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European Registry of Next Generation Imaging in Advanced Prostate Cancer (RING): protocol for an international, prospective registry study

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ABSTRACT

Introduction Next-generation imaging (NGI), particularly with prostate-specific membrane antigen positron emission tomography (PSMA PET) tracers, enables earlier and more accurate detection of metastases. However, conventional imaging (CT and bone scan) remains more affordable and widely accessible and was the standard used in most pivotal trials that established current survival outcomes. As PSMA PET becomes more widely adopted, a stage migration effect is emerging. However, key uncertainties persist regarding the actual proportional employment of NGI in clinical practice, main indications for its use and the mid-term and long-term effects of an NGI-driven treatment pathway. Furthermore, when or whether CI alone might remain enough informative for the treatment decision-making is still unclear.

Methods and analysis The European Registry of Next-Generation Imaging in Advanced Prostate Cancer is a non-profit, non-interventional, multi-centre, international, prospective, investigator-initiated registry that is intended to collect real-world data on how patients with prostate cancer at risk of harbouring metastasis (high-risk at initial diagnosis, or after primary treatment) are managed according to the type of imaging used for the systemic work-up. The registry is conducted in two phases: (1) cross-sectional analysis of imaging choices and their effect on clinical decision-making and (2) longitudinal follow-up evaluating survival outcomes such as progression-free survival (PFS), disease-specific survival (DSS) and skeletal-related events (SSEs). Statistical analyses will include descriptive analysis of demographic and clinical variables, comparative analysis between different imaging pathways, survival and prognostic analyses using Kaplan–Meier tests. The expected minimum sample size of the registry is 600 patients, and the planned follow-up duration is 24 months for the longitudinal follow-up.

Ethics and dissemination The study protocol was approved by the ethics committee of Fundació Puigvert (#C2024/30), and ethics approval is required at all participating sites. All patients will provide written informed consent. The results will be disseminated widely and transparently to maximise their effect on clinical practice, research and patient care through peer-reviewed publications, presentations at international conferences as well as through patient advocacy groups and relevant patient websites.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The European Registry of Next-Generation Imaging in Advanced Prostate Cancer is the first multinational and multi-centre observational registry designed to collect real-life data on how different imaging techniques are used in patients with advanced prostate cancer.
⇒ Real-world data collection makes it possible to evaluate the diversity of the imaging scenarios and assess how European Association of Urology guidelines are followed across different countries.
⇒ One of the possible limitations could be a relatively short follow-up duration (24 months), which may be insufficient to capture long-term outcomes such as disease-specific survival and progression-free survival.
⇒ To address the potential selection bias arising from the observational nature of the registry, where not all patients undergo both next-generation imaging and conventional imaging, specific sub-analyses will focus on the subgroup of patients who underwent both modalities.

Trial registration number NCT06866782.

INTRODUCTION

The advent of MRI and positron emission tomography (PET)/CT technologies in advanced prostate cancer (APC) is affecting both disease diagnosis pathways and post-treatment follow-up. The recent approvals by the US Food and Drug Administration and the European Medicines Agency of several prostate-specific membrane antigen (PSMA)-targeted PET tracers have facilitated broader clinical adoption. Owing to their superior diagnostic accuracy compared with conventional imaging (CI) modalities—namely, CT and bone scintigraphy—PSMA PET is increasingly employed for initial staging, or recurrence, and monitoring disease progression.[1]

The diagnostic utility of next-generation imaging (NGI) is now well established across multiple clinical contexts. Emerging evidence demonstrates enhanced accuracy of PSMA PET/CT not only in patients with high-risk PC but also among those with intermediate-risk disease,[2–5] which has prompted the European Association of Urology (EAU) to expand its recommendations accordingly.[6] Several studies and meta-analyses have suggested that given the high negative predictive value of PSMA PET/CT, pelvic lymph node dissection may be safely omitted in selected patients with intermediate risk and negative imaging findings.[7–10] However, owing to spatial resolution limitations and weak tracer uptake in small lymph node metastases (<5 mm), some pathological lymph nodes may go undetected. As a result, the current standard of care for N staging in PC remains surgical lymphadenectomy during prostatectomy.[11 12]

In patients with biochemical recurrence (BCR) of PC, PSMA PET/CT has demonstrated clear advantages over CI techniques, particularly in terms of sensitivity at low prostate-specific antigen (PSA) levels. Meta-analyses by Perera *et al* showed that PSMA PET/CT detects recurrent disease even at low PSA levels after prostatectomy, with positive scan rates of 33% for PSA <0.2 ng/mL and increasing to 97% for PSA ≥2 ng/mL.[13 14] This high sensitivity at low PSA values allows for early and precise localisation of recurrent lesions and thereby facilitates a more tailored therapeutic approach. Although MRI remains valuable for guiding biopsy post-radiotherapy, PSMA PET/CT has emerged as the modality of choice for restaging, as also reflected in the latest EAU guidelines on PC.[6] Moreover, data from the proPSMA trial highlight the prognostic significance of PSMA-positive nodal disease, which has been associated with shorter time to treatment failure.[15]

Notably, PSMA PET has been shown to reclassify disease extent in approximately 40% of patients when compared with CI, potentially altering treatment strategies by enabling both escalation and de-escalation of therapeutic intensity.[16] However, the majority of pivotal clinical trials informing current treatment paradigms for APC were conducted using CI for patient stratification.[17 18] Whether the same treatment approaches can be reliably extrapolated to cases staged with NGI remains an open question.[19] Moreover, evidence is still scarce in proving that an earlier initiation of systemic treatment prompted by stage migration by PSMA PET/CT will provide survival benefits for patient.[19–22] The cost of PSMA PET varies significantly across regions and healthcare systems and may represent a barrier to widespread adoption, particularly in resource-limited settings. Additionally, the availability of PET cameras capable of performing PSMA PET and the supply of PSMA-targeted radiotracers might not be universal, particularly in smaller centres or developing countries. Although the diagnostic benefits of NGI in APC are well documented, the associated financial burden and disparities in accessibility across Europe underscore the need for comprehensive studies evaluating real-world adherence to EAU guidelines in diverse clinical environments.

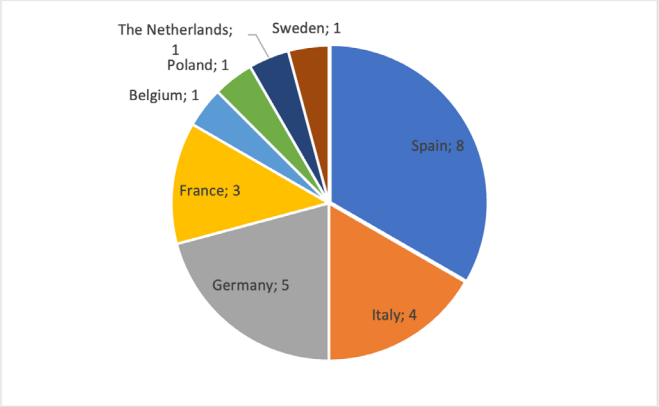


Figure 1 Distribution of invited centres across Europe.

Another topic of interest is the prognostic value of NGI for the prediction of survival outcomes, which has been recently addressed in the PSMA PET Prostate Cancer Molecular Imaging Standardized Evaluation (PPP2) study: the authors were able to create a nomogram after identifying PSMA PET/CT variables associated with the events in observation, allowing for a risk stratification of patients according to the PSMA PET/CT finding.[23]

With the RING registry, this study aims to understand when, which and why NGI investigations are undertaken in the assessment of real-life APC populations, to satisfy the following:

- Better identify patients who potentially benefit from an earlier/finer assessment of metastatic PC at baseline with NGI.
- Better identify patients for whom CI is informative enough for making a clinical decision.
- Assess the change in management prompted by NGI versus CI in usual clinical practice, when both imaging modalities are employed.

METHODS AND ANALYSIS

Study design and population

RING is a non-profit, non-interventional, multi-centre, prospective (observational cohort), investigator-initiated registry in several European countries (figure 1). It is designed to include at least 600 male patients (an average of 50 patients per at least 12 active recruiting centres) among patients with the suspicion of harbouring metastatic deposits at the hormone-sensitive stage, who require imaging exploration (CI, NGI or their combination) either at the diagnostic work-up of a treatment-naïve patient or at biochemical relapse/progression after local treatment.

These subgroups of patients are defined by the latest version of the EAU Prostate Cancer guidelines:

- Treatment-naïve group: intermediate-unfavourable and high-risk EAU groups [biopsy International Society of Urological Pathology (ISUP) grade group (GG) 2+PSA 10–20 ng/mL or biopsy ISUP GG≥3 or PSA≥20 ng/mL or cT2c or higher)[6]

Table 1 Inclusion and exclusion criteria for participation in the RING study

Inclusion criteria	Exclusion criteria
Adult male patients (≥18 years with no upper age limit).	Patients participating in other interventional or non-interventional studies that require new generation imaging (NGI) as a triage test for metastatic assessment.
Histologically proven prostate cancer.	Patients with evidence of any other clinically significant disease or condition which, in the opinion of the investigator, discourages their participation in the study.
Patients who require imaging exploration (conventional, NGI or their combination) are at high risk for harbouring metastatic deposits at the hormone-sensitive stage, either at the diagnostic work-up of a 'naïve' patient or at biochemical relapse/progression after local treatment.	Patients who cannot sign the ICF.
Patients who authorise their participation in the study by signing a written ICF.	

ICF, informed consent form; NGI, new-generation imaging; RING, European Registry of Next Generation Imaging in Advanced Prostate Cancer.

- Recurrent group: EAU high-risk group for BCR (PSA-DT ≤1 year for patients after radical prostatectomy, interval to biochemical failure ≤18 months for patients after radiotherapy or ISUP GG 4–5 for either local treatment.[24]

However, recruitment of patients not fulfilling the above criteria but still at risk of harbouring metastatic deposits according to the clinical assessment of the local principal investigator (PI) is also allowed (eg, patient *BRCA2* carrier, strong family history of PC or aggressive histological variants at biopsy).

The registry's inclusion and exclusion criteria are summarised in (table 1. An informed consent form will be obtained from each patient.

The recruitment phase is expected to last 18 months with the follow-up of 24 months. Invited centres (table 2) are specialised tertiary/university hospitals that have already obtained an ethical approval or are still waiting for approval. The selected centres are among those who have been accredited as European Prostate Cancer Centre of Excellence by the EAU or are part of the Genitourinary Alliance for Research and Development or of the members' centres of the EAU Section of Urological Imaging.

Table 2 List of the invited centres

Name of the centre	Participation decision
Fundació Puigvert, Barcelona, Spain	Participating
Hospital Universitario de Canarias, Spain	Not participating
Hospital Universitario Marqués de Valdecilla, Spain	Participating
Hospital Universitario de Reina Sofia, Spain	Participating
Hospital Universitario La Paz, Spain	Participating
Hospital Universitario Santiago de Compostela, Spain	Not participating
Hospital Universitario Ramon y Cajal, Spain	Participating
Hospital de la Santa Creu i Sant Pau, Spain	Participating
Skåne University Hospital, Malmö, Sweden	Not participating
AOUC Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy (two sites)	Participating
IRCCS Ospedale San Raffaele, Milan, Italy	Pending
IRCCS Humanitas Clinical and Research Institute, Milan, Italy	Pending
Azienda Sanitaria Universitaria Friuli Centrale	Pending
IRCCS Universitaria di Bologna, Bologna, Italy	Participating
München LMU, LMU-University Clinic, Munich, Germany	Participating
Universitätsklinik Tübingen, Tübingen, Germany	Not participating
Martini Klinik, Hamburg, Germany	Not participating
Bonn University Hospital, Bonn, Germany	Participating
Urologische Klinik München – Planegg, Planegg, Germany	Participating
Hospices Civils de Lyon, Lyon, France	Participating
University Hospital La Pitié-Salpêtrière, Paris, France	Pending
Centre Hospitalier Universitaire de Lille, Lille, France	Participating
University Hospital of Bern, Bern, Switzerland	Not participating
ERASMUS MC and Franciscus Hospital, Rotterdam, The Netherlands	Pending
UZ Leuven, Leuven, Belgium	Participating
Jagiellonian University Medical College, Kraków, Poland	Not participating

The project has also been endorsed by the EAU Research Foundation.

Data collection

Each participating centre will form a local team of investigators, including a urologist and an imaging expert (radiologist or nuclear medicine physician), led by a PI. Patients will be screened for eligibility during outpatient visits. Eligible patients will receive an informed consent form (ICF) detailing the registry's aims, data collection

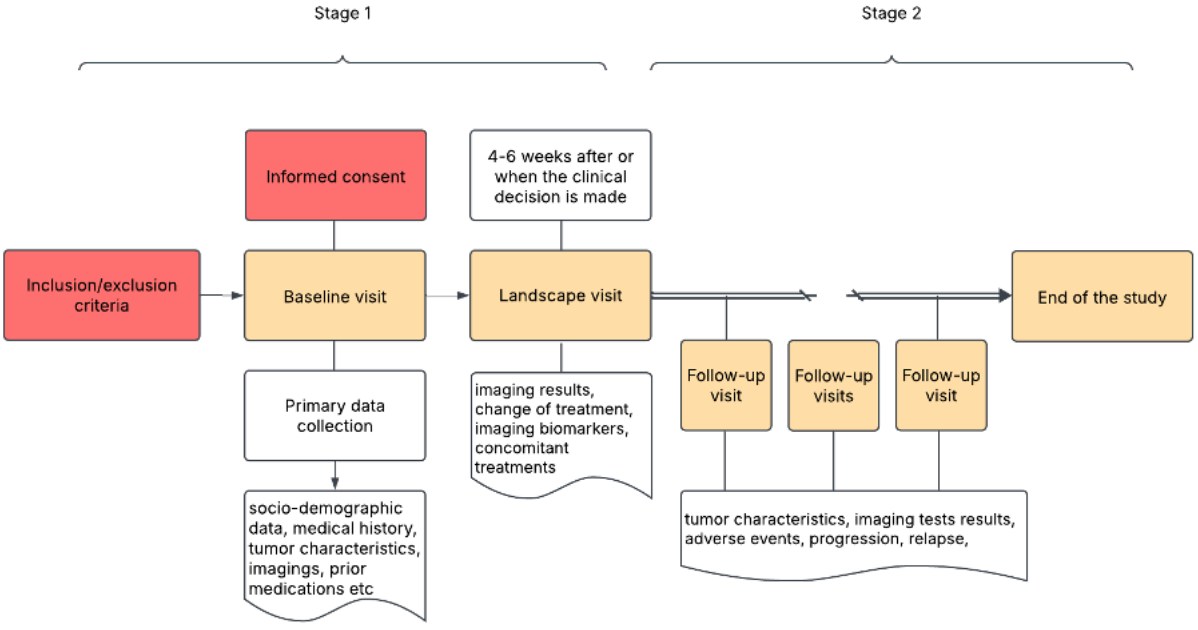


Figure 2 Study flowchart showing the stages of the RING study, planned visit schedule and characteristics to be analysed.

and management. A signed ICF is required before data entry into the registry's electronic Case Report Form (eCRF).

Imaging explorations will follow local standard clinical practice, with no modifications prompted by study participation. The registry will operate in two stages (figure 2):

- Stage 1: cross-sectional observation of patients recruited according to selection criteria.
- Stage 2: longitudinal observation of patients with treatment decision made and in follow-up.

Patient characteristics at the baseline visit will be collected during the diagnostic work-up, including family history of PC, general medical history, initial serum PSA value and clinical tumour stage assessed by digital rectal examination and MRI. The timeline of visits for tumour staging will be planned according to the routine schedule of the sites, without any alteration of the standard clinical practice. For patients with BCR, additional data will be collected, including details of the previous imaging explorations (if any), type of local treatment undertaken and PSA values at nadir and recurrence. Data for all the imaging explorations will be recorded according to the local radiological and nuclear medicine reports. To standardise and facilitate the reporting process, specific validated scoring systems will be used, such as the Prostate Imaging Reporting and Data System scores for MRI and Prostate-specific Membrane Antigen Reporting and Data System (PSMA-RADS),[25] PSMA PET to MRI Imaging Triage in Diagnosis of PC (PRIMARY[26]) score, Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) score v.1[27] and v.2[28] for PSMA-PET explorations.

A landscape visit will take place 4–6 weeks after the baseline visit, or as soon as the diagnostic work-up is completed, and a decision is made for the treatment type the patient

will undertake: all this information will be requested as mandatory fields for the site PIs to feed in the registry.

Follow-up monitoring will take place according to local protocol schedule, and data will be collected every 3 months concerning the closest visit to each time point. Taking into consideration the different clinical scenarios that could be included in the registry (non-metastatic, oligo-metastatic and high-volume metastatic disease), the events to satisfy the main survival outcomes (PFS and/or metastasis-free survival (MFS), DSS) and the time of their sufficient achievement can differ significantly. Even though the ideal follow-up time to collect most of the survival events should be 3–5 years for PFS and 5–10 years for the overall survival, a minimum of 24-month follow-up has been estimated to get a sufficient number of progression events.[29] At follow-up timepoints, clinical and imaging information will be collected, among which imaging explorations undertaken (if any), change of treatment (if any), PSA/PSA doubling time (DT), description of any management events (biochemical/radiological/clinical progression) and relevant concomitant treatments.

Study objectives

This registry is intended to collect real-world data on patient demographics, medical history, clinical endpoints, histological tumour characteristics and imaging explorations of patients with PC at high risk for harbouring metastatic deposits at the hormone-sensitive stage, who require imaging exploration (CI, NGI or their combination)

either at the diagnostic workup of a 'naïve' patient or at biochemical relapse/progression after local treatment.

Working (exploratory) hypothesis: there is a high heterogeneity of usage of different imaging modalities in patients with APC, including differences in indication, modality (eg, CI vs PSMA PET/CT with different tracers vs MRI) and frequency across different centres and countries, which can lead to relevant differences in patients' management.

The objectives of the study are as follows:

Stage 1: cross-sectional observation

Primary objective:

To identify the proportion of patients who will be staged at the baseline either with NGI or CI, or their combination according to the decision of treating physician, based on local protocols and/or national or international guidelines.

Secondary objectives:

1. To assess management prompted by NGI versus CI in usual clinical practice.
2. To identify the proportion of patients for whom CI is considered informative enough for making a clinical decision, according to the decision of the treating physician based on local protocols and/or national or international guidelines.
3. To evaluate the rate and type of reclassification of hormone-sensitive PC based on NGI with respect to CI when both imaging modalities are used.[17 30]

Stage 2: longitudinal observation

1. Evaluation of survival outcomes and their relationship with the imaging pathway undertaken (overall and per subgroup of imaging modality).
2. Identification of prognostic factors related to treatment response and disease progression.

Study endpoints

Stage 1: landscape analysis

1. Proportion of patients requiring NGI, CI or their combination.
2. The association between clinical characteristics (age, ethnicity, comorbidities, PSA, PSA DT, ISUP grade at biopsy or at specimens, etc) and type of imaging explorations to identify (if any) clinical variables associated with each imaging pathway.
3. Proportion of patients with a change of treatment determined by the imaging test result, when multiple imaging tests have been realised.

Stage 2: follow-up analysis

1. PFS (biochemical, clinical and radiological) or need for change of treatment (overall and per imaging subgroups)
2. DSS (overall and per imaging subgroups).
3. Symptomatic skeletal events (SSE) and SSE-free survival (overall and per imaging subgroups).
4. Imaging biomarkers related to treatment response and disease progression (Standardized Uptake Value (SUV), type of tracer, scoring system used and relevant scores, etc).
5. External validation of the PPP2 nomogram for risk stratification to assess its predictive accuracy for disease staging and management decisions.[23]

Project timeline

The project was started in 2024 with the first centre opening in September 2024 and starting the recruitment. The estimated milestones of the project are to enroll 300 patients before the end of 2025. The estimated time for the last patient to be included is the second quarter of 2026.

As soon as the 50%+1 patients are recruited, an interim analysis will be conducted.

The interim analysis is supposed to be written and submitted in the first quarter of 2026. The end of the study is defined as data entry for the last patient visit. The final study results are anticipated to be published in the fourth quarter of 2026.

Sample size

As the RING registry is a prospective, observational study designed to collect real-world data, no clinical question will be addressed but different endpoints to be explored. Accordingly, an effect sample size requiring a formal power calculation for the cohort of patients in observation cannot be applied. The registry is intended to include at least 600 male patients (an average of 50 patients per at least 12 active recruiting centres). The target sample size of 600 patients was pragmatically determined based on a balance between the feasibility of recruitment across participating European centres and the need for a sufficiently large cohort to enable robust statistical analyses. This sample size is expected to allow for reliable descriptive statistics of the various patient characteristics and imaging pathways for the primary objective.

Data management and analysis

All collected data will be pseudonymised and entered to the Research Electronic Data Capture database with patient names replaced by site codes and sequential numbers in accordance with General Data Protection Regulation (GDPR) requirements.

Different analyses have been planned using baseline and follow-up data. Analysis will be conducted with R statistical software (version 4.5.2). All statistical tests will be two-sided, and a p value<0.05 will be considered statistically significant. Primary analysis will be done in the full analysis set: all patients with at least one imaging event with follow-up data recorded. Subgroup analysis will be done for specific endpoints (eg, subgroup underwent both NGI and CI). Categorical variables (eg, imaging modality, presence of metastases and choice of treatment) will be described as frequencies and percentages. Continuous variables (eg, PSA level and age) will be described as means and SD or medians with IQRs, depending on

the distribution. Normality of continuous variables will be tested using the Kolmogorov–Smirnov test.

Rates of patients undergoing NGI, CI or both will be reported. The $\chi 2$ tests or Fisher's exact tests will be used to examine associations between imaging approach and clinical features (age, ISUP grade, PSA, PSA DT, family history, etc). The percentage of patients with treatment change due to NGI or CI will be reported. Logistic regression models will identify predictors of treatment change (binary outcome: change vs no change), with covariates including imaging modality, disease burden, PSA and clinical site. Subgroup analysis will be made for patients who have undergone both NGI and CI to assess reclassification rates (eg, M0 → M1) and corresponding treatment changes. Kaplan–Meier estimates will be used to calculate time-to-event endpoints.

Patient and public involvement

Patients and members of the public were not involved in the design, recruitment or conduct of this study. The RING registry is an observational study focused on real-world imaging practices in APC, and as such, it was designed based on current clinical standards and consensus among specialists in urology, nuclear medicine and radiology. However, the findings from the study are intended to inform more personalised imaging strategies and improve decision-making processes that ultimately benefit patients. On study completion, a plain-language summary of the results will be disseminated to participating centres for patient access and public communication.

Ethics and dissemination

The RING protocol was approved by the ethics committee of Fundació Puigvert (#C2024/30). The study has received (or will receive) approval from institutional ethics committees of all participating sites. All patients will provide written informed consent before data entry into the registry's electronic Case Report Form.

The results will be disseminated widely and transparently to maximise their effect on clinical practice, research and patient care through peer-reviewed publications, presentations at international conferences, patient advocacy groups and relevant patient websites.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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