40% (19–64%, CI 95%) for primary staging and 76% (66–85%, CI 95%) for biochemical recurrence (BCR). The first value was lowered after a sensibility test to 27% (15–42%, CI 95%) when subpopulations with a sample size of less than ten were excluded. PSA and PSAdt as predictors of positivity were analyzed in subgroups and meta-regression. Results were presented in detailed Forest Plots and Scattering Plot. This study presented an extensive discussion about the interpretation of the meta-analysis effect size, high heterogeneity found (I^2), and sensitivity to RoB, especially in recurrent disease. The authors were clear about the restrains and limitation of their conclusion, but were incisive about the quality of their findings. Important information on different Tables and Funnel Plots to assess publication bias was available as supplementary data.

The second SR/MA was performed by von Eyben et al. [20] covered 15 studies (1256 patients) with overall [^{68}Ga]PSMA PET positivity of 74% for primary staging and detected sites of recurrence in 81% of the patients. Among the primary stage patients, 273 patients presented a cancer inside the prostate bed (60%), 12 patients (4%) presented malignancy in pelvic lymph nodes, and 28 patients (10%) presented multiple malignant sites in more than one body region. Restaging [^{68}Ga]PSMA patients with an early rise of PSA values presented a detection rate of 50%. Among these patients, 79 presented a site in the prostate bed (10%), 164 patients (22%) presented a site in pelvic lymph nodes, and 272 patients (36%) presented sites in more than one region. Although pooled values were assigned, no Forest plot was presented, heterogeneity and RoB were not

assessed or calculated, and no publication bias evaluation was documented.

von Eyben et al.'s [20] findings on PET positivity were similar to those published by Perera et al. [19]. Mainly, because from the 15 studies selected by von Eyben, 11 were included in Perera et al. SR/MA. Considering the number of patients, von Eyben shared the same *N* in approximately 90% of their evaluation. Therefore, on the HTA interest, these two meta-analyses should be considered complimentary to each other and not true independent evaluations.

A restaging [^{68}Ga]PSMA PET/CT positivity of 50% for an early rise in PSA (< 2 ng/mL) was stated at von Eyben et al. [20] conclusions. However, the original data or the statistics behind it were not clearly presented. The statements that support the findings are comments about the other systematic reviews [19, 29].

Sensitivity and specificity of [^{68}Ga]PSMA PET/CT

Again the same output was considered by Perera et al. [19] and von Eyben et al. [20]. In addition, the original primary studies are the same in both SR/MA. True positive, false positive, and true negative findings of [^{68}Ga]PSMA imaging were assessed in an SR/MA from von Eyben et al. [20] against histopathological results. Summarizing, 15 studies (1256 patients) [^{68}Ga]PSMA sensibility and specificity ranged from 61 to 70% and 84 to 97%, respectively. Some of the data were discussed through the receiver-operating characteristics (ROC) analyses [35], a decision method based on the relation of gain/noise (i.e., sensibility/specificity) values that help to discriminate between two categorized groups (normal/abnormal findings). The ROC model applied is suitable to non-parametric data, but is very sensitive to effect size [35]. From 15 studies included in the meta-analysis, six studied more than 48 patients, which allowed an effect size comparison between studies with > 48 or < 48 patients. The main indication for imaging was only the increased PSA level, recurrence, which was also positively correlated with the PET/CT detection rate.

Perera et al. [19] performed similar histopathologic correlation with [^{68}Ga]PSMA PET/CT positivity per patient and per lesion. However, the similar findings cannot be considered totally independent, since both meta-analysis studies share four of the five studies applied in the ROC analysis.

Change of management

A PRISMA registered SR/MA included evaluation of 15 studies (1163 patients) about the impact of [^{68}Ga]PSMA PET/CT on the management of prostate cancer patients was assessed [18]. On average, a 54% change on management (ranging from 47 to 61%, CI 95%) occurred and was attributed to the [^{68}Ga]PSMA PET/CT findings, mainly due to the correlation observed between the PET positivity rate and the change on management of prostate cancer patients. Meta-analysis was presented in forest plots considering implemented and, as supplementary data Intended changes, showing pooled proportion of management changes due to [^{68}Ga]PSMA PET/CT stratified to PSA level categories.

The management decisions before and after [^{68}Ga]PSMA were compared and a significant change was observed on decisions to prescribe surgery and radiotherapy increased from 1 to 7% and from 2 to 6%, respectively. Concurrently, the systemic treatment prescriptions decreased from 26 to 12%.

The effect variability (heterogeneity) was extensively analyzed, and since it was elevated, explanatory subgroup analysis and a meta-regression were performed. There was 79% heterogeneity estimated with all the studies. As high heterogeneity values mean that a true effect is, indeed, present, it makes sense to investigate what causes the true effect and how the effect changes within studies variability.

Han et al. [18] states that primary staging versus BCF, types of initial treatment and baseline characteristics (Serum PSA, Gleason score, D'Amico risk classification) and different practice patterns between institutionscould explain the heterogeneity, but, with all data collected, no heterogeneity subgroup evaluation was performed considering the change of management study, the heterogeneity between studies (I^2) was reported to be affected significantly by the PET positivity as a whole. However, with all data collected, no statistical evaluation on the heterogeneity was performed in subgroups. Therefore, as an estimate of the total meta-analysis variance that is not random and that could be attributed to the true studied effect Higgins et al. [36], the next subgroup evaluation would be the next required step, as detailed in the discussion section. Finally, this study presents a funnel plot and Egger's test to assess publication bias.

The statistical expertise and awareness of meta-analysis capabilities intends to assess the real information hidden inside collected data. In this sense, Han et al. [18] performed an impressive data collection and compilation, as well as correct meta-analytical data treatment. However, to report the change on the management as an effect of PET positivity (an average of 54%) is just part of the picture. The intention of the meta-analysis should be to identify if a significant event is present and what causes the effect among the evaluated studies. When a true effect is identified such as the PET positivity linked to the change of management, in the present approach; the total true variation (heterogeneity or I^2) is estimated apart from random variation. The next step is to assess how the true effect would change inside a smaller part of the same studies to assess if the variation pattern remains the same or changes. This step reflects the differences observed on the effect size. A useful tool is to repeat the statistical analysis with subgroups which is often

described as meta-analysis sensitivity test as performed by Perera et al. [19]. For instance, studies that had a smaller change on the management could be compared with studies that presented larger changes.

As Han et al. [18] reported, it seems logical to find a low PET positivity linked to low change on the management. The same is valid to an increase in the positivity which leads to a more frequent change in the medical conduct.

But the real question to be posed would be on what causes this pattern change? Primary staging or BCF? Initial selected treatment? PSA, Gleason score, D'Amico risk classification? A more practical question would be related to HTA. Would a health system provider approve a procedure, simply based on the larger rate of management change? Does it make sense to approve a procedure that points simply to another medical procedure? A change on the management could be really a reliable indicator of the imaging procedure efficiency and sensibility? Especially when many other variables such as medical training, hospital culture, patient flow, patient personal choice, and staging could also affect the change of management in a clearer way than simply a test result.

In this sense, the clinical research and meta-analysis of diagnostic tests must focus on the proof of the procedure benefit to the patient, or on the early diagnostic probability, or on the accurate restaging, and not simply on the management change.

On the change of management study, a meta-regression analysis was used on the heterogeneity exploration. No change of management correlation was observed with several categories or cut-offs. For the Gleason Score and to D' Amico risk classification, no linear correlation would be expected to the change of management. For the study design (prospective or retrospective) and for the responding entity (physician versus multidisciplinary oncology committee), it was a positive outcome for the study that no correlation was observed within the change of management outcome. Possibly that indicates that no significant bias was present due to these two cut-offs. A certain degree of management change correlation would be expected with a prePET PSA level, as Perera et al. [19] and von Eyben et al. [20] reported previously, although, in recent multi-center study [37] on clinical management intent, no significant difference was observed between groups of low PSA level (<0.2, 0.2–0.5, and >0.5 ng/mL). The same would be expected with PSA doubling time. The single variable that presented a correlation with the change of management was the PET positivity (%).

The meta-regression was used to evaluate the heterogeneity. As a linear model, it only looks to the mean of the variables. At the same time, the linear regression is susceptible to outliers' effect. These two limitations could compromise the assessment: to evaluate the heterogeneity using subgroups, allows the comparison of the subgroup heterogeneity (variance) with the whole data set, identifying which variable carries the largest variance; to choose between these two models of heterogeneity assessment requires the knowledge of its advantages and drawbacks, as well as to evaluate how well the model fits to the real information available.

Discussion

A stricter adherence to reporting guidelines, such as PRISMA, as stated by Lu and Ioannidis [38] does not say much regarding the findings of the research activity. Instead, this statement is an evidence-based minimum set of items for reporting in SR/MA. The fact that the assessed studies have adopted it indicates a genuine commitment of authors with quality. The same could be said about the use of methods for quality assessment as QUADAS-2 and GRADE adopted by the authors of the three meta-analyses. However, all of these methodologies were developed with the intention of put in evidence critical aspects of a well-conducted SR/MA in a clear and transparent way. Shea et al. [17] state that the quality of reporting of a systematic review may more accurately reflect authors' ability to write in a comprehensible manner rather than the way which they conducted their review. AMSTAR-2 evaluates the way in which reviews are planned and conducted. As a good contribution, we can remark the requirement of providing a list of excluded studies and justify the exclusions. This is considered a critical domain and, like for the non-critical question 10, possibly authors opted by omit it in publications due to space requirements. The other two critical questions with flaw at least in one meta-analysis (13 and 15) point to the necessity of discussion of the results of analysis qualitative and/or quantitative of RoB and Publication bias. Extract data and performed quantitative analysis must result in an interpretation about how it interferes in the results of the SR/MA. Many flaws in non-critical questions, like 12 and 14, indicate the same. This points to the necessity of the existence of a synergetic multidisciplinary team to perform these reviews.

Statistical requirements of SR/MA

The clinical information about the use of [^{68}Ga]PSMA PET/CT has been mostly retrospective and susceptible to elevated RoB. The RoB assessment is easily performed, but its effects are quite difficult to correct in the results. To achieve powered evidence, the recommendations point to larger studies and to low-bias meta-analysis [6].

Under EANM and SNMMI procedure guidelines [15], some uses are highlighted as appropriated to be performed with [^{68}Ga]PSMA PET/CT as research studies. Medicine agencies and Health system providers would be mostly

interested to gather evidence-based information about the following main uses:

- Localization of tumor tissue in recurrent prostate cancer.
- Primary staging in high-risk disease before surgical or radiation therapy.
- Other emerging clinical applications could be assigned:
- Staging before and during PSMA-directed radiotherapy (mainly in metastatic castration-resistant prostate cancer).
- Previous negative biopsy patients with high suspicion of prostate cancer.
- Systemic treatment in metastatic prostate cancer.

In this sense, one single systematic review organized to answer one very specific question could disregard many other possibilities of [^{68}Ga]PSMA PET/CT use.

A multi-center study could be designed to gather information to all simultaneous investigation and uses, using health technology, electronic medical records (ERM), and statistical tools [39, 40].

One of the first examples of the multi-center prospective study was organized in Australia [37]. The most remarkable findings were related to a significant decrease in the number of patients with disease recurrence with site unknown and the significant increase of presumed oligometastatic and polymetastatic disease. An increase of detection of additional local disease previously unknownwas also reported. Several advantages are observed within this study design. Continuous and systematic data collection less prone to biases is the most evident advantages. More interesting possibilities are linked to future data assessment to smaller disease subgroups that will become more robust with time, such as previous negative biopsy patients or groups assign to go to surgical or radiotherapy procedures.

Considering these aspects, the research about [^{68}Ga]PSMA PET/CT could largely profit if future studies met some requirements to improve the statistical evaluation, such as:

- increase the observation number of patients and of any particular cohort (staging and restaging, PSA levels, PSAdt, etc.);
- systematically register positive and negative findings (to work to improve the personal awareness about bias on data registers);
- perform systematic re assessments under the same study design over a time period (1, 2, 5 years);
- consolidate clinical data within a multiple center study or within a country health system database;
- include in the research group a team member with biostatistical background in charge of the data consolidation and evaluation.

HTA on [^{68}Ga]PSMA PET/CT

To perform a complete HTA, beyond answer the specific PICO question, other new technologies available to the same application must be evaluated. In nuclear medicine, PET/CT imaging can be performed with the other technologies (radiopharmaceuticals) for the same patient. At the moment, different radiopharmaceuticals for prostate cancer imaging [11, 12, 41] are available. Presently, some most prevalent options are ^{18}F-fluorodeoxyglucose ([^{18}F]FDG), [^{11}C]Acetate, [^{11}C] or [^{18}F]Choline, anti-1-amino-3- ^{18}F-fluorocyclobutane-1-carboxylic acid ([^{18}F]FACBC), gastrin-releasing peptide receptor ([^{68}Ga]RM2), and radio-labeled ligand targeted to prostate-specific membrane antigen (PSMA). Each of them has specific aspects to be considered, like normal biodistribution. The change in the tracer, such as in case of ^{68}Ga and ^{18}F in the case of PSMA molecule, can provide a changed image [13, 42].

In prostate cancer imaging, HTA must evaluate the whole technological context too. The requirements will be different to maintain robustness, confidentiality, volume, and data nature.

Meta-analysis is a powerful tool to deal with so many variables affecting clinical outputs. Systematic reviews without meta-analysis can be done, but, to be considered as a good evidence, authors must adopt some quality statement. Even without a meta-analysis, RoB exists and plays a central role in systematic reviews of observational studies. To appraise is fundamental to reach a good level of confidence in the results.

As known, imaging diagnostic is a hard area to be assessed with many treatments options [3]. Among its challenges, one particularly important is the [^{68}Ga]PSMA PET/CT evaluation, in the context of its effect on the patient pathway of care under staging or restaging, at different temporal moments and scenarios. As the final medical conduct, the test decision depends not only on the imaging but also on the PSA scenario and clinical evaluation. Han et al. [18] showed that the change of management is linked to positivity of [^{68}Ga]PSMA PET/CT but not as a straight forward variable.

Since August 30th 2018, two more studies were published [43, 44]. Kim et al. [44] present good data treatment to objective data. The subjective evaluation estimates low risk of bias and applicability concerns to almost all included studies. A total of six studies were evaluated, including one new study [45], and one study on ^{64}Cu-PSMA [46] that were not evaluated in the previous meta-analysis.

Hope et al. [43] present a larger data collection with several studies not included in previous meta-analysis, considering two indexes tests (PET/CT and PET/MRI), staging, and BCR. For staging, registered in PROSPERO platform, five studies were considered and authors could assess accuracy confirming von Eyben's paper with narrower confidence

interval. However, 2616 patients in 41 papers assessed only 15 studies and 256 patients with BCR have data from pathological correlation. Due to the difficulties on the histological verification of the technique accuracy, the HSROC curve used the same studies presented by Perera et al. [19] and von Eyben et al. [20]. This study uses the positive predictive value and not the calculated sensitivity and specificity for BCR. The approach acknowledges and could correct part of the routine practice positive bias on which only avid PSMA lesions are biopsied, although limits the accuracy assessment.

Those studies present two different technologies: ^{64}Cu-PSMA and PET/MRI. While ^{64}Cu and ^{68}Ga have different physical properties, which can result in different biodistributions and image quality, PET/CT and PET/MRI consider two approaches to correct attenuation. Therefore, both should be clinically validated before being considered equivalent.

Future systematic reviews need to assess the accuracy following a validated statement as PRISMA and QUADAS-2, and analyze and discuss properly the origins of RoB, heterogeneity and publication bias, and its impact on the results. However, it is also important to conduct primary long-term studies, following all the patient's health pathway to be able to assess the real value associated with the [^{68}Ga]PSMA PET/CT on prostate cancer.

Accuracy studies are probably the only part of HTA for diagnostic tests that could be conducted in a joint work—task way. However, the final decision should be made considering local or regional economical evaluations, like cost-effectiveness. However, these studies could be done once accuracy is already assessed. And accuracy in clinical context, in turn, should be assessed after the market authorization. Although this is the common pathway followed to decide for the medicament reimbursements, it seems not to be ideal for nuclear medicine procedures using new radiopharmaceuticals. One possibility to optimize efforts and time could be to explore Early Dialogues [47] and/or Coverage with Evidence Development (CED) tools [48, 49].

Conclusions

This paper intends to create awareness about the several requirements on [^{68}Ga]PSMA PET/CT studies to provide evidence-based information to support HTA decisions. The aim was to assess [^{68}Ga]PSMA PET/CT secondary studies to find improvement opportunities on the subject to propose a vision that could profit the most from systematic and clinical research efforts.

We acknowledge the efforts performed from the early stages of the individual clinical study up to the giant information gathering and data treatment required in SR/MA. We also believe that the PSMA has many promising applications to be evaluated that, on time, will be proven as beneficial to prostate cancer patients.

However, many more studies must be performed on [^{68}Ga]PSMA PET/CT accuracy. The present data base must be enlarged by collaborative long-term studies, which should be multi and interdisciplinary. This is interesting to all the clinical community, patients, and health care providers. The authorization for commercialization of new radiopharmaceuticals or imaging equipments alone does not support the continuity and increase of the role of nuclear medicine. Multi-centric studies, with a strong multidisciplinary permanent team designed to conduct HTA accordingly, should be addressed and supported by institutions interested in expanding the benefits of diagnostic and therapeutic possibilities of nuclear medicine.

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Author contributions LP was responsible for conception, search and data extraction, analysis, writing, and revision. LRM was responsible for statistical analysis evaluation, writing, and revision. JJC and SF were responsible for clinical discussion and revision. ET was responsible for study selection and revision. AN was responsible for HTA discussion and revision.

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