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Nature Reviews Urology

Consensus Statement:

Unanswered questions in prostate cancer: Findings of an international multi-stakeholder consensus by the PIONEER Consortium

Muhammad Imran Omar, Steven MacLennan, Maria Ribal, Monique J. Roobol, Konstantinos Dimitropoulos, Thomas van den Broeck, Sara MacLennan, Susan Evans Axelsson, Giorgio Gandaglia, Peter-Paul Willemse, Ken Mastris, John Butler, Zsuzsanna Devecseri, Thomas Abbott, Bertrand De Meulder, Anders Bjartell, Alex Asiimwe, James N'Dow, and The PIONEER Consortium*
*The PIONEER Consortium (will submit as a list containing names of all consortium members)

Abstract

PIONEER is a European network of excellence for big data in prostate cancer, consisting of 37 private and public stakeholders from 9 countries across Europe. Major stakeholders including healthcare professionals and patients were consulted to propose the most critical questions in the field of prostate cancer to be answered using big data. Through this process, 44 key questions were identified. The PIONEER consortium conducted a two-round modified Delphi survey aiming to build consensus between the two stakeholder groups: healthcare professionals and prostate cancer patients. Respondents were asked to consider what impact answering the proposed questions would have on better diagnosis and treatment outcomes for prostate cancer patients, while scoring these questions on a scale of 1 (not important) to 9 (critically important). In total, 73 healthcare professionals and 57 patients participated in round one. Twelve additional questions were proposed during this first round. For the second round 169 patients (including 53 English; 19 French; 31 German; 53 Italian; 13 Spanish) participated. The results were analysed by calculating the percentage of respondents scoring each question as not important, important, or critically important. The mean of the percentages across the two stake-holder groups scoring each of the 56 questions as "critically important" was calculated and used to rank the questions in terms of those scoring highest in the "critically important" category. Three questions (Q1, Q2 and Q4) focused on prognostic factors and two (Q4 and Q5) on the role of medical interventions on patient outcomes. The disease stages that were covered are also varied, including localized (Q1, Q2, Q3), recurrent

(Q4) and metastatic (Q5) disease. Hence prioritisation does not seem to be biased towards the opinion of a subgroup of HCPs (urologists versus medical oncologists for example). Although the prioritisation of the first 5 questions was overall similar between HCPs and patients, for two questions (Q3 and 4) there was a +/- 10% difference in the percentage of respondents categorizing the question as critically important. For Q3 this was 91.8% by HCPs versus 82.3% by patients and for Q4 79.6% versus 92.5%. Identification of critical questions will help the PIONEER consortium to answer those questions that are critical to various stakeholders.

Background information

Prostate cancer represents the most common cancer diagnosed in men in Europe with more than 1,400,000 estimated cases in the year 2020 and the fifth cause of mortality for cancer with more than 375,000 new deaths per year worldwide (1). Although prostate cancer is characterized by a relatively prolonged natural history, the outcomes of prostate cancer patients are heterogeneous and profoundly vary according to disease features as well as individual characteristics (2). Over the last few years, the introduction of novel imaging modalities, biomarkers, genomics and personalized medicine revolutionized the management of prostate cancer patients (3, 4) (5). Nonetheless, several questions on the most optimal management of prostate cancer at different stages of the disease still remain unanswered and further research is needed in all stages of the disease with the aim of developing approaches that improve oncologic control and survival and minimize the detrimental effects on health-related quality of life.

Prostate cancer management is typically based on stratification into risk categories, which provide an estimate of the probability of experiencing recurrence after primary treatment or indeed the likelihood of disease progression should a non-curative intent management strategy such as Active Surveillance (AS) was adopted. However, this classification relies mainly on clinical factors such as PSA values, clinical stage, and biopsy grade group (6). Moreover, its accuracy in the identification of men who would die from the disease itself or who would suffer from side effects of the disease versus those who are more likely to die from other causes and has no burden of his prostate cancer is suboptimal. Therefore, the impact of novel available tools on risk stratification at diagnosis still needs to be clarified.

When focusing on patients with clinically localized disease, deferred treatment, which mainly consists of active surveillance (AS) and watchful waiting (WW), as well as curative intent treatments such as surgery to remove the prostate (radical prostatectomy) and radiation treatment, all represent valid options. Although both AS and WW aim at avoiding unnecessary therapies and their treatment-related side effects, they have substantial differences. AS represents an alternative for selected patients with low- or intermediate-risk localized disease with the aim of avoiding treatment-related side effects without missing the correct timing for the delivery of curative-intent therapies (7). Several selection criteria for the inclusion in AS protocols have been proposed. However, which are the patient- and tumor-specific factors that could accurately guide the prognosis in this setting and identify the optimal AS candidates are still unknown (8). For example, multiparametric MRI and genetic testing has been proposed to identify men suitable for the inclusion in AS protocols (9, 10). Nonetheless, the role of these factors and their impact on survival still needs to be elucidated. Similarly, the optimal follow-up and triggers for intervention in patients enrolled in AS protocols have been poorly addressed so far.

Patients considered for WW are deemed as unsuitable for curative treatments due to their life expectancy or significant comorbidities and therefore, are typically monitored until the development of local or systemic symptoms. The natural history of contemporary patients managed with WW and the rates of disease progression and survival still need to be investigated. Moreover, the improved life expectancy and different impact of comorbidities on survival would preclude the generalizability of their results to contemporary cohorts.

When focusing on men with more advanced disease (i.e., locally advanced or metastatic prostate cancer), several questions remain unanswered. Recent studies suggested that the treatment of the primary tumor in oligo-metastatic patients at diagnosis, as well as the delivery of metastases-directed therapies in the oligo-recurrence setting, might improve outcomes (12, 13). However, the impact of these local therapies on long-term outcomes in the metastatic setting still remains unknown.

Over the last few years, several novel systemic therapies have been introduced for the treatment of metastatic hormone-sensitive and castration-resistant prostate cancer, such as novel androgen-receptor targeted therapies (ARTA), chemotherapy, PARP inhibitors or immunotherapy. However, which is the best sequencing of these molecules is still largely unknown. Similarly, little is known regarding the use of biomarkers for the delivery of an individualized approach.

Finally, it should be highlighted that each local or systemic therapy for the management of prostate cancer patients is associated with specific treatment-related side effects which have a profound impact on health-related quality of life. One of the main challenges in the management of prostate cancer patients in the next decade would be to identify which is the therapeutic approach with the best trade-off between toxicity and efficacy for each patient in order to improve oncologic control without affecting quality of life.

PIONEER project

PIONEER (Prostate Cancer DIagnOsis and TreatmeNt Enhancement through the power of big data in EuRope) is a European network of excellence for big data in prostate cancer project, consisting of 37 private and public stakeholders from 9 countries across Europe. Launched by the Innovative Medicines Initiative 2 under grant agreement No.777492 and part of the Big Data for Better Outcomes Programme (BD4BO), the overarching goal of PIONEER is to provide high-quality evidence on prostate cancer management to improve health outcomes and healthcare systems in Europe by unlocking the potential of big data.

Prostate cancer is the most common cancer diagnosed in men in Europe, representing 1 in 10 of all cancer deaths in men (14) Prostate cancer healthcare costs were estimated at €8.43 billion per year in the EU in 2009 and accounted for 7% of all cancer costs in Europe (15). At present, there are a number of critical knowledge gaps in relation to the screening, diagnosis and treatment of prostate cancer patients, including:

- lack of standardisation of prostate cancer outcomes definitions across all stages of the disease;
- insufficient knowledge of the risk factors for developing prostate cancer;

- insufficient knowledge of appropriate patient stratification and patient prognostic characteristics, including genetic profiles, for optimal stratification of patients at time of diagnosis;
- lack of meaningful engagement of all key stakeholders, including patients, when defining disease-specific core outcome sets (COS);
- ineffective implementation of knowledge and real-world clinical data into clinical practice including care pathways.

The vision of PIONEER is to transform the management and clinical practice of prostate cancer across all disease stages (Stage I to IV) towards a data-driven and outcome-driven, value-based, and patient-centric health-care system. By applying advanced big data analytics, and developing a data platform of unparalleled scale, quality and diversity, PIONEER will empower meaningful improvement in clinical practice, prostate cancer disease-related outcomes, and health economic outcomes across the European health care landscape (16). Specific objectives of PIONEER project include:

1- To improve disease understanding and deliver a core set of clinically relevant standardised prostate cancer -related outcomes
2- To optimise diagnosis and therapeutic management of prostate cancer patients across different stages of the disease and across multiple geographies by delivering valuable insights from real-world data and sharing best practices
3- To provide unique tools for standardisation and analysis of complex prostate cancer data sets from a variety of sources, using different data models and different terminology, whilst comprising different layers of information (e.g., genetic, omics, imaging, biomarkers)
4- To develop a large and harmonised repository of prostate cancer data that can be used to improve evidence-based decision-making for all prostate cancer patients, and enable a wide variety of data re-use scenarios

Knowledge gap and PIONEER's approach

It is PIONEER's ultimate vision to re-orient the management and clinical practice of prostate cancer across all stages of the disease towards a more outcome-driven, value-based, and patient-centric healthcare system. Clinical research is traditionally led by scientists, clinical

professionals or commercial interest. In 2009, Chalmers and Glasziou, among others, argued strongly for a more efficient research culture in which scientists study health conditions that are not only the greatest burden on the population, but also address questions about interventions and outcomes that patients and clinicians consider to be the most important (17). Although the distinction between a scientific problem and a research question is perhaps not always clear, we can consider a research question as identifying the particular piece of knowledge a project seeks to generate to (partially) solve a problem. Generating relevant research questions, with respect to novelty, scientific and practical impact, feasibility, and clarity requires different types of pre-existing knowledge. Despite the fact that PIONEER will have the availability of ample data, we must remain critical on what will be feasible to address. In general, available patient-centered prostate cancer datasets can be divided into three categories i.e., clinical, genomics and imaging, and availability of each category will influence feasibility of solving a particular research question. However, as shown above, the success of big data analysis does not solely depend on access to data. The interaction between prostate cancer experts, patients, IT and data experts is crucial and calls for a multi-disciplinary approach (18, 19).

The PIONEER consortium initiated a research prioritisation exercise aiming to identify the major unmet questions in the field. First, the PIONEER consortium identified critical prostate cancer evidence gaps from the perspectives of academic and industry professionals and patients and then used modified Delphi methods to come to a consensus on a prioritised list of research questions.

Methods

The most important stakeholder groups for identifying the top unanswered questions in prostate cancer are healthcare professionals (HCPs), because they design and administer care and drive the research agenda and the patient group because they are the recipients of the benefits and harms of care and research. The modified Delphi method was identified as appropriate to assess agreement within and between these stakeholder groups, and to facilitate consensus (20). The modified Delphi method allows for anonymous controlled feedback, whereby participants are first asked to score a series of items, then, in subsequent

rounds are shown a summary of the scores that other participants attributed to each item in the previous round. They are then asked to re-score the items (21).

Key Opinion Leaders including EAU Prostate Cancer Guideline panel members and other urologists, oncologists, radiologists, nurses, health economists, and researchers were consulted to propose the most critical questions in the field of prostate cancer to be answered using big data. These KOLs work in a variety of different setting including academic/university environments, hospitals, and primary care. They were asked to provide critical unanswered research questions for prostate cancer, considering what we do not know for sure about prostate cancer but would be important to know and answering these questions can/could transform practice and patient outcomes. Through this process, 44 key questions were identified. Afterwards, the PIONEER consortium conducted a two-round modified Delphi survey in order to assess and build consensus between the two stakeholder groups: healthcare professionals (including representatives from pharmaceutical companies who are medically qualified and work in either R&D or medical affairs branches of industry and not from marketing departments) and prostate cancer patients. Several organisations helped us with the dissemination of the surveys including the EAU, EAUN, Ecancer, ECPC, EUROPA UOMO, Prostate Cancer UK, and UCAN. Respondents were asked to consider what impact answering the proposed questions would have on better diagnosis and treatment outcomes for prostate cancer, while scoring these questions on a scale of 1 (not important) to 9 (critically important). The results were analysed by calculating the percentage of respondents scoring each question as: not important (score 1 to 3), important (score 4 to 6) or critically important (score 7 to 9). In the second round, participants were shown a summary of the percentage of other participants' (patients and healthcare professionals) who considered the question "critically important" in round one.

Results:

In total, 73 healthcare professionals and 57 patients participated in round one of the modified Delphi survey. Twelve additional questions were proposed during this first round. For the second round, the patients' surveys were translated into French, German, Italian and Spanish. 49 healthcare professionals and 169 patients (including 53 English; 19 French; 31 German; 53 Italian; 13 Spanish) participated in round two of the surveys (**Figure 1**).

The mean of the percentages across the two stake-holder groups scoring each of the 56 questions as "critically important" was calculated and used to rank the questions in terms of those scoring highest in the "critically important" category. The top ten questions are listed in **Table 1** and the process is illustrated in **Figure 2**. The complete results are in **Appendix 1**.

The five questions with highest prioritisation were overall deemed critically important by more than 85% of all respondents **(Table 1).** None of the questions that were added after the first modified Delphi round were retained within the final top 10 prioritised questions. All top 5 questions were also part of the top 10 questions after the first modified Delphi voting round. Three questions (Q1, Q2 and Q4) focused on prognostic factors and two (Q4 and Q5) on the role of medical interventions on patient outcomes. The disease stages that were investigated are also varied, including localized (Q1, Q2, Q3), recurrent (Q4) and metastatic (Q5) disease. Hence prioritisation does not seem to be biased towards the opinion of a subgroup of HCPs (urologists versus medical oncologists for example). Although the prioritisation of the first 5 questions was overall similar between HCPs and patients, for two questions (Q3 and 4) there was a +/- 10% difference in the percentage of respondents categorizing the question as critically important. For Q3 this was 91.8% by HCPs versus 82.3% by patients and for Q4 79.6% versus 92.5%.

The remaining 5 questions (Q6 – Q10) had an overall prioritisation score around 85% with the exception of Q10 which scored lower, at 80.5%. Three questions (Q6, 7 and 9) were part of the top 10 questions identified by the healthcare professionals and patients after the first modified Delphi voting round. Two questions (Q8 and Q10) were also part of the 10 questions prioritised by the HCP group after Round 1. Three out of the 5 questions focused on treatment-related benefits and harms and sequencing of available treatment options (Q6, Q9 and Q10), while Questions 7 and 8 revolved around optimising patient selection for treatment at various clinical stages, and using genetic profile to maximise treatment effect. While prioritisation scores were similar between the groups of patients and HCPs for Questions 7 and 8 (~85%), patient prioritisation scores for Questions 6, 9 and 10 were ~10-15% higher than the scores provided by the HCPs (91.4%, 90.8% and 88.1% versus 79.6%, 77.6% and 72.9%, respectively).

Overall, both groups' prioritised questions related to four specific question types in their top ten. These question types were comparisons of treatments or specific diagnostic / treatment questions for specific stages e.g. CRPC, timing of treatment and care pathways, comparison of side effects, or genetics and understanding patient types / risk profiles and treatment. The main difference between the two groups was that the patients also prioritised questions related to co-ordination of care and skill of care provider within their top ten list of priorities.

The top ten priorities for patients relate to five specific question types – comparisons of treatments or specific treatment questions for specific stages e.g. CRPC, timing of treatment and care pathways, understanding of side effects, co-ordination of care and skill of care provider or genetics and understanding patient types and treatment. Examples include questions related to the comparison of rates of side effects between different treatments; questions related to tumour-specific and patient-specific variables, prognosis and active surveillance; and questions related to sequencing of therapeutic options to support best outcomes. The most rated question was around treatment options and timing of treatment following recurrence of prostate cancer (for full details see **Appendix 1**).

These are all key dimensions of evidence-based decision making which would help increase patient understanding of their diagnosis, their potential treatment options and inform their outcome expectancies. Greater evidence to support a more complete understanding of these questions would support appropriate decision-making and could minimise decisional regret. The co-ordination of care and skill sets of care providers are important dimensions of confidence and trust in the process of care.

The top ten priorities for healthcare providers relate to four specific question types comparisons of treatments or specific diagnostic / treatment questions for specific stages e.g. CRPC, timing of treatment and care pathways, comparison of side effects, or genetics and understanding patient types / risk profiles and treatment. Examples include questions related to best models for risk stratification; questions related to understanding which specific groups of patients benefit from specific treatments such as upfront chemotherapy; questions related to diagnosis and use of pre-biopsy mpMRI (for full details see **Appendix 1**).

Interestingly, whilst there was a clear emphasis on developing better understanding of treatment options and aspects of tailoring these to specific patient groups, there was less emphasis on the delivery and co-ordination of care or the particular expertise or skill set of the healthcare professionals involved in care.

Discussion

Both the abandonment of the paternalistic model of the doctor-patient relationship and the increasing knowledge of prostate cancer biology has led to a change in how prostate cancer patients are treated. General cancer treatments made way for patient-tailored treatments, not only taking tumour features into consideration, but also patients' quality of life, their personal expectations and desires. Although practice has already dramatically changed, the plethora of unanswered questions identified from this prioritisation exercise clearly reflects that this transition is not yet complete. The prioritised questions reflect the main concerns of both patients and HCPs on the natural history of prostate cancer, importance of improved disease stratification, its treatment options, their effectiveness and associated side effects or complications.

Notably, the two highest ranked questions are focussed on conservative strategies and are focussed on identifying patients who can be treated conservatively and safely in the active surveillance (AS) and watchful waiting (WW) setting. Although both treatment options are being used in daily practice, many uncertainties still exist. Among others, this is reflected by the recently published DETECTIVE Study, which was designed to formulate consensus statements on AS due to the lack of higher levels of evidence {Lam, 2019, EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study)}.

Questions 3-5 and 8 are also a reflection of the increasing appreciation of disease and patient heterogeneity {Joniau, 2015, Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study}{Van den Broeck, 2019, Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A

Systematic Review}. Big data will allow for a better risk stratification of patients and disease with meaningful real world clinical endpoints. Further, this big data could lead to optimised risk stratification using both clinical and omics data (Q7), which could ultimately lead to the development of clinical prediction models, allowing for more patient-tailored treatment strategies with less toxicity and higher efficacy.

Not only would big data allow for the development of prognostic models, it could also allow for better prediction of therapeutic response. Management of the various stages of prostate cancer is becoming more challenging as we gain more knowledge on disease biology and with the introduction of new technologies and treatments. In an ever-changing field, understanding the safety profile of the available treatments, and determining the optimal sequencing of the various types of multimodal treatments that are now part of the treatment armamentarium are critical (Q 6 and Q10). Finally, the management of complex and less common clinical scenarios (such as the management of oligometastatic disease) remains unclear (Q9), which could be answered using big data as well.

Future directions

PIONEER is a consortium dedicated to improving the diagnosis, treatment and care of patients with prostate cancer through the development and implementation of research studies to address clinical knowledge gaps. Members of the PIONEER Consortium can form Research Question (RQ) Teams. . These RQ Teams are dedicated to address specific Research Questions and each data contributor has the right to participate in the research teams developing the protocols. Any PIONEER beneficiary or data contributor (including industry participants) can propose the creation of a new Research Question Team to focus on specific Research Questions identified from either the list of 56 prioritized questions or by proposing a new question (non-prioritized questions must be justified).

In order to support and sanction the establishment of RQ Teams, a PIONEER RQ Oversite Committee was formed with membership designated by the PIONEER Executive Committee. The RQ Oversite Committee is made up of senior clinicians and researchers from both public and private partners with the aim of ensuring transparency and efficiency when using the PIONEER big data platform to answer the most relevant questions pertaining to prostate cancer patients, and generate high-quality publications with results that provide evidence-

based data to underpin clinical practice guideline recommendations as well as informing the decision-making processes by healthcare providers and patients.

The committee process is covered in the Research Committee Charter, which is available to all PIONEER members. Briefly, to initiate the formation of a new RQ Team , the beneficiary or associated partner will submit an application to the Chair of the RQ Oversite Committee at least 7 days prior to the next Research Committee Meeting, which are held once monthly. A thorough review of the merits of the proposed application is made on the basis of:

a) Does the proposed team address a scientifically or clinically relevant question?
b) Does the proposed team overlap an existing team's activities?
c) Does PIONEER have sufficient data to support the proposed investigation?
d) Does the proposed team meet the basic qualifications as set out in the application?

In addition to the above criteria, there are a number of points that must be addressed before approval is given. To warrant a true collaborative team, the RQ Team membership must include a minimum of 2 Public and 2 EFPIA partners. Once the application is approved then membership to the RQ Team is open to all PIONEER partners. Also within the proposal, the applicant should clearly explain the RQ to be tackled, address the knowledge gaps that are associated with the question, present the study design and methods to be used, state the key variables (inclusion/exclusion criteria, endpoints, covariates/controls) and indicate expected key findings; including how the findings will be used to improve patient care, outcomes and lives.

Finally, the applicant must identify a list of at least 3 datasets that will be used to answer the question along with a timeline and publication/dissemination plan.

The Research Committee bylaws state that in order for a proposal to be considered, a minimum of 80% of the RQ Oversite Committee members must be present at the meeting and a decision to sanction a new RQ team will require at least 60% majority of the committee members present at the meeting. The decision will be announced to the applicant within 3 days of the committee meeting.

For example, the research question 1 which focuses on the natural history of PCa patients and the impact of life expectancy and comorbidities on outcome of conservative management, was approved by the PIONEER Research Committee. The research team organised the

PIONEER Study-A-Thon held in March 2020 in collaboration with EHDEN (The European Health Data & Evidence Network) and OHDSI The Observational Health Data Sciences and Informatics) aimed to characterise the long-term outcomes (clinical characterisation) of prostate cancer patients managed with conservative treatment and to build a prediction model to generate risk scores that could inform patients about their possible risks. Out of 12 data bases analysed at the time of the Study-A-Thon, there were 1,557,114 PCa patients identified (patients diagnosed between 1989 and 2021). Out of these patients, 896,318 received immediate treatment whereas 536,235 received conservative management. Critically, patients were actively participated from start to finish of the Study-A-Thon, they shared their experiences of living with prostate cancer, impact of treatment and their experiences of survivorship including gaps in care that exist and outcomes of most importance for them. Results will be presented in a separate publication. PIONEER has formed other RQ teams to answer some of the top questions. Patients will again be central to the planning, protocol development and execution of the research questions.

By successfully answering the prioritised research questions, the expectation is that the findings would constitute real world evidence that would be relevant and used to fill gaps in clinical practice guidelines (underpinning recommendations) and further improving clinician-patient shared decision making.

Strengths and weaknesses of the study

Main strengths of our modified Delphi approach are that the online format facilitated a large and diverse sample, and the anonymous feedback allowed participants to know both stakeholder groups' scores without giving undue influence to dominant voices or to those with perceived authority. A limitation of our approach is that additional patient group participants were added in round two, whereas methods guidance supports not adding participants (21). Although we did accept this as a limitation, the decision to invite further participants was to boost sample size, target maximum diversity in opinion and to mitigate against the anticipated critique that our original English speaking-only sample may not have adequately included opinions from other native European languages, in case these opinions systematically deviated from the English-speaking sample.

A further limitation was the inclusion of pharmaceutical industry representatives who may be seen as having a conflict of interest in driving the prioritisation of research questions. Nonetheless, our anonymous scoring process, and the definition of consensus being applied as a percentage and to the two stakeholder groups separately means that industry voice has been considered, but had no more weight than any other stakeholder group in the results.

Conclusions

PIONEER has conducted an international multi-stakeholder consensus in order to identify and prioritise the most important questions in the field of prostate cancer. Identification of critical questions will help the PIONEER consortium to answer those questions that are critical to key stakeholders including patients.

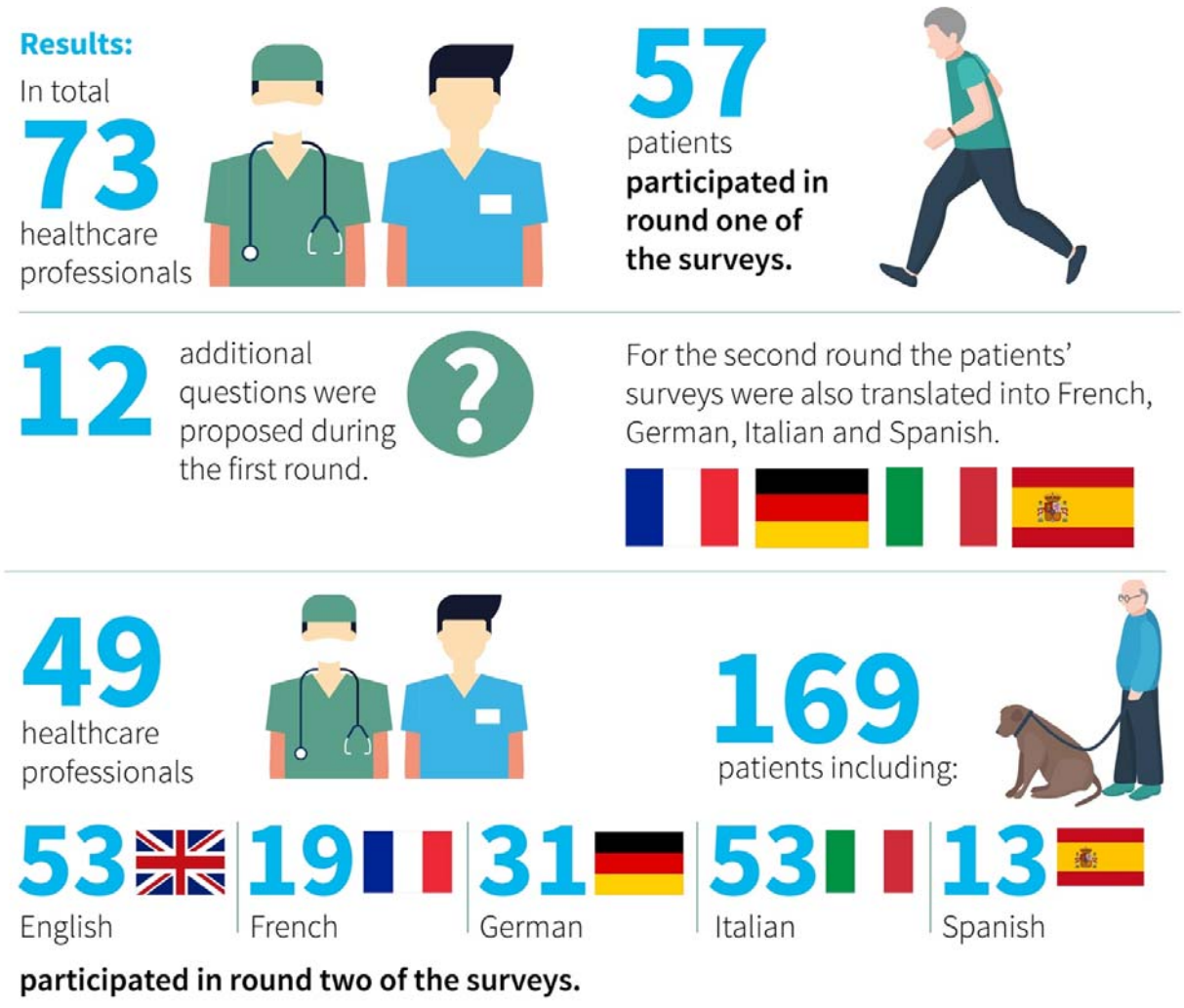

Figure 1: Graphical illustration of participants who took part in an international multi-stakeholder consensus by PIONEER Consortium

	PIONEER - Unanswered questions in prostate cancer: Findings of an international multi-stakeholder consensus by the PIONEER Consortium			
Final Ranking	**Questions**	HCPs centred prioritiation	Patients centred prioritiation	**All respondents**
1	What are the relevant tumour-specific and patient-specific variables that affect prognosis of PCa patients suitable for active surveillance? (Q4)	89.6	90.2	**89.9**
2	What is the natural history of PCa patients undergoing conservative management (i.e., watchful waiting) and what is the impact of comorbidities and life expectancy on long-term outcomes?	85.4	89.0	**87.2**
3	Currently, the scientific community generally applies the EAU Guidelines PCa risk stratification, stratifying patients into low-, intermediate- and high-risk PCa. This is based on the risk of recurrent disease of patients after radical treatments. However, this risk stratification still has its limits and patients still have very heterogeneous outcomes especially in the high-risk group. What we still do not know is what differentiates patients with lethal vs non-lethal disease, irrespective of their risk stratification.	91.8	82.3	**87.1**
4	When should we treat patients who experience prostate cancer recurrence after primary treatment and which are the most effective therapeutic approaches?	79.6	92.5	**86.0**
5	Which specific patient groups benefit most of upfront chemotherapy? What are the side effects and What is impact on quality of life in real-life practice of chemotherapy in this setting? the benefit of potentially toxic upfront chemotherapy appears to be highly individual. Other factors to predict who would benefit most are needed. the benefit of chemotherapy in the subgroup patients who have recurrence after primary treatment is not known.	87.8	83.3	**85.5**
6	How does the rate of side effects / local problems (including secondary / palliative treatments needed) compare between treatments (open, laparoscopic, robot surgery, with or without lymph node dissection; brachytherapy, different forms of external beam radiation therapy), and which patient specific factors are associated with these adverse secondary endpoints?	79.6	91.4	**85.5**
7	What is the clinical benefit of determining patients' genetic risk profile regarding PCa management, especially in the screening setting? (Q1)	85.1	84.8	**85.0**
8	Which specific patient benefits from different available treatment options for CRPC?	85.1	84.7	**84.9**
9	Is there a therapeutic benefit of treating the local tumour in patients diagnosed with (oligo)metastatic PCa?	77.6	90.8	**84.2**
10	How should the available therapeutical options be sequenced in order to achieve response and best outcomes in individual patients and in specific settings? effects ideally need to be maximized while limiting side effects.	72.9	88.1	**80.5**
11	We still do not know whether in a real life setting, pre-biopsy mpMRI would be successful at predicting biopsy and patient outcomes. Furthermore, the added value of targeted biopsies in positive mpMRI investigations remains unclear as well.	79.2	79.6	**79.4**
12	Which is the best prognostic marker for prostate cancer patients treated with active surveillance?	77.6	79.8	**78.7**
13	At the moment we still do not know whether PSA screening is a viable strategy to detect PCa and if there are any other strategies defining patients who should under PSA screening. For example in patients with a positive family history, BRCA screening has been proposed and its results could be applicable to increase PSA screening efficiency. Up to now, this is based on small but valuable studies. Furthermore, other genetic tests (germline mutations in DNA damage repair genes or SNP studies for example) could be proposed to define this subset of patients that could benefit from PSA screening.	77.1	75.8	**76.4**
14	Which is the best test to be used during follow-up in prostate cancer patients?	64.6	85.8	**75.2**
15	What is the rate of long-term side effects specified per treatment type (surgery versus radiation)? How does surgeon training and experience impact outcomes?	59.2	87.6	**73.4**
16	Should we individualize follow-up according to treatment modality and disease characteristics in patients with prostate cancer?	71.7	74.1	**72.9**
17	Which are the most clinically relevant functional and oncologic outcomes that should be collected during follow-up in prostate cancer patients?	58.3	83.9	**71.1**
18	How best to co-ordinate care between multiple health professionals during and following completion of treatment for prostate cancer?	55.1	86.2	**70.6**
19	Are PSA screening policies for men aged 50 years and early diagnosis improving survival as compared to opportunistic screening?	59.2	78.8	**69.0**
20	Although mpMRI in expert hands overall has good NPVs and PPVs, still some tumors will never be captured by imaging. We do not know whether these tumors are pathologically different.	61.2	76.5	**68.9**
21	How can we improve patient-physician communication in patients diagnosed with prostate cancer and what is its impact on quality of life patient-reported outcomes?	55.1	75.9	**65.5**
22	Which are the most clinically relevant outcomes in PCa patients that should be collected by all cancer registries?	56.3	73.5	**64.9**
23	Which are the most effective strategies to improve functional outcomes recovery and mitigate side effects associated with systemic therapies in prostate cancer patients?	46.7	80.9	**63.8**
24	What is the rate of adherence to international guidelines for the diagnostic and treatment pathways of prostate cancer?	69.4	56.7	**63.0**
25	Which patients [demographics] experience side effects and late effects of different treatment modalities for prostate cancer? What are these side effects and late effects? When do they occur in the cancer care and aftercare pathway?	47.9	73.3	**60.6**
26	Should there be specialized Prostate Cancer Centers certified and re-certified according to the same criteria throughout Europe with public reporting of identical outcomes?	45.8	73.8	**59.8**
27	Although there is an excellent correlation between the newly introduced histological grading groups (ISUP groups) and prognosis, these results are all based on biochemical recurrence, which is a surrogate endpoint for PCa outcomes such as prostate cancer specific mortality and overall mortality. We do not know yet whether these grading groups are actually associated with hard end points such as prostate cancer specific survival.	51.1	66.1	**58.6**
28	Are results obtained using currently available data sources generalizable to all PCa patients?	41.7	74.1	**57.9**
29	Are available markers able to predict stronger endpoints such as metastases-free survival in prostate cancer patients?	54.2	59.0	**56.6**
30	What are the most important outcomes across different parts of the prostate cancer care pathway? The outcome domains can be subdivided into the following groups: a. Oncologicalb. Functionalc. Process and recoveryd. Complications and/or adverse eventse. Quality of lifef. Health economic and cost effectiveness	43.8	68.5	**56.1**
31	What are the oncologic and functional outcomes of patients with clinically localized prostate cancer undergoing experimental therapies that are not currently recommended by international guidelines (e.g., high-intensity focused ultrasound) as compared to the standard of care?	52.1	59.7	**55.9**
32	Should we routinely implement quality control initiatives to improve the quality of data collected?	44.7	66.9	**55.8**
33	How can we integrate clinical and biomarker data in prostate cancer data sources to develop novel predictive tools?	52.1	59.3	**55.7**
34	We do not know which risk calculator is the best risk calculator and whether there are differences between their efficiencies between populations. Furthermore, up to now it is not known either whether the use of a risk calculator would make the use of a pre-biopsy mpMRI obsolete.	47.9	57.3	**52.6**
35	How can we reduce heterogeneity in the outcomes reported by different data sources?	40.8	61.5	**51.2**
36	Can we integrate data coming from randomized trials into population-based and prospective cancer registries?	50.0	50.9	**50.5**
37	What is the best way of measuring those outcomes identified above (question 37)? The outcome measures can be sub-stratified further into the following domains: a. Definitions (e.g. biochemical recurrence following radical prostatectomy or radical radiotherapy) b. Thresholds c. Outcome measuring instrument (including PROMS for functional or quality of life outcomes) d. Metrics of measurement (change from baseline or discrete endpoints) e. Reporting statistic f. Time point of measurement	45.8	54.4	**50.1**
38	What are the rates of incidence, prevalence, and mortality of prostate cancer across Europe?	46.9	53.2	**50.1**
39	How does focal therapy compare to standard of care in terms of oncological and functional outcomes in patients affected by localized prostate cancer?	46.9	50.3	**48.6**
40	How do we routinely collect cancer survivorship data including current disease status, functional ability, current medications, co-morbidities, quality of life, psychological wellbeing, social outcomes, cancer treatment history and modalities used?	35.4	59.6	**47.5**
41	Should we offer imaging during follow-up in men treated with androgen deprivation therapy for prostate cancer?	38.8	53.7	**46.2**
42	Although it is generally assumed that a Gleason pattern 5 (most dedifferentiated histological subtype) is a major determinant in PCa mortality, we do not know whether a tertiary Gleason 5 component <5% in ISUP group 2 or 3 on a RP specimen has an impact on patients' outcome and whether there is a differential outcome in patients with ISUP group 4 with a Gleason 5 component >5% compared to only Gleason 4 pattern. It has been suggested before that this tertiary component is correlated with a more extensive tumor phenotype, mainly in lower grade tumors.	35.4	56.7	**46.1**
43	We do not know whether there is a difference in (significant) PCa occurrence based on geographical location within Europe when corrected for differential PCa management (differences in PSA screening, treatment decisions etc).	49.0	40.7	**44.8**
44	For each part of the prostate cancer care pathway, what important baseline or pre-intervention characteristics are important? What is the best way of measuring them?	27.1	59.3	**43.2**
45	What support is needed for psychosocial late effects (fear, anxiety, distress, ptsd, employment) (+ = strengthened relationships, empowerment, appreciation of life) following detection? When is this needed in the cancer care and aftercare pathway? What triggers the delivery of this support?	29.2	56.8	**43.0**
46	At this moment, multiple commercially available biomarker tests have shown success in increasing PCa diagnosis efficiency. However, we do not know how this has contributed to PCa diagnosis dynamics in Europe.	44.7	40.9	**42.8**
47	What support is needed for physical late effects (include musculoskeletal issues, fatigue, last of stamina, urinary / bowel problems, lymphedema, premature menopause, cognitive deficits and sexual dysfunction) following detection? When is this needed in the cancer care and aftercare pathway? What triggers the delivery of this support?	26.5	58.6	**42.6**
48	How does state-of-the-art risk assessment and treatment regimes for PC compare across major cancer centers, and how has this changed over the past decade?	26.5	57.1	**41.8**
49	When should we stop follow-up in patients with localized prostate cancer?	27.1	52.8	**39.9**
50	What is the impact of satellite low-volume lesions next to the index lesion in patients suitable for focal therapy?	28.6	45.6	**37.1**
51	How do various PC data-sources/databases compare in terms of quality, size, geography, and overlap?	28.6	44.8	**36.7**
52	What is the risk of prostate cancer death for men on five alpha reductase inhibitors?	25.0	48.4	**36.7**
53	We do not know which of the proposed environmental risk factors are actually causative or protective for (significant) PCa?	36.7	29.5	**33.1**
54	Are men aged 50-75 years old who underwent vasectomy at increased incidence of prostate cancer as compared to individuals who did not receive a vasectomy?	21.3	30.8	**26.0**
55	Are currently available predictive models for prostate cancer outcomes generalizable to a population level?	16.3	26.3	**21.3**
56	Which individuals are most likely to drop out of employment during and following completion of treatment for prostate cancer? When does this occur in the cancer care and aftercare pathway?	14.3	22.4	**18.3**

Table 1: Unanswered questions in prostate cancer: Findings of an international multi-stakeholder consensus by the PIONEER Consortium

Percentage (%) of agreement indicate the mean of the percentages across the two stakeholder groups scoring each of the 56 questions as “critically important” was calculated and used to rank the questions in terms of those scoring highest in the “critically important” category.

* Blue-12 additional questions proposed in Round 1

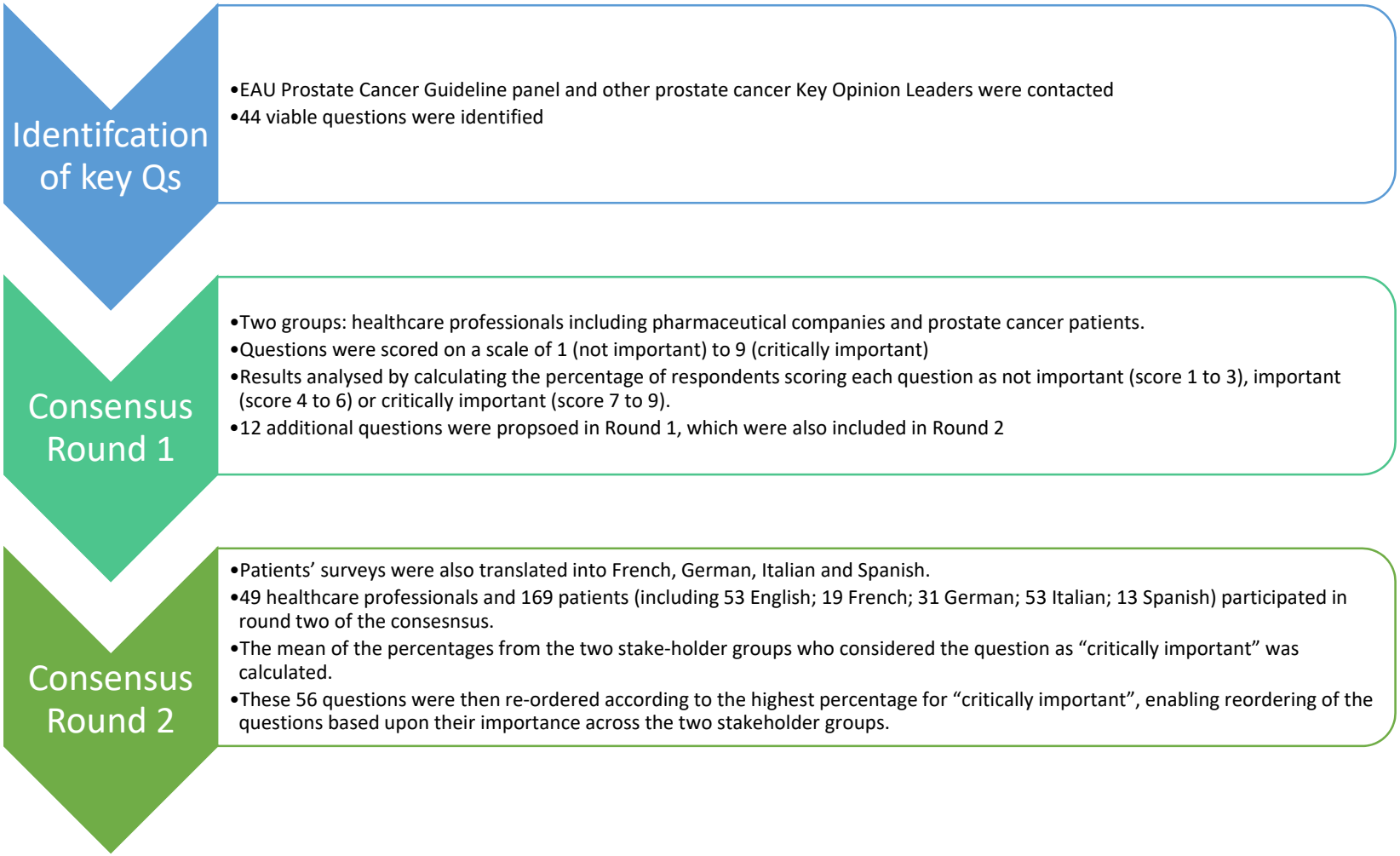

Figure 2: Consensus process

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