Clinical Practice Guideline - Screening for Prostate Cancer
The Massachusetts Prostate Cancer Screening Guideline Panel
June 2013

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Summary of Recommendations

Table 1 below summaries the key recommendations on PSA screening supported by the Panel. In the sections that follow, the rationale for the recommendations is reviewed in more detail and some recommendations for implementation and future efforts to improve the guideline are presented.

Table 1: Summary of Panel Recommendations

Recommendation	Strength of Recommend-ation and Panel Support	Supporting Evidence	Related Values and Assumptions
1. All eligible men should be offered the opportunity to find out if they have a clear preference for PSA screening and receive PSA screening if they express that preference.	Strength: B Consensus of the Panel	Inconsistent, limited quality patient-oriented evidence including two recently reported randomized trials of invitation to regular PSA screening compared to usual practice.	There is a reasonable probability that PSA screening may offer a small but meaningful survival benefit to some patients, but there is controversy about the evidence supporting that benefit and about the balance of benefits and harms. The Panel believes that given the facts and the controversy that individual patients, rather than guideline panels, are in the best position to weigh the evidence and balance of benefit and harms if they have the opportunity to engage in a meaningful shared decision making (SDM) process.
2. All eligible men should receive a basic message about PSA screening when they reach the age at which screening could begin or at the next available opportunity.	Strength: C Consensus of the Panel	No specific evidence is available on implementation of the proposed basic message.	The underlying assumption is that key information required for men to decide if they would possibly consider screening can be provided in a short statement
3. Men who express an interest in learning more about PSA screening after receiving the basic information should be offered an opportunity to engage in a SDM process.	Strength: A Consensus of the Panel	Limited and good quality, consistent, patient oriented evidence that SDM reduces decisional conflict, and improves satisfaction with decisions.	The panel believes that the uncertainty about benefit that an individual may receive from screening and the high likelihood of men experiencing significant harm from screening make it imperative that men fully appreciate these issues before making a decision about screening. A systematic SDM process is the best approach to assuring that men are fully prepared to make an informed decision.
4. Men who are uncertain	Strength: N/A	No specific evidence.	The harms of PSA screening are both

Recommendation	Strength of Recommend-ation and Panel Support	Supporting Evidence	Related Values and Assumptions
about PSA screening and/or do not express clear preference for PSA screening after participating in an SDM process should receive a recommendation that they NOT undergo PSA screening.	Consensus of the Panel		reasonably probable and clinically important, so avoidance of harm should be paramount in counseling men who do not highly value the small probability of avoiding death from prostate cancer that may be possible with PSA screening.
5. The earliest age to begin PSA screening for men who express a clear preference for screening after SDM is for: • All men except for African Americans: – Average Risk: Age 50 years, – High Risk[1]: Age 45 years • African Americans: – Average Risk : Age 45 years, – High Risk: Age 40 (	Strength: C Supported by a majority[2] of the Panel (n=15).	Models that assumed that the benefit of screening shown in the ERSPC[3] trial (2) (29% PrCA mortality reduction after 11 years) Consistent, limited quality evidence from observational studies that African Americans experience PrCA incidence and mortality levels of average risk white men about 5 years earlier,.	The Panel sought to minimize harms related to biopsy and treatment that may follow screening while maintaining a reasonable level of possible benefit.
6. Criteria for stopping or not starting screening are : • Life expectancy < 10 years or • Age 70 years	Strength: C Consensus of Panel	Models (3) that show increasing harms with limited additional benefit when screening is continued from age 70-74. The survival benefit from screening does not appear until about 10 years after starting screening.	The Panel sought to minimize harms related to biopsy and treatment that may follow screening while maintaining a reasonable level of possible benefit
7. The recommended screening interval is every 2 years	Strength: C Consensus of Panel	Models (3) that show increasing harms with limited additional benefit when screening is performed annually	The Panel sought to minimize harms related to biopsy and treatment that may follow screening while maintaining a reasonable level of possible benefit
8. The recommended criterion for considering prostate biopsy is PSA >4.0 ng./ml. Men should engage in an SDM process	Strength: C Consensus of Panel	Models (3) showing less harm with limited loss of benefit using this criterion rather than other lower PSA levels.	The Panel sought to minimize harms related to biopsy and treatment that may follow screening while maintaining a reasonable level of possible benefit

Recommendation	Strength of Recommend-ation and Panel Support	Supporting Evidence	Related Values and Assumptions
informing him of the benefits and harms of seeking a diagnosis of PrCA through biopsy.			

[1] High Risk: 1st degree relative with PrCA at age <65)

[2] A minority (n=2) recommended a starting age of 50 for African American men and 55 for all other men. Four members favored a starting age of 55 but were willing to support age 50. Three members have not weighed in on this issue yet.

[3] ERSPC – European Randomized Study of Screening for Prostate Cancer

Grading Recommendations

In the summary table below and the rest of this document we use the Strength of Recommendation Taxonomy (SORT) proposed by Ebell and colleagues (1) to grade recommendations based on the quality and consistency of relevant evidence:

Strength of Recommendation	Best Available Supporting Evidence
A	Consistent and good quality patient-oriented evidence[1]
B	Inconsistent and/or limited quality patient-oriented evidence
C	Consensus, usual practice, opinion, disease-oriented[2] evidence or, case series

[1]Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction and quality of life.

[2]Disease-oriented evidence measure intermediate, physiologic, or surrogate end points that may or may not reflect improvement in patient-oriented outcomes.

The Guideline Panel

The Massachusetts Prostate Cancer Screening Guideline Panel (MPCSGP) included 21 members (patients, primary care providers, urologists, representatives of Massachusetts health care payers, institutional providers and Department of Public Health staff) identified and selected by the research and facilitation teams established through a grant from the Patient Centered Outcomes Research Institute (PCORI) to the University of Massachusetts Medical School with the assistance of the staff of Massachusetts Health Quality Partners (MHQP).

The Panel met face to face on 4 occasions and engaged in other virtual meetings and discussions to assess the scientific evidence about screening for prostate cancer (PrCA) with the prostate specific antigen (PSA) test. Table 1 below summarizes the key recommendations and related strength of recommendation along with supporting evidence and related value judgments made by the Panel.

Background/Introduction

Patient-oriented evidence of limited quality suggests that screening for prostate cancer (PrCA) with the prostate specific antigen (PSA) test and early treatment of selected cancers identified by screening may reduce the risk of metastatic disease and death from PrCA. However, good quality patient-oriented evidence documents the frequent occurrence of several significant harms related to prostate biopsies prompted by an abnormal screening PSA test result and the treatment and follow-up of screen-detected PrCAs: 1) adverse effects (e.g. urinary incontinence, erectile dysfunction) of the treatment of cancers that would never have been identified or caused clinical symptoms during a man's lifetime ("overtreatment"), 2) exposing men to the adverse effects of treatment years earlier in life than would have occurred without screening ("early treatment"), 3) reduced quality of life (QOL) in men with elevated PSA levels or low risk PrCA because of anxiety and repeated testing over time, and 4) adverse physical and psychological effects of prostate biopsies. Because of the strong evidence for and significance of these harms and the uncertainty of any benefit, the U.S. Preventive Services Task Force (USPSTF) recommends against the use of PSA for PrCA screening. Other national organizations (American College of Physicians (ACP), American Cancer Society (ACS), and American Urological Association (AUA)) recommend that men be offered PSA screening only if they make a clear request for screening after demonstrating a full understanding of the limited, uncertain benefit and significant harms.

The Panel has concluded that a reasonable case can be made both for and against screening based on currently available evidence, depending on the interpretation of the evidence and the values placed on possible benefit and harms. The balance of benefits and harms of PSA screening and the likelihood of experiencing a benefit will be perceived differently by men with different preferences and values. Some men may conclude that the possible benefit is adequately supported by the evidence and outweighs the harms and seek PSA screening, while others may reject screening because they believe the evidence supporting a benefit is weak and/or the harms of screening outweigh any likely benefit.

Therefore the Panel recommends that all men eligible for PrCA screening (see Section B below) receive a brief basic message about the availability of PSA screening and the possible benefits and the harms. The responsibility for assuring that eligible men receive the basic message lies primarily with individual and institutional health care providers who provide access to PrCA screening and with the Department of Public Health. Men who express an interest in getting PSA screening after hearing the basic message should engage in a comprehensive, shared decision making (SDM) process facilitated by a health care provider or qualified counselor before the PSA test is performed. Providers should recommend against PSA screening for men who do not wish to participate in SDM and for those who remain uncertain after SDM. Only men who express a clear preference for PSA screening after engaging in a process of SDM should receive PSA screening.

The Panel acknowledges that many health care providers have reached the conclusion that the evidence supporting a benefit of PSA screening is weak and/or that the harms of testing outweigh any possible benefit. These providers will continue to recommend against PSA screening. The Panel agrees that a reasonable case can be made for their conclusion and that men who choose testing assume significant risk of harm with no guarantee of any benefit. However, the Panel has also concluded that many men are capable of and willing to assess the uncertainty of benefit and the balance of benefit and harm themselves, and that the potential for a benefit is high enough that eligible men should be given an opportunity to participate in decision making about PSA screening.

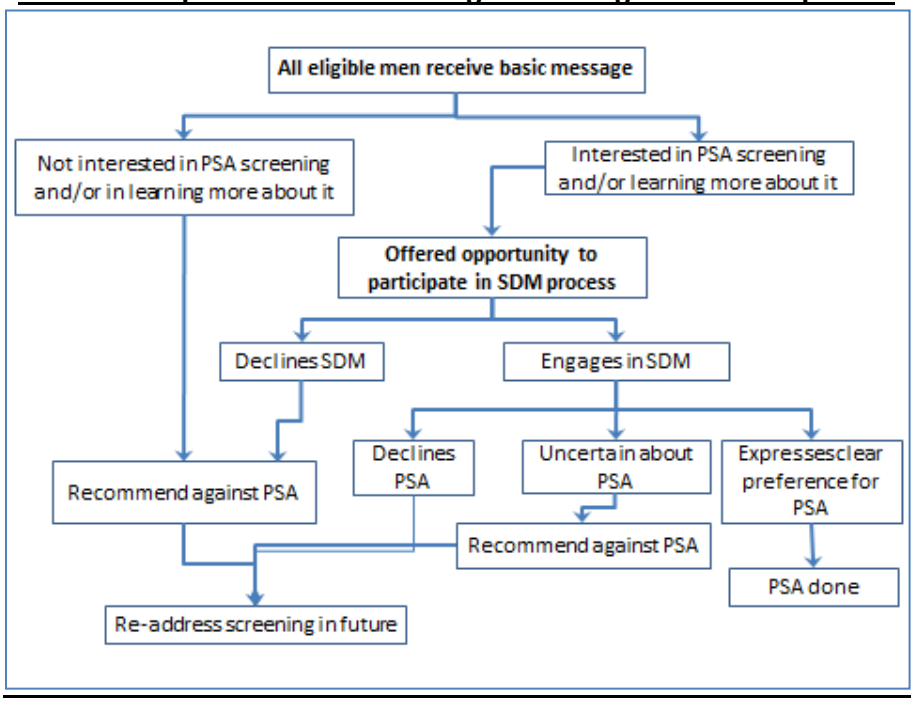
The Panel acknowledges that many men interested in PSA testing may not have ready access to an optimal SDM process and that some health care providers will not be able or willing to directly provide comprehensive SDM support. For that reason, the Panel urges payers, the Department of Public Health and health care

systems in Massachusetts to address the need for SDM support as soon as possible. Further, the Panel urges all payers to provide a reimbursement mechanism for providers who engage men in SDM and to educate providers how to effectively bill for SDM. Health care providers who do not provide comprehensive SDM support should direct patients to internet and print resources that may be adequate for some men to learn about the uncertainty, benefits, and harms of PSA testing. Health care providers should, to the best of their ability, confirm that men requesting PSA testing understand and are prepared to accept the harms of testing, appreciate the limited, uncertain benefit, and have decided the potential benefit outweighs the harms for a person with their values.

Recommendations

Overview: Based on inconsistent, limited quality patient-oriented evidence and other evidence of limited and good quality the Panel recommends that all eligible men be offered the opportunity to find out if they have a clear preference for PSA screening. That opportunity should begin with providing all men a basic message about PSA screening (see section A). Based on consistent, good quality patient-oriented evidence and good quality and consistent other evidence, the Panel strongly recommends that men still interested in PSA screening after receiving the basic message be offered the opportunity to participate in an SDM process. The Panel strongly recommends that only men who express a clear preference for PSA screening after participating in an SDM process by offered the PSA test. Figure 1 shows possible pathways a man may follow after receiving the basic message. In the sections that follow each pathway and related outcomes are described in detail.

Figure 1
Recommended Approach to Educating Men
About the Option of PSA Screening and Acting on Their Responses



A. Educating Men about Screening for PrCA

1. **Provide basic information**: All men eligible for PrCA screening should be informed about the availability of PSA screening for early detection of PrCA and that there is uncertainty and controversy over the effectiveness of screening in reducing the risk of death from PrCA. This basic message should include the following:

   - **A brief description of what the PSA test is.**
   - **An acknowledgment that experts disagree about whether men should get PSA screening.**
   - **An explanation of the possible benefit and related evidence:**

     Some studies have found that a few men may avoid prostate cancer death by getting PSA screening and, if cancer is found, being treated for it; however, other studies have concluded that PSA screening has no benefit for two reasons: 1) most prostate cancers (about 9 out of 10 in one study) grow so slowly that men die from something else before the cancer becomes a problem, and 2) many of the prostate cancers that are fast growing and dangerous are not cured by treatment.

   - **An enumeration of most common potential harms:**

     Significant harms may occur when screening leads to a biopsy, a PrCA diagnosis, and possibly treatment. These harms include pain and infection (due to biopsy) and loss of control of urine and loss of ability to have sex (due to prostate cancer treatment).

   - **A statement regarding factors that increase the risk for PrCA (African American race, brother or father with prostate cancer) and their impact on benefit/harms.**
   - **A recommendation that men interested in PSA screening engage in a shared decision making process.**
   - **A statement about ongoing research that may in the future reduce potential harms and show which men may most likely benefit from screening.**

2. **Provide access to decision support**: Men who express an interest in learning more about PSA testing after receiving the basic information should be offered an opportunity to engage in an SDM process leading to a personal decision for or against getting tested based on each man's values and preferences. Health care professionals facilitating SDM should complete the following 6 steps:
   1. Invite patient to participate
   2. Present options
   3. Provide information on benefits and harms
   4. Assist patient in evaluating options based on their goals, values and concerns
   5. Facilitate deliberation and decision making
   6. Assist with implementation

   The second and third steps may be completed independently by patients, who can read or view presentations on PSA testing such as the ones available from the following organizations at these websites:
   - American Cancer Society
     www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-024618.pdf
   - American Society of Clinical Oncology
     www.asco.org/sites/www.asco.org/files/psa_pco_decision_aid_71612.pdf

- The Prostate Cancer Research Foundation and European Randomized Study of Screening for Prostate Cancer
  www.prostatecancer-riskcalculator.com
- Mayo Clinic
  www.mayoclinic.com/health/prostate-cancer/HQ01273
- U.S. Preventive Services Task Force
  www.uspreventiveservicestaskforce.org/prostatecancerscreening/prostatecancerfact.pdf

The SDM discussion with a health care provider or other qualified counselor should include the following:

- Review of the possible benefits and all the harms of PSA screening related to biopsies, treatments, and the option for active surveillance of low risk cancers along with the information that most men opting for active surveillance end up choosing treatment within a few years, even if there is no evidence of change in their cancers.

- Clarification of the patient's view of his personal goals for healthcare, which could include the following: maximize lifespan, maximize symptom free period, minimize suffering from disease, minimize suffering from treatment, avoid consequences of disease, and avoid consequences of treatment.

- Conversation with patient regarding his goals and related values in which the health care provider or counselor assists the patient in matching his goals and values to a decision about PSA testing.

- Reaching a decision about PSA testing when possible, or agreeing uncertainty remains and the issue may be revisited in the future.

3. **Tailor SDM as needed**: Men should not be tested with PSA to screen for PrCA without engaging in an SDM process tailored to their level of literacy and their capacity to understand numeric estimates of benefit and harm.

4. **Uncertainty after SDM process**: Men who are uncertain about PSA testing after participating in an SDM process should receive a recommendation that they NOT be tested with PSA.

5. **Update information when available**: When clinically significant new information about benefits and/or harms of screening becomes available, that information should be conveyed to men in a timely fashion and a repeat of the SDM process should be offered if indicated.

B. Specific Elements of the Screening Program

Overview: The Panel concluded that modeling of PrCA incidence, rate of screen detection, and outcome of treatment provided the best approach to comparing the lifetime outcomes of screening programs starting and stopping at different ages, with different screening intervals, and various thresholds for biopsy. Published models (3) reviewed by the Panel provide estimates of the probability of avoiding prostate cancer death and the probability of major harms for different screening programs for white men at average risk of prostate cancer. The Panel members all agreed that the optimal screening program would be one that minimized major harms from biopsies and treatment and still offered a reasonable opportunity for screened men to avoid death from prostate cancer over their lifetime. The Panel acknowledges that the choice to minimize harm at the cost of a reduced benefit is a value judgment that others with different values could legitimately reject.

The Panel reviewed 35 screening programs and related model-based estimates of outcomes evaluated by Gulati and colleagues (3), as well as an additional 10 other programs that the Panel requested be tested in the Gulati model. Based on this review of evidence from modeling, the Panel reached a consensus on a biennial screening interval and a PSA threshold for referral for biopsy of 4.0.

The Panel considered two possible starting ages for screening for average risk white men who express a clear preference for screening: age 50 and 55. The Panel focused on these two ages because of the starting ages recommended by the ACP (age 50) and the AUA (age 55) in recently published statements and because of the well-established practice among clinical guideline developers of referencing starting ages for screening and treatment programs ending with "0" or "5". A majority of the Panel favored a starting age of 50 and a minority a starting age of 55. The starting age for screening for men who choose screening is also the age at which the Panel recommends men first receive the basic message about PSA screening.

Based on outcomes from the Gulati models, men who start PSA screening at age 50, who receive a PSA test every 2 years, who receive a prostate biopsy if the PSA is greater than 4, and who receive a prostatectomy if the biopsy shows cancer have a probability of 4.1/1000 of avoiding death from prostate cancer compared to men who are not screened. They also have 140/1000 chance of having a false positive PSA test (i.e. PSA>4.0 and negative biopsy), and a 13.0/1000 chance of receiving a prostatectomy for a cancer that would not have caused symptoms during their lifetime (i.e. "overdiagnosis"). A similar program followed exactly as specified but starting at age 55 would, according to the model, modestly increase major harms as well as the benefit of avoiding a prostate cancer death. Starting screening at age 55 would reduce the total number of screening tests a man following the biennial protocol would receive by 2.

The differences in the estimated probabilities of major harms and of avoiding prostate cancer death between the models with starting ages 50 and 55 are driven primarily by the fact that screening ends at age 68 for men who are screened every 2 years starting at 50 and ends at 69 for men with a starting age of 55. For men who do not follow the screening protocol exactly (e.g. starting at an age other than 50 or 55, screening at one or more 3 year intervals, stopping screening at age 67 etc.) the probability of harms of benefits would be different. Without prior knowledge of the distribution of the actual intervals between screens in a population, it is not possible to compare the outcomes to be expected from different starting ages in practice. Thus Panel members had to base their preference for starting age on small differences in model outcomes and on other factors such as the recommendations of the ACP and AUA, and the fact that the age group 55-69, is the only age group for which randomized trial data supports a prostate cancer mortality reduction, given that the ERSPC analysis was limited to this age group A factor considered important to some Panel members was the fact that the number of screens would .almost certainly be lower for most men starting at age 55, regardless of the distribution of screening intervals and the stopping age.

The Panel acknowledges that reasonable arguments can be made for several different approaches to screening based on different interpretations of screening trials and clinical evidence, on varying assumptions about the potential for mitigating harms, and on different values for the trade-offs between potential harms and benefits. The Panel recommends that other possible screening programs involving complex age and PSA dependent screening intervals and criteria for biopsy be tested in existing validated models to determine if a program with less estimated harm than the selected program and as much or more benefit can be identified. At the same time, the Panel recommends that barriers to implementing complex screening protocols be identified and that means of overcoming those barriers be developed.

Based on evidence that increased PrCA- specific survival does not usually appear until 8-10 years following treatment in the treatment and screening trials that show a benefit, the Panel agreed that men with a life expectancy of less than 10 years should not undergo PSA testing. The panel also decided that men with higher and lower risk of PrCA should first be offered the opportunity to consider screening at the age when their incidence of PrCA approaches the incidence in average risk men at the age screening may begin for those average risk men. Therefore, the Panel recommends that men in high risk groups (African Americans, men with a family history of PrCA) be offered the opportunity to consider screening at an age 5 years earlier than the age recommended for average risk men. A significant family history means a history of PrCA in a brother or father of the patient before the relative's 65th birthday.

1. **Starting and stopping screening for men who express a clear preference for screening**: Based on the estimated balance of benefit and harm from a model (2), and on the other principles stated above, the Panel suggests the following approach to starting and stopping PSA testing as a reasonable approach until more and/or better evidence identifies a more optimal approach:

    a. Starting age:

        - All men except for African Americans : Average risk start at age 50 (45 with family history of PrCA at age <65)

        - African American men: Average risk start age 45 (40 with family history of PrCA at age <65)

    a. Opportunity to consider screening and screening should be discontinued when a man's life expectancy is less than 10 years or he reaches the age of 70. The Panel acknowledges that estimating life expectancy is challenging for both clinicians and researchers. Even when a reasonably accurate estimate of life expectancy can be calculated, the definition of life expectancy means that 50% of men with a specific life expectancy will live longer than the estimate. So for men with a life expectancy of 10 years, at least 50% might possibly receive some, albeit minimal, benefit from PSA screening. Ideally for men age 50-69 with one or more diagnoses of a disease that may limit life expectancy, primary care providers should offer an SDM process that includes review of the best available evidence on survival for men with the disease profile of the patient. Based on a discussion of this evidence, the estimates of harms and benefit from PSA screening, and the patient's values, an informed, shared decision would be reached about starting, stopping, or continuing PSA screening for that individual.

    b. The Panel recommends against PSA screening in men who are not eligible for screening based on age, risk, and life expectancy

2. **Screening interval:** Men should receive a PSA test every 2 years. In comparing similar Gulati models with annual and biennial screening, the Panel found that biennial screening offered a meaningful reduction in harms at the cost of only a minor reduction in benefit.

3. **PSA threshold for consideration of biopsy and referral to a urologist:** Men with a PSA greater than 4 ng./ml should be offered a repeat PSA test on a blood sample taken after abstinence from ejaculation for 48 hours or more. If the result of both PSA tests is above 4 ng./ml., then the patient should engage in an SDM process, usually facilitated by a urologist, about the benefits and harms of a prostate biopsy. The Panel acknowledges the importance of clinical judgment in making a recommendation about prostate biopsy. Based on other factors besides the PSA, a provider may appropriately refer a patient with a PSA <= 4.0 ng./ml. for consideration of a biopsy, and a urologist may recommend against a

biopsy even when the PSA is >4.0 based on a number of clinical factors. The biopsy criterion of PSA >4.0 ng./ml. reflects the Panel's inclination to minimize harm based on current best model-based evidence and to facilitate ease of use and adoption of the threshold at which a biopsy should be considered.

a. As part of the SDM process when a biopsy is being considered, the patient should receive information about the risk of finding any PrCA and high risk PrCA on the biopsy. The Sunnybrook PrCA Risk Calculator (or some other approach to risk estimation) may be used to estimate the probability of finding PrCA on biopsy. This information may be useful in the SDM process.

b. Urologists and primary care providers with adequate understanding of PSA-based PrCA risk estimation, treatment options and treatment outcomes are best suited to engage patients with elevated PSA results in SDM regarding biopsy.

c. The Panel did not identify any SDM support tools for the biopsy decision and encourages all stakeholders to advocate for the development of such tools.

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3. Gulati R, Gore JL, Etzioni R. Comparative effectiveness of alternative prostate-specific antigen–based prostate cancer screening strategies model estimates of potential benefits and harms. *Ann Intern Med* 2013;158:145-153.