Review

Xavier Filella*, María Dolores Albaladejo, Juan Antonio Allué, Miguel Angel Castaño, Daniel Morell-Garcia, Maria Àngels Ruiz, María Santamaría, María José Torrejón and Nuria Giménez

Prostate cancer screening: guidelines review and laboratory issues

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Abstract

Background: Prostate-specific antigen (PSA) remains as the most used biomarker in the detection of early prostate cancer (PCa). Clinical practice guidelines (CPGs) are produced to facilitate incorporation of evidence into clinical practice. This is particularly useful when PCa screening remains controversial and guidelines diverge among different medical institutions, although opportunistic screening is not recommended.

Methods: We performed a systematic review of guidelines about PCa screening using PSA. Guidelines published since 2008 were included in this study. The most updated version of these CPGs was used for the evaluation.

Results: Twenty-two guidelines were selected for review. In 59% of these guidelines, recommendations were graded according to level of evidence ($n=13$), but only 18% of the guidelines provided clear algorithms ($n=4$). Each CPG was assessed using a checklist of laboratory issues, including pre-analytical, analytical, and post-analytical factors. We found that laboratory medicine specialists participate in 9% of the guidelines reviewed ($n=2$) and laboratory issues were frequently omitted. We remarked that information concerning the consequences of World Health Organization (WHO) standard in PSA testing was considered by only two of 22 CPGs evaluated in this study. **Conclusions:** We concluded that the quality of PCa early detection guidelines could be improved properly considering the laboratory issues in their development.

Keywords: clinical practice guidelines; prostate cancer; prostate-specific antigen (PSA); screening.

***Corresponding author: Xavier Filella**, Evidence Based Laboratory Medicine Commission and Biological Markers of Cancer Commission, Spanish Society of Laboratory Medicine (SEQC-ML), Barcelona, Spain; and Department of Biochemistry and Molecular Genetics (CDB), Hospital Clinic, IDIBAPS, Barcelona, Spain, E-mail: xfilella@clinic.cat

María Dolores Albaladejo: Evidence Based Laboratory Medicine Commission, Spanish Society of Laboratory Medicine (SEQC-ML), Barcelona, Spain; and Department of Clinical Analysis and Biochemistry, Hospital General Universitario Santa Lucía, Cartagena, Spain

Juan Antonio Allué: Evidence Based Laboratory Medicine Commission, Spanish Society of Laboratory Medicine (SEQC-ML), Barcelona, Spain; and Synlab Diagnosticos Globales, Sevilla, Spain

Miguel Angel Castaño: Evidence Based Laboratory Medicine Commission, Spanish Society of Laboratory Medicine (SEQC-ML), Barcelona, Spain; and Department of Biochemistry, Hospital Clínico Universitario Juan Ramón Jiménez, Huelva, Spain

Daniel Morell-Garcia: Evidence Based Laboratory Medicine Commission, Spanish Society of Laboratory Medicine (SEQC-ML), Barcelona, Spain; and Department of Laboratory Medicine, Hospital Universitari Son Espases, Palma de Mallorca, Spain

Maria Àngels Ruiz: Evidence Based Laboratory Medicine Commission, Spanish Society of Laboratory Medicine (SEQC-ML), Barcelona, Spain; and Department of Laboratory Medicine, Fundació Hospital de l'Esperit Sant, Santa Coloma de Gramenet, Barcelona, Spain

María Santamaría: Evidence Based Laboratory Medicine Commission, Spanish Society of Laboratory Medicine (SEQC-ML), Barcelona, Spain; and Department of Biochemistry, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

María José Torrejón: Evidence Based Laboratory Medicine Commission, Spanish Society of Laboratory Medicine (SEQC-ML), Barcelona, Spain; and UGC of Clinical Analysis, Hospital Clínico San Carlos, Madrid, Spain

Nuria Giménez: Evidence Based Laboratory Medicine Commission, Spanish Society of Laboratory Medicine (SEQC-ML), Barcelona, Spain; Committee of Evidence-Based Laboratory Medicine (C-EBLM), International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), Milano, Italy; Research Unit, Research Foundation Mútua Terrassa, Universitat de Barcelona, Barcelona, Spain; and Laboratory of Toxicology, Universitat Autònoma de Barcelona, Barcelona, Spain

Introduction

Prostate cancer (PCa) is the most prevalent cancer in males in Western countries. In Europe, an incidence of 450,000 new cases and a mortality of 107,000 cancer deaths per year have been estimated for 2018 [1]. Prostate-specific antigen (PSA) remains as the most used biomarker in the detection of early PCa. However, since 2009, PSA usefulness in PCa screening has been widely argued following the opposite results obtained in the two largest randomized screening studies. The European Randomized Study of Screening for Prostate Cancer (ERSPC), enrolling 162,387 men between 50 and 74 years old from seven European countries, found a PCa-specific mortality reduction of 20% in the screened group after a median follow-up of 9 years [2]. In evident contrast, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial, based on 76,693 men, found no differences in the PCa-specific mortality after 7 years of follow-up between the screened group and the control group [3]. Furthermore, these opposite results were confirmed by both groups increasing the time of follow-up and differences were confirmed by the ERSPC trial [4].

In 2011 the United States Preventive Services Task Force (USPSTF) strongly advise against PSA screening based on a review of six well-done trials, underlying harms related to subsequent evaluation and treatments [5]. Nevertheless, several studies showed the evidence that screening reduces the risk of metastasis both at diagnosis and during follow-up [6, 7]. Furthermore, Gulati et al. [8] suggested that discontinuing PSA screening for all men may generate many avoidable cancer deaths in the next years. On the other hand, Stephan et al. [9] remarked on methodological limitations in the meta-analysis showing no evidence of a PCa-specific mortality reduction, suggesting the value of multivariable risk-prediction tools to select appropriate treatment or active surveillance. Additionally, in a recent review, Carlsson and Roobol [10] underlined data emerging in last years that suggest a new approach to PCa screening according to PSA-based risk stratification at an early age. Similarly, Eapen et al. [11] postulated in favor of a smarter screening approach, based on relatively infrequent PSA testing, consistent use of multivariable risk stratification, and selective treatment focused on patients with high grade PCa.

Clinical practice guidelines (CPGs) are produced to facilitate incorporation of evidence into clinical practice. This is particularly useful when PCa screening remains controversial and guidelines diverge among different medical institutions. Ideally CPGs from different organizations should be based on high quality methodology to achieve similar clinical recommendations. Unfortunately,

despite of the enormous energies invested in its realization, the value of CPGs varies considerably. Clinicians should consider recommendations of varying evidence levels differently. A multidisciplinary approach, the description of the sources of information used, and recommendations graded according to level of evidence are necessary items to be considered in a high-quality CPG.

The evidence-based laboratory medicine commission of the Spanish Society of Laboratory Medicine (SEQC-ML) has observed that, despite the obvious involvement of the clinical laboratory in the PCa screening using PSA, some technical aspects have been unremarked among clinicians [12].

We critically review the characteristics of guidelines about PCa detection, focusing the attention on the laboratory issues considered. In addition, we propose a checklist including several laboratory issues related to PSA measurement that in our opinion should be considered during the development of clinical practice guidelines.

Materials and methods

Information sources, search strategy and study selection

A systematic search was undertaken using several electronic databases: Medline/PubMed, Web of Science and Scopus. A strategic search was done by one reviewer looking for combinations of the following search terms: as publication type (“Guideline”, “Practice Guideline”), as medical subject heading MeSH (“Guidelines as Topic”, “Prostatic Neoplasms”, “Prostate-Specific Antigen”, “Mass Screening”, “Early Detection of Cancer”, “Diagnosis”) and as free search terms (“guideline”, “prostate cancer”, “prostate specific antigen”, “screening”, “diagnosis”). Guidelines published since 2008 were included in this study. The most updated version of these CPGs was used for the evaluation. This scientific literature search was complemented with three international guideline websites: National Guidelines Clearinghouse [13], Guidelines International Network Web site [14] and National Institute for Health and Care Excellence (NICE) [15].

Eligibility criteria

All the guidelines were considered eligible for inclusion if they met the following criteria: publication type guideline, published in the last 10 years, written in English language.

Data collection process

Two of the authors participated in the final process of guideline selection. The main information, overall recommendation and remarkable quality information of each guideline was extracted by two researcher and independently checked for accuracy by the other researchers. Disagreements between researchers were resolved by discussion.

Each CPG was assessed using a checklist of laboratory issues following the criteria described by Aakre et al. [16]. These criteria were adapted for the PSA assay. Previous versions of the selected GPCs were also checked for this purpose.

The Appraisal of Guidelines Research and Evaluation II (AGREE II) instrument was used to assess the quality of guidelines. This tool has 23 items distributed in six domains: scope and purpose (1), stakeholder involvement (2), rigor of development (3), clarity of presentation (4), applicability (5) and editorial independence (6). Each guideline was rated by four independent appraisers trained using the online training tools recommended by the AGREE collaboration. We also followed the AGREE II instrument guideline to calculate all the scores.

Figure 1: Study selection process.

Results

The study selection process is summarized in Figure 1.

A summary of the most relevant characteristics of the 22 selected PCa guidelines are shown in Table 1 [17–38], including information concerning, among others, overall recommendation, laboratory issues considered, the description of the sources of information used, and recommendations graded according to the level of evidence. Shared decision considering benefits and harms of PCa screening is a frequent criterion in the evaluated guidelines, while mass screening is not recommended in any guideline. Differences among guidelines go from the non-restricted criteria counseled by the Canadian Urological Association to the recommendation against screening counseled by the American College of Physicians or the Australian Government National Health and Medical Research Council. Furthermore, in the majority of CPGs, screening is explicitly not recommended for men higher than 70 years old or with a life expectancy <10 years.

Table 2 shows a list of laboratory issues that should be examined for PSA measurement. CPGs should report information about these laboratory requirements for high quality results. The list was adapted from Aakre et al. [16]

but modified according to the specific criteria for PSA [39]. The issues were classified following three categories: pre-analytical, analytical and post-analytical phases. Specifically, guidelines should report information about the standard reference material used in the measurement of PSA and how reference ranges were established.

We found data concerning consequences of the adoption of the standard reference material from the World Health Organization (WHO) in PSA testing in only two of 22 CPGs evaluated in this study, the National Academy of Clinical Biochemistry (NACB) and the National Comprehensive Cancer Network (NCCN) guidelines. Also, the guideline of the Canadian Urological Association informs of 20%–25% differences in the concentration of PSA among laboratories.

Previous versions of the selected GPCs were also checked for this purpose. We found relevant data in previous versions of American Urological Association (AUA) guidelines, corresponding to 2009, and the European Association of Urology (EAU) guidelines, corresponding to 2013 and 2015, respectively.

Three of the six CPGs considering laboratory issues remark that assays using the WHO standard offer results 20%–25% lower than those using the initial Hybritech® standard. The other three guidelines only refer that results

Table 1: Summary of characteristics of PCa screening guidelines.

Guidelines	Institution, year	Focused on PCa early detection	Overall recommendation (Level of evidence and grade of recommendation)	Additional biomarkers recommended	Shared decision	Clinical algorithms	Laboratory issues were considered	Laboratory medicine specialists participating in the guideline	Description of the sources of information used	Recommendations graded according to level of evidence
National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers [17]	National Academy of Clinical Biochemistry, 2008	No	These guidelines do not endorse a general recommendation for mass screening. More studies are necessary to decide to recommend the implementation of PSA as screening test (LE: III; GR: A)	The use of %fPSA is recommended as an aid in the detection of PCa in men with PSA 4–10 µg/L and DRE negative	Yes	Not provided	Yes	Yes	Review of the literature on PSA screening	Yes
The Japanese Guideline for Prostate Cancer Screening [18]	Japanese Research Group for Development of Cancer Screening Guidelines, 2009	Yes	There was no conclusive evidence that PSA screening reduces PCa mortality. Opportunistic screening: PSA and DRE were not recommended for population-based screening programs, but they could be conducted as individual-based screening (LE: I)	Not recommended	Yes	Not provided	No	No	Systematic literature review	Yes
Updated Japanese Urological Association Guidelines on prostate-specific antigen-based screening for prostate cancer in 2010 [19]	The Committee for Establishment of the Guidelines on Screening for Prostate Cancer and Japanese Urological Association, 2010	Yes	PSA screening should be offered to all men at risk of developing PCa with fact sheets showing updated benefits and drawbacks of screening for PCa	Not recommended	Yes	Not provided	No	No	Systematic literature review	No
American Cancer Society Guideline for the Early Detection of Prostate Cancer [20]	American Cancer Society, 2010	Yes	Asymptomatic men who have at least a 10-year life expectancy should have an opportunity to make an informed decision about screening for PCa	Not recommended	Yes	Not provided	No	No	Systematic literature review	No
Prostate cancer screening: Canadian Guidelines [21]	Canadian Urological Association, 2011	Yes	Prostate cancer screening should be offered to all men 50 years of age with at least a 10-year life expectancy (LE: I) Strong consideration should be given to discontinuing PSA screening for Canadian men over 75 years of age (LE: III)	The PSA velocity, PSAD and PSA free to total ratio may improve PSA sensitivity and specificity	Yes	Not provided	Yes	No	Systematic literature review	Yes
Screening for Prostate Cancer with Prostate-Specific Antigen Testing [22]	American Society of Clinical Oncology, 2012	Yes	In men with a life expectancy <10 years, it is recommended that general screening for prostate cancer with total PSA be discouraged, because harms seem to outweigh potential benefits In men with a life expectancy >10 years, it is recommended that physicians discuss with their patients whether PSA testing for prostate cancer screening is appropriate for them (Evidence based: strong)	Not recommended	Yes	Not provided	No	No	Systematic literature review	Yes

Table 1 (continued)

Guidelines	Institution, year	Focused on PCa early detection	Overall recommendation (Level of evidence and grade of recommendation)	Additional biomarkers recommended	Shared decision	Clinical algorithms	Laboratory issues were considered	Laboratory medicine specialists participating in the guideline	Description of the sources of information used	Recommendations graded according to level of evidence
Prostate Cancer Taskforce. Diagnosis and Management of Prostate Cancer in New Zealand Men [23]	Recommendations from the Prostate Cancer Taskforce. Wellington: Ministry of Health, 2012	No	Population screening for asymptomatic men with PSA testing is currently not recommended However, for men with a request for PCa screening, primary health care should provide high-quality, culturally appropriate information on prostate cancer and PSA testing to men aged 50–70 years	PSA modifications (%PSA, PSA velocity, PSA doubling time, PSAD, age adjusted reference ranges) should be restricted in their use to those men in whom the decision on whether or not to biopsy is difficult	Yes	Not provided	No	No	Systematic literature review	No
Screening for PCa: a guidance statement from the Clinical Guidelines Committee of the American College of Physicians [24]	American College of Physicians, 2013	Yes	The guideline recommends that clinicians inform men from 50 to 69 years old about the limited potential benefits and substantial harms of screening for PCa ACP recommends that clinicians base the decision to screen for PCa using PSA based on the risk for PCa, a discussion of the benefits and harms of screening, the patient's general health and life expectancy, and patient preferences	Not recommended	Yes	Not provided	No	No	Search on the National Guideline Clearinghouse for guidelines on screening for prostate cancer	No
The Melbourne Consensus Statement on the early detection of PCa [25]	Multidisciplinary group of the world's leading experts, 2013	Yes	While routine population-based screening is not recommended, healthy, well-informed men aged 50–69 years should be fully counseled benefits and harms of screening Experts disagree about whether PCa screening causes more benefit or harm (LE: I)	New tools, such as PHI and PCA3, can help to better risk stratify men, potentially reducing overdiagnosis and overtreatment of indolent PCa	Yes	Not provided	No	No	An appraisal of existing guideline statements and an overview of published data about the early detection of PCa	Yes
University of Michigan Health System. Cancer screening [26]	University of Michigan Health System, 2014	No	If PCa screening is considered, for men who have at least a 10-year life expectancy, an informed decision-making process should precede a decision to perform screening (LE: I; GR: A)	PCA3, is currently being studied; It may be most useful for men with elevated PSA and a prior negative prostate biopsy	Yes	Not provided	No	No	Systematic literature review	Yes
Recommendations on screening for prostate cancer with the prostate-specific antigen test [27]	Canadian Task Force on Preventive Health Care, 2014	Yes	We recommend not screening for PCa with the PSA test (Strong recommendation against screening for men <55 or ≥70; weak recommendation for the rest) Because of recent efforts to encourage screening for PCa, some men may be interested in PSA screening despite the current recommendations. The PSA test should not be used for screening without a detailed discussion with the patient about benefits and harms of screening	Not recommended	Yes	Not provided	No	No	Systematic literature review	Yes

Table 1 (continued)

Guidelines	Institution, year	Focused on PCa early detection	Overall recommendation (Level of evidence and grade of recommendation)	Additional biomarkers recommended	Shared decision	Clinical algorithms	Laboratory issues were considered	Laboratory medicine specialists participating in the guideline	Description of the sources of information used	Recommendations graded according to level of evidence
PSA Testing for Prostate Cancer in symptomatic Men. Information for Health practitioners [28]	Australian Government. National Health and Medical Research Council, 2014	Yes	The present evidence is inconsistent as to whether PSA testing affects the risk of dying from PCa	Not recommended	Yes	Not provided	No	No	Summary of the evidence	No
National Collaborating Centre for Cancer, PCa: diagnosis and treatment [29]	National Institute for Health and Care Excellence, 2014	No	Give men information, support and adequate time to make a decision. Include explanation of the risks and benefits of screening (LE: 2+)	%PSA or cPSA have been employed to increase specificity, particularly in the PSA range 2–10 µg/L and might reduce the number of unnecessary biopsies A raised PCA3 level was associated with PCa in men with a negative first prostate biopsy	Yes	Yes	No	No	Systematic literature review	Yes
Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [30]	European Society for Medical oncology, 2015	No	Population-based PSA screening for PCa reduces PCa mortality at the expense of over diagnosis and overtreatment and is not recommended (LE: I; GR: C) The decision whether or not to have a prostate biopsy should be made in the light of DRE findings, ethnicity, age, co-morbidities, PSA values, %fPSA, history of previous biopsy and patient values Testing for PCa in asymptomatic men should not be done in men >70 years old (LE: I; GR: B)	%PSA is considered to decide prostate biopsy	Yes	Not provided	No	No	The relevant literature has been selected by the expert authors	Yes (LE: I; GR: C, for population-based PCa screening; B for testing in men >70 years old)
Prostate Cancer, Clinical Practice Guideline [31]	Alberta Health Services, 2015	No	Serum PSA should be checked in fit men between the ages of 50 and 75 years, where clinically indicated Serum PSA screening increases the detection rate of early stage clinically significant PCa; early detection may improve overall survival Fit men between the ages of 50 and 75 years with at least 10 years life expectancy should be made aware of the availability of PSA as a detection test for PCa; they should be aware of the potential benefits and risks of early detection so they can make an informed decision as to whether to have the test performed	Not recommended	Yes	Not provided	No	No	Systematic literature review	No

Table 1 (continued)

Guidelines	Institution, year	Focused on PCa early detection	Overall recommendation (Level of evidence and grade of recommendation)	Additional biomarkers recommended	Shared decision	Clinical algorithms	Laboratory issues were considered	Laboratory medicine specialists participating in the guideline	Description of the sources of information used	Recommendations graded according to level of evidence
Choosing Wisely® in Preventive Medicine [32]	American College of Preventive Medicine Prevention Practice Committee, 2016	No	Men should only consent to being screened for PCa after they clearly understand the associated benefits and risks	Not recommended	Yes	Not provided	No	No	Each task force member developed two to three recommendations based on their individual evidence searches	No
The Memorial Sloan Kettering Cancer Center Recommendations for Prostate Cancer Screening [33]	Memorial Sloan Kettering Cancer Center, 2016	Yes	The best evidence suggests that more restricted indication for prostate biopsy and a more focused approach to pursue screening in men at highest risk of lethal cancer would retain most of the mortality benefits of aggressive screening schema, while importantly reducing harms from overdetection and overtreatment	Commercially available reflex tests that have been shown to be associated with the risk of high-grade disease include blood tests such as the %tPSA, the PHI, the 4Kscore, and the urinary testing of <i>PCA3</i>	Yes	Yes	No	Yes	Systematic review of literature was discarded The evidence base was to focus on three well-known high-quality studies: ERSPC, PLCO and Malmö Project Study These studies were complemented by other data for a limited number of uncontroversial areas	No
Guidelines for preventive activities in general practice. 9th edition [34]	Royal Australian College of General Practitioners, 2016	No	Screening of asymptomatic (low-risk) men for prostate cancer by PSA testing is not recommended If after an informed process a man still requests PCA screening, a PSA is acceptable	Not recommended	Yes	No	No	No	The recommendations are based on current, evidence-based guidelines	No
EAU–ESTRO–SIOG Guidelines on Prostate Cancer [35]	European Association of Urology, European Society for Radiotherapy and Oncology and International Society of Geriatric Oncology, 2017	No	Mass screening of PCA is not indicated. However, early diagnosis on an individual basis is possible offering an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status and a life expectancy of at least 10–15 years (LE: III; GR: B)	The %tPSA stratifies the risk of PCA in men with 4–10 µg/L total PSA and a previous negative biopsy Novel assays for risk stratification including the PHI and the 4Kscore are intended to reduce the number of unnecessary biopsies in men with a PSA between 2 and 10 µg/L	Yes	No	No	No	Systematic literature review	Yes (LE: III; GR: B)
Early detection of Prostate Cancer: AUA Guideline [36]	American Urological Association, 2018	Yes	For men ages 55–69 years the panel recognizes that the decision to undergo PSA screening involves weighing benefits and harms associated with screening and treatment (GR: B) The Panel recommends against PSA screening in men under age 54 years at average risk or in men age 70 years or more, or any man with less than a 10–15- year life expectancy (GR: C)	PSA derivatives (PSAD, age specific reference ranges, PSA kinetics (velocity and doubling time), %tPSA, proPSA, and <i>PCA3</i> should be considered secondary tests with potential utility for determining the need for a prostate biopsy—or repeat biopsy—after PSA screening	Yes	Yes	No	No	Systematic review and meta analysis	Yes (GR: B for men from 55 to 69 years old; C for the rest)

Table 1 (continued)

Guidelines	Institution, year	Focused on PCa early detection	Overall recommendation (Level of evidence and grade of recommendation)	Additional biomarkers recommended	Shared decision	Clinical algorithms	Laboratory issues were considered	Laboratory medicine specialists participating in the guideline	Description of the sources of information used	Recommendations graded according to level of evidence
Prostate Cancer early detection (version 2.2018) [37]	National Comprehensive Cancer Network, 2018	Yes	Men opting to participate in an early detection program after receiving the appropriate counseling on benefits and harms The guidelines for when to start and stop screening, at what intervals to conduct screening, and when to biopsy were recommended by most panel members, but a consensus was not reached (LE: II, GR: A)	%fPSA <10%, PHI >35 or 4Kscore (which provides an estimate of the probability of high-grade PCa) are potentially informative in patients who have never undergone biopsy or after a negative biopsy A PCA3 score >35 is potentially informative after a negative biopsy	Yes	Yes	Yes	No	Systematic literature review	Yes (LE: II, GR: A)
Screening for Prostate Cancer US Preventive Services Task Force Recommendation Statement [38]	US Preventive Services Task Force, 2018	Yes	For men aged 55–69 years, the decision to undergo periodic PSA-based screening for PCa should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision (GR: C) The panel recommends against PSA-based screening for prostate cancer in men 70 years and older (GR: D)	Not recommended	Yes	No	No	No	Systematic literature review	Yes (Gr: C for men aged 55–69 years; D for men older than 70 years)

cPSA, complexed PSA; DRE, digital rectal examination; ERSPC, European randomized study of screening for prostate cancer; %fPSA, percentage of free PSA to total PSA; PCA3, prostate cancer 3 gene; LE, level of evidence; PHI, prostate health index; PCa, prostate cancer; PLCO, prostate, lung, colorectal and ovarian cancer screening trial; GR, grade of recommendation; PSA, prostate specific antigen; PSAD, prostate specific antigen density.

Table 2: List of laboratory issues that should be considered for PSA assays in a clinical practice guideline.

Pre-analytical phase	Analytical phase	Post-analytical phase
Sampling handling: sample type; stability of specimen on storage; maximum number of freezing/thawing cycles Prostate manipulation: digital rectal examination; prostate massage; cystoscopy; transrectal ultrasound; prostate biopsy; bladder catheterization Sexual activity (ejaculation) Interferences caused by medication (5- α -reductase inhibitors) Genetic factors (polymorphisms in the <i>KLK3</i> gene) Intraindividual variability	Methodology: information about the assay used in the measurement of PSA; standard used in the calibration of the assay Quality issues: imprecision intra- and inter-assay; external quality assessment; accreditation of the laboratory Analytical interferences caused by lipemia, hemolysis or bilirubin Interference from heterophilic or human anti-mouse antibodies (HAMA)	Assay specific reference range

between different PSA assays are not interchangeable. A summary of these characteristics is shown in Table 3 [17, 37, 45, 48, 50]. The references cited in these guidelines about PSA standardization are also indicated.

We used the AGREE II instrument to evaluate the quality of the guidelines (Table 4). The overall assessment score ranged from 39.5% to 97% and 13 (59%) of the 22 guidelines obtained an overall assessment score higher to 70%. The highest score was reached by the NICE, the Canadian Task Force on Preventive Health Care and the AUA guidelines.

Discussion

The usefulness of PSA as a screening test for reducing PCa mortality has been an area of intense controversy. Nowadays, PCa guidelines recommend against routine PSA testing or emphasize that the decision to undergo early PSA testing should be a shared decision between the patient and his physician, considering potential benefits and harms. Nonetheless, discussion about the opportunity of screening remains. Actually, a balance between benefits and harms is the key point to decide to screen. So, active surveillance has been proposed to mitigate harms related with overtreatment in patients with indolent PCa. On the other hand, recently, several studies have noted a reduction in PSA screening rates following the USPSTF [5, 52] recommendation against systematic PSA screening in general population [53–55]. Fleshner et al. [56] have recently remarked that the withdrawal of PSA screening would prevent all cases of overdiagnosis, but would fail to prevent 100% of avoidable deaths, leading to a 13%–20% increase in PCa-related deaths. These data demonstrate that harms associated with no screening

must be also considered and suggest that the process of reviewing evidences and updating recommendations must be continuous. This is reflected in the remarkable changes in the recommendations of the US Preventive Services Task Force along the last decade. In 2008, the panel indicated for men younger than 75 years old that current evidence was insufficient to assess the balance of benefits and harms of PCa screening [57]. Later on, in 2012, the group recommended against PCa screening [52], but, more recently, in 2018, the panel recommends a shared decision considering benefits and harms for men aged from 55 to 69 years [38].

On the other hand, additional reflex tests in blood (Prostate Health Index, 4Kscore) or urine (*PCA3*) has been proposed by several guidelines [25, 26, 29, 33, 35–37] to increase PSA specificity and potentially to decrease the overdiagnosis of indolent PCa. Furthermore, recent data have demonstrated that these biomarkers can also improve the cost-effectiveness of PCa screening [58, 59], showing that is more cost-effective the use and development of screening tests than the use of tests after a negative biopsy [60].

The quality of PCa CPGs is heterogeneous according to published data. Heterogeneity of results has been emphasized by Gupta et al. [61] using the AGREE II instrument to assess the quality of 13 CPGs selected from 1999 to 2014. The authors showed that the guidelines from the NICE and AUA had the best scores in most domains using this tool. We share the same conclusion, remarking the heterogeneity of quality in guidelines and having obtained a high overall score for NICE and AUA guidelines, as well. In contrast, Qaseem et al. [24] gave a low overall quality rate to the AUA guideline, remarking the high quality of the American Cancer Society (ACS) guideline. All these results show the need for improving CPGs methodology and quality.

Table 3: Information about results concerning variability between PSA assays.

Guidelines	Institution, year	Information about PSA standardization	References concerning PSA assay cited in the guideline
National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers [17]	National Academy of Clinical Biochemistry, 2008	Two reference standards currently are commonly used for PSA assays: those traceable to the WHO International Standards and those traceable to the Hybritech, Inc. standard The initial Hybritech PSA values are about 20% higher than the WHO First International Standard for PSA Although several studies suggest that between-method comparability has improved since introduction of the International Standards, there are still differences in PSA assays that may lead to clinical misinterpretation if different PSA assays are used when evaluating a single patient	Sturgeon and Ellis [40] Rafferty et al. [41] Roddam et al. [42] Kort et al. [43] Stephan et al. [44]
Prostate-Specific Antigen Best Practice Statement: 2009 Update [45]	American Urological Association, 2009	Importantly, laboratory variability can range from 20% to 25% depending upon the type of standardization used. Assays using the 1999 WHO standard yield results 20%–25% lower than those using the Hybritech standard. It is necessary to use the same assay for longitudinal monitoring because PSA assays are not interchangeable and there is no acknowledged conversion factor between them. Consideration should be given to confirming an abnormal PSA before proceeding to biopsy	Etzioni et al. [46] Slev et al. [47]
Prostate cancer screening: Canadian Guidelines EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013 [48] EAU Guidelines on Prostate Cancer [50]	Canadian Urological Association, 2011 European Association of Urology, 2013 European Association of Urology, 2015	The variation between laboratories is 20%–25%; therefore using the same laboratory may reduce variability A PSA cut-off of 3 or 3.1 µg/L should be considered for WHO-calibrated assays to achieve the same sensitivity and specificity profile found with a cut-off of 4 µg/L in traditionally calibrated assays There are no agreed standards defined for measuring PSA	Etzioni et al. [46] Slev et al. [47] Stephan et al. [49] Semjonow et al. [51]
Prostate Cancer early detection (version 2.2018) [37]	National Comprehensive Cancer Network, 2018	PSA measures obtained using different commercial assays are not directly comparable or interchangeable, since the values are calibrated against different standards	Not provided

PSA, prostate specific antigen; WHO, World Health Organization.

Table 4: Quality appraisal of guidelines about PSA screening using the AGREE II instrument.

Institution (reference)	AGREE-II domains						Overall guideline assessment	
	1	2	3	4	5	6	Overall assessment	Rate the overall quality of this guideline (mean)
National Institute for Health and Care Excellence [29]	100%	97%	96%	97%	94%	98%	97.00	7.00 4 Yes
Canadian Task Force on Preventive Health Care [27]	90%	81%	90%	99%	73%	98%	88.50	6.50 4 Yes
American Urological Association [36]	100%	78%	87%	99%	52%	100%	86.00	6.00 3 Yes; 1 Yes, with modifications
American Cancer Society [20]	94%	82%	80%	75%	78%	90%	83.17	6.00 4 Yes
US Preventive Services Task Force [38]	96%	69%	78%	94%	51%	96%	80.67	5.75 3 Yes; 1 Yes, with modifications
National Comprehensive Cancer Network [37]	97%	86%	82%	97%	35%	75%	78.67	5.75 4 Yes
European Association of Urology, European Society for Radiotherapy and Oncology and International Society of Geriatric Oncology [35]	90%	81%	55%	93%	30%	100%	74.83	5.25 2 Yes; 2 Yes, with modifications
American College of Physicians [24]	92%	72%	48%	90%	69%	75%	74.33	5.25 3 Yes; 1 Yes, with modifications
National Academy of Clinical Biochemistry [17]	81%	76%	60%	94%	30%	96%	72.83	6.00 4 Yes
Japanese Research Group for Development of Cancer Screening Guidelines [18]	79%	64%	69%	89%	38%	96%	72.50	4.75 3 Yes, with modifications; 1 No
University of Michigan Health System [26]	83%	71%	64%	86%	35%	96%	72.50	5.00 2 Yes; 2 Yes, with modifications
American Society of Clinical Oncology [22]	90%	50%	53%	88%	54%	88%	70.50	4.75 1 Yes; 3 Yes, with modifications
Sloan Kettering Cancer Center [33]	99%	74%	51%	83%	34%	81%	70.33	5.25 3 Yes; 1 Yes, with modifications
Royal Australian College of General Practitioners [34]	93%	65%	57%	82%	40%	65%	67.00	4.00 1 Yes; 3 Yes, with modifications
American College of Preventive Medicine Prevention Practice Committee [32]	92%	51%	48%	69%	59%	75%	65.67	4.75 2 Yes; 2 Yes, with modifications
Recommendations from the Prostate Cancer Taskforce. Wellington: Ministry of Health [23]	89%	88%	40%	96%	67%	13%	65.50	5.00 2 Yes; 2 Yes, with modifications
Alberta Health Services [31]	79%	57%	46%	65%	28%	90%	60.83	4.25 1 Yes; 2 Yes, with modifications; 1 No
Canadian Urological Association [21]	78%	46%	65%	88%	21%	67%	60.83	5.00 2 Yes; 2 Yes, with modifications
Multidisciplinary group of the world's leading experts [25]	88%	67%	28%	94%	17%	52%	57.67	4.50 4 Yes, with modifications
European Society for Medical oncology [30]	57%	35%	46%	96%	29%	73%	56.00	4.25 1 Yes; 2 Yes, with modifications; 1 No
Australian Government. National Health and Medical Research Council [28]	93%	49%	15%	82%	33%	0%	45.33	3.50 2 Yes, with modifications; 2 No
The Committee for Establishment of the Guidelines on Screening for Prostate Cancer and Japanese Urological Association [19]	78%	39%	22%	63%	35%	0%	39.50	3.75 1 Yes, with modifications; 3 No
Total	88 (57–100)	67 (35–97)	58 (15–96)	87 (63–99)	46 (17–94)	74 (0–100)	70.01 (39.5–97)	5.1 (3.5–7.0)

In our study, we found that recommendations were graded according to the level of evidence only in 12 of 22 guidelines evaluated and clear algorithms were only provided for four CPGs. On the other hand, we reviewed the sources of information used in every guideline evaluated in this study. It is remarkable that only one of 22 guidelines was not based on a wide review of data (Table 1). This procedure was specifically discarded by Vickers et al. [33], focusing their attention on three well-known screening high quality studies (ERSPC, the Prostate Cancer Prevention Trial and the Malmö Project Study), and arguing that regarding to other questions (frequency of PSA testing, indications for biopsy) a systematic review of the literature would be uninformative.

Finally, we found that laboratory issues are frequently (86%) omitted in GPCs. In our opinion, the no inclusion of laboratory medicine specialists in the development process of the guidelines is the main reason for it. The laboratory medicine experts can provide the perspective of the clinical laboratory that sometimes goes unmarked among clinicians [12].

We found that laboratory medicine specialists participate in only two of the 22 CPGs reviewed in our study, one of them corresponding to the NACB guideline. This guideline widely considers factors in the pre-analytical, analytical and post-analytical phases, which can affect the clinical interpretation of PSA results. We suggest a list of laboratory issues for PSA assays (Table 2) that should be examined in the CPGs, following Aakre et al. [16] and the specific criteria for PSA reported by Schmelzer [39].

The lack of harmonization of the assays is a major problem in the interpretation of PSA results. The establishment of the 1st International Standard for PSA (World Health Organization 96/670) in 2000 and its adoption as primary calibrator by most manufacturers of PSA assays decreases differences between assays, but concordance has not yet been achieved [49]. Additionally, the reference cut-off of 4 µg/L used to select patients for biopsy was obtained using the traditional Hybritech® standard. Information concerning the influence of WHO standard in the PSA cut-off was directly or indirectly reported by six guidelines (Table 3). Furthermore, the NACB, the 2009 AUA and the 2013 EAU guidelines explain that the initial Hybritech® PSA values are about 20% higher than the assays using the WHO 96/670 standard. The information furnished by the Canadian Urological Association guidelines is less precise, only reporting a 20%–25% variation among laboratories. In consequence, it would be necessary to change the cut-off of 4 µg/L for a cut-off of 3.1 µg/L to obtain similar clinical

results. However, published data show that this is not absolutely true. Initial results comparing Access® PSA test using WHO and Hybritech® standards showed that PSA serum levels were 20%–25% lower when WHO standard is adopted [62]. Similar results have been observed for other assays using the reference material from WHO, but there are assays where the differences with the Hybritech® PSA assay are minimal despite the fact that the WHO standard is used. This point was remarked by Stephan et al. [44] showing that PSA serum levels measured with Elecsys® (using the WHO standard) were very similar to the Hybritech® PSA values. More recently, Foj et al. [63] compared different assays calibrated against the WHO standard in relation to the Hybritech® PSA values. The authors showed lower PSA results when Advia Centaur®, and Architect® were used, but results for Elecsys®, Lumipulse G 1200®, and Immulite 2000® were substantially similar to the Hybritech® PSA values.

Despite the availability of numerous CPGs considering PCa screening, consensus is currently lacking among them, although opportunistic screening is not recommended. Discrepant methodologies have been applied in the development of these CPGs, even in one case a systematic review of the literature has been explicitly rejected. Also, differences in the quality of the CPGs available have been reported by several authors. We focused our attention on the laboratory issues, because they are frequently omitted in the development of GPCs. The mechanical transfer of the established Hybritech® reference range of <4.0 µg/L to other assays could lead to clinical mistakes in the selection of patients for biopsy. Differences between assays in the measurement of PSA serum levels are not taken into account by the majority of these guidelines. Furthermore, we detected some errors in three of the CPGs about the consequences of the calibration of PSA assays against the WHO. In conclusion, in our opinion, the quality of PCa early detection guidelines could be adequately improved considering the laboratory issues in their development.

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