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Evidence-Based Series 24-3 Version 2 IN REVIEW

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Referral of Suspected Prostate Cancer by Family Physicians and Other Primary Care Providers

The Prostate Cancer Referral Expert Panel

An assessment conducted in January 2026 placed Evidence-Based Series (EBS) 24-3 Version 2 IN REVIEW. This means it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 24-3 Version 2 is comprised of 4 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/221

Section 1: Guideline Recommendations (ENDORSED)
Section 2: Evidentiary Base
Section 3: Development Methods, Recommendations Development and External Review Process
Section 4: Document Assessment and Review

December 19, 2016

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Oct. 2016	1999 – 2011	Full Report	Web publication	NA
Current Version 2 December 2016	2012 - 2016	New data found in section 4: Document Review Summary and Tool		2012 recommendations ENDORSED

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Evidence-Based Series 24-3 Version 2: Section 1

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Referral of Suspected Prostate Cancer by Family Physicians and Other Primary Care Providers

S. Young, P. Bansal, E. Vella, A. Finelli, C. Levitt, A. Loblaw, and the Prostate Cancer Referral Expert Panel

December 19, 2016

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.

Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2012 and 2016, and for details on how this Clinical Practice Guideline was ENDORSED

GUIDELINE OBJECTIVE

How should patients presenting to family physicians and other primary care providers (PCPs) with signs and/or symptoms of prostate cancer, including incidental prostate specific antigen (PSA) test results, be managed? The following questions are the factors considered in answering the overall question:

RESEARCH QUESTIONS

1. What signs, symptoms, and other clinical features that present in primary care are predictive of prostate cancer?
2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of prostate cancer?
3. What major, known risk factors increase the likelihood of prostate cancer in patients presenting with signs and/or symptoms of prostate cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers or system-related factors? Does a delay in the time to consultation affect patient outcome?

TARGET POPULATION

Adult male patients presenting in primary care settings with signs, including incidental PSA results (defined as results not ordered by the attending FP or other primary care provider [PCP]), or symptoms suggestive of prostate cancer comprise the target population. This guideline does not provide recommendations for screening healthy patients or opportunistic PSA testing.

INTENDED USERS

This guideline is targeted to family physicians (FPs), general practitioners (GPs), emergency room physicians, other PCPs (nurse practitioners, registered nurses, and physician assistants), and urologists. For the purposes of this document, we have referred to FPs, GPs, emergency room physicians, and other PCPs as "FPs and other PCPs". The guidelines are also intended for policymakers to help ensure that resources are in place so that target wait times are achieved. They are intended to coincide with the introduction of prostate cancer Diagnostic Assessment Programs (DAPS) in Ontario. DAPs provide a single point of referral, coordination of care using a clinical navigator, fast tracking of diagnostic tests, and a multidisciplinary team approach. They are an Ontario-wide strategic priority designed to improve patient access and outcomes, as outlined in the Ontario Cancer Plan, 2005-2011 and 2011-2014 (1).

Added in December 2019: Formal Cancer Care Ontario DAPs no longer exist in Ontario, but many hospitals provide ongoing multidisciplinary team approaches to diagnosing prostate cancer.

RECOMMENDATIONS

The following recommendations were adapted from the New Zealand Guidelines Group (NZGG) guideline "Suspected Cancer in Primary Care: Guidelines for Investigation, Referral and Reducing Ethnic Disparities" and the National Institute for Health and Clinical Excellence (NICE 2005), "Referral Guidelines for Suspected Cancer" (2,3).The recommendations below reflect the integration of the NZGG 2009 and NICE 2005 recommendations, an updated systematic review of the research evidence since the NZGG 2009 and the NICE 2005 guidelines, and consensus by the PEBC Prostate Cancer Referral Working Group (see Section 2: Appendix 1 for a list of members) (2,3). The recommended wait times for referral were based on consensus as opposed to strong evidence from well-conducted studies.

During the review process for this document in December 2016 when Version 2 of this guideline was ENDORSED, the Expert Panel noted that these wait time targets should be the goal, but may not always be possible.

Recommendation 1: Actions for Patients with Unexplained Symptoms of Metastatic Prostate Cancer

A man aged 40 years or older should have a digital rectal examination (DRE) and a PSA test if he has any **unexplained** symptoms suggestive of metastatic prostate cancer:

- Suspicious lower back pain symptoms such as those associated with reproducible percussion tenderness
- Severe bone pain
- Weight loss, especially in the elderly

Guidance for referral is as follows:

a. If the prostate is hard or irregular on DRE or PSA is 20 ng/ml or more, then patients should be referred urgently, which may include additional communication (e.g., telephone call, fax), and expect a consultation with a urologist or a prostate DAP within one week.

b. If the PSA is between 10 and 20 ng/ml, then patients should be referred semi-urgently and expect a consultation with a urologist or a prostate DAP within two weeks.

c. If the PSA is less than 10, then consider other metastatic cancers. If there is still a suspicion for prostate cancer, then patients should be referred non-urgently and expect a consultation with a urologist or a prostate DAP within four weeks.

Recommendation 2: Actions for Patients with Lower Urinary Tract Symptoms (LUTS)

For a man presenting with lower urinary tract symptoms (LUTS) (irritative and obstructive voiding symptoms), a DRE should be performed and a discussion about the benefits and risks of PSA testing should occur with the patient (refer to Individual Risk Assessment from the Canadian Partnership Against Cancer PSA toolkit) (4). Lower urinary tract infection should be excluded before PSA testing, especially in men presenting with LUTS. The PSA test should be postponed for at least one month after treatment for a proven urinary infection.

Guidance for referral is as follows:

a. If the prostate is hard or irregular on DRE, a PSA test should be ordered, and the patient should be referred non-urgently and expect a consultation with a urologist or a prostate DAP within four weeks.

b. If the prostate is hard or irregular on DRE and the age-based PSA is elevated but less than 10 ng/ml, then the patient should be referred non-urgently and expect a consultation with a urologist or a prostate DAP within four weeks.

c. If the prostate is hard or irregular on DRE and the PSA is between 10 and 20 ng/ml, then the patient should be referred urgently, which may include additional communication (e.g., telephone call, fax), and expect a consultation with a urologist or a prostate DAP within one week.

d. If the PSA is 20 ng/ml or more, then the patient should be referred urgently, which may include additional communication (e.g., telephone call, fax), and expect a consultation with a urologist or a prostate DAP within one week.

e. If the prostate is normal on DRE and the PSA is between 10 and 20 ng/ml, then the patient should be referred semi-urgently and expect a consultation with a urologist or a prostate DAP within two weeks.

f. If the prostate is normal on DRE and the age-based PSA is elevated but less than 10 ng/ml, then appropriate nomograms* should be used to determine the risk of high grade prostate cancer (5).

    i. If the risk of high grade prostate cancer is less than 5%, then annual monitoring of PSA and DRE is recommended. This is based on the premise that repeated PSA testing is supported by the patient and FP or other PCP.

    ii. If the risk of high-grade prostate cancer is between 5% and 20%, then discussion about other management options should occur with the patient. Based on patient preference, this could include referral to a urologist or a prostate DAP or annual or more frequent follow-up of PSA testing and DREs. This is based on the premise that repeated PSA testing is supported by the patient and FP or other PCP.

    iii. If the risk of high-grade prostate cancer is greater than 20%, then the patient should be referred non-urgently and expect a consultation with a urologist or a prostate DAP within four weeks.

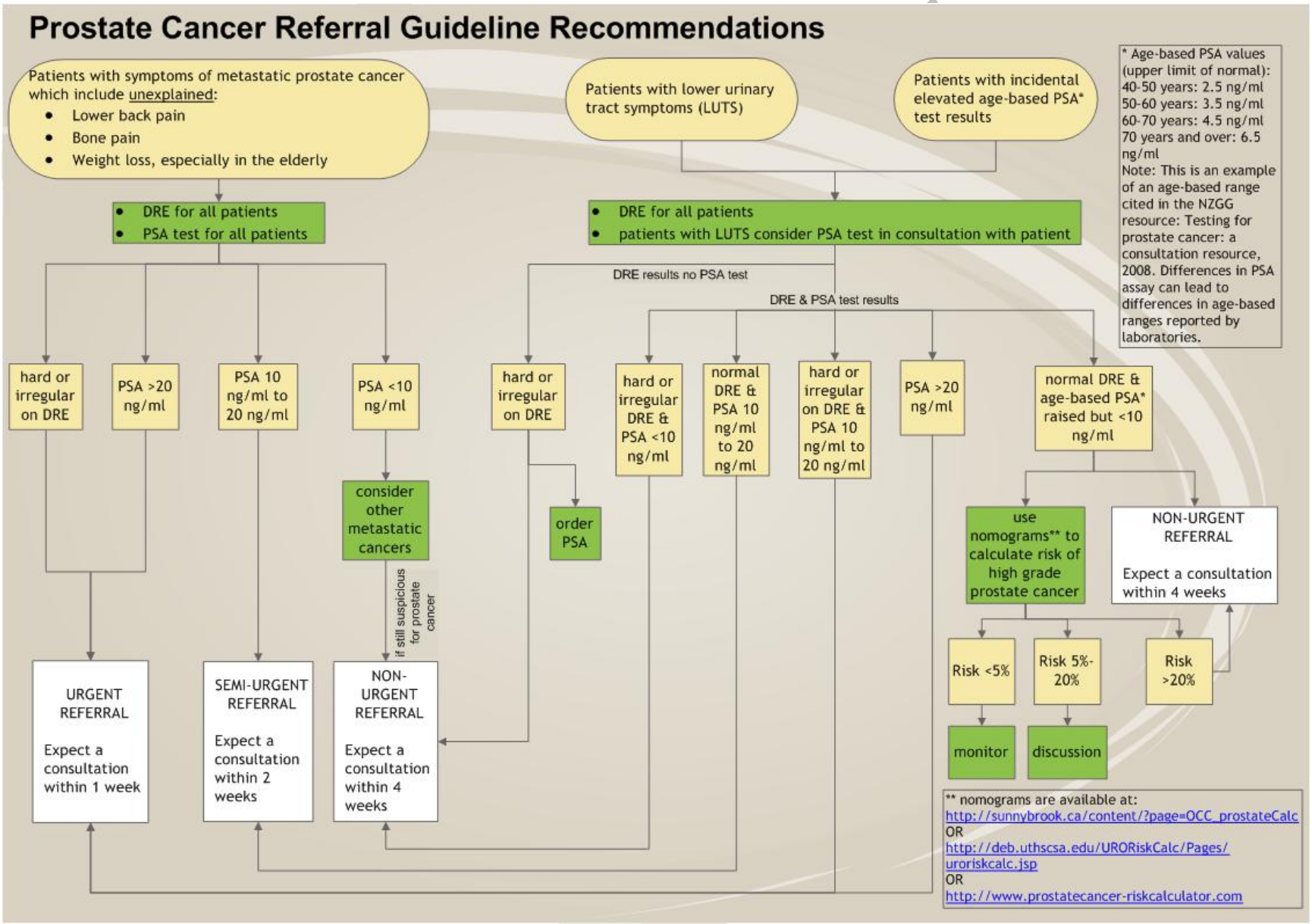
*If a nomogram is not used, then the patient should be referred non-urgently and expect a consultation with a urologist or a prostate DAP within four weeks.

Recommendation 3: Actions for Patients with Incidental PSA

For incidental elevated age-based PSA findings, a DRE should be performed for all patients. Rule out other reasons for elevated PSA values (e.g. age-related hypertrophy [benign prostatic hypertrophy; BPH], infection, inflammation, prostatitis, recent sexual activity,

etc.). Repeat PSA test if unsure. The recommendations b) through f) for LUTS (see Recommendation 2: above) should be followed.

ALGORITHM



POST-ENDORSEMENT: The recommended wait times for referral were based on consensus rather than strong evidence from well-designed studies. These targets are the goal, but may not always be possible.

KEY EVIDENCE AND JUSTIFICATION

All recommended wait times were based on consensus of the Working Group. The Canadian Association of Radiation Oncology recommended a wait time from referral to consultation with a radiation oncologist of no longer than 10 working days (6). This was taken into consideration when developing the wait times in this guideline.

The primary care literature evidence examining the diagnostic accuracy of tests for prostate cancer was very weak. Two studies suggested that DREs performed by FPs may be useful in identifying patients who should be referred (7,8), and four studies suggested that PSA values were good predictors of prostate cancer with PPVs ranging from 34.3% to 47% (7,9-11). The working group chose to endorse the recommendations from NICE 2005 and NZGG 2009 to recommend a DRE and PSA test for all patients with symptoms of metastatic prostate cancer (2,3). NICE 2005 recommended performing a DRE and PSA test for all men with LUTS and NZGG 2009 recommended these tests only for older men with LUTS (2,3). The working group chose to recommend a DRE for all men with LUTS and a PSA test for selected patients with LUTS, following discussion and treatment. The limited evidence from the systematic review suggested that men with LUTS may not be at any higher risk for prostate cancer or have a poorer prognosis than asymptomatic men would be (9,12). The Canadian Urological Association's benign prostatic hyperplasia guideline for men presenting with LUTS recommended a DRE for all men and a PSA test for selected patients (13). The working group chose to be consistent with this guideline.

Recommendation 1. Actions for Patients with Symptoms of Metastatic Prostate Cancer

The NZGG 2009 guideline recommendation that patients with symptoms of metastatic prostate cancer should have a DRE and PSA was endorsed (3). An age threshold of 40 years was included at the suggestion of the Expert Panel and due to the few cases of prostate cancer in men under 40 years in Canada (14). The working group did not think it necessary for a man with erectile dysfunction to undergo a DRE and PSA test and therefore excluded it as a symptom of metastatic prostate cancer. This is consistent with the NZGG 2009 guideline but in contrast to the NICE 2005 guideline (2,3). The working group also excluded unexplained hematuria as a symptom of metastatic prostate cancer because although it can be associated with advanced prostate cancer, the Working Group believed the vast majority of men with gross hematuria usually have a different underlying cause such as benign prostate hyperplasia, bladder or renal cancer, stones or infections. The working group believed hematuria requires urologic assessment but is not part of a prostate cancer care algorithm.

a-c. The cut-off values of 10 and 20 ng/ml were taken from the D'Amico classification system for categorizing patients at low risk (cT1-cT2a, Gleason <7 and PSA ≤10 ng/ml), intermediate risk (cT2b, Gleason = 7 or [PSA >10 and ≤20 ng/ml]) or high risk (cT2c or PSA >20 ng/ml or Gleason >7) for prostate cancer (15,16). Although this was not developed in the primary care population, the working group chose to include this classification system because it is widely used to classify risk of prostate cancer and using these thresholds provides guidance for family physicians in determining their course of action.

Recommendation 2. Actions for Patients with Lower Urinary Tract Symptoms (LUTS)

The recommendation that a man with LUTS should have a DRE and a discussion about PSA testing was consistent with the Canadian Urological Association's guideline for benign prostatic hyperplasia (13). The working group referred to the individual risk assessment developed by the Canadian Partnership Against Cancer as a guide to who should be given a PSA test (4). This document describes the benefits and harms of PSA testing. The working group also endorsed the recommendations to exclude urinary infection before PSA testing and to postpone

PSA testing for at least one month after treatment from the NICE 2005 and NZGG 2009 guidelines (2,3).

a. This recommendation was endorsed from the NICE 2005 guideline (2).
b. The age-based PSA values were endorsed from the NZGG 2009 guidelines (3).
c-e. Please refer to a-c in the previous section under Recommendation 1: Actions for Patients with Symptoms of Metastatic Prostate Cancer.
f. i. A cut-off risk value of 5% was chosen because in Ontario, Canada, the hospital admission rate for urological complications within 30 days of TRUS-guided biopsy was found to be 4.1% in 2005 (17). The working group decided to use 5% as a cut-off to separate patients into a higher risk category because for these patients the risk of high-grade prostate cancer would be higher than the risk of complications from TRUS-guided biopsy.
ii-iii. The prostate risk calculator developed at Sunnybrook Hospital, Toronto, Ontario, Canada, showed a net benefit (the relative value of false-positive versus false-negative results) when a risk of 15% for aggressive prostate cancer was chosen as a threshold to agree to a biopsy (18). Based on the consensus of the working group a conservative cut-off risk value of 20% was chosen.

Recommendation 3. Actions for Patients with Incidental PSA

Although this guideline excludes patients in a screening program, the working group thought that FPs and other PCPs need guidance on how to manage patients with incidental PSA test results, a frequently encountered occurrence in practice. Opportunistic screening has been excluded because it is beyond the scope of this guideline.

The working group believed that if an incidental PSA test was abnormal, then standard practise would be to perform a DRE. A hard or irregular prostate on DRE may increase the urgency of referral.

Cases with enlarged, smooth prostates were excluded because it was beyond the scope of this guideline since it was not considered to be a sign of prostate cancer. Also, although a rising PSA level could be considered a sign of prostate cancer, the working group believed the guideline was sufficiently thorough to include most possible scenarios for prostate cancer using the absolute PSA values. Furthermore, there were no studies examining the factors associated with delayed referral that could directly inform these recommendations.

FUTURE RESEARCH

Further studies are required that specifically investigate the diagnostic performance of signs, symptoms, or tests for prostate cancer in the primary care setting.

GLOSSARY

Age-based PSA

Age-based PSA values (upper limit of normal):
40–50 years: 2.5 ng/ml
50–60 years: 3.5 ng/ml
60–70 years: 4.5 ng/ml
70 years and over: 6.5 ng/ml
Note: This is an example of an age-based range cited in the NZGG resource:
Testing for prostate cancer: a consultation resource, 2008 (19). Differences in PSA assay can lead to differences in age-based ranges reported by laboratories.

Nomograms

Prostate Risk Calculator developed by Nam et al 2011 is available here: http://sunnybrook.ca/content/?page=OCC_prostateCalc (5). The prostate risk calculator includes the free:total PSA ratio, which is the ratio of free PSA, unbound to serum proteins, to total PSA. This ratio is decreased in men with prostate cancer (20). The free:total PSA ratio in some cases may be charged a laboratory fee to the patient. If this ratio is not determined, then a value of 0.1 can be entered into the risk calculator.

The Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator developed by Thompson et al 2006 using data from the Prostate Cancer Prevention Trial is available here: http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp (21)

The Prostate Cancer Risk Calculator developed by the Prostate Cancer Research Foundation, Rotterdam, in partnership with the European Randomized Study of Screening for Prostate Cancer is available here: http://www.prostatecancer-riskcalculator.com/assess-your-risk-of-prostate-cancer (22)

Case Examples

1. ***Symptoms of metastatic prostate cancer***

   A healthy 70 year old vigorous gentleman, on no medications, who ran marathons yearly in the spring presented to a FP. He lived in Florida in the winter and usually was seen only once yearly in the spring. He came home to Canada earlier than usual as he had urinary retention in Florida, was catheterized but was having tremendous lower back pain. This thin, muscular man had never complained about lower back pain before. On examination, a firm fixed pelvic mass was noted. DRE noted a firm, irregular, fixed, and enlarged prostate. The urologist saw him within two days. A presumptive diagnosis of prostate cancer with bone metastasis was made. The PSA was 20ng/ml. Although diagnosis of prostate cancer was likely, the patient refused a biopsy and further diagnostic tests. His pain was quite severe and he was admitted to a palliative care unit for pain control and died within three weeks.

2. ***LUTS***

   A healthy 72 year old man with some symptoms of urinary retention and urgency presented to a FP. His older brother was diagnosed with prostate cancer at age 76. Urine analysis was negative and DRE found a smooth, normal prostate. The FP and patient discussed having a PSA test but the patient refused and asked to see a urologist to discuss the LUTS and his family history and was seen two months later. After a discussion with the urologist, the patient agreed to have a PSA and the result was 4.9ng/ml. The urologist explained to the patient that the result was within normal limits for his age. The patient elected to be followed with serial PSAs and DREs by his family physician. No

treatments were initiated for the patient's symptoms of some urinary retention and urgency which seemed to resolve spontaneously. Since the first visit with the urologist, the PSA has been monitored every three months and has not increased beyond 6.8ng/ml in two years.

3. ***Incidental PSA***

A healthy 49 year old banker had a PSA test as part of a comprehensive medical examination offered through his insurance company. The physical examination was normal but the PSA was elevated for his age. He presented to his family doctor with a PSA of 3.5ng/ml and no other symptoms. The family doctor on DRE found a smooth, normal prostate. The family doctor evaluated the patient's risk for prostate cancer at 10-20% using the Prostate Risk Cancer nomogram and the patient elected to repeat the PSA and DRE in a few months. However, after further consideration at home, the patient called and asked to be referred to a urologist for a consultation.

Funding

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Updating

All PEBC documents are maintained and updated as described in the PEBC Document Assessment and Review Protocol at http://www.cancercare.on.ca/.

Disclaimer

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Contact Information

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Evidence-Based Series 24-3 Version 2: Section 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Referral of Suspected Prostate Cancer by Family Physicians and Other Primary Care Providers: Evidentiary Base

S. Young, P. Bansal, E. Vella, A. Finelli, C. Levitt, A. Loblaw, and the Prostate Cancer Referral Expert Panel

Report Date: October 31, 2012

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.

Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2012 and 2016, and for details on how this Clinical Practice Guideline was ENDORSED.

GUIDELINE OBJECTIVE

How should patients presenting to family physicians and other primary care providers (PCPs) with signs and/or symptoms of prostate cancer, including incidental prostate specific antigen (PSA) test results, be managed? The following questions are the factors considered in answering the overall question:

RESEARCH QUESTIONS

1. What signs, symptoms, and other clinical features that present in primary care are predictive of prostate cancer?
2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of prostate cancer?
3. What major, known risk factors increase the likelihood of prostate cancer in patients presenting with signs and/or symptoms of prostate cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers or system-related factors? Does a delay in the time to consultation affect patient outcome?

INTRODUCTION

Prostate cancer is the most common cancer diagnosed in men and is the third leading cause of death due to cancer in men in Canada (1). In most men, however, the disease progresses slowly over time, and the five-year survival rate is 96% in Canada (1). Because some men may be diagnosed with prostate cancer but survive unaffected, the challenge for family physicians (FPs) and other primary care providers (PCPs) is not only to determine when to

suspect prostate cancer in their patients but also to decide, in consultation with their patients, when to refer patients for further testing.

In healthy asymptomatic men, screening for prostate cancer using Prostate Specific Antigen (PSA), may lead to a diagnosis of prostate cancer disease, but a type that does not affect overall survival. Prostate cancer includes a wide spectrum of malignancy that ranges from low-grade indolent disease to high-grade cancers that have a propensity to spread. Organized screening programs for prostate cancer have been discouraged by experts in Canada, but despite this, opportunistic screening is very common, and current PSA testing practices have already led to large numbers of men being screened (2). Depending on the province, 35-75% of men aged 50-70yrs have had at least one PSA test (2). The merits of screening asymptomatic men for prostate cancer are beyond the scope of this report, but the consequential positive result of a PSA test is included as it is considered as a sign that raises suspicion of prostate cancer

The CCO's Primary Care Program has collaborated with the Program in Evidence-based Care (PEBC) to develop guidelines for patients who present with signs and symptoms that could be suspicious of prostate cancer. The New Zealand Guidelines Group (NZGG) 2009 guideline *Suspected Cancer in Primary Care: Guidelines for Investigation, Referral and Reducing Ethnic Disparities* and the National Institute for Health and Clinical Excellence (NICE) 2005 guideline *Referral Guidelines for Suspected Cancer in Adults and Children* were chosen as baseline documents for the development of this systematic review (3,4). The aim of this guideline is to assist FPs and other PCPs to recognize signs and symptoms that should raise their suspicions about the presence of prostate cancer in their patients leading to ordering and interpreting the results of diagnostic tests and referrals to specialists that will ultimately lead to more timely diagnosis and treatment.

METHODS

The evidence-based series guidelines developed by CCO PEBC use the methods of the Practice Guidelines Development Cycle (5). A priori, the Prostate Cancer Referral Working Group chose the evidence-based NZGG 2009 and NICE 2005 documents as a foundation, because they were considered to be of high quality, comprehensive, recent in publication, and relevant to this topic (3,4). In addition, the working group chose to use the modified research questions from the NZGG guideline (4). The working group updated the literature searches of the NZGG and the NICE systematic reviews (3,4). Evidence was selected and reviewed by five members of the Prostate Cancer Referral Working Group and one methodologist (Appendix 1).

The body of evidence in this review is primarily comprised of guidelines, systematic reviews, and prospective and retrospective studies. This evidence forms the basis of the recommendations developed by the Prostate Cancer Referral Working Group and Expert Panel found in Section 1. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through CCO. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

To determine if there were other higher quality guidelines compared to NICE 2005 or NZGG 2009, or guidelines with more recent systematic reviews, or what other agencies were recommending, a targeted search of the websites of international guideline developers and key organizations was conducted (2009-June 2, 2011) for documents about primary care referral for suspected prostate cancer using the Standards and Guidelines Evidence (SAGE) database (6).

Following this search for other guidelines, the Prostate Cancer Referral Working Group considered the NICE 2005 and NZGG 2009 guidelines to be highly relevant and updated the

literature searches (3,4). The search strategies from NZGG 2009 and NICE 2005 were kindly provided to us for this systematic review by those guideline developers (3,4). NZGG 2009 performed systematic reviews for questions concerning the diagnostic accuracy of signs, symptoms, and diagnostic tests and for the clinical questions investigating factors associated with delay in referral (4). For these clinical questions, a search, updated since the NZGG 2009 publication, of MEDLINE (Ovid, August 2007 – April 2012) and EMBASE (Ovid, 2007 - 2012 week 16) was performed using the NZGG 2009 literature search strategy (4). For the clinical question investigating risk factors for prostate cancer, NZGG 2009 did not perform a systematic review. Therefore, an updated search, since the NICE 2005 publication, of MEDLINE (Ovid, June 2004-April 2012) and EMBASE (Ovid, 2004 - 2012 week 16) using the NICE 2005 search strategies for systematic reviews for prostate cancer was performed (3). The search strategies can be found in Appendix 2.

Study Selection Criteria

Guidelines were included if they addressed at least one of our research questions, were not cited in the NZGG 2009 or NICE 2005 guidelines, and included recommendations not found or different from those in either the NICE 2005 or NZGG 2009 guidelines (3,4).

For the clinical question about the predictive accuracy of signs or symptoms, all prospective or retrospective case series or cohort or case control studies of symptom recognition/identification for prostate cancer conducted in the primary care setting were included. The working group felt that nomograms may be useful in the primary care setting to assist FPs and other PCP in their management. Nomograms are prediction tools that incorporate a number of factors and can be used to enhance PSA and DRE results and help decide which treatment approaches will result in the greatest benefit for men at various stages of prostate cancer. Therefore, the working group chose to include studies assessing the accuracy of nomograms to predict prostate cancer. Screening studies were excluded because they include asymptomatic patients. This report focuses on patients presenting to primary care with signs or symptoms of prostate cancer.

For the question concerning the diagnostic accuracy of investigations, studies were sought in which symptomatic patients underwent one or more investigations, including an abnormal rectal examination, PSA testing, urine microscopy, trans-rectal ultrasound, computed tomography scan, urine cytology, and bone scan (for metastatic disease) in primary care. Some diagnostic measurements, such as the positive predictive value, are affected by the prevalence of the disease in the population. Therefore, although some of these tests are not performed by the FP or other PCPs, it would be important for an FP or other PCP to order them so that the prevalence of the disease is reflected in the primary care setting as opposed to the general population, where the prevalence of prostate cancer may be lower, or the secondary care setting, where the prevalence of prostate cancer may be higher. Screening studies were excluded.

For the research questions concerning risk factors and delay in referral, a search for practice guidelines, systematic reviews (with meta-analyses), and systematic reviews (without meta-analyses) was performed. If these articles did not definitively answer the particular clinical question, then searches for randomized phase III trials and randomized phase II trials followed by prospective or retrospective case series or cohort or case-control studies were performed. If information from systematic reviews definitively answered the question(s), then articles from the time of publication of the systematic review and onwards were retrieved. To develop recommendations with feasible wait times for Ontario, articles assessing wait times in Canada were also included, regardless of study design.

Publications in a language other than English were not eligible because of the lack of funding for translation. Non-systematic reviews, abstracts, case studies, letters, editorials, and commentaries were excluded.

Synthesizing the Evidence

Because considerable heterogeneity between the studies was expected that would be identified in terms of study type and the selection of the patient population, no meta-analysis was planned.

Quality Appraisal of Evidence-Based Guidelines

The Appraisal of Guidelines Research and Evaluation (AGREE II) scores were taken from the SAGE Inventory of Cancer Guidelines developed by the Canadian Partnership Against Cancer (6,7). The AGREE II instrument is a tool to assess the methodological rigour and transparency in which a guideline is developed. Systematic reviews and meta-analyses were assessed for quality using the 'assessment of multiple systematic reviews' or 'AMSTAR' tool (8). The AMSTAR tool is an 11-item questionnaire that assesses the methodological quality of systematic reviews.

RESULTS

Literature Search Results

Of 16,596 articles identified in the updated literature search since the NICE and the NZGG guidelines searches, 257 were deemed relevant for a full-article review (3,4). Of these, one systematic review and 15 primary studies that met the study selection criteria were included (9-24). Four studies were found from the reference lists (25-28). From the NICE systematic review, four primary studies were included in this review (29-32). Two primary studies were included from the NZ review (33,34). Table 1 summarizes the included articles for each research question. No additional practice guidelines were identified other than the NICE and NZGG guidelines that were identified a priori.

Table 1. Summary of included articles for each research question.

Research Question	Guideline	Systematic review	Prospective studies	Retrospective studies	Case-control studies
Signs /symptoms	2*	1	7**	5**	1**
Tests	2*	0	2**	4	1**
Risk factors	2*	0	0	0	1
Delay	2*	0	0	8**	0
Total number	**2**	**1**	**7**	**16**	**2**

*Two guidelines for each research question were from NICE and NZGG (3,4).

**Three studies addressed research questions about signs or symptoms and tests (30,32,34) and one study addressed both the research questions about signs and symptoms and the research question about the factors associated with delayed referral (31).

Study Design and Quality

Guidelines

The AGREE scores for the NICE and NZGG guidelines are presented in Table 2. The AGREE domain of rigour of development assesses the process used to gather and synthesize the evidence and the methods to formulate the recommendations (6,7). From a methodological perspective, this is one of the more important domains. The NZGG scored fairly low on this domain, but this may be because systematic reviews were not performed for all of the research questions (4). The NZGG guideline was based on the NICE guideline and updated their literature only for the clinical questions for signs, symptoms, and investigations for prostate cancer.

The NICE guideline scored higher on the rigour of development domain, but sometimes the links between the evidence and the recommendations were not always clear (3). For example, it was unclear how the symptoms associated with prostate cancer, which included erectile dysfunction, hematuria, lower back pain, bone pain and weight loss, especially in the elderly, were selected.

The research questions and the literature review in the NICE and NZGG guidelines were highly relevant to this review, and therefore the studies included in those reviews are described in detail below (3,4).

Table 2. Results of AGREE Tool quality rating of evidence-based guidelines.

Guideline	AGREE Domain Scores					
	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)
NICE 2005 (3)	97.2	66.7	77.1	61.1	79.2	25.0
NZGG 2009 (4)	80.6	58.3	54.2	83.3	62.5	58.3

Abbreviations: NICE, National Institute for Health and Clinical Excellence; NZGG, New Zealand's Guideline Group

Reviews

Only one systematic review of nomograms for prostate cancer, by Shariat et al 2009, was included (20). The AMSTAR scores are provided in Table 3 (8). This review scored low for several reasons: the types of studies searched and how they were selected and extracted were not described in detail, only one electronic database was searched and AMSTAR suggests at least two should be searched, no meta-analyses were performed, and a list of excluded studies was not provided. However, this review does provide a comprehensive list of available nomograms and whether they have been internally or externally validated.

Three systematic reviews met the criteria for inclusion, but two of them included only the paper by Hamilton et al 2006, previously included in the NZGG review (4,35,36). The other systematic review by Schroder et al 2008 evaluated nomograms and artificial neural network ability to predict prostate cancer over PSA levels alone (37). However, some of the studies were from screening studies, and some studies evaluated nomograms for the prediction of prostate cancer on repeat biopsy and not initial biopsy, which is more relevant for FPs and other PCPs. Therefore, the reference lists from these reviews were searched for relevant references, but the results of these reviews are not discussed further.

Table 3. Evaluation of included publication using AMSTAR.

ITEM	Shariat et al 2009 (20)
1. Was an 'a priori' design provided?	Y
2. Was there duplicate study selection and data extraction?	CA
3. Was a comprehensive literature search performed?	N
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	CA
5. Was a list of studies (included and excluded) provided?	N
6. Were the characteristics of the included studies provided?	Y
7. Was the scientific quality of the included studies assessed and documented?	Y
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y
9. Were the methods used to combine the findings of the studies appropriate?	NA
10. Was the likelihood of publication bias assessed?	N
11. Was the conflict of interest stated?	Y
TOTAL AMSTAR POINTS	**5**

Abbreviations: CA, can't answer; N, no; NA, not applicable; Y, yes.

Primary Studies

Seven prospective cohort studies (9,16,17,19,29,30,32), nine retrospective cohort studies (12-15,18,24-27), seven retrospective case series studies (10,21-23,28,31,33), and two case-control studies (11,34) were included. Based on the Cochrane Collaboration method for assessing the methodological quality of diagnostic studies, using a modified QUADAS tool, several factors affected the quality of the included prospective, retrospective, and case-control diagnostic studies (38). The details of these study characteristics can be found in Table 4. The main concern with these studies in addressing our research questions is that all of the studies except for two (9,34) were not conducted in the primary care setting. Because of the lack of studies performed in the primary care setting, a post hoc decision was made to include studies conducted in the secondary care setting if they included patients who were referred from the primary care setting. For studies assessing nomograms, only those studies that included patients from a referred population and that included variables that were available before referral to a specialist were included. Other methodological concerns were that some studies did not recruit consecutive patients or were not blinded to the patients' signs, symptoms, or diagnoses.

Table 4. Study characteristics for clinical questions about signs, symptoms, investigations or risk factors for prostate cancer.

Author	Study, country, setting	No. of patients	No. of patients with prostate cancer (%)	Investigations used	Consecutive patients	Blinded to index	Missing / uninterpretable data explained	Withdrawals explained
Prospective								
Baughan 2011 (9)	Prospective during six months, Scotland, primary care	582 referred with suspected prostate cancer	306 (53)	Not given	no	no	yes	no
Fowler 2000 (29)	Prospective over eight years, USA, tertiary care referred mainly from primary care	536 with abnormal DRE and PSA ≥ 4 ng/ml, 179 black and 357 white men	103 (19)	Various biopsy techniques	yes	yes	yes	yes
Gjengsto 2004 (30)	Prospective over 4 years, Norway, secondary care referred from primary care	872 mostly aged <70 yrs without serious comorbidity, PSA <20 µg/l and no locally advanced disease on DRE	360 (41)	2D transrectal ultrasound-guided modified sextant biopsy	no	no	yes	Yes
Nam 2007 (17)	Prospective over six years, Canada, mainly a referred population	3,108 with abnormal DRE and PSA ≥ 4 ng/ml	1,304 (42)	6 to 15 ultrasound-guided needle core biopsies	yes	no	yes	yes
Nam 2011 (16)	Prospective over two years, Canada, referred population	2,130 with abnormal DRE and PSA > 2.6 ng/ml	867 (41)	transrectal ultrasound-guided needle core biopsy	no	yes	yes	yes
Powell 1989 (32)	Prospective, UK, secondary care referred from primary care	287 with symptoms of bladder outflow obstruction	19 (6.6)	All patients with elevated PSA had cystoscopy and TRUS or	yes	no	yes	Yes

Author	Study, country, setting	No. of patients	No. of patients with prostate cancer (%)	Investigations used	Consecutive patients	Blinded to index	Missing / uninterpretable data explained	Withdrawals explained
				Tru-cut biopsy; 30% with normal PSA had TRUS				
Serag 2012 (19)	Prospective, UK, tertiary care referred from primary care	397	169 (43)	Biopsy or high-index of suspicion warranting androgen deprivation therapy, follow-up 12 months	yes	yes	no	no
Retrospective								
Allen 2004 (25)	Retrospective over one year, UK, two-week wait referral	35 referred for elevated PSA	11 (31)	various	yes	no	no	no
Borre 2009 (10)	Retrospective, Denmark, secondary care referred from primary care	585 with prostate cancer treated with radical prostatectomy	585, 350 with LUTS, 188 no LUTS	Not given	yes	no	yes	yes
Hawary 2008 (13)	Retrospective over six months, UK, secondary care referred from primary care	41 with elevated age-specific PSA	18 (44)	Not given	yes	No	yes	yes
Karakiewicz et al 2005 (26)	Retrospective, Canada and Germany, mainly a referred population	For nomogram 2: internal validation 1,762, external validation 514, ≤50 ng/ml with abnormal DRE and/or abnormal PSA or free PSA	For nomogram 2: internal validation 739 (42), external validation 189 (37)	Sextant biopsy	unclear	No	no	no
Kawakami et al 2008a (15)	Retrospective, Japan, referred population	For nomogram 1: 1083, PSA <20 ng/ml, for Karakiewicz nomogram: 1762	For nomogram 1: 37%, for Karakiewicz nomogram: 42%	Extended biopsy	unclear	No	no	no
Kawakami et al 2008b (14)	Retrospective, Japan, referred population	External validation: 544 PSA <10 ng/ml	External validation: 221 (41)	Mostly extended biopsy	yes	No	no	no
Mansson 1999 (31)	Retrospective over five years, Sweden, primary care	63 with prostate cancer	63	Swedish Cancer Registry	yes	No	yes	yes
Mathew 2009 (27)	Retrospective during six month period, UK,	115 referred for elevated PSA, 3 referred for	45 (39) with elevated PSA, 3 (100) with	Imaging and pathology reports	yes	no	no	no

Author	Study, country, setting	No. of patients	No. of patients with prostate cancer (%)	Investigations used	Consecutive patients	Blinded to index	Missing / uninterpretable data explained	Withdrawals explained
	secondary care referred from primary care	elevated PSA and abnormal DRE, 4 referred for elevated PSA and LUTS	elevated PSA and abnormal DRE, 2 (50) with elevated PSA and LUTS					
Quinlan 2009 (18)	Retrospective, Ireland, tertiary care some referred from primary care	200 with LUTS, 148 referred from primary care	3 (2)	Not given	yes	no	yes	yes
Case-control								
Buckley 2011 (11)	Case-control over five years, Scotland, primary care linked with secondary care records	Cases: 984, controls: 1968	984	Not given	yes	no	yes	yes
Hamilton 2006 (34)	Case control, UK, primary care records	217 cases, 1080 controls	217	Electronic records	no	yes	yes	yes

Abbreviations: DRE, digital rectal examination; LUTS, lower urinary tract symptoms; No., number; PSA, prostate specific antigen; TRUS, transurethral resection of the prostate; UK, United Kingdom; USA, United States of America

Outcomes

What Signs, Symptoms, and Other Clinical Features Are Predictive of Prostate Cancer?

Evidence from NICE 2005 and NZGG 2009

The NICE 2005 systematic review included three review articles, none of which included studies conducted in primary care (3). A NICE 2001 review was included but the methods were not described in detail, and it was more an advice document with the recommendations based on consensus (39). The systematic review by Muris et al 1993 assessed the diagnostic accuracy of rectal examination (40). However, no studies were conducted in the primary care setting. The systematic review by Selley et al 1997 included a chapter on the diagnosis of prostate cancer (41). Although no studies were conducted in primary care, one study in their review included patients referred from primary care with bladder outflow obstruction (32). Prostate cancer was positively suggested in eight of 287 patients' primary care referral letters, and four of these had histologically confirmed prostate cancer.

The NICE 2005 review also included five primary studies. Two studies would not have met our inclusion criteria. One study, by Brett 1998, assessed the acceptability of DRE and PSA in general practice (42). However, only asymptomatic men were offered DRE and PSA testing. The second study, by Haid et al 1994, was performed in the secondary care setting to assess the diagnostic accuracy of TRUS and DRE (43).

A study by Gjengsto et al 2004 included in the NICE 2005 review examined patients' reasons for consulting their FP (30). A total of 360 of 872 (41.3%) patients were diagnosed with prostate cancer. Among the 373 patients who consulted their FP because of LUTS, 34.3% were diagnosed with prostate cancer, whereas of the 462 patients without urological symptoms who

consulted their FP (those attending for a health check, non-urological disease, or concerns with having cancer), 47% were diagnosed with prostate cancer.

Fowler et al 2000, included in the NICE 2005 review, found no differences in the detection rate of prostate cancer between black and white men with abnormal DRE (29). The study was conducted in a tertiary care setting, but patients were mainly referred from primary care.

NICE 2005 also included a retrospective study by Mansson et al 1999 (31). Using a Swedish database of patients with prostate cancer, they reported the sensitivity of symptoms presented to FPs at first consultation. Skeletal or abdominal pain was reported in 22% of patients with prostate cancer, followed by the general symptoms of weight loss, dyspnea, tiredness, vertigo, fever in 11% of patients, urgency in 7.9% of patients, nocturia in 7.9% of patients, and urinary tract infection in 6.3% of patients. Other isolated local symptoms, including urinary retention, incontinence, macroscopic hematuria, starting problems, poor stream, or terminal dribbling, were reported by 9.5% of patients. Two or more local symptoms were reported by 49% of patients, and 13% were found by chance on routine rectal examination.

Based on the systematic review, NICE concluded that prostate cancer often presents with symptoms of urinary outflow obstruction (3). Other presenting symptoms include urinary tract infection, and features of metastasis such as bone pain. An additional conclusion was that most prostate cancers can be palpated by the general practitioner through DRE, although an abnormal result may be caused by other conditions besides cancer.

NZGG 2009 included one primary case-control study by Hamilton et al 2006 conducted in the primary care setting (34). Using multivariable analysis, eight features were associated with prostate cancer. The PPVs against a background risk of 0.35% were: urinary retention 3.1% (95% confidence interval [CI],1.5 to 6.0); impotence 3.0% (95% CI, 1.7 to 4.9); frequency 2.2% (95% CI, 1.3 to 3.5); hesitancy 3.0% (95% CI, 1.5 to 5.5); nocturia 2.2% (95% CI, 1.2 to 3.6); hematuria 1.0% (95% CI, 0.57 to 1.8); weight loss 0.75% (95% CI, 0.38 to 1.4); abnormal rectal examination, deemed benign 2.8% (95% CI, 1.6 to 4.6); and abnormal rectal examination, deemed malignant 12% (95% CI, 5.0 to 37). They suggest that lower urinary tract symptoms, especially urinary retention, frequency, hesitancy, and nocturia, as well as impotence, should prompt PSA testing.

Evidence from Newly Identified Reviews

A review by Shariat et al 2009 described studies with nomograms for the prediction of prostate cancer at initial biopsy (20). Although none of these studies were conducted in the primary care setting, eight of 14 were from referral populations, none of which stated that the patients were referred only from a primary care setting. Three studies from referral populations were internally and externally validated. Two of these studies contained variables (previous prostate biopsy and sampling density) in their models that would not be available before referral to a specialist (44,45). Only one internally and externally validated nomogram by Karakiewicz et al 2005 was from a referral population and had variables available to a FP or other PCP before referral (26). These variables included age, DRE, PSA, and percent free PSA. The cancer detection rate for this model was 35% to 42%, and the discrimination rate was 77%.

Evidence from Newly Identified Primary Studies

A prospective multi-institutional study by Nam et al 2011 evaluating two nomograms for prostate cancer, one from the Prostate Cancer Prevention Trial (PCPT) and another from Sunnybrook Hospital (the prostate risk calculator), was performed in Canada (16). Patients were included if they had an abnormal PSA level (>2.6 ng/ml) or an abnormal DRE test, but it was unclear if all patients were from a primary care setting. They found the area under the curve (AUC) for the Sunnybrook nomogram was significantly higher than for the PCPT nomogram for

predicting prostate cancer, as well as for aggressive prostate cancer with a Gleason score of seven or higher. In addition, if patients chose a risk of 30% for prostate cancer as a threshold to agree to a biopsy, then the net benefit (the relative value of false-positive versus false-negative results) was better for the Sunnybrook model compared to the PCPT nomogram. The Sunnybrook nomogram also provided better net benefit at a risk threshold of 15% for aggressive prostate cancer. The variables for the Sunnybrook nomogram included age, urinary prostate symptom score, PSA, free:total PSA ratio, ethnic background (Asian, Caucasian, African descent, other), family history of prostate cancer, and DRE. All of these factors were found to be significantly associated with prostate cancer using multivariable analysis when this nomogram was developed with patients referred with abnormal PSA values or DREs, although it was unclear whether patients were referred from primary care (17).

Kawakami et al 2008a provided an internally and externally validated nomogram using variables available prior to prostate biopsy (15). Their model along with a nomogram developed by Karakiewicz et al 2005 was externally validated with a dataset of Japanese men with serum PSA levels <20 ng/ml who had been referred and had undergone extended biopsy (15,26). Kawakami et al 2008a found that their nomogram, which included age, DRE, PSA, and percent free PSA, had a significantly more accurate area under the curve (AUC=0.73) compared to the Karakiewicz et al 2005 (AUC=0.71) nomogram ($p<0.01$).

Kawakami et al 2008b also developed a nomogram in a Japanese population using age, PSA, DRE, family history of prostate cancer, and number of previous malignancies other than the prostate as variables (14). Using data from Japanese patients with PSA less than 10 ng/ml derived from the same retrospective cohort in Kawakami et al 2008a, they externally validated this nomogram and calculated the AUC to be 0.67 (14,15).

Borre et al 2009 investigated the difference in tumour characteristics and treatment outcome in men undergoing radical prostactectomy for prostate cancer who had either lower urinary tract symptoms (n=350) or were asymptomatic (n=188) (incidental PSA screening) (10). Men with a familial predisposition for prostate cancer were excluded. Patients were categorized as asymptomatic or symptomatic by asking them their reason for consulting their FP. No differences were found in tumour characteristics and treatment outcome except for a higher Gleason score of the radical prostactectomy specimen among asymptomatic patients compared to symptomatic patients. This suggests a poorer prognosis for asymptomatic compared to symptomatic patients for patients undergoing radical prostatectomy. The median PSA value before radical prostactectomy was identical in both groups. The authors question the recommendation by the Danish Urological Society to perform PSA testing in men with LUTS.

An audit of urgent referrals by GPs in Scotland found that 53% (306/582) of patients who were urgently referred were diagnosed with prostate cancer (9). Likewise, a prospective study in the United Kingdom (UK) found that the overall prostate cancer detection rate for men referred by their general practitioner based on the NICE guideline was 43%, with 80% being assessed with intermediate- or high-risk prostate cancer and 15% with metastatic presentation (19). These rates were not significantly different compared to rates in a historical cohort of men referred prior to the NICE guideline. However, more low-risk and fewer high-risk prostate cancers were found among younger men (aged 50-69 years) in the cohort after the implementation of the NICE guideline compared to the historical cohort.

What Is the Diagnostic Accuracy of Investigations for Prostate Cancer?

Evidence from NICE 2005 and NZGG 2009

NICE 2005 included five references that looked at the diagnostic accuracy of investigations in their review (3). Three references were reviews that were not focused on primary care and included screening studies (41,46,47). One reference was a population-based study not focused on the primary care population (48). The final reference was a pamphlet intended as an advice document for FPs or other PCPs (49). None of these studies would have met our inclusion criteria.

However, the Selley et al 1997 systematic review, mentioned for the previous research question in the NICE 2005 review, included a study by Powell et al 1989 that selected patients referred from primary care with bladder outflow obstruction (32,41). In 23% of 287 patients a digital rectal examination of the prostate was not performed or not recorded in primary care referral letters. Of the 211 patients who had their PSA levels measured, 36 had elevated PSA levels (>10 µg/l) and underwent further urological assessment. Seventeen patients with elevated PSA levels had histologically confirmed prostate cancer (PPV=47%). Only 30% of patients with normal PSA levels had further assessment, and two of these patients had prostate cancer (sensitivity = 17/19 or 89.5%). Although they report a specificity of 90% for PSA, the exclusion of 70% of patients with normal PSA levels who were not further evaluated results in a specificity of 72% or 73%.

In addition, from the NICE 2005 review mentioned previously, Gjengsto et al 2004 examined FPs reasons for referral (30). An elevated PSA was the most frequent reason for FPs to refer patients. Of the 647 patients with an elevated PSA, 222 (34.3%) were diagnosed with prostate cancer. The PPV for detecting prostate cancer was highest when the reason for referral was both an elevated PSA and a suspicious DRE (125/185 [67.6%]). The PPV was lower (7/24 [29.2%]) when the reason for referral was suspicious DRE alone.

NZGG 2009 found no additional articles in their systematic review since the publication of the NICE 2005 guideline for this research question (4). However, Hamilton et al 2006 included in the previous section also addressed this question (34). The PPV for an abnormal rectal exam assessed as benign by a general practitioner was 2.8%, whereas the PPV was 12% for those assessed as malignant. The authors suggest this shows that FPs are good at discriminating between benign and malignant enlarged prostates. As well, for PSA testing, this study found that, once the PSA result was added to the multivariable analysis, a PSA >4 ng/mL was the only variable significantly associated with prostate cancer. The authors suggest this finding can provide useful information for the sequential diagnostic assessment of patients with symptoms of prostate cancer. If LUTS is identified, the authors suggest a PSA test be performed as the PSA result would be the best predictor of prostate cancer; the symptoms would no longer be relevant.

Evidence from Newly Identified Primary Studies

Hawary et al 2008 reviewed 41 men referred with an elevated age-specific PSA from a two-week wait referral clinic in the UK (13). Eighteen (44%) prostate cancers were diagnosed in this group, and two (4.9%) cancers were suitable for radical prostatectomy. Suitability was defined as those patients with localised/locally-advanced prostate cancer (with respect to age and PSA only) with a possible life expectancy of greater than 10 years. In addition, all patients diagnosed with prostate cancer were over 50 years old.

A retrospective study reviewed all patients referred under the two-week-wait initiative in the UK to a single urological clinic (25). Eleven of 35 (31%) patients referred with a raised PSA (ranging from 3.4-480 ug/L, median 13.9 ug/L) were diagnosed with prostate cancer. Five of these patients were metastatic at presentation.

Similarly another retrospective audit of all two-week wait referrals to a single urological department in the UK found that 39% (45/115) of the men referred for elevated PSA were diagnosed with prostate cancer (27). As well, two out of four men with elevated PSA and LUTS were diagnosed with prostate cancer, and all three men with elevated PSA and abnormal DRE were found to have prostate cancer.

Quinlan et al 2009 reviewed patients referred with LUTS in their tertiary referral centre in Ireland (18). Of 148 men referred by their GP, 48 (32%) received a DRE and 3 (6%) of them had prostate cancer. Two DREs were reported as benign, and one as hard. However, 39/41 (95%) DREs that were reported by GP as benign, enlarged, or normal were eventually diagnosed with benign prostatic hyperplasia. Seven of these patients had a PSA level greater than 4 ng/mL, and four had no PSA level checked. The authors suggest that DREs be performed in order that abnormal DREs result in an expedited referral.

Summary/Interpretation for accuracy of signs, symptoms, and diagnostic tests to predict prostate cancer

In summary, two studies showed that patients without urological symptoms appear to have higher rates of prostate cancer or poorer prognosis with prostate cancer compared to patients with LUTS (10,30). In addition, using multivariable analysis, Hamilton et al 2006 found that PSA testing was the only variable significantly associated with prostate cancer, whereas other urological symptoms were not predictive (34). This finding suggests that LUTS are not highly predictive of prostate cancer. However, three studies suggest that FPs are good at discriminating between patients with and without prostate cancer (18,32,34). Four out of eight patients, where referral letters suggested possible prostate cancer, were later diagnosed with prostate cancer (32). As well, the Quinlan et al 2009 and Hamilton et al 2006 studies suggest that DREs performed by FPs are useful tools in evaluating suspected prostate cancer (18,34). Four published audits of the NICE guideline found that a high proportion of men referred for suspected prostate cancer were diagnosed with the disease (9,19,25,27). Furthermore, PSA testing showed good predictive value for detecting prostate cancer, with PPVs ranging from 34.3% to 47% (13,30,32). Therefore, although LUTS may not be good predictors of prostate cancer within the primary care population, DRE and PSA testing appear to be valuable tests for determining the possibility of prostate cancer. The nomogram by Nam et al 2011 included urological symptoms in their model and found a composite score of LUTS, rather than individual symptoms as suggested in Hamilton et al 2006 study, was a significant predictor of prostate cancer, using multivariable analysis with PSA results in the model (16,34). Although it was unclear whether the patients were referred from primary care in the Nam et al 2011 paper, their nomogram includes factors that are easily available to FPs and other PCPs (16). Furthermore, their nomogram was predictive of aggressive prostate cancers with a Gleason score of seven or higher. Hawary et al 2008 pointed out that, while it is necessary to reveal the signs and symptoms that are predictive of prostate cancer, it is also important to differentiate which prostate cancers are potential candidates for curative treatment (13).

What Major, Known Risk Factors Are Predictive of Prostate Cancer?

Evidence from NICE 2005

NICE 2005 identified two reviews that examined the risk factors for prostate cancer (3). One review suggested the primary risk factor for prostate cancer is age, and the other review performed a meta-analysis on the risk of prostate cancer among relatives of affected patients (50,51). Neither review was focused on symptomatic patients in the primary care setting.

Evidence from Newly Identified Primary Studies

One additional study beyond NICE's review was found. A retrospective case-control study linking primary and secondary care records, found that the risk of prostate cancer is higher within six months of being diagnosed for the first time with benign prostate hyperplasia but afterward the risk for prostate cancer is low and not significantly different from men without benign prostate hyperplasia (11). The authors suggest that a possible explanation for the association within the first six months is that physicians may diagnose benign prostate hyperplasia initially until prostate cancer has been ruled out.

Which Factors Are Associated with Delayed Referral? Which Factors Influence Delay by Patient and Which Delay by Provider? Does a Delay in the Time to Consultation Affect Patient Outcome?

Evidence from NICE 2005 and NZGG 2009

No articles were identified in the NICE 2005 systematic review (3). However, NICE 2005 did include a study by Mansson et al 1999, previously mentioned, that found a longer delay, between the first visit to the doctor for signs or symptoms for prostate cancer and a confirmed diagnosis, for patients visiting their FP compared to patients visiting another physician (31). No significant differences were found for colorectal, breast or pulmonary cancer.

The NZGG 2009 review included two studies (4). One was a qualitative study and would have been excluded from this review (52). Another study by Allgar and Neal 2005 was based on secondary analysis of the National Survey of NHS Patients: Cancer and found that patients who saw their FP had a longer delay from first symptom to referral for prostate cancer than those who did not (33). They suggest this may be explained because patients who see FPs may have less aggressive cancers and there may be more system delays in primary versus secondary care. For example, there may be quicker access to diagnostic tests in secondary care. Allgar and Neal 2005 also found longer delays from the first symptom to contact with a FP and also longer delays to referral for patients with prostate cancer compared to patients with breast, lung, ovarian, non-Hodgkin's lymphoma, and colorectal cancer (33).

Evidence from Newly Identified Primary Studies

Stapleton et al 2008 reviewed Australian hospital records of patients with prostate cancer, referred from primary care, with at least one serum PSA recorded before referral (21). They found the median time from first abnormal PSA (defined as >4 ng/mL) to referral was 1.15 months for men aged <75 years and 1.87 months for men aged 75 years and older. PSA levels increased from the first test through to referral to diagnosis and treatment. Patients with delays greater than six months, between first abnormal PSA and referral, had median PSA levels significantly lower than patients with delays less than or equal to six months. PSA velocity or the probability of biochemical recurrence was not significantly different between the two groups of patients.

Turner et al 2011 searched a US database for men with first-time, abnormal PSA levels (≥10 ng/mL) that had been ordered by a primary care clinician (24). Using Cox proportional hazards models, adjusting for demographic, clinical and health care factors, there was no difference in time to first follow-up (included a urology appointment, a new prostate diagnosis or repeat PSA test) between black men and nonblack men. However, black men had higher index PSA levels and were more likely to have had prior urology care. The unadjusted hazard ratio also showed that men aged at least 75 years had a longer delay to first follow-up than men aged 74 years or less.

Neal and Allgar's 2005 secondary analysis of the UK National Survey of NHS Cancer Patients, using general linear modelling, found that younger people with prostate cancer had

longer referral delays than did older people with prostate cancer (28). For pre-hospital delay, age, sex, marital status, ethnic group, and social class were not significant factors.

Sunny et al 2008 sent questionnaires to 591 patients diagnosed with prostate cancer in Sweden (23). Using multivariable analysis with the 219 men who reported having clinical symptoms before the diagnosis of prostate cancer, they found that self-employed men were more likely to have had an early first contact (less than three weeks from symptoms to first contact) with the health care system compared to pensioners or men with other employment. Also, men who obtained moderate or much information from the internet were more likely to have had early contact with the health care system. Men who obtained moderate or much information from health care staff, written information from any doctor and moderate or much information from family members or acquaintances had less than three weeks delay between first contact and first visit to health care.

A retrospective observational study of 350 patients conducted in The Ottawa Hospital found that the median time from referral for symptoms suggestive of prostate cancer to a first diagnostic consult was 35 days and the median time from referral to a confirmed diagnosis was 65.5 days (12). Another retrospective observational study of 41 patients with prostate cancer conducted in Toronto, Canada found a median wait time from suspicion to consultation with a urologist of 40 days and a median interval from consultation to biopsy of 26 days (22).

Summary/Interpretation for factors influencing delay

Limited conclusions can be drawn from these studies. Two studies showed that patients who visited their FP with signs or symptoms of prostate cancer had longer delays than patients who visited other physicians (31,33). No other factors were shown to be significant in more than two studies except for age. Two studies found that older men aged 75 years and older experienced greater delays to referral or follow-up (21,24). One study found the opposite with longer referral delays for younger men (28). The median wait times found by Grunfeld 2009 and Stevens 2010 may be useful in setting realistic benchmarks for FPs and other PCPs in Ontario (12,22).

DISCUSSION

The findings from this review suggest that there are no signs or symptoms that are good predictors of prostate cancer. LUTS has been examined in a few studies but it appears that patients with LUTS are not at any greater risk of developing prostate cancer or having a poorer prognosis with prostate cancer than asymptomatic patients. However, as suggested in a systematic review by Hamilton and Sharp 2004, patients with LUTS may be seeking reassurance that they do not have prostate cancer (53). Furthermore, the treatment for enlarged prostate is very different than for prostate cancer. Therefore, FPs and other PCPs might consider DREs and PSA testing in patients with LUTS as recommended in the BPA guidelines by the Canadian Urological Association and refer those with suspicious findings to a urologist for investigation (54). There is some evidence to suggest that FPs can use DRE and PSA testing to distinguish prostate cancer from benign disease, but there was little evidence to suggest that DRE or PSA testing could predict aggressive prostate cancer in the primary care setting (18,32,34). The nomogram by Nam et al 2011 may be an appropriate model for FPs to use to assess the risk of aggressive prostate cancer (16).

Very few studies investigated the association of risk factors with prostate cancer or the factors associated with delayed referral. Only age was shown to be a factor contributing to delay in a few studies, and even then the results were mixed (21,24,28).

Since there is little evidence for these research questions, and those reported in this systematic review come mainly from secondary and tertiary care sources and the study designs are weak for primary care diagnosis of prostate cancer, the recommendations in this guideline

will be based on consensus of the working group and approved by the Expert Panel, incorporating recommendations from NICE 2005 and NZGG 2009 (3,4,54,55).

CONFLICT OF INTEREST

The conflict of interest details are shown at the end of Section 3.

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Appendix 1. Members of the Prostate Cancer Referral Working Group and Expert Panel.

Prostate Cancer Referral Working Group	
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Joseph Chin Urologist London Health Sciences Centre, London, ON	Robert Siemens Urologist Kingston General Hospital, Kingston, ON

Appendix 2. Literature search strategies.

MEDLINE

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1 Prostate-Specific Antigen/ (16552)
2 psa.mp. (19443)
3 prostate specific antigen.mp. (22171)
4 prostate-specific antigen.mp. (22171)
5 (elevated adj serum adj psa).mp. (128)
6 (elevated adj (psa or prostat$)).mp. (787)
7 (elevated adj serum adj prostat$).mp. (131)
8 (urinary adj (urgency or frequency or hesitancy)).mp. (1545)
9 exp Urination Disorders/ (85582)
10 (hematuria or haematuria).mp. (18570)
11 exp urological manifestations/ (58196)
12 dysuria.mp. (2740)
13 nocturia.mp. (1780)
14 voiding symptom$.mp. (917)
15 exp urinary bladder diseases/ (76331)
16 interstitial cystitis.mp. (2023)
17 Urinary Incontinence, Urge/ (407)
18 urge incontinence.mp. (1903)
19 exp urinary tract infections/ (36319)
20 (urinary tract adj3 infection$).mp. (40693)
21 Prostatitis/ (4301)
22 prostatitis.mp. (5443)
23 Impotence/ (13670)
24 erectile dysfunction$.mp. (16729)
25 (nodule$ adj2 testic$).mp. (49)
26 (pain$ adj3 testic$).mp. (558)
27 exp blood cell count/ (110544)
28 (CBC or FBC or full blood count).mp. (2499)
29 C-reactive protein/ (24972)
30 c-reactive protein$.mp. (38279)
31 Blood sedimentation/ (9634)
32 erythrocyte sedimentation rate.mp. (7842)
33 Urine/cy [Cytology] (2412)
34 urine cytology.mp. (1029)
35 Urinalysis/ (3912)
36 urine microscopy.mp. (182)
37 Tomography, X-Ray Computed/ (251576)
38 ct.mp. (179013)
39 exp ultrasonography/ (223170)
40 ultrasound.mp. (130447)
41 Urography/ (19038)
42 intravenous urogram$.mp. (433)
43 intravenous pyelogram$.mp. (614)
44 ((per rect$ or pr) adj exam$).mp. (45)
45 Digital rectal examination/ (410)
46 DRE.mp. (1688)
47 bone scan.mp. (4156)
48 (delay$ adj3 diagnos$).mp. (14969)
49 (delay$ adj3 practitioner$).mp. (66)
50 (delay$ adj3 patient$).mp. (9901)
51 early diagnosis/ (9418)

52 diagnos$ earl$.mp. (3049)
53 earl$ diagnosis.mp. (54937)
54 (earl$ adj detect$).mp. (37032)
55 (earl$ adj present$).mp. (922)
56 (earl$ adj symptom$).mp. (2406)
57 exp health behavior/ (82742)
58 exp attitude to health/ (255261)
59 Physician-patient relations/ (55356)
60 disease progression/ (84065)
61 time factors/ (920295)
62 Physician's practice patterns/ (35025)
63 "referral and consultation"/ (46989)
64 referral$.mp. (90746)
65 (earl$ adj refer$).mp. (1365)
66 (late$ adj refer$).mp. (572)
67 exp ethnic groups/ge (7672)
68 ethnic$.ti,ab. (69854)
69 $racial.ti,ab. (20642)
70 race.ti,ab. (53811)
71 heredit$.ti,ab. (56189)
72 inherit$.ti,ab. (78037)
73 (genetic$ or gene or genes).ti,ab. (1557508)
74 or/1-73 (4003495)
75 mass screening/ (73866)
76 74 not 75 (3977349)
77 exp prostate neoplasms/ (80065)
78 (prostat$ adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or
aden?carcinoma$ or polyp$)).mp. (94101)
79 77 or 78 (94101)
80 76 and 79 (46110)
81 limit 80 to english language (40922)
82 (200708: or 200709: or 20071: or 2008: or 2009: or 2010: or 2011: or 2012:).ed. (4154827)
83 81 and 82 (14062)
84 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient
education handout or case report or historical article).pt. (1596408)
85 83 not 84 (13203)
86 exp "Sensitivity and Specificity"/ (353520)
87 false negative reactions/ or false positive reactions/ (31607)
88 (sensitivity or specificity or accura$).ab,ti. (967231)
89 diagnos$.ab,ti. (1433092)
90 predictive value$.ab,ti. (57170)
91 reference value$.ab,ti. (10127)
92 ROC.ab,ti. (16104)
93 (likelihood adj ratio$1).ab,ti. (7054)
94 monitoring.mp. (360283)
95 (false adj (negative$1 or positive$1)).ab,ti. (49131)
96 (randomized controlled trial or controlled clinical trial).pt. (404640)
97 double-blind method/ or single-blind method/ (129520)
98 practice guideline.pt. (16527)
99 consensus development conference$.pt. (8066)
100 review.pt. (1686238)
101 review.ab. (594136)
102 (meta-analysis or metaanalysis).ab. (29706)

103 meta-analysis.pt. (33106)
104 meta-analysis.ti. (19468)
105 (cohort adj stud$).ab,ti. (63171)
106 exp cohort studies/ (1164614)
107 (single blind$3 or double blind$3 or triple blind$3).ab,ti. (112717)
108 Primary health care/ (47274)
109 Family physician/ (14219)
110 ((family or general) adj practitioner$).mp. (34799)
111 gp.mp. (24225)
112 family physician$.mp. (10417)
113 family doctor$.mp. (3383)
114 Family practice/ (59203)
115 ((family or general) adj practice$).mp. (80447)
116 primary care.mp. (59231)
117 primary health care.mp. (53338)
118 meta-analysis/ (33106)
119 "review literature"/ (1686238)
120 meta-analy$.mp. (59167)
121 metaanal$.mp. (1404)
122 (systematic$ adj (review$ or overview$)).mp. (36475)
123 review.ti. (215778)
124 (sensitivity or specificity).mp. (1116692)
125 exp Diagnostic Errors/ (85660)
126 predictive value$.mp. (154535)
127 "predictive value of tests"/ (118992)
128 ROC.mp. (30693)
129 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).mp. (28941)
130 (false adj (negative or positive)).mp. (61578)
131 accuracy.mp. (186526)
132 reference value$.mp. (141914)
133 likelihood ratio$.mp. (7072)
134 ((pre-test or pretest) adj probability).mp. (1043)
135 post-test probability.mp. (289)
136 Diagnosis, differential/ (352117)
137 Diagnostic tests, routine/ (5938)
138 exp DIAGNOSIS/ (5892781)
139 exp PATHOLOGY/ (38999)
140 (diagnosis or diagnostic).mp. (1505325)
141 exp primary health care/ (68225)
142 exp family practice/ (59203)
143 exp general practice/ (60683)
144 exp physicians, family/ (14219)
145 (gp$ or general practi$ or family physician$ or family doctor$ or primary health care or primary care).ti,ab.
(217381)
146 (gp$ or general practi$ or family physician$ or family doctor$ or primary health care or primary care).mp.
(250397)
147 or/86-146 (9467254)
148 85 and 147 (9862)

EMBASE

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1 Prostate-Specific Antigen/ (27484)
2 psa.mp. (25786)
3 prostate specific antigen.mp. (29760)
4 (elevated adj serum adj psa).mp. (132)
5 (elevated adj (psa or prostat$)).mp. (895)
6 (elevated adj serum adj prostat$).mp. (130)
7 (urinary adj (urgency or frequency or hesitancy)).mp. (5764)
8 urinary frequency/ (3160)
9 Urinary Urgency/ (2677)
10 exp Urinary Tract Hemorrhage/ (17028)
11 (hematuria or haematuria).mp. (19181)
12 dysuria.mp. (5525)
13 nocturia.mp. (3337)
14 exp Micturition Disorder/ (59698)
15 urge incontinence.mp. (4068)
16 interstitial cystitis.mp. (2709)
17 Interstitial Cystitis/ (2310)
18 exp Urogenital Tract Infection/ (49358)
19 (urinary tract adj3 infection$).mp. (35875)
20 exp Prostatitis/ (4146)
21 prostatitis.mp. (4657)
22 exp Impotence/ (21277)
23 impotence.mp. (8564)
24 erectile dysfunction$.mp. (18336)
25 (nodule$ adj2 testic$).mp. (43)
26 (pain$ adj3 testic$).mp. (521)
27 exp Scrotal Pain/ (754)
28 exp blood cell count/ (111420)
29 (CBC or FBC or full blood count).mp. (3504)
30 c-reactive protein.mp. or C Reactive Protein/ (61594)
31 erythrocyte sedimentation rate/ (14770)
32 erythrocyte sedimentation rate.mp. (16264)
33 Urine Cytology/ (1521)
34 urine cytology.mp. (1864)
35 exp urinalysis/ (45639)
36 urine microscopy.mp. (189)
37 cancer cytodiagnosis/ (4123)
38 Computer Assisted Tomography/ (317272)
39 ct.mp. (190059)
40 ULTRASOUND/ or ultrasound.mp. (173626)
41 intravenous urography/ or intravenous pyelography/ (3918)
42 (intravenous adj (urogra$ or pyelogra$)).mp. (4688)
43 ((per rect$ or pr) adj exam$).mp. (50)
44 Digital rectal examination/ (3250)
45 (delay$ adj3 diagnos$).mp. (16184)
46 (delay$ adj3 practitioner$).mp. (54)
47 (delay$ adj3 patient$).mp. (11520)
48 diagnos$ delay$.mp. (1742)
49 Cancer diagnosis/ (58064)
50 Early diagnosis/ (49460)
51 (diagnos$ adj earl$).mp. (19526)
52 (earl$ adj detect$).mp. (32994)
53 (earl$ adj present$).mp. (996)

54 (earl$ adj symptom$).mp. (5233)
55 Patient attitude/ (34864)
56 Attitude to health/ or Attitude to illness/ or Illness behavior/ (57854)
57 Delayed diagnosis/ (3401)
58 doctor patient relation/ (46832)
59 Patient referral/ (45265)
60 referral$.mp. (88288)
61 (earl$ adj refer$).mp. (1731)
62 (late$ adj refer$).mp. (800)
63 Time factors/ (199881)
64 exp disease course/ (1328389)
65 exp ethnic group/ (128675)
66 ethnic$.ti,ab. (72992)
67 $racial.ti,ab. (19036)
68 race.ti,ab. (52713)
69 heredit$.ti,ab. (41425)
70 inherit$.ti,ab. (64326)
71 (genetic$ or gene or genes).ti,ab. (1426576)
72 or/1-71 (3883284)
73 cancer screening/ (34583)
74 72 not 73 (3860421)
75 exp prostate cancer/ (83440)
76 (prostat$ adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or
aden?carcinoma$ or polyp$)).mp. (111599)
77 75 or 76 (111599)
78 74 and 77 (73044)
79 limit 78 to english language (66826)
80 (2007: or 2008: or 2009: or 2010: or 2011: or 2012:).ew. (4699865)
81 79 and 80 (33600)
82 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/ (1429694)
83 abstract.pt. (689288)
84 82 or 83 (2113572)
85 81 not 84 (21136)
86 "sensitivity and specificity"/ (159172)
87 false negative result/ or false positive result/ (11321)
88 (sensitivity or specificity or accura$).ab,ti. (791632)
89 diagnos$.ab,ti. (1226418)
90 predictive value$.ab,ti. (59057)
91 reference value$.ab,ti. (9439)
92 ROC.ab,ti. (21881)
93 (likelihood adj ratio$1).ab,ti. (7691)
94 monitoring.mp. (371112)
95 (false adj (negative$1 or positive$1)).ab,ti. (40117)
96 double blind procedure/ or single blind procedure/ or triple blind procedure/ (94414)
97 exp controlled clinical trial/ (373860)
98 double blind procedure/ or single blind procedure/ or triple blind procedure/ (94414)
99 exp practice guideline/ (255109)
100 review.pt. (1352756)
101 review.ab. (613367)
102 (meta-analysis or metaanalysis).ab. (36038)
103 Meta Analysis/ (58177)
104 meta-analysis.ti. (22657)
105 (cohort adj stud$).ab,ti. (74174)

106 cohort analysis/ (115216)
107 (single blind$3 or double blind$3 or triple blind$3).ab,ti. (90598)
108 exp Primary health care/ (72022)
109 general practitioner/ (40318)
110 ((family or general) adj practitioner$).mp. (54267)
111 gp.mp. (38273)
112 Family physician/ (40318)
113 family physician$.mp. (8961)
114 family doctor$.mp. (3269)
115 general practice/ (38211)
116 ((family or general) adj practice$).mp. (49129)
117 primary care.mp. (62862)
118 primary health care.mp. (32866)
119 "systematic review"/ (48857)
120 (meta-analy$ or metaanaly$).mp. (82982)
121 (systematic adj (review$ or overview$)).mp. (70364)
122 review.ti. (160586)
123 sensitivity.mp. (571116)
124 specificity.mp. (394522)
125 "prediction and forecasting"/ (22714)
126 predictive value$.mp. (67046)
127 predictive value$ of test$.mp. (466)
128 roc curve/ (5694)
129 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).mp. (22428)
130 exp diagnostic error/ (37364)
131 (false adj (positive or negative)).mp. (39499)
132 diagnostic accuracy/ (142337)
133 accuracy.mp. (337179)
134 reference value/ (34762)
135 reference value$.mp. (39682)
136 likelihood ratio$.mp. (7929)
137 ((pre-test or pretest) adj probability).mp. (1332)
138 post-test probability.mp. (330)
139 differential diagnosis/ (175179)
140 or/86-139 (4431440)
141 85 and 140 (11856)

Evidence-Based Series 24-3 Version 2: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Referral of Suspected Prostate Cancer by Family Physicians and Other Primary Care Providers: Development Methods, Recommendations Development and External Review Process

S. Young, P. Bansal, E. Vella, A. Finelli, C. Levitt, A. Loblaw, and the Prostate Cancer Referral Expert Panel

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2001 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Provincial Primary Care and Cancer Network of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on primary care referral for suspected prostate cancer, developed through review of an updated evidentiary base since the National Institute for Health and Clinical Excellence (NICE) 2005 and New Zealand Guidelines Group (NZGG) 2009 guidelines, an adaptation of existing guidelines, consensus of the Prostate Cancer Referral Working Group, and input from external review participants in Ontario (3,4).

Development of the Recommendations

The recommendations from NZGG 2009, Suspected Cancer in Primary Care: Guidelines for Investigation, Referral and Reducing Ethnic Disparities (http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?guidelineID=158) and NICE 2005, Referral guidelines for suspected cancer http://www.nice.org.uk/Guidance/CG27) were considered during the development of the recommendations (see Appendix 1). The updated evidentiary base was also considered. The evidentiary base consisted mainly of cohort and case series studies. The working group (Section 2, Appendix 1) held a teleconference to develop the recommendations through informal consensus. Each of the recommendations in Appendix 1 was discussed taking into consideration any evidence found in the systematic review. The recommendations were written and approved by all members during the meeting. The Prostate Cancer Referral Expert Panel (Section 2, Appendix 1) reviewed and approved the guideline as well.

Report Approval Panel Review and Approval

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. Key issues raised by the report approval panel and the working group responses (italicized) were the following:

- The guideline as written addresses the objectives of the review. It indirectly addresses the asymptomatic patient with an elevated PSA however this is not one of the stated objectives. It should be included as a stated objective as it is a relevant question for patients and physicians alike.
  - *Incidental PSA test results have been included in the objective. A definition has been included under Section 1.Target Population.*
- Why not refer to the intended users as primary care providers (PCPs) only?
  - *Family physicians (FPs) also look after people in secondary and tertiary care and therefore are not restricted to the primary care setting. The working group chose to keep the distinction between FPs and PCPs to reflect this difference.*
- Very little information has been provided on the risks or downstream effects of further investigations.

- *The benefits and risk of PSA testing can be found in the reference "PSA Toolkit: PSA Screening and Testing for Prostate Cancer" developed by the Canadian Partnership against Cancer. This sentence was added to the recommendations "The benefits and risks of PSA testing can be found in a PSA Toolkit developed by the Canadian Partnership against Cancer".*

- The selection criteria on page 3 indicated that predictive accuracy and diagnostic accuracy within the primary care setting was sought. However, the text as well as the study characteristic table would suggest some of the studies were not conducted within the primary care setting. It would be helpful to clarify this in the selection criteria.
  - *This was decided post hoc and therefore cannot be included in the selection criteria. This statement was added in the Results section under primary studies: "Because of the lack of studies performed in the primary care setting, a post hoc decision was made to include studies conducted in the secondary care setting if they included patients that were referred from the primary care setting. For studies assessing nomograms, only those studies that included patients from a referred population and that included variables that were available before referral to a specialist were included."*
- An additional explanation needs to be added as to why diagnostic accuracy for investigations, particularly of PSA, would be different as a function of setting.
  - *The following was added under the study selection criteria "Some diagnostic measurements, such as the positive predictive value, are affected by the prevalence of the disease in the population. Therefore, although some of these tests are not performed by the FP or other PCPs, it would be important that they are ordered by a FP or other PCP so that the prevalence of the disease is reflected in the primary care setting as opposed to the general population, where the prevalence of prostate cancer may be lower, or the secondary care setting, where the prevalence of prostate cancer may be higher."*
- AGREE and AMSTAR tools: while these are recognized tools for guideline developers and systematic reviewers, the intended user of this guideline may not be as familiar. A statement or two to put into context what the scores mean (high quality reviews scores tend to be etc) may improve the usefulness of this information to the reader.
  - *Statements were included in the Methods section.*
- Reference to Incidental PSA, Sunnybrook Calculator seems to appear for the first time in the key evidence and justification but cannot be linked to the evidence that is presented.
  - *The Sunnybrook Calculator was referred to as the 'prostate risk calculator' in Section 1 but not in Section 2. The term 'prostate risk calculator' was added to the evidence in Section 2 to be consistent with Section 1.*
- The readability of the recommendations and algorithm can be improved. The way the algorithm/recommendations were used to decide on the "action" is not the easiest to follow. The colour scheme of the algorithm is difficult to understand. For example, what is shared between the green boxes and the yellow boxes?
  - *The colour scheme was changed so that red represents 'refer', yellow represents a sign/symptom, and green represents an actionable item.*
  - *The headers for each recommendation for each patient group was reworded, and the following phrase was added "And guidance for referral is as follows:"*

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Prostate Cancer Referral Working Group circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the working group.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review July 23, 2012)

GUIDELINE OBJECTIVE

How should patients presenting to family physicians and other primary care providers (PCPs) with signs and/or symptoms of prostate cancer, including incidental prostate specific antigen (PSA) test results, be managed? The following questions are the factors considered in answering the overall question:

RESEARCH QUESTIONS

1. What signs, symptoms, and other clinical features that present in primary care are predictive of prostate cancer?
2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of prostate cancer?
3. What major, known risk factors increase the likelihood of prostate cancer in patients presenting with signs and/or symptoms of prostate cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers or system-related factors? Does a delay in the time to consultation affect patient outcome?

TARGET POPULATION

Adult male patients presenting in primary care settings with signs, including incidental PSA results (defined as results not ordered by the attending FP or other primary care provider [PCP]), or symptoms suggestive of prostate cancer comprise the target population. This guideline does not provide recommendations for screening healthy patients.

INTENDED USERS

This guideline is targeted to family physicians (FPs), general practitioners (GPs), emergency room physicians, other PCPs (nurse practitioners, registered nurses, and physician assistants), and urologists. For the purposes of this document, we have referred to FPs, GPs, emergency room physicians, and other PCPs as "FPs and other PCPs". The guidelines are also intended for policymakers to help ensure that resources are in place so that target wait times are achieved. They are intended to coincide with the introduction of prostate cancer Diagnostic Assessment Programs (DAPS) in Ontario. DAPs provide a single point of referral, coordination of care using a clinical navigator, fast tracking of diagnostic tests, and a multidisciplinary team approach. They are an Ontario-wide strategic priority designed to improve patient access and outcomes, as outlined in the Ontario Cancer Plan, 2005-2011 and 2011-2014 (5).

RECOMMENDATIONS

The following recommendations were adapted from the New Zealand Guidelines Group (NZGG) guideline Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities and the National Institute for Health and Clinical Excellence (NICE 2005), Referral guidelines for suspected cancer (3,4).The recommendations below reflect the integration of the NZGG 2009 and NICE 2005 recommendations, an updated systematic review of the research evidence since the NZGG 2009 and the NICE 2005 guidelines, and consensus by the PEBC Prostate Cancer Referral Working Group (see Section 2: Appendix 1 for a list of members) (3,4). The recommended wait times for referral were based on consensus as opposed to strong evidence from well-conducted studies.

Recommendation 1: Actions for Patients with Symptoms of Metastatic Prostate Cancer
A man aged 40 years or older should have a digital rectal examination (DRE) and a PSA test if he has any unexplained symptoms suggestive of metastatic prostate cancer:

- Suspicious lower back pain symptoms such as those associated with reproducible percussion tenderness
- Severe bone pain
- Weight loss, especially in the elderly

Guidance for referral is as follows:

a. If the prostate is hard or irregular on DRE or PSA is 20 ng/ml or more, then patients should be referred urgently, which may include additional communication (e.g., telephone call, fax), and expect a consultation with a urologist or a prostate DAP within one week.

b. If the PSA is between 10 and 20 ng/ml, then patients should be referred semi-urgently and expect a consultation with a urologist or a prostate DAP within two weeks.

c. If the PSA is less than 10, then patients should be referred non-urgently and expect a consultation with a urologist or a prostate DAP within four weeks.

Recommendation 2: Actions for Patients with Lower Urinary Tract Symptoms (LUTS)
For a man presenting with lower urinary tract symptoms (LUTS) (irritative and obstructive voiding symptoms), a DRE should be performed and a discussion about PSA testing should occur with the patient (refer to Individual Risk Assessment from the Canadian Partnership Against Cancer PSA toolkit) (4). Urinary infection should be excluded before PSA testing, especially in men presenting with LUTS. The PSA test should be postponed for at least one month after treatment for a proven urinary infection.
Guidance for referral is as follows:

a. If the prostate is hard or irregular on DRE, a PSA test should be ordered, and the patient should be referred non-urgently and expect a consultation with a urologist or a prostate DAP within four weeks.

b. If the prostate is hard or irregular on DRE and the age-based PSA is elevated but less than 10 ng/ml, then the patient should be referred non-urgently and expect a consultation with a urologist or a prostate DAP within four weeks.

c. If the prostate is hard or irregular on DRE and the PSA is between 10 and 20 ng/ml, then the patient should be referred urgently, which may include additional communication (e.g., telephone call, fax), and expect a consultation with a urologist or a prostate DAP within one week.

d. If the PSA is 20 ng/ml or more, then the patient should be referred urgently, which may include additional communication (e.g., telephone call, fax), and expect a consultation with a urologist or a prostate DAP within one week.

e. If the prostate is normal on DRE and the PSA is between 10 and 20 ng/ml, then the patient should be referred semi-urgently and expect a consultation with a urologist or a prostate DAP within two weeks.

f. If the prostate is normal on DRE and the age-based PSA is elevated but less than 10 ng/ml, then appropriate nomograms such as the Prostate Risk Calculator developed by Nam et al 2011 may be used to determine the risk of high grade prostate cancer, in consultation with a urologist and following a discussion with the patient about the benefits and risks of PSA testing (5).The benefits and risks of PSA testing can be found in a PSA Toolkit developed by the Canadian Partnership against Cancer (4).

i. If the risk of high grade prostate cancer is less than 5%, then annual monitoring of PSA and DRE is recommended. This is based on the premise that repeated PSA testing is supported by the patient and FP or other PCP.

ii. If the risk of high-grade prostate cancer is between 5% and 20%, then discussion about other management options should occur with the patient. Based on patient preference, this could include referral to a urologist or a prostate DAP or annual or more frequent follow-up of PSA testing and DREs. This is based on the premise that repeated PSA testing is supported by the patient and FP or other PCP.

iii. If the risk of high-grade prostate cancer is greater than 20%, then the patient should be referred non-urgently and expect a consultation with a urologist or a prostate DAP within four weeks.

Recommendation 3: Actions for Patients with Incidental PSA

For incidental elevated age-based PSA findings, a DRE should be performed for all patients. Rule out other reasons for elevated PSA values (e.g. age-related hypertrophy [benign prostatic hypertrophy; BPH], infection, inflammation, prostatitis, recent sexual activity, etc.). Repeat PSA test if unsure. The recommendations b) through f) for LUTS (see Recommendation 2: above) should be followed.

KEY EVIDENCE AND JUSTIFICATION

All recommended wait times were based on consensus of the Working Group. The Canadian Association of Radiation Oncology recommended a wait time from referral to consultation with a radiation oncologist of no longer than 10 working days (6). This was taken into consideration when developing the wait times in this guideline.

The primary care literature evidence examining the diagnostic accuracy of tests for prostate cancer was very weak. Two studies suggested that DREs performed by FPs may be useful in identifying patients who should be referred (7,8), and four studies suggested that PSA values were good predictors of prostate cancer with PPVs ranging from 34.3% to 47% (7,9-11). The Working Group chose to endorse the recommendations from NICE 2005 and NZGG 2009 to recommend a DRE and PSA test for all patients with symptoms of metastatic prostate cancer (3,4). NICE 2005 recommended performing a DRE and PSA test for all men with LUTS and NZGG 2009 recommended these tests only for older men with LUTS (3,4). The Working Group chose to recommend a DRE for all men with LUTS and a PSA test for

selected patients with LUTS, following discussion and treatment. The limited evidence from the systematic review suggested that men with LUTS may not be at any higher risk for prostate cancer or have a poorer prognosis than asymptomatic men would be (9,12). The Canadian Urological Association's benign prostatic hyperplasia guideline for men presenting with LUTS recommended a DRE for all men and a PSA test for selected patients (13). The Working Group chose to be consistent with this guideline.

Recommendation 4. Actions for Patients with Symptoms of Metastatic Prostate Cancer

The NZGG 2009 guideline recommendation that patients with symptoms of metastatic prostate cancer should have a DRE and PSA was endorsed (4). An age threshold of 40 years was included at the suggestion of the Expert Panel and due to the few cases of prostate cancer in men under 40 years in Canada (14). The Working Group did not think it necessary for a man with erectile dysfunction to undergo a DRE and PSA test and therefore excluded it as a symptom of metastatic prostate cancer. This is consistent with the NZGG 2009 guideline but in contrast to the NICE 2005 guideline (3,4). The Working Group also excluded unexplained hematuria as a symptom of metastatic prostate cancer because although it can be associated with advanced prostate cancer, the Group believed the vast majority of men with gross hematuria usually have a different underlying cause such as benign prostate hyperplasia, bladder or renal cancer, stones or infections. The Working Group believed hematuria requires urologic assessment but is not part of a prostate cancer care algorithm.

a-c. The cut-off values of 10 and 20 ng/ml were taken from the D'Amico classification system for categorizing patients at low risk (cT1-cT2a, Gleason <7 and PSA ≤10 ng/ml), intermediate risk (cT2b, Gleason = 7 or [PSA >10 and ≤20 ng/ml]) or high risk (cT2c or PSA >20 ng/ml or Gleason >7) for prostate cancer (15,16).

Recommendation 5. Actions for Patients with Lower Urinary Tract Symptoms (LUTS)

The recommendation that a man with LUTS should have a DRE and a discussion about PSA testing was consistent with the Canadian Urological Association's guideline for benign prostatic hyperplasia (13). The Working Group referred to the individual risk assessment developed by the Canadian Partnership Against Cancer as a guide to who should be given a PSA test (17). This document describes the benefits and harms of PSA testing. The Working Group also endorsed the recommendations to exclude urinary infection before PSA testing and to postpone PSA testing for at least one month after treatment from the NICE 2005 and NZGG 2009 guidelines (3,4).

c. This recommendation was endorsed from the NICE 2005 guideline (3).
d. The age-based PSA values were endorsed from the NZGG 2009 guidelines (4).
c-e. Please refer to a-c in the previous section under Recommendation 1: Actions for Patients with Symptoms of Metastatic Prostate Cancer.
f. i. A cut-off risk value of 5% was chosen because in Ontario, Canada, the hospital admission rate for urological complications within 30 days of TRUS-guided biopsy was found to be 4.1% in 2005 (18). The Working Group decided to use 5% as a cut-off to separate patients into a higher risk category because for these patients the risk of high-grade prostate cancer would be higher than the risk of complications from TRUS-guided biopsy.
ii-iii. The prostate risk calculator developed at Sunnybrook Hospital, Toronto, Ontario, Canada, showed a net benefit (the relative value of false-positive versus false-negative results) when a risk of 15% for aggressive prostate cancer was chosen

as a threshold to agree to a biopsy (19). Based on the consensus of the Working Group a conservative cut-off risk value of 20% was chosen.

Recommendation 6. Actions for Patients with Incidental PSA

Although this guideline excludes patients in a screening program, the working group thought that FPs and other PCPs need guidance on how to manage patients with incidental PSA test results, a frequently encountered occurrence in practice. Opportunistic screening has been excluded because it is beyond the scope of this guideline.

The Working Group believed that if an incidental PSA test was abnormal, then standard practise would be to perform a DRE. A hard or irregular prostate on DRE may increase the urgency of referral.

Cases with enlarged, smooth prostates were excluded because it was beyond the scope of this guideline since it was not considered to be a sign of prostate cancer. Also, although a rising PSA level could be considered a sign of prostate cancer, the Working Group believed the guideline was sufficiently thorough to include most possible scenarios for prostate cancer using the absolute PSA values. Furthermore, there were no studies examining the factors associated with delayed referral that could directly inform these recommendations.

FUTURE RESEARCH

Further studies are required that specifically investigate the diagnostic performance of signs, symptoms, or tests for prostate cancer in the primary care setting.

GLOSSARY

age-based PSA
Age-based PSA values (upper limit of normal):
40–50 years: 2.5 ng/ml
50–60 years: 3.5 ng/ml
60–70 years: 4.5 ng/ml
70 years and over: 6.5 ng/ml
Note: This is an example of an age-based range cited in the NZGG resource:
Testing for prostate cancer: a consultation resource, 2008 (20). Differences in PSA assay can lead to differences in age-based ranges reported by laboratories.

Prostate Risk Calculator
The nomogram developed by Nam et al 2011 was chosen as an example because it was externally validated in Ontario, Canada and is available online (http://sunnybrook.ca/content/?page=OCC_prostateCalc) (21). The prostate risk calculator includes the free:total PSA ratio, which is the ratio of free PSA, unbound to serum proteins, to total PSA. This ratio is decreased in men with prostate cancer (22). The free:total PSA ratio in some cases may be charged a laboratory fee to the patient. If this ratio is not determined, then a value of 0.1 can be entered into the risk calculator.

Case Examples

4. Symptoms of metastatic prostate cancer

   A healthy 70 year old vigorous gentleman, on no medications, who ran marathons yearly in the spring presented to a FP. He lived in Florida in the winter and usually was seen only once yearly in the spring. He came home to Canada earlier than usual as he had urinary retention in Florida, was catheterized but was having tremendous lower back pain. This thin, muscular man had never complained about lower back

pain before. On examination, a firm fixed pelvic mass was noted. DRE noted a firm, irregular, fixed, and enlarged prostate. The urologist saw him within two days. A presumptive diagnosis of prostate cancer with bone metastasis was made. The PSA was 20ng/ml. Although diagnosis of prostate cancer was likely, the patient refused a biopsy and further diagnostic tests. His pain was quite severe and he was admitted to a palliative care unit for pain control and died within three weeks.

5. LUTS

A healthy 72 year old man with some symptoms of urinary retention and urgency presented to a FP. His older brother was diagnosed with prostate cancer at age 76. Urine analysis was negative and DRE found a smooth, normal prostate. The FP and patient discussed having a PSA test but the patient refused and asked to see a urologist to discuss the LUTS and his family history and was seen two months later. After a discussion with the urologist, the patient agreed to have a PSA and the result was 4.9ng/ml. The urologist explained to the patient that the result was within normal limits for his age. The patient elected to be followed with serial PSAs and DREs by his family physician. No treatments were initiated for the patient's symptoms of some urinary retention and urgency which seemed to resolve spontaneously. Since the first visit with the urologist, the PSA has been monitored every three months and has not increased beyond 6.8ng/ml in two years.

6. Incidental PSA

A healthy 49 year old banker had a PSA test as part of a comprehensive medical examination offered through his insurance company. The physical examination was normal but the PSA was elevated for his age. He presented to his family doctor with a PSA of 3.5ng/ml and no other symptoms. The family doctor on DRE found a smooth, normal prostate. The family doctor evaluated the patient's risk for prostate cancer at 10-20% using the Prostate Risk Cancer nomogram and the patient elected to repeat the PSA and DRE in a few months. However, after further consideration at home, the patient called and asked to be referred to a urologist for a consultation.

Methods

Targeted Peer Review: During the guideline development process, ten targeted peer reviewers from Ontario considered to be clinical and/or methodological experts on the topic were identified by the Prostate Cancer Referral Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Six reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on July 23, 2012. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Prostate Cancer Referral Working Group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All health care professionals with an interest in prostate cancer including family physicians, urologists, radiologists and surgeons in the PEBC database were contacted by email to inform them of the survey. Also, members of the Canadian Cancer Society, the Nurses Practitioner Association of Ontario, the Ontario College of Family Physicians, the Ontario Hospital Association, the Ontario Medical Association, the Canadian Association of Radiation Oncology, the Canadian Urological Association, and the Genitourinary Radiation Oncologists of Canada were invited to review this guideline.

Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on July 23, 2012. The consultation period ended on September 14, 2012. The Prostate Cancer Referral Working Group reviewed the results of the survey.

Results

Targeted Peer Review: Six responses were received from six reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=6)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	1	0	0	4	1
2. Rate the guideline presentation.	0	0	1	4	1
3. Rate the guideline recommendations.	1	0	2	2	1
4. Rate the completeness of reporting.	1	0	1	2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	1	0	0	3	1
6. Rate the overall quality of the guideline report.	1	0	1	2	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	3	0	0	2	1
8. I would recommend this guideline for use in practice.	1	0	1	3	1

9. What are the barriers or enablers to the implementation of this guideline report?

One of the main barriers is the lack of evidence to justify the recommendations. One targeted peer reviewer felt the document was confusing and might be difficult to implement in communities with limited resources.

Table 2. Summary of written comments by targeted peer reviewers and modifications/actions taken.

Summary of Written Comments	*Modifications/Actions/Comments*
1. Recommendation 1: D'Amico PSA levels used to direct wait times. These were never meant for this purpose. If there is suspicion of metastatic disease with PSA between <10 or 10-20 it may seem that an appointment isn't needed for up to 4 weeks, but this is wrong.	The working group felt that although the D'Amico system is used to classify risk of prostate cancer in patients that have localized prostate cancer, not in a primary care population, there is no study that classifies the risk of prostate cancer for patients according to PSA levels in the primary population. The limited evidence in

	the primary care population does suggest that PSA is associated with risk of prostate cancer. In order to simplify the recommendations, thresholds were chosen based on the D'Amico system. Using a continuum of PSA values for the recommendations would have made them more confusing. This statement was added to the justification section in section one "Although this was not developed in the primary care population, the working group chose to include this classification system because it is widely used to classify risk of prostate cancer and using these thresholds provides guidance for family physicians in determining their course of action."
2. An isolated, especially first-time, "Incidental PSA" should be confirmed with a repeat reading before implementing the recommended actions.	The working group felt if the PSA is high then ordering a repeat PSA would delay referral. Also, the guidelines do mention to repeat the PSA if unsure. This is left to clinical judgement. Furthermore, consideration can be given to repeat a PSA before undergoing biopsy.
3. Although I like nomograms, leaning on Nams' seems strange given the requirement for free/total and IPSS scores which are not discussed in the recommendations?	The working group agrees with this comment. Nam's nomogram was used as an example. Other examples have been provided.
4. Furthermore, although Nam's risk calculator has been validated in external populations, it has never been shown to add to any outcome in a screening population or case detection. How patients and physicians perceive risk is important to validate (but never has) for these calculators and simply saying annual follow-up based on a calculator and risk <5 is foolish and paternalistic. It is an important and in depth discussion with a well-informed patient expert to lead to informed/shared decision. There is much more to discuss with this patient with LUTS and a PSA of 7 (use and follow-up of 5-alpha reductase inhibitors, etc). I believe this is too specific and paternalistic.	The working group felt that the guideline does recommend the physician consult with a urologist and discuss with the patient about the benefits and risks of PSA testing, before using the Nam nomogram. Also, this guideline is for referring based on suspicion of prostate cancer and not benign prostate hyperplasia. Physicians will have to refer to other guidelines for LUTS that is benign prostate hyperplasia.
5. History of presence/absence of recent sexual activity, specifically ejaculation, should be elicited when the GO is faced with an elevated PSA	The working group felt that although we know sexual activity can have an effect on PSA values it should not change the risk stratification for patients. Also, ruling out sexual activity is mentioned in the guideline.
6. Although Incidental PSA may be important and the report specifies that opportunistic testing has not been included because it is beyond the scope of this report, many PCP may not appreciate the difference between the two and would use the Incidental guidelines and apply it to the opportunistic group.	A statement that this guideline is not about opportunistic PSA testing was added under the target population.

Professional Consultation: Eighty-eight responses were received. Key results of the feedback survey are summarized in Table 3.

Table 3. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	*3*	***3***	*14*	*55*	*25*
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	*5*	*8*	*9*	*51*	*27*
3. I would recommend this guideline for use in practice.	*5*	*7*	*7*	*48*	*33*

4. What are the barriers or enablers to the implementation of this guideline report?
Again, several reviewers felt that the lack of evidence to support the recommendations was a major barrier. Some of the professional consultants believed that the algorithm was helpful for dissemination whereas others found it too detailed and confusing. Several reviewers felt the timelines were unrealistic and would be difficult to follow. Other reviewers felt there would be problems accessing urologists and the cost to the patients for a free PSA test would not be feasible. Several reviewers felt that barriers included disseminating the guidelines, educating family physicians and getting buy-in from the family physicians and specialists. Other reviewers suggested that family physicians do not commonly do DREs and this would be a barrier. Also, there may be non-compliant patients and patients' demands for PSA testing may be a barrier.

Table 4. Summary of Written Comments by professional consultants and Modifications/Actions Taken.

Summary of Written Comments	*Modifications/Actions/Comments*
1. The guidance for referral is completely unrealistic and bears no relationship to the underlying biologic course of the disease. Prostate cancer is slow growing even at higher grades compared to other tumours. Your "a" one week and "b" 2 weeks and "c" 4 weeks recommendations would actually have the unintended consequence of delaying evaluation of other cancers (red cell, bladder, testicular) because of the sheer volume of prostate cancer referrals. These recommendations might work in a teaching centre, but show complete ignorance of the practice realities (and urgency of care expectations) in a peripheral environment. Your time to assessment recommendation will have no impact on disease outcome, will foster unreasonable and unobtainable expectations, and will cause other more urgent conditions to be delayed in their assessment.	The working group acknowledges that prostate cancer is slow-growing and patients may have other cancer/diseases with the signs/symptoms mentioned in the recommendations. That is why the word 'unexplained' is underlined and bolded in the recommendations. It implies that after proper triaging of the patient, prostate cancer may be considered if other cancers/diseases do not explain the signs/symptoms.

2. With regards to Recommendation#1: The word "suspected" should be added before "symptoms of metastatic cancer".	The word 'unexplained' was included in the title of the recommendation.
3. The guidelines are clear which will help enable its use. What was not clear was in the metastatic setting whether the FP or PCP should be ordering other investigations (ie bone scan) at the same time as the referral to a urologist or treatment centre.	The working group felt that this should be left to the discretion of the physician. They did not include this in the recommendations because it would be difficult to include all possible scenarios.
4. The recommendations assume that it is more urgent to diagnose metastatic prostate cancer than LUTS. The decision to agree or adopt existing recommendations where appropriate will reduce the likelihood of confusion from conflicting recommendations. Do we need early diagnosis centres in an era where we have discouraged the use of opportunistic screening? It sounds like a WAIT (until it is metastatic before it is diagnosed) and then HURRY (because you regret not picking it up earlier) policy. Adherence to this would be only slightly better than advise to not do "routine" PSAs.	The working group understands that practices will vary as to their philosophy to do PSA screening. The Working Group's intention is to write this guideline so that referral is done in an appropriate manner.
5. Recommendation#2: "discussion about PSA testing" should be elaborated to include "discussion about pros and cons of testing" or "It is an individual decision based on patient wishes once education provided to better inform the patient's decision". "Urinary infection" is potentially misleading term. In this context, it should be changed to "urinary infections including prostatitis" The urgency of a referral for PSA > 20 is dependent on the degree of associated clinical symptoms and on the risk of symptom progression to urgent complications (i.e. risk of obstruction).	The working group felt that this was not in the scope of this guideline and that there are different points of view on PSA screening. They also decided to change 'urinary infection' to 'lower urinary tract infection' as it is more of an inclusive term.
6. It is also not clear what to do when LUTS or incidental elevated PSA and risk by nomogram below 5% or between 5-20% occurs. How often should one monitor and with what?	The working group tried to give some guidance on this topic but did not want to be overly prescriptive.
7. I notice there is no recommendation for obtaining a biopsy by the FP or PCP. A large group of patients will fit the category of LUTS or incidental elevated PSA with normal exam and PSA <10. In my experience urologists will normally obtain biopsies on these patients. Is there a role for arranging a biopsy in advance of (or to obviate the need for) a referral to urology?	The working group felt this was beyond the scope of this guideline.
8. The nomogram for risk calculation is mentioned several times but is not included. I think the nomogram for calculating risk needs to be provided with this document.	The working group decided to include the links on the algorithm for the nomograms.
9. I have one big problem with this report: It's the use of age-based PSA ranges. It is not only out of date but potentially dangerous to suggest that the normal PSA for a man aged 40-50 is <2.5. This is based on decades old data. We now know that a man at this age with a PSA above 1 ng/ml is at much increased	These cut-points were taken from the NZGG guideline. In the glossary it indicates that differences in PSA assay can lead to differences in age-based ranges reported by laboratories. This guideline is not used to diagnose low-risk patients, but rather those

risk of having prostate cancer and that the risk of ultimately fatal prostate cancer rises sharply. I believe the advice should be to repeat any PSA above 1 at this age, and to refer to a urologist if confirmed. Similarly in their young 50's a PSA up to 3.5 is slightly high. One could go so far as to say there is no normal range, only a continuum of risk, but this is completely lost in the guideline which implies hard cut points below which everything is "OK	that are at high risk for prostate cancer. Likewise, the nomograms use age and PSA in their equations. Also, the recommendations do suggest to repeat a PSA if unsure.
10. Clear straight forward algorithm to follow, but don't like the colour scheme particularly the red....seems alarming especially when used for urgent as well as non-urgent.	The working group decided to change the colour from red to white.
11. Doesn't address the issue of the incidental abnormality detected on DRE.	The working group felt this could occur during a routine general assessment or when looking for other diseases i.e. rectal lesions. Physicians would treat this as an opportunity to discuss the possibility of prostate cancer and whether to proceed with further investigation.
12. In the flow sheet and guidelines, there are no suggestions for "LUTS with normal DRE and decision to not perform PSA"	These patients are not at greater risk for prostate cancer and are therefore not part of the target population
13. It does not address TRUS.	The working group felt that TRUS in the absence of biopsy has limited value in the diagnosis of prostate cancer and should be discouraged.
14. No advice regarding screening. When to do PSA.	The working group believed that screening for prostate cancer is controversial. The focus of this document is to give guidance when PSA is available or when there are signs or symptoms for prostate cancer.

The chairs from CCO's Disease Pathway Management for prostate cancer suggested two clarifications to the algorithm that have been incorporated. One is to recommend non-urgent referral for patients with a normal DRE and an elevated age-based PSA that is lower than 10ng/ml if a nomogram has not been used. The other adjustment was to consider other metastatic cancers for patients with possible symptoms of metastatic prostate cancer and a normal DRE but a PSA that is lower than 10ng/ml. If there is still a suspicion of metastatic prostate cancer, than a non-urgent referral is recommended.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the Prostate Cancer Referral Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest.

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Appendix 1 Table 1. Recommendations from existing guidelines.

NZGG 2009*	NICE 2005**
	Patients presenting with symptoms suggesting prostate cancer should have a digital rectal examination (DRE) and prostate specific antigen (PSA) test after counselling. Symptoms will be related to the lower urinary tract and may be inflammatory or obstructive.
	If a hard, irregular prostate typical of a prostate carcinoma is felt on rectal examination, then the patient should be referred urgently. The PSA should be measured and the result should accompany the referral. Patients do not need urgent referral if the prostate is simply enlarged and the PSA is in the age-specific reference range. The age-specific cut-off PSA measurements recommended by the Prostate Cancer Risk Management Programme are as follows: aged 50–59 years ≥ 3.0 ng/ml; aged 60–69 years ≥ 4.0 ng/ml; aged 70 years and older ≥ 5.0 ng/ml. (Note that there are no age-specific reference ranges for men aged over 80 years. Nearly all men of this age have at least a focus of cancer in the prostate. Prostate cancer only needs to be diagnosed in this age group if it is likely to need palliative treatment.)
A man presenting with lower urinary tract symptoms and found to have a hard, irregular prostate on digital rectal examination should be referred urgently to a specialist.	
A man presenting with lower urinary tract symptoms and a high PSA (10 ng/ml or more) should be referred urgently to a specialist.	Symptomatic patients with high PSA levels should be referred urgently.
A man with lower urinary tract symptoms in whom the prostate is normal on digital rectal examination but the age-specific PSA† is raised or rising, should be urgently referred to a specialist. For a man whose clinical state is compromised by other comorbidities, a discussion about management options with the man and/or a specialist in urological cancer may be more appropriate † Age-based PSA values (upper limit of normal): 40–50 years: 2.5 ng/ml 50–60 years: 3.5 ng/ml 60–70 years: 4.5 ng/ml 70 years and over: 6.5 ng/ml Note: This is an example of an age-based range cited in the NZGG resource: Testing for prostate cancer: a consultation resource, 2008. Differences in PSA assay can lead to differences in age-based ranges reported by laboratories	In a male a patient with or without lower urinary tract symptoms and in whom the prostate is normal on DRE but the age specific PSA is raised or rising, an urgent referral should be made. In those patients whose clinical state is compromised by other comorbidities, a discussion with the patient or carers and/or a specialist in urological cancer may be more appropriate.
A man should be recommended to have a digital rectal examination and a PSA test if he has any unexplained symptom suggestive of metastatic prostate cancer: • lower back pain	Prostate cancer is also a possibility in male patients with any of the following unexplained symptoms: • erectile dysfunction • hematuria

• bone pain • weight loss, especially in the elderly	• lower back pain • bone pain • weight loss, especially in the elderly. These patients should also be offered a DRE and a PSA test.
Prior to PSA testing, a practitioner should exclude urinary infection, especially in a man presenting with lower urinary tract symptoms. The PSA test should be postponed for at least 1 month after treatment of a proven urinary infection	Urinary infection should be excluded before PSA testing, especially in men presenting with lower tract symptoms. The PSA test should be postponed for at least 1 month after treatment of a proven urinary infection.
A man presenting with macroscopic haematuria should be referred urgently to a specialist	
A man found to have an enlarged, smooth prostate on digital rectal examination and a normal PSA should *only* be referred to a specialist if they have macroscopic haematuria	
An older man presenting with lower urinary tract symptoms (frequency, hesitancy, nocturia) should be recommended to have a digital rectal examination and a PSA test	
	If there is doubt about whether to refer an asymptomatic male with a borderline level of PSA, the PSA test should be repeated after an interval of 1 to 3 months. If the second test indicates that the PSA level is rising, the patient should be referred urgently.

* National Collaborating Centre for Primary Care. Referral guidelines for suspected cancer. London: National Institute for Health and Clinical Excellence (NICE); 2005 Jun. Clinical Guideline No.: 27.2005.
**New Zealand Guidelines Group. Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities. Wellington (NZ): New Zealand Guidelines Group (NZGG); 2009

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 24-3 Version 2: Section 4

Referral of Suspected Prostate Cancer by Family Physicians and Other Primary Care Providers

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Prostate Cancer Referral Expert Panel

December 19, 2016

The 2012 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2012.

In 2015, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. The methods and results of the search are summarized below. A clinical expert (Dr. Praveen Bansal) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The prostate cancer referral expert panel endorsed the recommendations found in Section 1 (Clinical Practice Guideline) on December 19, 2016.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. What signs, symptoms, and other clinical features that present in primary care are predictive of prostate cancer?
2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of prostate cancer?

3. What major, known risk factors increase the likelihood of prostate cancer in patients presenting with signs and/or symptoms of prostate cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers or system-related factors? Does a delay in the time to consultation affect patient outcome?

Literature Search and New Evidence
The new search (April 2012 to September 2016) yielded 22 new studies evaluating referrals of suspected prostate cancer patients by family physicians and other primary care providers. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations
The results of this new evidence are somewhat in line with the original recommendations specifying elevated PSA, abnormal DREs, and symptoms of LUTS as being appropriate reasons for referral (questions 1 and 2). However, only one study actually presented statistical measures on the accuracy of DRE in predicting a diagnosis of prostate cancer and none assessed the diagnostic accuracy of the other types of testing. Few studies examined major risk factors and delay in referral for prostate cancer (questions 3 and 4), and their conclusions were varied depending on data available to the researchers. Basically, all 22 studies in this review were observational and most relied on retrospectively extracted chart data to answer the four questions. Given these limitations, the evidence from this review does not appear to alter the current recommendations.

Document Review Tool

Number and title of document under review	24-3 **Referral of Suspected Prostate Cancer by Family Physicians and Other Primary Care Providers**
Current Report Date	**October 31, 2012**
Clinical Expert	Dr. Praveen Bansal
Research Coordinator	Judy A Brown
Date Assessed	October 10, 2016
Approval Date and Review Outcome (once completed)	December 19, 2016 ENDORSED

Original Question(s):
1. What signs, symptoms, and other clinical features that present in primary care are predictive of prostate cancer?
2. What is the diagnostic accuracy of investigations commonly considered for patients presenting with signs and/or symptoms of prostate cancer?
3. What major, known risk factors increase the likelihood of prostate cancer in patients presenting with signs and/or symptoms of prostate cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers or system-related factors? Does a delay in the time to consultation affect patient outcome?

Target Population:

Patients presenting to primary care with signs or symptoms of prostate cancer.

Study Section Criteria:

For the clinical question about the predictive accuracy of signs or symptoms, all prospective or retrospective case series or cohort or case control studies of symptom recognition/identification for prostate cancer conducted in the primary care setting were included.

For the question concerning the diagnostic accuracy of investigations, studies were sought in which symptomatic patients underwent one or more investigations, including an abnormal rectal examination, PSA testing, urine microscopy, trans-rectal ultrasound, computed tomography scan, urine cytology, and bone scan (for metastatic disease) in primary care.

For the research questions concerning risk factors and delay in referral, a search for practice guidelines, systematic reviews (with meta-analyses), and systematic reviews (without meta-analyses) was performed. If these articles did not definitively answer the particular clinical question, then searches for randomized phase III trials and randomized phase II trials followed by prospective or retrospective case series or cohort or case-control studies were performed.

Search Details:

For these clinical questions, a search, updated since the original report, of MEDLINE (Ovid, April 2012 – September 2016) and EMBASE (Ovid, 2012 - 2016 week 40) was performed using the original search strategy (see appendix 1).

Brief Summary/Discussion of New Evidence:

The new search from April 2012 to September 2016 yielded 22 studies (all observational studies) [1-22] from 26 articles [1-26] evaluating referrals of suspected prostate cancer patients by family physicians and other primary care providers. A 2015 update of the 2005 NICE guideline, "Suspected Cancer: recognition and referral" was used as a foundation, because it was considered to be of high quality, comprehensive, recent in publication, and relevant to this topic https://www.nice.org.uk/guidance/ng12. The NICE report found five articles [1,27-30] asking the question, "What is the risk of prostate cancer in patients presenting in primary care with symptom(s)?" One article was relevant to this report [1] and is included in the 22 studies listed above. Of the remaining four articles, two were out of the time range of this report [28,29], one was non-English [27] and the other was included in the 2012 original version of this report [30]. Table 1 show the articles included in this report (pages 5-9).

Sixteen of the 22 studies explicitly stated that patient were referred from a primary care setting [1,4,5,7-15,17-20]. Referral source was unclear in the remaining six studies [2,3,6,16,21,22] but were included since they occurred in secondary care setting and are presumed to include at least some patients referred from a primary care setting; this was decided in the original version of this report because of the small number of studies conducted in the primary care setting at the time (see Section 2, pg. 16).

Twelve studies addressed question 1 [1,2,4,6,7,10-17] and 13 addressed question 2 [1,2,4,6,7,11-13,15,17,19-21]. Ten of the 12 studies suggested that rising or elevated PSA values [4,6,7,10,12,13,15-17] were strong predictors of referral for prostate cancer. Of those studies referring for abnormal PSA tests, five also referred men on the basis of an abnormal digital rectal exam (DRE) [6,7,13,15,16], and two referred men with lower urinary tract symptoms (LUTS) [6,7,13]. In two studies, men were referred with symptoms of haematuria [1] and haematospermia [11]. The percentage of men diagnosed with prostate cancer ranged from under 1% and 5.7% in studies examining men presenting with haematuria [1] or

haematospermia [11] respectively to just over 50% among men referred because of raised PSA levels [4,12]. In another study, 38% of men with elevated PSA were diagnosed with prostate cancer, compared to 20% with normal PSA [7]. The only study presenting statistical measures of diagnostic accuracy found that DRE alone had a sensitivity and specificity of 81% and 40% respectively in diagnosing prostate cancer, with a positive predictive value of 42% [13].

Three studies addressed question 3 (major risk factors) [6,9,15]. One study found that men living in more deprived areas were more likely to be diagnosed at a more advanced stage, while non-white and younger men less likely to be diagnosed at a more advanced stage [9]. This same study also found GP practice deprivation and practices with higher rates of colonoscopy, sigmoidoscopy and endoscopy to be associated with a higher percentage diagnosed at a more advanced stage [9]. One study's results suggested that being referred from primary care with symptomatic presentation may be an independent negative prognostic indicator for survival [6].

Six studies addressed question 4 [2,3,5,10,18,22]. Priority of referral by GPs, compared to other cancer, was sighted as the reason for delay in referring prostate cancer patients [5] with men waiting on average 11 days between first presenting with symptoms to a GP and being referred to secondary care; much higher than for other cancer types. An Australian study found that men that presented with symptoms without private health insurance were more likely to wait more than 70 days between consultation and receiving a diagnosis [3]. For treatment interval, men without private health insurance or who were treated with radiotherapy alone were more likely to wait more than 70 days. Treatment intervals were shorter when men received androgen deprivation therapy combined with radiotherapy [3]. A study examining men who went through TRUS biopsy for abnormal age-related PSA and/ or abnormal clinical examination found that delay in referral of 12 months or more was significantly associated with higher PSA titers, clinically palpable disease and likelihood of diagnosis with prostate cancer. A delay of 18 months or more led to a significantly higher risk of being diagnosed with a leading grade 4 prostate cancer [22].

Clinical Expert Interest Declaration:

None declared.

Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No.
2. Does the newly identified evidence support the existing recommendations?	Yes.
3. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	Yes.
4. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	No.

Review Outcome	ENDORSE
DSG/GDG Approval Date	December 19, 2016
DSG/GDG Commentary	The Expert Panel suggested some minor changes in the recommendations to help clarify the practicalities of the referral process.

Table 1: Referral of Suspected Prostate Cancer		
Author	**Study, country, setting** **Population age:**	**Results** **Q1:Signs/symptoms (reason for referral)** **Q2: Diagnostic accuracy** **Q3: Major risk factors** **Q4: Delayed referrals**
1. Alghamdi 2015 [2][ab]	Cancer registry used to determine RO referral, ADT+RT and prostatectomy rates in 2005 (n=1792) and 2012 (n=2148) and to examine associated patient, disease, and treatment factors (n=3940). **Age:** median 71 yrs	**Q1:** Older age (odds ratio [OR] 0.60, 95% CI: 0.49-0.73) and 2012 year of diagnosis (OR 0.54, 95% CI: 0.37-0.79) were associated with lower RO referral rates; Referral rates to RO decreased from 63% in 2005 to 56% in 2012 (P=.06). **Q2:**2005 PC patient 295/1792 (16%) high risk; 2012 PC patient 504/2148 923%) high risk **Q3:**NA **Q4:**Median time to referral radiation oncologist was significantly shorter in 2012 (1.1months vs 2.0 months, P<.001). In 2005, 61% of patients were treated with RT+ADT compared to 35% in 2012 (P<.001).
2. Baade 2012 [3]	Men diagnosed with prostate cancere recruited through participating urologists and hospital outpatient clinics in Queensland, Australia (n=1064). **Age:** 34% 40–59 yrs at diagnosis, 45% 60–69 yrs, 20% 70 yrs and over.	**Q1:** NA **Q2:** NA **Q3:** NA **Q4:**Median time to diagnosis was 73 days (IQR = 41-144) and median treatment interval was 65 days (IQR = 36-107); men were more likely to wait more than 70 days for diagnosis when they initially presented with symptoms (p < 0.001) (compared with a general checkup) or did not have private health insurance (p <0.001). For treatment interval, men without private health insurance (p < 0.001) or who were treated with radiotherapy alone (p < 0.001) more likely to wait more than 70 days. Treatment intervals were shorter when men received androgen deprivation therapy combined with radiotherapy.
3. Baughan 2009 [5]	Patients identified with a new diagnosis of cancer in Scotland (2006-2008) (n=874) **Age:** NR	**Q1:**NA **Q2:**NA **Q3:**NA **Q4:**Median time from first presentation to time of referral 11 days (IQR 19 days) (priority in referrals by GP sighted as major reason), median time to see specialist 32 days routine, 17 days urgent
4. Baughan 2011 [4]	Prospective audit of urgent suspected cancer referrals from 516 general practices in Scotland (all cancers) (n=582). **Age:** NR	**Q1:**Elevated PSA **Q2:**306/582 (52.6%) **Q3:**NA **Q4:**NA

Table 1: Referral of Suspected Prostate Cancer		
Author	**Study, country, setting** **Population age:**	**Results** **Q1:Signs/symptoms (reason for referral)** **Q2: Diagnostic accuracy** **Q3: Major risk factors** **Q4: Delayed referrals**
5. Beckmann 2016 [6]	Men with localized PCa referred for urinary/prostatic symptoms or elevated PSA from the South Australia Prostate Cancer Clinical Outcomes Collaborative database (n=4841). **Age:** majority 60-79 yrs	**Q1:**1) elevated or rising PSA, 2) prostatic or lower urinary tract symptoms (LUTS) or 3) 'other' symptoms; predominantly bone or pelvic pain, paralysis or erectile dysfunction. **Q2:** NA **Q3:** All-cause mortality (HR=1.31, CI 1.16-1.47), disease-specific mortality (HR=1.42, CI 1.13-1.77) and risk of metastases (HR=1.36, CI 1.13-1.64) were higher for men presenting with symptoms at referral compared to elevated PSA. Risk of intermediate grade (Gleason score=7), intermediate PSA levels (10-20ng/mL) and having NCCN intermediate and high risk disease factors. Older age, earlier diagnostic period and public-sector management independently associated with symptomatic presentation. **Q4:**NA
6. Bhindi 2015 [21]	Men who underwent transrectal ultrasound guided prostate biopsy identified from an institutional Genitourinary BioBank Project at University Health Network in Toronto - referred by 13 academic urologists in network (60%), community urologists (approximately 30%) or directly by PCPs (10%) (n=3408) **Age:** mean 63.4 yrs	**Q1: NA** **Q2:**1,601/3,408 (47%) **Q3:**NA **Q4:**NA
7. Foley 2015 [15]	Men referred to prostate cancer clinic (RAPCC) with an East of Ireland based catchment area (primary setting). (n=337) **Age:** mean 62.89 yrs	**Q1:**abnormal DRE or two abnormal PSA levels at 6-week intervals. **Q2:**146/337 (43%) **Q3:**age, abnormal PSA, abnormal DRE (p<.001). **Q4:** NA
8. Friedlander 2014 [1]	Retrospective cohort study, using claims data and laboratory values from the Vanderbilt University Medical Centre's (VUMC) located in Tennessee in the USA (n=2455). **Age:** 40 yrs or over	**Q1:** haematuria **Q2:**15/2455 **Q3:**NR **Q4:**NR
9. Guy 2016 [16]	Patients diagnosed with PCa at a North York diagnostic assessment program (n=1277). **Age:** median at diagnosis 67.2	**Q1:**elevated PSA in the absence of instrumentation, abnormal digital rectal examination (DRE) or abnormal imaging suggestive of PCa. **Q2:**NA **Q3:**NA **Q4:**NA
10. Hodgson 2012 [7]	Five Waikato general practices investigated looking at PSA laboratory tests of men ≥40 years in 2010 (n=65). **Age:** 40 and over	**Q1:**normal PSA test (n=10) LUTS, abnormal DRE, previous prostate cancer, previous elevated PSA; referred with elevated PSA (n=55); reason for PSA testing

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		in primary care screening (71%), history of prostate problems (14.3), patient request (3.9%), LUTS (10.8%) **Q2:**elevated PSA 21/55 (38%); normal PSA 2/10 (20%) **Q3:**NA **Q4:** NA
11. Kim 2016 [ab] [17]	Retrospective analysis of all prostate MRIs performed between 2005 and 2015 at a single large volume academic institution (under 15% referred by primary care) (n=2273) **Age:** mean 63.9 yrs (SD 8.51)	**Q1:** initial staging/restaging patients who had not undergone treatment and were not on active , rising prostate-specific antigen (PSA) with negative biopsy (18.5%), active surveillance (10.9%) and surveillance following prostatectomy or radiation (7.7%). **Q2:**28.6% positive 17.4% indeterminate, 23.7% negative **Q3:**NA **Q4:**NA
12. Lacey 2016 [18]	Cross-sectional survey in 2013 of patients treated for cancer in five of the member hospitals of the Victorian Comprehensive Cancer Centre (VCCC) that cover the inner city and western suburbs of Melbourne (n=159). **Age:** 18 yrs and over	**Q1:**NA **Q2:**NA **Q3:**NA **Q4:**73/159 with PC (46%) patients seeing a GP regarding symptoms 3 or more times before being referred to hospital physician vs. fewer than 3 times OR=2.15 (95% CI, 1.05 to 4.39); interval of at least 3 months (vs. less than 3 months) elapsing between suspecting problem and being seen in hospital 53/152 with PC (35%) OR=1.52 (0.73 to 3.16) (reference = rectal cancer*).
13. Lyratzopoulos 2012 [8] see also Lyratzopoulos 2013 [26]	Data from the 2010 National Cancer Patient Experience Survey in England through the UK Data Archive (n=4059). **Age:** NR	**Q1:**NA **Q2:**NA **Q3:**NA **Q4:**912/4059 (22.5) patients with 3 or more pre-referral GP consultations before hospital referral (reference rectal cancer* OR=1.10 (0.98 to 1.24)
14. Maclean 2015 [9]	Data obtained from England's National Cancer Registration Service, Quality Outcomes Framework, GP survey and GP workforce census, linked by practice code (n=34,458). **Age:** NR	**Q1:** NA **Q2:** NA **Q3:** Men living in more deprived areas more likely to be diagnosed at a more advanced stage than those living in less deprived areas (Q5 vs. Q1 RD 4.7 % (95 % CI 2.7 % to 6.8 %), p trend <0.001). Non-white vs. white men and younger men less likely to be diagnosed at a more advanced stage (RD −6.0 % (95 % CI −10.3 % to −1.7 %) p = 0.01; 45-64 years vs. 65+ RD −8.1 % (95 % CI −9.4 % to −6.8 %) p < 0.001, 15-44 years vs. 65+ RD −19.0 % (95 % CI −29.5 % to −8.5 %) p < 0.001). GP practice deprivation and practices with higher rates of colonoscopy, sigmoidoscopy and endoscopy were associated with a higher percentage

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		diagnosed at a more advanced stage (Q5 vs. Q1 RD 1.8 % (95 % CI −0.6 % to 4.2 %) p-value for trend 0.04; tertile 3 vs. tertile 1 RD 2.4 % (95 % CI 0.9 % to 3.9 %) p for trend = 0.002). **Q4:** NR
15. Moss 2016 [10]	Clinical Practice Research Datalink (CPRD) for men aged 45–84 years who had a PSA test during 2010–2011, registered in practices in England with linked Hospital Episode Statistics (HES) data (n=9425). **Age:** 45 to 85 years	**Q1:**raised PSA 22.4% **Q2:** NA **Q3:** NA **Q4:**Of men with raised PSA according to age specific guidelines, 22.4% (2113/9425) were referred to secondary care within 14 days, with 36.2% of the remainder retested within 6 months.
16. Ng 2013 [11]	Observational case series of consecutive patients referred from primary care to a tertiary urology referral centre presenting with haematospermia (n=300). **Age:** NR	**Q1:** presenting with haematospermia **Q2:** 5.7% **Q3:** NA **Q4:** NA
17. O'Kelly 2013 [22]	Men identified through rapid access prostate clinic who underwent TRUS biopsy for abnormal age-related PSA and/or abnormal clinical examination (n=350). **Age:** mean 62.3 yrs	**Q1:** NA **Q2:** NA **Q3:** NA **Q4:** delay in referral of 12 months or more significantly associated with higher PSA titers, clinically palpable disease and likelihood of diagnosis with prostate cancer (p<0.001). A delay of 18 months or more led to a significantly higher risk of being diagnosed with a leading grade 4 prostate cancer, which as further supported using PSA velocity as a diagnostic tool (p<0.001) (change >0.4 ng/ml/year).
18. Perez 2015 [12]	Men referred to institution for newly elevated PSA level from June 2011 to June 2013 pre-and post US Preventive Services Task Force (USPSTF) on PSA screening period (n=413). **Age:** mean 65 yrs	**Q1:**newly evaluated PSA levels **Q2:** 53.4% pre and 57.7% post-USPSTF among men who had biopsy **Q3:** **Q4:** NR
19. Serag 2011[ab] [25] see also Serag 2012 [19]	Prospective of two separate tertiary centres both of which undertake prostate cancer diagnostic clinics based on the UL Department of Health national referral guidelines. The study was performed over two separate time periods (n=394). **Age:** NR	**Q1:** NR **Q2:**166/394 (42%); 68/200 (34%) 50-69 yrs olds **Q3:** NR **Q4**: NR
20. Thomsen 2016 [20]; see also	All men diagnosed with PC at the Department of Urology at Frederiksberg Hospital(primary referral centre.) Based	**Q1:** NR

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Thomsen 2016 [24]	on the referral date, patients were categorised as pre-Movember (1 January 2007–31 January 2011) and Movember (1 February 2011–31 January 2014), respectively (n=1934). **Age:** NR	**Q2:** incidence rate of men diagnosed with PCa in the Movember period was 168/100.000 person years compared to 63/100.000 person years in the pre-Movember period (RR 1.08 [95% CI 0.97–1.21],*p*=0.17). **Q3:** NR **Q4:** NR
21. Walsh 2014 [13]	A retrospective analysis study of a cohort of Irish men who underwent TRUS guided biopsy of the prostate in a single Irish tertiary referral centre, despite a normal PSA level (n=103). **Age:** mean 63.3 yrs	**Q1:**67% referred on basis of DRE alone (all normal PSA); 33% referred because PSA level perceived as raised, with an absolute PSA threshold of >4.0 g/L rather than age-specific PSA cutoffs. Five of these men were referred on the basis of their PSA readings being perceived as raised; they were also found to have an abnormal DRE. **Q2:**36/103 (35%); DRE alone had a sensitivity and specificity of 81% and 40% respectively in diagnosing prostate cancer, with a positive predictive value of 42%. Seventy-six per cent of these men had high-grade disease. **Q3:**NA **Q4:**NA
22. Yafi 2011 [23]; see also Yafi 2010 [ab] [14]	Level of awareness and indications for urologic consultations by GPs in patients treated with 5-ARIs in Quebec (n=599). **Age:** NR	**Q1:**74% do not refer to urology if PSA does not decline after 6-12 months of 5-ARI treatment. **Q2:**NA **Q3:**NA **Q4:**NA
*Rectal cancer was selected as the reference category because it is common in both sexes; LUTS = lower urinary tract symptoms; DRE = digital rectal exam; PPV = Positive Predictive Value; PSA= prostate specific antigens;		

Appendix 1. Literature search strategies.

MEDLINE

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1 Prostate-Specific Antigen/
2 psa.mp.
3 prostate specific antigen.mp.
4 prostate-specific antigen.mp.
5 (elevated adj serum adj psa).mp.
6 (elevated adj (psa or prostat$)).mp.
7 (elevated adj serum adj prostat$).mp.
8 (urinary adj (urgency or frequency or hesitancy)).mp.
9 exp Urination Disorders/
10 (hematuria or haematuria).mp.
11 exp urological manifestations/
12 dysuria.mp.
13 nocturia.mp.
14 voiding symptom$.mp.
15 exp urinary bladder diseases/
16 interstitial cystitis.mp.
17 Urinary Incontinence, Urge/
18 urge incontinence.mp.
19 exp urinary tract infections/
20 (urinary tract adj3 infection$).mp.
21 Prostatitis/
22 prostatitis.mp.
23 Impotence/
24 erectile dysfunction$.mp.
25 (nodule$ adj2 testic$).mp.
26 (pain$ adj3 testic$).mp.
27 exp blood cell count/
28 (CBC or FBC or full blood count).mp.
29 C-reactive protein/
30 c-reactive protein$.mp.
31 Blood sedimentation/
32 erythrocyte sedimentation rate.mp.
33 Urine/cy [Cytology]
34 urine cytology.mp.
35 Urinalysis/
36 urine microscopy.mp.
37 Tomography, X-Ray Computed/
38 ct.mp.
39 exp ultrasonography/
40 ultrasound.mp.
41 Urography/
42 intravenous urogram$.mp.
43 intravenous pyelogram$.mp.
44 ((per rect$ or pr) adj exam$).mp.
45 Digital rectal examination/
46 DRE.mp.
47 bone scan.mp.
48 (delay$ adj3 diagnos$).mp.
49 (delay$ adj3 practitioner$).mp.
50 (delay$ adj3 patient$).mp.

51 early diagnosis/
52 diagnos$ earl$.mp.
53 earl$ diagnosis.mp.
54 (earl$ adj detect$).mp.
55 (earl$ adj present$).mp.
56 (earl$ adj symptom$).mp.
57 exp health behavior/
58 exp attitude to health/
59 Physician-patient relations/
60 disease progression/ (
61 time factors/ (920295)
62 Physician's practice patterns/
63 "referral and consultation"/
64 referral$.mp.
65 (earl$ adj refer$).mp.
66 (late$ adj refer$).mp.
67 exp ethnic groups/ge
68 ethnic$.ti,ab.
69 $racial.ti,ab.
70 race.ti,ab.
71 heredit$.ti,ab.
72 inherit$.ti,ab.
73 (genetic$ or gene or genes).ti,ab.
74 or/1-73
75 mass screening/
76 74 not 75
77 exp prostate neoplasms/
78 (prostat$ adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or
aden?carcinoma$ or polyp$)).mp.
79 77 or 78
80 76 and 79
81 limit 80 to english language (
82 (200708: or 200709: or 20071: or 2008: or 2009: or 2010: or 2011: or 2012:).ed.
83 81 and 82
84 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient
education handout or case report or historical article).pt.
85 83 not 84
86 exp "Sensitivity and Specificity"/
87 false negative reactions/ or false positive reactions/
88 (sensitivity or specificity or accura$).ab,ti.
89 diagnos$.ab,ti.
90 predictive value$.ab,ti.
91 reference value$.ab,ti.
92 ROC.ab,ti.
93 (likelihood adj ratio$1).ab,ti.
94 monitoring.mp.
95 (false adj (negative$1 or positive$1)).ab,ti.
96 (randomized controlled trial or controlled clinical trial).pt.
97 double-blind method/ or single-blind method/
98 practice guideline.pt.
99 consensus development conference$.pt.
100 review.pt.
101 review.ab.

102 (meta-analysis or metaanalysis).ab.
103 meta-analysis.pt.
104 meta-analysis.ti.
105 (cohort adj stud$).ab,ti.
106 exp cohort studies/
107 (single blind$3 or double blind$3 or triple blind$3).ab,ti.
108 Primary health care/
109 Family physician/
110 ((family or general) adj practitioner$).mp.
111 gp.mp.
112 family physician$.mp.
113 family doctor$.mp.
114 Family practice/
115 ((family or general) adj practice$).mp.
116 primary care.mp.
117 primary health care.mp.
118 meta-analysis/
119 "review literature"/
120 meta-analy$.mp.
121 metaanal$.mp.
122 (systematic$ adj (review$ or overview$)).mp.
123 review.ti.
124 (sensitivity or specificity).mp.
125 exp Diagnostic Errors/
126 predictive value$.mp.
127 "predictive value of tests"/
128 ROC.mp.
129 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).mp.
130 (false adj (negative or positive)).mp.
131 accuracy.mp.
132 reference value$.mp.
133 likelihood ratio$.mp.
134 ((pre-test or pretest) adj probability).mp.
135 post-test probability.mp.
136 Diagnosis, differential/
137 Diagnostic tests, routine/
138 exp DIAGNOSIS/
139 exp PATHOLOGY/
140 (diagnosis or diagnostic).mp.
141 exp primary health care/
142 exp family practice/
143 exp general practice/
144 exp physicians, family/
145 (gp$ or general practi$ or family physician$ or family doctor$ or primary health care or primary care).ti,ab.
146 (gp$ or general practi$ or family physician$ or family doctor$ or primary health care or primary care).mp.
147 or/86-146
148 85 and 147

EMBASE

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1 Prostate-Specific Antigen/
2 psa.mp.
3 prostate specific antigen.mp.
4 (elevated adj serum adj psa).mp.
5 (elevated adj (psa or prostat$)).mp.
6 (elevated adj serum adj prostat$).mp.
7 (urinary adj (urgency or frequency or hesitancy)).mp.
8 urinary frequency/
9 Urinary Urgency/
10 exp Urinary Tract Hemorrhage/
11 (hematuria or haematuria).mp.
12 dysuria.mp.
13 nocturia.mp.
14 exp Micturition Disorder/
15 urge incontinence.mp.
16 interstitial cystitis.mp.
17 Interstitial Cystitis/
18 exp Urogenital Tract Infection/
19 (urinary tract adj3 infection$).mp.
20 exp Prostatitis/
21 prostatitis.mp.
22 exp Impotence/
23 impotence.mp.
24 erectile dysfunction$.mp.
25 (nodule$ adj2 testic$).mp.
26 (pain$ adj3 testic$).mp.
27 exp Scrotal Pain/
28 exp blood cell count/
29 (CBC or FBC or full blood count).mp.
30 c-reactive protein.mp. or C Reactive Protein/
31 erythrocyte sedimentation rate/
32 erythrocyte sedimentation rate.mp.
33 Urine Cytology/
34 urine cytology.mp.
35 exp urinalysis/
36 urine microscopy.mp.
37 cancer cytodiagnosis/
38 Computer Assisted Tomography/
39 ct.mp.
40 ULTRASOUND/ or ultrasound.mp.
41 intravenous urography/ or intravenous pyelography/
42 (intravenous adj (urogra$ or pyelogra$)).mp.
43 ((per rect$ or pr) adj exam$).mp.
44 Digital rectal examination/
45 (delay$ adj3 diagnos$).mp.
46 (delay$ adj3 practitioner$).mp.
47 (delay$ adj3 patient$).mp.
48 diagnos$ delay$.mp.
49 Cancer diagnosis/
50 Early diagnosis/
51 (diagnos$ adj earl$).mp.
52 (earl$ adj detect$).mp.
53 (earl$ adj present$).mp.

54 (earl$ adj symptom$).mp.
55 Patient attitude/
56 Attitude to health/ or Attitude to illness/ or Illness behavior/
57 Delayed diagnosis/
58 doctor patient relation/
59 Patient referral/
60 referral$.mp.
61 (earl$ adj refer$).mp.
62 (late$ adj refer$).mp.
63 Time factors/
64 exp disease course/
65 exp ethnic group/
66 ethnic$.ti,ab.
67 $racial.ti,ab.
68 race.ti,ab.
69 heredit$.ti,ab.
70 inherit$.ti,ab.
71 (genetic$ or gene or genes).ti,ab.
72 or/1-71
73 cancer screening/
74 72 not 73
75 exp prostate cancer/
76 (prostat$ adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or neoplas$ or malignan$ or carcinoma$ or sarcoma$ or aden?carcinoma$ or polyp$)).mp.
77 75 or 76
78 74 and 77
79 limit 78 to english language
80 (2007: or 2008: or 2009: or 2010: or 2011: or 2012:).ew.
81 79 and 80
82 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
83 abstract.pt.
84 82 or 83
85 81 not 84
86 "sensitivity and specificity"/
87 false negative result/ or false positive result/
88 (sensitivity or specificity or accura$).ab,ti.
89 diagnos$.ab,ti.
90 predictive value$.ab,ti.
91 reference value$.ab,ti.
92 ROC.ab,ti.
93 (likelihood adj ratio$1).ab,ti.
94 monitoring.mp.
95 (false adj (negative$1 or positive$1)).ab,ti.
96 double blind procedure/ or single blind procedure/ or triple blind procedure/
97 exp controlled clinical trial/
98 double blind procedure/ or single blind procedure/ or triple blind procedure/
99 exp practice guideline/
100 review.pt.
101 review.ab.
102 (meta-analysis or metaanalysis).ab.
103 Meta Analysis/
104 meta-analysis.ti.
105 (cohort adj stud$).ab,ti.
106 cohort analysis/
107 (single blind$3 or double blind$3 or triple blind$3).ab,ti.

108 exp Primary health care/
109 general practitioner/
110 ((family or general) adj practitioner$).mp.
111 gp.mp.
112 Family physician/
113 family physician$.mp.
114 family doctor$.mp.
115 general practice/
116 ((family or general) adj practice$).mp.
117 primary care.mp.
118 primary health care.mp.
119 "systematic review"/
120 (meta-analy$ or metaanaly$).mp.
121 (systematic adj (review$ or overview$)).mp.
122 review.ti.
123 sensitivity.mp.
124 specificity.mp.
125 "prediction and forecasting"/
126 predictive value$.mp.
127 predictive value$ of test$.mp.
128 roc curve/
129 (ROC adj (analys$ or area or auc or characteristic$ or curve$)).mp.
130 exp diagnostic error/
131 (false adj (positive or negative)).mp.
132 diagnostic accuracy/
133 accuracy.mp.
134 reference value/
135 reference value$.mp.
136 likelihood ratio$.mp.
137 ((pre-test or pretest) adj probability).mp.
138 post-test probability.mp.
139 differential diagnosis/
140 or/86-139
141 85 and 140

OUTCOMES DEFINITION

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY** – A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.

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