

# Consensus on molecular imaging and theranostics in prostate cancer

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Rapid developments in imaging and treatment with radiopharmaceuticals targeting prostate cancer pose issues for the development of guidelines for their appropriate use. To tackle this problem, international experts representing medical oncologists, urologists, radiation oncologists, radiologists, and nuclear medicine specialists convened at the European Association of Nuclear Medicine Focus 1 meeting to deliver a balanced perspective on available data and clinical experience of imaging in prostate cancer, which had been supported by a systematic review of the literature and a modified Delphi process. Relevant conclusions included the following: diphosphonate bone scanning and contrast-enhanced CT are mentioned but rarely recommended for most patients in clinical guidelines; MRI (whole-body or multiparametric) and prostate cancer-targeted PET are frequently suggested, but the specific contexts in which these methods affect practice are not established; sodium fluoride-18 for PET-CT bone scanning is not widely advocated, whereas gallium-68 or fluorine-18 prostate-specific membrane antigen gain acceptance; and, palliative treatment with bone targeting radiopharmaceuticals (rhenium-186, samarium-153, or strontium-89) have largely been replaced by radium-223 on the basis of the survival benefit that was reported in prospective trials, and by other systemic therapies with proven survival benefits. Although the advances in MRI and PET-CT have improved the accuracy of imaging, the effects of these new methods on clinical outcomes remains to be established. Improved communication between imagers and clinicians and more multidisciplinary input in clinical trial design are essential to encourage imaging insights into clinical decision making.

## Introduction

Worldwide, more than 1 000 000 men are diagnosed with prostate cancer and over 300 000 men die from it annually,<sup>1,2</sup> with an increasing incidence as a result of greater life expectancy.<sup>3–5</sup> Developments in diagnosis and treatment of prostate cancer are evolving very rapidly, and the 5-year relative survival for patients has increased from 73·4% (95% CI 72·9–73·9) in 1999–2001 to 81·7%

(81·3–82·1) in 2005–07. With several clinical trials showing improved overall survival with new drugs, it is likely to further improve in the coming years.<sup>4,6</sup>

The costs of prostate cancer management are also increasing, with an overall cost in the EU of €8·43 billion for 2009.<sup>7</sup> High costs underscore the need for improved communication and cooperation among the medical specialties involved in the diagnosis and treatment of patients with prostate cancer to generate pertinent data in clinical trials to facilitate the rational integration of imaging into clinical decision making.

Several imaging methods for the evaluation of prostate cancer have been suggested, and these include methods that have been available for decades (eg, CT, bone scintigraphy, and transrectal ultrasound), as well as those that were introduced more recently (eg, whole-body MRI [WB-MRI], multiparametric MRI, and PET). However, there has been little consensus about the usefulness of these approaches.<sup>8–11</sup>

Promotion of the use of the most appropriate diagnostic and therapeutic interventions in clinical practice, guidelines, and consensus statements, are of paramount importance for the medical community, although they cannot replace scientific evidence. The availability of an increasing number of therapeutic and diagnostic options requires more careful choices. Evidence-based data (eg, meta-analyses) are often unable to inform the appropriate use of available medical options, and most guidelines that are promoted by professional organisations tend to lead to bias because experts are usually selected from within the same specialty. In the area of prostate cancer, most clinical guidelines have been promoted by urological societies (including the European Association of Urology [EAU] and American Urological Association [AUA]), oncological societies (including the European Society for Medical Oncology [ESMO], Society of Urologic Oncology [SUO], American Society for Clinical Oncology, International Society of Geriatric Oncology [SIOG], and National Comprehensive Cancer Network [NCCN]), and radiation oncology societies (including the American Society for Radiation Oncology [ASTRO], and the European Society for Radiotherapy and Oncology

[ESTRO]), and attempts at producing collaborative guidelines have been made recently (eg, AUA with ASTRO and SUO,<sup>12</sup> and EAU with ESTRO and SIOG<sup>13,14</sup>). The Advanced Prostate Cancer Consensus Conference is the sole attempt to obtain consensus globally on areas of diagnostic and treatment uncertainty, including imaging.<sup>11</sup> Representing nuclear medicine specialists who have led advances in novel molecular imaging techniques for prostate cancer, the European Association of Nuclear Medicine (EANM) decided to promote a project named Focus 1 to develop consensus statements in prostate cancer with a well-balanced and structured methodology.

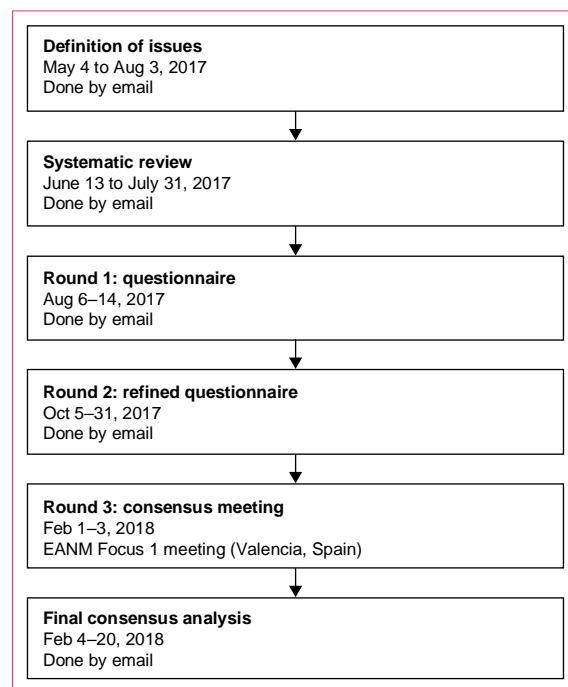


Figure: Details of all stages of the modified Delphi process

For this purpose, a multidisciplinary panel of international experts was established with representation from all involved specialties that included a balanced number of oncologists, urologists, radiation oncologists, radiologists, and nuclear medicine specialists, to achieve a less biased consensus than those conducted with more restrictive representation of specialties; patient advocates were also involved.

## Data collection

### Panellist selection

Panellists were selected on the basis of their expertise and publication record in the diagnosis or treatment of prostate cancer as well as on their involvement in the development of guidelines. We sought representation of all core clinical disciplines listed previously, and panellists were actively involved in all



stages of a modified Delphi consensus process (figure). Preference was given to candidates already involved in similar guideline projects. Availability for the modified Delphi consensus process and the Focus 1 meeting (Feb 1–3, 2018, in Valencia, Spain) helped determine the final selection of experts. Overall, the panellist selection process assured broad representation from the respective disciplines for prostate cancer.

### Search strategy and selection criteria

We first identified the clinical needs of patients and the clinical team in conjunction with areas in which the use of imaging to inform disease status and radiopharmaceuticals for therapy is known to be useful. We did a comprehensive literature search on PubMed from Jan 1, 2007, to May 31, 2017, using Mesh vocabulary keywords and free-text words for studies published in English (appendix p 2). We included studies assessing the diagnostic accuracy or the detection rate of the eight imaging methods (bone scintigraphy,<sup>15</sup> CT,<sup>16</sup> fluoride PET-CT,<sup>17</sup> choline PET-CT,<sup>15,18–23</sup> prostate specific membrane antigen [PSMA] PET-CT,<sup>24</sup> fluciclovine PET-CT,<sup>25</sup> whole-body MRI,<sup>16,26,27</sup> and multi-parametric MRI<sup>28</sup>) for staging of prostate cancer at the first diagnosis, detection of the site of recurrence at biochemical relapse, and detection of the sites and the spread of metastases at metastatic castration-resistant prostate cancer. We included the efficacy of radium-223, PSMA therapeutic radiopharmaceuticals, or other radiopharmaceuticals on overall survival or progression-free survival in patients with advanced prostate cancer (advanced castration-resistant prostate cancer). To avoid repetition of information and of primary studies, only the best systematic reviews were considered. The criteria for selection of the best and most useful reviews were: correlation between the inclusion criteria of the review and our objectives, the methodological quality of the review, use of up-to-date literature, the overall number of included studies, and the availability of meta-analysis. For therapy of advanced prostate cancer with radiopharmaceuticals, when no systematic reviews were found (namely for radium-223), we searched for primary studies,<sup>29–31</sup> which largely consisted of randomised controlled trials, although if none were found, we enlarged our search to include controlled, non-randomised studies and uncontrolled case series. We assessed the methodological quality of the included studies and produced evidence tables and summary documents, which were made available to the panellists.

### Questionnaire

With the results of the literature review (appendix) used as a basis to tackle the most pertinent questions relating to prostate cancer imaging, a questionnaire was proposed and agreed upon among the panellists. A modified Delphi process was then used to gain a structured consensus on each of these identified and researched topics.<sup>32</sup> Anonymised summaries of the first two rounds of the modified Delphi process served as the basis for live presentations and further discussions during the EANM Focus 1 meeting. For questions that did not achieve consensus during Delphi rounds 1 and 2, the panellists were asked to vote again at the meeting after presentation of the data from these rounds and moderated discussion (round 3). We adopted a 70% cutoff point to determine consensus. An agreement between 60% and 80% is considered substantial according to the classification of Landis and Koch,<sup>33</sup> and a threshold of 70% is consistent with other consensus procedures.<sup>34–38</sup>

For all questions, unless stated otherwise, we assumed that all treatments and diagnostic procedures mentioned were readily available and affordable, and that there were no treatment or imaging contraindications. All questions referred to non-frail patients and patients with prostate adenocarcinoma, unless stated otherwise. We note that separating frail and non-frail patients is mandatory for guidelines for patient management and particularly therapies used in treatment, but our report mostly concerns imaging for diagnosis and is, thus, applicable to both frail and non-frail patients. During preparation of the questionnaire, panellists were asked about the separation of subgroups of patients on the basis of various clinical categories (eg, castration-naïve or castration-resistant prostate cancer and intermediate-risk or high-risk). Although separation of castration-naïve prostate cancer from castration-resistant prostate cancer was requested, separation of patients according to life expectancy was not. The questionnaire was sent to a total of 25 panellists. If a panellist did not answer a question, it was either because they abstained, did not feel qualified to answer, or did not provide a response. These panellists did, however, answer other questions.

### Findings

Four clinical topics were identified from the systematic review that informed the subsequent modified Delphi process. These were imaging for staging of prostate cancer, imaging at biochemical recurrence of prostate cancer, imaging of advanced prostate cancer, and therapy of metastatic castration-resistant prostate cancer with radiopharmaceuticals.

Findings that were asked in the questionnaire can be found in the table.

### Imaging for staging of prostate cancer

Consensus on which patients with prostate cancer should have imaging for staging was consistent with the EAU- ESTRO-SIOG guidelines that recommend no additional imaging for staging purposes for low-risk, localised prostate cancer.<sup>13,14</sup> The panellists considered bone scintigraphy necessary in a minority of selected patients at staging based on risk and symptoms, although two panellists considered it necessary only if other methods were not available, whereas one panellist considered it necessary for the majority of patients. This consensus is similar to clinical guidelines<sup>13,14</sup> in which bone scintigraphy is recommended in the presence of high-risk features and symptoms (eg, prostate-specific antigen [PSA]). The panellists also preferred the use of CT at staging only in a minority of patients selected on the basis of risk and symptoms.

Overall, little evidence exists that sodium fluoride (NaF) PET-CT scans change patient management, because the overall prevalence of metastases from prostate cancer is low and bone scans detect at least one metastasis in patients in whom several metastases might be detected by NaF scans; a solitary metastasis is detected by NaF PET-CT in only a few patients.<sup>39</sup>

Panellists did not recommend routine fluoride PET at staging, and only two panellists felt it could be recommended in a minority of patients, if available, to replace bone scintigraphy. This outcome is in line with published results on SPECT-CT,<sup>40</sup> which suggest that the sensitivity of NaF PET-CT and SPECT-CT were not statistically superior to bone scintigraphy. Consensus was not reached on routine use of WB-MRI at staging, with just over half of panellists recommending it in a minority of patients selected on the basis of risk and symptoms, while a third do not recommend it. Low availability and scarce expertise in this technique, as well as the absence of strong validation data, probably explain why no consensus was reached on this point.

Prostate cancer-targeted PET was considered necessary in a minority of patients based on risk and symptoms, and the panellists preferred prostate-specific membrane antigen (PSMA)-targeted PET/CT imaging (19 of 21 panellists), which is in concordance with consensus statements from Advanced Prostate Cancer Consensus Conference 2017.<sup>11</sup> This preference of the panellists for PSMA PET over the other PET imaging agents is mirrored by the attention paid to PSMA PET in the literature: 286 papers on PSMA PET were published in 2017, 80

papers on choline PET, and 19 on fluciclovine PET (based on the literature search, up to May 31, 2017, conducted in preparation of the study questionnaire; appendix).

For comparative purposes, the EAU-ESTRO-SIOG prostate cancer guidelines<sup>13,14</sup> recommend including at least cross-sectional abdominopelvic imaging and a bone scan for metastatic screening or multiparametric MRI for local staging of intermediate-risk prostate cancer with predominantly Gleason pattern 4 (International Society of Urological Pathology grade  $\geq 3$ ) and for high-risk or locally-advanced prostate cancer to include at least cross-sectional abdominopelvic imaging and a bone scan for metastatic screening as well as multiparametric MRI for local staging.<sup>13,14</sup>

### Imaging at biochemical recurrence

For patients who should be studied with imaging methods at biochemical recurrence, the questionnaire distinguished between castration-naïve prostate cancer (referring to biochemical recurrence following initial curative therapies and short durations of adjuvant androgen-deprivation therapy) and castration-resistant prostate cancer (referring to relapse following primary androgen-deprivation therapy for locally advanced disease); however, in both groups the consensus was that all patients with biochemical recurrence should be studied with imaging.

Furthermore, for both castration-naïve and castration-resistant prostate cancer the panellists felt that PSA values, kinetics, and previous and ongoing therapy should all be considered for deciding whether to refer patients with biochemical recurrence to imaging. The panellists suggested a PSA concentration of less than 0.5 ng/mL at early relapse for patients with castration-naïve prostate cancer presenting with biochemical recurrence after radical prostatectomy as a cutoff for starting imaging, because they thought the EAU-ESTRO-SIOG guidelines,<sup>13,14</sup> which set the PSA concentration at 1 ng/mL, are too restrictive. No consensus was reached for a PSA cutoff concentration in patients with castration-resistant prostate cancer at biochemical recurrence, but just over half of panellists (11 of 21 in round 3) were in favour of not using a cutoff.

If other methods are not available, bone scintigraphy was considered useful at biochemical recurrence in a minority of patients; conversely no consensus was reached on the usefulness of CT as the panellists remained fairly evenly distributed in round 3 in their responses: seven of 20 panellists

	Response	Consensus
Which patients should be studied with imaging methods at presentation?	Only intermediate and high-risk patients should be studied with imaging methods at presentation	Round 1: 14 (61%) of 23; Round 2: 18 (82%) of 22
Do you consider bone scintigraphy necessary at staging?	Bone scintigraphy is necessary in a minority of selected patients at staging (based on risk and symptoms)	Round 1: 14 (61%) of 23; Round 2: 19 (86%) of 22
Do you consider CT necessary at staging?	CT is necessary in a minority of selected patients at staging (based on risk and symptoms)	Round 1: 9 (39%) of 23; Round 2: 12 (54%) of 22; Round 3: 18 (90%) of 21
Do you recommend routine fluoride PET at staging?	Routine fluoride PET is not recommended at staging	Round 1: 14 (61%) of 23; Round 2: 20 (87%) of 23
Do you consider prostate cancer-targeted PET necessary at staging?	Prostate cancer-targeted PET is necessary in a minority of patients at staging (based on risk and symptoms)	Round 1: 7 (30%) of 23; Round 2: 13 (59%) of 22; Round 3: 17 (81%) of 21
If you perform a prostate cancer-targeted PET at staging, which tracer would you prefer?	If prostate cancer-targeted PET is performed at staging, then PSMA is the preferred tracer	Round 1: 19 (86%) of 21
Which castration-naive prostate cancer should be studied with imaging methods at biochemical recurrence?	All castration-naive prostate cancer patients should be studied with imaging methods at biochemical recurrence (applying appropriate definitions for radiotherapy or surgical failure according to guidelines)	Round 1: 12 (54%) of 22; Round 2: 19 (86%) of 22
Which parameters should be considered for deciding to refer a patient with castration-naive prostate cancer biochemical recurrence to imaging?	PSA values, PSA kinetics, previous therapies, and ongoing therapies should all be considered for deciding to refer a patient with castration-naive prostate cancer biochemical recurrence to imaging	Round 1: 11 (50%) of 22; Round 2: 20 (95%) of 21
In patients with castration-naive prostate cancer presenting with biochemical recurrence after radical prostatectomy, what PSA concentration would you suggest as a cutoff for initiating imaging?	For initiating imaging in patients with castration-naive prostate cancer presenting with biochemical recurrence, PSA concentration to suggest as cutoff is PSA <0.5 ng/mL (early relapse)	Round 1: 9 (41%) of 22; Round 2: 12 (57%) of 21; Round 3: 16 (76%) of 21
Which patients with castration-resistant prostate cancer should be studied with imaging methods at biochemical recurrence?	All patients with castration-resistant prostate cancer should be studied with imaging methods at biochemical recurrence (applying appropriate definitions for radiotherapy or surgical failure according to guidelines)	Round 1: 12 (57%) of 21; Round 2: 18 (86%) of 21
Which parameters should be considered for deciding whether to refer a patient with castration-resistant prostate cancer biochemical recurrence to imaging?	PSA values, PSA kinetics, previous therapies, and ongoing therapies should all be considered for deciding whether to refer a patient with castration-resistant prostate cancer biochemical recurrence to imaging	Round 1: 11 (52%) of 21; Round 2: 20 (95%) of 21
Do you consider bone scintigraphy useful at biochemical recurrence?	Bone scintigraphy is useful at biochemical recurrence in a minority of patients (if other methods are not available)	Round 1: 8 (36%) of 22; Round 2: 15 (71%) of 21
Do you recommend performing fluoride PET at biochemical recurrence?	It is not recommended to perform fluoride PET at biochemical recurrence	Round 1: 15 (71%) of 21
Do you recommend performing WB-MRI at biochemical recurrence?	WB-MRI is not recommended at biochemical recurrence	Round 1: 7 (32%) of 22; Round 2: 9 (43%) of 21; Round 3: 15 (71%) of 21
Do you recommend performing multiparametric MRI at biochemical recurrence?	Performing multiparametric MRI at biochemical recurrence depends on clinical factors such as primary therapy method, pathologic status, and PSA kinetics	Round 1: 10 (45%) of 22; Round 2: 19 (86%) of 22
Do you recommend performing prostate cancer-targeted PET at biochemical recurrence?	Prostate cancer-targeted PET is recommended at biochemical recurrence in the majority of patients, to replace conventional imaging methods (bone scintigraphy or CT)	Round 1: 10 (48%) of 21; Round 2: 13 (65%) of 20; Round 3: 19 (91%) of 21
If you recommend performing a prostate cancer-targeted PET at biochemical recurrence, which tracer do you prefer?	PSMA is the preferred tracer if prostate cancer-targeted PET is performed at biochemical recurrence	Round 1: 20 (91%) of 22
If you use modern imaging methods at biochemical recurrence, which method do you prefer as first line?	If modern imaging methods are used at biochemical recurrence, prostate cancer-targeted PET alone is the preferred first-line method	Round 1: 10 (45%) of 22; Round 2: 11 (52%) of 21; Round 3: 17 (81%) of 21
If you perform modern imaging methods at biochemical recurrence, do you need confirmation for positive findings?	If modern imaging methods are performed at biochemical recurrence, then confirmation of positive findings is needed only in highly selected cases and with a biopsy when findings are equivocal	Round 1: 13 (59%) of 22; Round 2: 18 (86%) of 21
Which patients with advanced prostate cancer and castration-naive prostate cancer should be studied with imaging?	All patients with advanced prostate cancer and castration-naive prostate cancer should be studied with imaging	Round 1: 15 (68%) of 22; Round 2: 18 (82%) of 22

(Table continues on next page)



(Continued from previous page)	Response	Consensus
Which patients with advanced prostate cancer and castration-resistant prostate cancer should be studied with imaging?	All patients with advanced prostate cancer and castration-resistant prostate cancer should be studied with imaging	Round 1: 15 (68%) of 22; Round 2: 20 (91%) of 22
Which reason is most important for referring to imaging a patient with advanced prostate cancer?	Identifying anatomical locations of metastatic disease, evaluating the extent or volume of local or metastatic disease, evaluating complications of local or metastatic disease, and monitoring the response to therapy are the most important reasons for referring a patient with advanced prostate cancer to imaging	Round 1: 11 (50%) of 22; Round 2: 19 (86%) of 22
Do you consider bone scintigraphy necessary in patients with advanced prostate cancer?	Bone scintigraphy is considered necessary in the majority of patients with advanced prostate cancer	Round 1: 11 (50%) of 22; Round 2: 13 (59%) of 22; Round 3: 16 (76%) of 21
Do you consider CT necessary in patients with advanced prostate cancer?	CT is considered necessary in the majority of patients with advanced prostate cancer	Round 1: 12 (55%) of 22; Round 2: 15 (68%) of 22; Round 3: 18 (86%) of 21
Do you recommend performing fluoride PET in patients with advanced prostate cancer?	It is not recommended performing fluoride PET in patients with advanced prostate cancer	Round 1: 13 (62%) of 21; Round 2: 19 (91%) of 21
Do you recommend performing pelvic multiparametric MRI in patients with advanced prostate cancer?	Performing pelvic multiparametric MRI is recommended in a minority of patients with advanced prostate cancer (based on risk and symptoms)	Round 1: 11 (50%) of 22; Round 2: 15 (71%) of 21
If you perform a prostate cancer targeted PET in patients with advanced prostate cancer, which tracer do you prefer?	PSMA is the preferred tracer for prostate cancer targeted PET in patients with advanced prostate cancer	Round 1: 11 (48%) of 23; Round 2: 16 (73%) of 22
If you perform modern imaging methods in patients with advanced prostate cancer, which method do you prefer?	Prostate cancer targeted PET is the preferred imaging method for patients with advanced prostate cancer	Round 1: 11 (48%) of 23; Round 2: 16 (73%) of 22
If you do modern imaging methods in patients with advanced prostate cancer to evaluate extent of disease, which method do you prefer?	If modern imaging method in patients with advanced prostate cancer is performed to evaluate extent of disease, the preferred method is prostate cancer-targeted PET	Round 1: 11 (48%) of 23; Round 2: 14 (61%) of 23; Round 3: 16 (80%) of 20
Which patients with advanced metastatic castration-resistant prostate cancer qualify for treatment with therapeutic radiopharmaceuticals?	Qualification of patients with advanced metastatic castration-resistant prostate cancer for treatment with therapeutic radiopharmaceuticals varies as a function of available radiopharmaceuticals and respective indications.	Round 1: 18 (82%) of 22
Which patients with advanced metastatic castration-resistant prostate cancer do you refer for palliative treatment with bone targeting radiopharmaceuticals (eg, rhenium-186, samarium-153, and strontium-89)?	Almost no patients with advanced metastatic castration-resistant prostate cancer are referred for palliative treatment with bone targeting radiopharmaceuticals (such as rhenium-186, samarium-153 and strontium-89)	Round 1: 8 (42%) of 19; Round 2: 9 (50%) of 18; Round 3: 16 (89%) of 18
Which patients with advanced metastatic castration-resistant prostate cancer do you refer for treatment with PSMA therapeutic radiopharmaceuticals (given that they are PSMA PET positive)?	Metastatic patients with advanced metastatic castration-resistant prostate cancer (bone and nodal lesions) who have already been treated with or who have contraindications for all other available life-prolonging therapies with advanced metastatic castration-resistant prostate cancer (given that they are PSMA PET positive) should be considered for referral for treatment with PSMA-therapeutic radiopharmaceuticals	Round 1: 10 (59%) of 17; Round 2: 13 (77%) of 17
If you refer patients with metastatic castration-resistant prostate cancer for therapeutic radiopharmaceuticals, which treatment do you prefer?	Among the therapeutic radiopharmaceuticals available for patients with metastatic castration-resistant prostate cancer, radium-223 is preferred	Round 1: 10 (48%) of 21; Round 2: 16 (80%) of 20
In patients with metastatic castration-resistant prostate cancer would you consider therapy with PSMA radiopharmaceuticals?	Patients with metastatic castration-resistant prostate cancer should only be considered for therapy with PSMA radiopharmaceuticals within appropriate clinical trials	Round 1: 10 (53%) of 19; Round 2: 16 (84%) of 19
In patients with metastatic castration-resistant prostate cancer and candidates for radium-223 treatment, would you consider using other prostate cancer-specific therapies?	In patients with metastatic castration-resistant prostate cancer and candidates for radium-223 treatment, association of other prostate cancer specific therapies is considered only within appropriate clinical trial	Round 1: 9 (50%) of 18; Round 2: 11 (65%) of 17; Round 3: 18 (90%) of 20
In patients with metastatic castration-resistant prostate cancer and candidate for radium-223 treatment, which imaging methods are you recommending before treatment?	Bone scintigraphy is the imaging method recommended before treatment in patients with metastatic castration-resistant prostate cancer and candidate for radium-223 treatment	Round 1: 10 (48%) of 21; Round 2: 12 (60%) of 20; Round 3: 19 (91%) of 21

The number of panellists answering each question varies because panellists either abstained, did not feel qualified to answer, or did not provide a response.  
PSMA=prostate-specific membrane antigen. PSA=prostate-specific antigen. WB-MRI=whole-body MRI.

**Table: EANM consensus outcomes for imaging in prostate cancer**

recommended CT in a minority of patients (based on risk and symptoms), six did not consider it useful, five considered it useful in a minority of patients (if other methods are unavailable), and just two considered it useful in the majority of cases. Consensus on the ineffectiveness of fluoride PET or WB-MRI at biochemical recurrence was reached during round 1.

The use of multiparametric MRI of the pelvis at biochemical recurrence would be recommended depending on clinical factors such as primary therapy methods, pathological status, and PSA kinetics. Among the panellists, pelvic multiparametric MRI is, therefore, more popular than WB-MRI, but the questionnaire did not clarify the primary treatment method in which multiparametric MRI was most relevant.

The panellists (20 of 22) would recommend prostate cancer-targeted PET at biochemical recurrence to replace conventional imaging methods (bone scintigraphy or CT), and the preferred imaging method was PET-CT with a PSMA-targeting tracer. However, the availability of PSMA tracers is not uniform across cancer centres, and none have been approved by regulatory authorities so far. If the panellists were to use modern imaging methods at biochemical recurrence, 17 of 21 panellists (round 3) would choose prostate cancer-targeted PET-CT alone.

### Imaging of advanced prostate cancer

Imaging of advanced prostate cancer represents a wide spectrum of diseases from locally advanced prostate cancer to metastatic castration-resistant prostate cancer. To decide on which patients with advanced prostate cancer should be studied with imaging, panellists again agreed that all patients, both those with non-castration and those with castration-resistant prostate cancer, should be studied. This consensus is slightly different from the EAU-ESTRO-SIOG guidelines,<sup>13,14</sup> in that those guidelines recommend additional imaging methods guided by symptoms or possible subsequent treatments.<sup>24</sup> Identification of anatomical locations of metastatic disease, evaluation of the extent or volume of local or metastatic disease, evaluation of complications of local or metastatic disease, and monitoring of response to therapy, were all considered important reasons for referring a patient with advanced prostate cancer for imaging.

Bone scintigraphy and CT were considered necessary for most patients with advanced prostate cancer. These results are not exactly in line with guidelines. According to the Cancer Radiographic Assessments for Detection of Advanced Recurrence Group, bone scintigraphy and CT are recommended in

the context of their availability and cost-effectiveness, and additional tests are recommended instead (eg, plain radiography, MRI, and NaF PET), the modality of which is to be decided at the physician's discretion.<sup>41</sup> Consensus on fluoride PET-CT was reached, and the panellists (19 of 21) would not recommend it for patients with advanced prostate cancer. Consensus was not achieved on the recommendation of WB-MRI in patients with advanced prostate cancer:

12 of 21 would not recommend using it, whereas four would for a minority of patients, three in a majority of patients to replace conventional imaging methods, and two as a complementary method to conventional imaging. For pelvic multiparametric MRI, the consensus (15 of 21) was to recommend it for a minority of patients, if available, to replace conventional imaging to look for local pelvic complications, such as bladder and rectal invasion. Although prostate multiparametric MRI is becoming standard for guiding prostate biopsies in patients with suspected cancer, in the setting of advanced prostate cancer, the recommendations from the panellists focused on multiparametric MRI use for staging locally advanced disease and not for guiding prostate biopsies.

Combined pelvic MRI with WB-MRI can detect bone metastases with a higher sensitivity than bone scintigraphy with at least comparative performance to choline PET-CT. A distinct need exists, however, to standardise WB-MRI to assess its performance in advanced prostate cancer clinical trials, and probably to compare it to PSMA-targeted PET-CT, which is emerging as the preferred whole-body imaging technique.<sup>42,43</sup> With respect to prostate cancer-targeted PET in patients with advanced prostate cancer, the opinions of the panellists varied substantially. At the third round of the modified Delphi process, the majority of panellists (11 of 21) responded that they would recommend it for the majority of patients to replace conventional imaging methods, five panellists would use it for a minority of patients based on risk and symptoms, three as a complementary method to conventional imaging (bone scintigraphy or CT), one would recommend it in a minority of patients, if available, to replace conventional imaging, and one panellist would not recommend prostate cancer-targeted PET for any patients with advanced prostate cancer.

When using prostate cancer-targeted PET in patients with advanced prostate cancer, 20 of 23 panellists had reached a consensus in round 1 in which it was agreed that a PSMA-targeted drug should be the preferred tracer. For the form of imaging to recommend for the majority of men with advanced

prostate cancer, the panellists were divided in their opinions: ten of 21 recommended CT or bone scintigraphy, seven recommended prostate cancer-targeted PET, and four recommended modern imaging methods (MRI and PET). Imagers must design more appropriate trials so that referring clinicians can be provided with more comparative scientific data on relative utility.

Considering modern imaging methods (MRI and PET) in patients with advanced prostate cancer, the consensus opinion of panellists was to do prostate cancer-targeted PET for detecting metastases (16 of 22 panellists). In terms of detection, based on available data, PSMA-PET is superior, but WB-MRI could have advantages for response assessment.

With respect to the precise method preferred for identifying specific lesions or for addressing specific clinical problems, consensus was not achieved. Panellists had a wide range of opinions concerning the imaging method for the identification of bone metastases in patients with advanced prostate cancer: ten of 21 chose prostate cancer-targeted PET and six chose WB-MRI. To evaluate the extent of the disease in patients with advanced prostate cancer, 16 of 20 preferred prostate cancer-targeted PET as the imaging method.

### Therapy of metastatic castration-resistant prostate cancer with radiopharmaceuticals targeting bone

Predictably, qualification of patients with metastatic castration-resistant prostate cancer for treatment with therapeutic radiopharmaceuticals varies as a function of available radiopharmaceuticals and respective indications; approval and reimbursement issues should also be considered.

The panellists did not reach consensus regarding when to give radium-223 treatment for patients with metastatic castration-resistant prostate cancer. A clear division was apparent in round 3 between those panellists who would refer all patients with bone lesions and no visceral lesions and treated with, or unfit for, docetaxel and abiraterone or enzalutamide (11 of 20), and those who would refer patients with symptomatic bone lesions and no visceral lesions before using other life-prolonging therapy (eight of 20). According to ESMO 2015,<sup>44</sup> radium-223 is recommended for bone-predominant, symptomatic metastatic castration-resistant prostate cancer without visceral metastases; according to NCCN 2016,<sup>45</sup> radium-223 is indicated for symptomatic bone metastases (first-line use) or for bone-predominant disease (after systemic therapy) and no visceral metastases.

The panellists would recommend almost no patients for palliative treatment with bone-targeting radiopharmaceuticals (eg, rhenium-186, samarium-153, or strontium-89). These treatments are falling out of favour with the oncology community, and new systemic therapies exist that also target soft tissue disease and appear to be as effective as traditional radiopharmaceuticals.

For treatment with prostate cancer-directed PSMA therapeutic radiopharmaceuticals, the consensus (13 of 17 panellists) was that patients with metastatic disease (bone and nodal lesions) already treated with all other available life-prolonging therapies or with contraindications for them could be considered for referral for such treatment, with lutetium-177 PSMA being the only one with data in a larger number of patients. One study found <sup>68</sup>Ga-PSMA-HBED-CC PET imaging to be more accurate than morphological imaging in detecting lymph node metastases in patients with biochemical recurrence,<sup>46</sup> whereas another showed that PSMA PET was independently predictive of treatment response to salvage radiotherapy in men with rising PSA concentrations after radical prostatectomy.<sup>47</sup> A post-hoc analysis of

<sup>68</sup>Ga-PSMA-11 PET-CT mapping of prostate cancer biochemical recurrence was promising in another study, in that 52 of 270 patients had at least one PSMA-11-positive lesion not covered by the consensus clinical target volumes.<sup>48</sup> A phase 2 trial in 43 men with metastatic castration-resistant prostate cancer who progressed after conventional treatments showed high responses and low toxicity following treatment with <sup>177</sup>Lu-PSMA-617.<sup>49</sup> However, little evidence exists for the established treatments when they are used as third-line treatments.

Intermediate-term outcome for patients with recurrent high-risk prostate cancer showed PSMA-PET-guided planning of radiotherapy had well tolerated treatment toxicity and led to change of treatment in the majority of patients.<sup>50</sup> Similarly, PSMA-PET-CT-based radiotherapy in patients with biochemical recurrence after radical prostatectomy showed significant PSA response and led to deferral of long-term androgen-deprivation therapy or systemic therapy.<sup>51</sup> These results all warrant further study, and level 1 evidence to support PSMA therapy is awaited.<sup>52</sup> The panellists showed a clear preference for PSMA, not only among the nuclear medicine physicians, but also among the clinicians. Indeed, fluciclovine (fluorine-18) has been approved for detecting suspected recurrent disease, and fluciclovine and choline have a commercial licence, whereas PSMA is not approved in several countries.

The consensus (16 of 19 panellists) was that therapy



with PSMA radiopharmaceuticals should only be considered within the framework of appropriate clinical trials that might eventually lead to introduction of radiopharmaceuticals into clinical practice.<sup>53</sup>

Regarding the choice of therapeutic radiopharmaceuticals, consensus (16 of 20) was reached in support of radium-223, mainly in relation to the completed registration trial and marketing authorisation.<sup>54</sup> With respect to radium-223 treatment associated with other prostate cancer-specific therapies, consensus (18 of 20) was for the use of such combinations only within an appropriate clinical trial.

For imaging methods to evaluate radium-223 treatment, 19 of 21 panellists would recommend bone scintigraphy as the imaging method before radium-223 treatment, in line with St Gallen consensus.<sup>11</sup> Pending the results of ongoing clinical trials (eg, NCT02813226 and NCT02856100), no consensus was attained on the imaging methods to use for monitoring response to therapy, with the majority (14 of 21) of panellists again in favour of bone scintigraphy.<sup>11</sup> It was noted that bone scintigraphy is needed to determine dose.

## Discussion

### Guidelines and consensus

Development of guidelines and consensus statements is of paramount importance for the medical community to guide clinical decision making. The availability of an increasing number of diagnostic and therapeutic options for prostate cancer requires careful decision making to optimise the use of resources, while appreciating that evidence-based data, such as systematic reviews and meta-analyses, are not always sufficient to inform appropriate use of medical options.<sup>55</sup>

To address the clinical need for up-to-date imaging guidance on state-of-the-art evidence accumulation, and potential clinical utility, we established a multidisciplinary panel with representation of all involved specialties, with similar numbers of oncologists, urologists, radiation oncologists, radiologists, and nuclear medicine specialists to generate more balanced statements on imaging uses for prostate cancer care. The choice of topics was limited to clinically relevant patient grouping, and the positioning of cross-sectional imaging and therapeutic nuclear medicine procedures defined by the organisers of the EANM consensus meeting.

We recognise that rapid developments in imaging pose multiple issues when developing guidelines. New methods such as MRI and PET are often adopted into clinical practice before evidence-generating clinical

trials are done, resulting in a subsequent substantial increase in their use. With the growth in the use of medical imaging, concern that not all investigations are necessary has emerged, and it is argued that up to 40% of diagnostic imaging studies might be inappropriate.<sup>56</sup> Furthermore, intrinsic problems exist in building evidence-based literature for diagnostic imaging,<sup>57</sup> and these factors have led to disagreement in the field of prostate cancer. For example, at the 2017 Advanced Prostate Cancer Consensus Conference held in St Gallen, Switzerland, no consensus was reached on most questions related to advanced prostate cancer imaging.<sup>11</sup> However, the 2017 Advanced Prostate Cancer Consensus Conference was based on one round of questions that were answered at the conference itself. Although questions were circulated three times to improve precision, only clinicians were allowed to answer, not imaging specialists, because most questions dealt with therapy issues.

EANM Focus 1 adopted a different strategy. We did a systematic review of the literature, used this review to construct a questionnaire that was reviewed by expert panellists, and used a modified Delphi method to achieve consensus on clinically relevant imaging topics with a more balanced multidisciplinary group of panellists. We observed good agreement (>70% of consensus) on 36 of 47 questions.

### Specific areas of consensus on imaging

In all four covered clinical scenarios (staging, biochemical recurrence, advanced prostate cancer, and therapy for metastatic castration-resistant prostate cancer), consensus was reached regarding patient selection for imaging procedures (questions 1, 8, 11, 23, and 24; table); this consensus is a relevant and qualifying point because patient selection is not mentioned in most guidelines. The panellists agreed that at presentation only intermediate and high-risk patients should be studied with imaging methods. At biochemical recurrence and in presence of advanced disease all patients with prostate cancer (whether castration naive or resistant) should be studied with imaging.

With respect to specific imaging methods, bone scintigraphy was not recommended as a procedure applicable to most patients. The consensus among most panellists was that bone scintigraphy should be used in only a selected minority of patients at staging and at biochemical recurrence. Although no consensus was attained on the use of bone scintigraphy in advanced prostate cancer, 13 of 22 of the panellists did consider bone scintigraphy to still be necessary in this setting. These results differ

substantially from widely used clinical guidelines, in which bone scintigraphy is still regarded as a valuable imaging method. For example, EAU recommend that, for M staging at presentation, bone scanning should be performed in symptomatic patients, independent of PSA level, Gleason score, or clinical stage.<sup>13,14</sup> Data in the published literature that report a composite sensitivity for bone scintigraphy of 79% and specificity of 82%,<sup>15</sup> its ready availability, and its low cost, which have justified its use in the past, are clearly no longer considered relevant factors for continual use. A larger proportion of experts at this meeting probably have had either more experience of advanced imaging techniques or more exposure to information about these techniques than the general prostate cancer community, given that they are experts in the field and generally from centres of excellence.

With regards to the use of CT, 18 of 21 of the panellists considered CT necessary in the majority of patients with advanced prostate cancer. Some panellists suggested using CT in the majority of patients for staging (five of 22) and at biochemical recurrence (six of 21). CT, like bone scintigraphy, is still mentioned in most existing guidelines. For example, the 2016 NCCN guidelines for prostate cancer recurrence states that imaging should include chest x-ray, bone scan, and abdominal and pelvic CT or MRI with or without contrast.<sup>58</sup>

The panellists reached the consensus that they would not recommend fluoride PET in any clinical scenario, despite data in the published literature indicating a pooled sensitivity of 86.9% and specificity of 79.9%. It could be speculated that the small advantage in terms of diagnostic accuracy over bone scintigraphy is not considered sufficient to justify the higher costs. However, it has also been remarked that PET-CT could increase efficiency and, thereby, save costs through improved diagnosis and clinical decision making.<sup>59</sup>

With respect to WB-MRI, no consensus for any indication was achieved. A minority of panellists suggested using WB-MRI in most patients (three of 21 at presentation, six at biochemical recurrence, and eight at advanced disease), which could be related to some incomplete data in the published literature that shows low sensitivity for lymph node disease, but good sensitivity for bone metastasis detection. Additionally, problems with standardisation of methodologies and dearth of expertise were noted, and these factors have been addressed elsewhere.<sup>42,43</sup>

Consensus was reached for pelvic multiparametric MRI, which was recommended at biochemical recurrence to detect local recurrences (depending on clinical factors, such as primary therapy method,

pathological status, and PSA kinetics) and in advanced prostate cancer (in a minority of patients, based on risk and symptoms). Consensus could be related to more convincing evidence in the published literature, especially regarding the capability of identifying local recurrence, pelvic complications, and biopsy guidance.

Prostate cancer-targeted PET (ie, using choline, fluciclovine, or PSMA-targeted tracers) did not achieve consensus for any indication, but the use of PET was preferred by a majority of panellists (13 of 22 at presentation in a minority of patients based on risk and symptoms, 13 of 20 at biochemical recurrence in the majority of patients to replace bone scintigraphy or CT, ten of 21 in advanced prostate cancer in the majority of patients). This increasing acceptance of PET is probably related to the growing amount of supporting data in the published literature, although level 1 evidence is scarce and most of these data do not address the effect of PET on clinically relevant endpoints. It was noted by the panellists that the efficacy of treatment needs to translate into improved survival to avoid futile procedures or treatments that might lead to overdiagnosis and increased cost, but will not necessarily affect survival outcome.<sup>60</sup>

The increasing number of publications regarding PSMA PET is a major reason for the large agreement that PSMA drugs are increasingly preferred PET radiopharmaceuticals. This consensus might appear to conflict with the reality of PSMA PET availability and approval in most countries and might reflect the composition of the panel; they were largely from high-income countries in western Europe. However, it should be noted that the availability of a treatment option was only considered important by a small minority of panellists (three of 22, two of 22, and three of 23, in three questions). An issue for future consensus is the availability of many different forms of PSMA tracers (several ligands and isotopes). In the future, it would be advisable for nuclear medicine specialists to provide referring clinicians with precise recommendations and standard operating procedures concerning the use of these radioactive tracers.

Given that little consensus on the use of MRI and PET was observed, it was predictable that agreement was limited to the procedure of choice among modern imaging methods. In biochemical recurrence, prostate cancer-targeted PET was preferred over MRI (11 of 21 vs three of 21, with six of 21 in favour of a combination). In advanced prostate cancer, PET was preferred by seven of 21 panellists and WB-MRI by six, although eight recommended conventional imaging with bone scintigraphy and CT. These data indicate that more data are required to change



practice, although PET is preferred when early identification of recurrence site is the clinical question. Further data on the risk of false-negative results in prostate cancer not expressing PSMA or having heterogeneous PSMA expression are also needed to determine whether combinations of PET and WB-MRI can have clinical utility that can be cost effective. The consideration of patient preferences in such studies is imperative.

The clinical priorities for imaging in biochemical recurrence have been agreed by the Advanced Prostate Cancer Consensus Conference<sup>11</sup> and the EAU,<sup>13</sup> and a systematic analysis showed that multiparametric MRI is recommended for local recurrence.<sup>61</sup> However, no clear guidelines exist for multiparametric MRI in this setting, although the EAU have been clear in their recommendation of the need for multiparametric MRI.<sup>62</sup>

### Consensus on nuclear medicine therapy

No consensus was achieved on when to refer patients for treatment with radium-223. Panellists were divided between referring patients yet to be treated with other life-prolonging therapies (nine of 19) versus patients already treated with (or unfit for) docetaxel and abiraterone or enzalutamide (eight of 19). The positioning of radium-223 as a first, second, or third-line treatment is still a clinical challenge.

Treatment with rhenium-186, samarium-153, or strontium-89 was not recommended in view of an absence of level 1 evidence from randomised phase 3 trials. With regards to PSMA-targeted therapeutic radiopharmaceuticals, good consensus was reached on referring patients with metastatic disease (bone and nodal lesions) already treated with all other available life-prolonging therapies, but referral should be done within the framework of appropriate clinical trials. The need for properly designed trials (prospective, multicentre, and randomised, with clear objectives) was emphasised, so that the real value of PSMA-directed radionuclide therapies can be evaluated. Without such an approach, it will be difficult for these drugs to have major therapeutic roles.

Of note, radium-223 is indicated for patients with only bone metastases detectable, and anti-PSMA based radionuclides might have broader use based on their mechanism of action.

### General observations for clinical practice

Clinicians and imagers have different perspectives and ways of thinking, so more interaction and direct communication between them are needed. Nuclear medicine and radiology should be represented in

medical decision teams for prostate cancer, so that image interpretation can be integrated into the clinical background for making treatment decisions. The involvement of radiologists or nuclear medicine specialists should start with the indication or referral of the patient for imaging and therapy.

When they deem it necessary, the urologist and medical oncologist can refer a patient to a nuclear medicine physician or radiation oncologist for a specific purpose. Therefore, more cross-disciplinary interaction is needed among specialists in the field so that patient outcomes can be optimised. Imaging is not a histological diagnosis but can aid in disease characterisation. Similarly, progressive disease is not defined by imaging alone, but appropriate and timely feedback on imaging results that can enhance the quality of treatment.

### General observations for research

Referring clinicians need to involve radiologists and nuclear medicine specialists early in trial design, and, for their part, imagers need to adopt a proactive approach towards engagement in clinical trials. They need to develop robust imaging procedures with appropriate quality control and quality assurance and with definable endpoints that line up with the expectations and unmet needs of the clinicians. Only one acceptable approach exists for research in therapeutics: clinical trial design must adhere to accepted standards that generate high-level evidence. Clinical trials must be prospective, randomised (but not necessarily large) if an acceptable conventional management option that allows clinical balance exists, multicentred, and adequately powered. Without this approach, experimental treatments will not have a solid base, and the potential of nuclear medicine therapy will be diminished. Trials must be conducted at the right time. We cannot afford to miss the tipping point after which randomised trials will no longer be accepted or result in trials that fail due to poor accrual. An example of such an approach is the VISION trial (NCT03511664), which is currently ongoing and examining whether <sup>177</sup>Lu-PSMA-617 RLT is better than treatment without the radiopharmaceutical.

### Implications for imaging

We need to advance the current framework of grouping patients according to tumour location and move towards a more refined in-vivo characterisation of tumour biology and heterogeneity. In other words, we should move away from tumour imaging that emphasises sensitivity or specificity to more meaningful effects on clinically relevant endpoints that are associated with overall survival. Depending



on the clinical question at hand, use of the most advanced, expensive technology is not always necessary to meet clinical needs. Elimination of false-positives (or irrelevant positives) is needed and provision of thoughtful interpretation of findings in written reports suited to directing patient care, while the fact that patients receive and read their reports is recognised.

### Requirements for imaging

Imaging needs to move away from merely innovating that draws on feasibility studies and towards trials and clinical implementation. Imaging procedures must be standardised and validated, and quality control must progress beyond imaging instrumentation and radiopharmaceutical production. There is a need to spread knowledge concerning imaging impacts, and teaching efforts must continue to expand to shorten learning curves. Reporting of imaging results need to be standardised and effectively communicated. Additionally, imagers need to actively participate in clinical trial groups and guideline committees, and thereby enhance clinicians' appreciation of the benefits of the early engagement of imagers in their studies. Imaging methods and knowledge need to be rolled out from expert centres to general practice and we need to ensure that continuous dialogue between clinicians and imagers is maintained.

### Conclusion

EANM Focus 1 constitutes the efforts of a multi-disciplinary panel of international experts to produce a comprehensive series of statements on prostate cancer imaging and therapy with radiopharmaceuticals. This approach can be regarded as a useful method to build consensus on topics of relevant clinical value, in which differing views might exist. Consensus was achieved for many questions, and clear preferences were expressed for the remainder. The most relevant conclusions drawn regarding the use of imaging were that bone scintigraphy and CT have never been recommended for the majority of patients with prostate cancer, despite the fact that these methods are still largely used and advocated in most clinical guidelines. This disparity is in part a reflection of the dearth of engagement by imaging specialists in clinical guidelines development. The use of MRI (either WB-MRI or pelvic MRI) and prostate cancer-targeted PET have been frequently suggested, but there is still no clarity on usage within the imaging community. This disparity does not reflect efficacy but rather a divergence of views on appropriate use. Among PET tracers, fluoride has no clear advantage over

conventional bone scanning, but PSMA is rapidly gaining acceptance. Given the rapid progress in the field of prostate cancer imaging and the impressive amount of new literature, it would be useful to update this consensus statement in 2-3 years to see if the areas that have been identified in these consensus questions have improved.

### Contributors

SF, SM, and WJGO designed the study, did the research, and wrote the paper. GA, AB, IC, AC, NC, ME, JDB, KF, SGI, UH, KH, RJH, FL, RM, PO, JMO'S, ARP, JS, HIS, BT, RJAvm, HVP, HAV, JW, WAW, and H-JW were all members of the expert panel, designed the study, contributed to the content of the study, and reviewed the paper. IB and SGI designed the study, contributed to the content of the study, and reviewed the paper.

### Declaration of interests

SF has received research grants from Movember and Blue Earth Diagnostics, and has received speaker or advisory honoraria from General Electric (GE), Bayer, Astellas, Novartis, Janssen, Bristol-Myers Squibb, and Advanced Accelerator Applications (AAA). GA wrote articles for Visus and MedEcon Ruhr during the last 5 years. IC has received research grants from Bracco, Philips, GE, and Advanced Accelerator Applications, and has received speaker or advisory honoraria from Lilly, Endocyte, Philips, GE, Bayer, and AAA. AC received speaker honoraria from General Electric and Sirtex Medical System, acted as scientific adviser for Blue Earth Diagnostics and Advanced Accelerator Applications, and benefited from an unconditional research grant from Sanofi. JDB has received research funding or support from Movember, Prostate Cancer UK, Prostate Cancer Foundation, Stand Up to Cancer, National Institute of Health Research, UK Department of Health, Cancer Research UK, EU 7th Framework Programme, AstraZeneca, Genentech, Menarini, Pfizer Oncology, and Sanofi-Aventis. ME is a consultant for Blue Earth Diagnostics. KF held positions on advisory boards and received honoraria from Amgen, Astellas, AstraZeneca, Bayer, Clovis, Curevac, Essa, Genentech, Janssen, Merck Sharp & Dohme, Orion, and Sanofi. SGI is an adviser or consultant for AAA International, Amgen, Astellas, Bayer, Curevac, Dendreon, ESSA, Janssen Cilag, Millennium, Novartis, Orion, Pfizer, ProteoMediX, Roche, and Sanofi-Aventis. UH declares a patent application for PSMA-617 and PSMA-1007. KH is consultant or adviser for ABX, Bayer, Endocyte, Ipsen, Sirtex, and Siemens Healthcare. RJH is on the scientific advisory board of Telix Pharmaceuticals and is an adviser to Endocyte with honoraria donated to his institution. RJAvm is a consultant or adviser for Amgen, Astellas, AstraZeneca, Bayer, Janssen, and Sanofi-Genzyme. JMO'S is an adviser to Astellas, Bayer, Janssen, and Sanofi, and wrote articles for Bayer during the past 5 years. PO is a consultant for Bayer and Ferring, and receives support from Ferring and Merck. ARP is an adviser for Siemens Healthineers. JS is an adviser or speaker for Astellas, Bayer, Sanofi, and MDxHealth. HIS is a consultant for Clovis, Pfizer, Janssen Research, Janssen, Sanofi, and Menarini, on the advisory board for WCG, has grant or research support from Janssen and Janssen Research, is in collaboration with EPIC Sciences, and is a recipient of National Institutes of Health/National Cancer Institute Prostate SPOR Grant P50-CA92629 and Cancer Center Support Grant P30 CA008748. BT is a consultant or adviser for Astellas, Amgen, Bayer, Ferring, Janssen, Pfizer, Takeda, Myovant, and Sanofi Genzyme, and has written articles for Astellas, Amgen, Bayer, Ferring, Janssen, Pfizer, Takeda, Myovant, and Sanofi Genzyme during the last 5 years. JW is a consultant, assessor or adviser for Blue Earth Diagnostics, Exact Imaging, and Supersonic, and was a Speaker and received honoraria from ANNAcTRUS, Hitachi, Supersonic, Takeda, and Astellas. WAW is a consultant for Endocyte and BMS and is a recipient of National Institutes of Health grants 1 R01 CA222049-01, 1R01CA207645-01, 1 R01 CA213448-01, and 1R01CA207645-01. H-JW is scientific adviser for and shareholder of Scintomics. WJGO is an adviser for Bayer. The remaining authors declare no competing interests.

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