EARLY DETECTION OF PROSTATE CANCER: AUA GUIDELINE

H. Ballentine Carter, Peter C. Albertsen, Michael J. Barry, Ruth Etzioni, Stephen J. Freedland, Kirsten Lynn Greene, Lars Holmberg, Philip Kantoff, Badrinath R. Konety, Mohammad Hassan Murad, David F. Penson and Anthony L. Zietman

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This Guideline was re-viewed and confirmed current as of June 2018.

Purpose: This guideline addresses prostate cancer early detection for the purpose of reducing prostate cancer mortality with the intended user as the urologist. This document does not make a distinction between early detection and screening for prostate cancer. Early detection and screening both imply detection of disease at an early, pre-symptomatic stage when a man would have no reason to seek medical care –an intervention referred to as secondary prevention. This document does not address detection of prostate cancer in symptomatic men, where symptoms imply those that could be related to locally advanced or metastatic prostate cancer (e.g., new onset bone pain and/or neurological symptoms involving the lower extremities).

Methods: The AUA commissioned an independent group to conduct a systematic review and meta-analysis of the published literature on prostate cancer detection and screening. The protocol of the systematic review was developed *a priori* by the expert panel. The search strategy was developed and executed by reference librarians and methodologists and spanned across multiple databases. This search covered articles in English published between 1995 and 2013. This document was later reviewed in 2015 and 2018 with additional literature incorporated into the original report. These publications were used to inform the statements presented in the guideline as Standards, Recommendations or Options. When sufficient evidence existed, the body of evidence for a particular intervention was assigned a strength rating of A (high), B (moderate) or C (low).

GUIDELINE STATEMENTS

1. The Panel recommends against PSA screening in men under age 40 years. (Recommendation; Evidence Strength Grade C)

    - *In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.*

2. The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C)

    - *For men younger than age 55 years at higher risk, decisions regarding prostate cancer screening should be individualized. Those at higher risk may include men of African American race; and those with a family history of metastatic or lethal adenocarcinomas (e.g., prostate, male and female breast cancer, ovarian, pancreatic) spanning multiple generations, affecting multiple first-degree relatives, and that developed at younger ages.*

3. For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of reducing the rate of metastatic prostate cancer and prevention of prostate cancer death against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B)

    - *The greatest benefit of screening appears to be in men ages 55 to 69 years.*

    - *Multiple approaches subsequent to a PSA test (e.g., urinary and serum biomarkers, imaging, risk calculators) are available for identifying men*

more likely to harbor a prostate cancer and/or one with an aggressive phenotype. The use of such tools can be considered in men with a suspicious PSA level to inform prostate biopsy decisions.

4. To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. As compared to annual screening, it is expected that screening intervals of two years preserve the majority of the benefits and reduce overdiagnosis and false positives. (Option; Evidence Strength Grade C)

    - *Additionally, intervals for rescreening can be individualized by a baseline PSA level.*

5. The Panel does not recommend routine PSA screening in men over age 70 years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C)

    - *Some men over age 70 years who are in excellent health may benefit from prostate cancer screening.*

PURPOSE

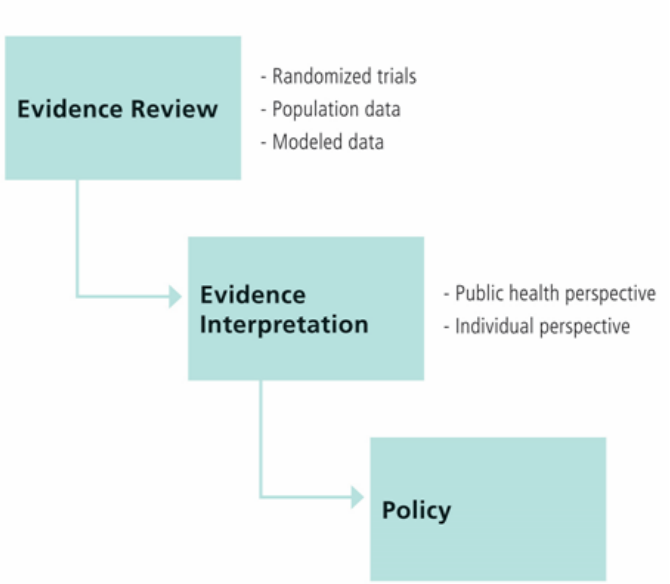
This guideline addresses prostate cancer early detection for the purpose of reducing prostate cancer mortality with the intended user as the urologist. This document does not make a distinction between early detection and screening for prostate cancer. Early detection and screening both imply detection of disease at an early, pre-symptomatic stage when a man would have no reason to seek medical care –an intervention referred to as secondary prevention.[1] In the US, early detection is driven by prostate specific antigen (PSA)-based screening followed by prostate biopsy for diagnostic confirmation. While the benefits of PSA-based prostate cancer screening have been evaluated in randomized-controlled trials, the literature supporting the efficacy of digital rectal exam (DRE), PSA derivatives and isoforms (e.g. free PSA, -2proPSA, prostate health index, hK2, PSA velocity or PSA doubling time) and novel urinary markers and biomarkers (e.g. PCA3) for screening with the goal of reducing prostate cancer mortality provide limited evidence to draw conclusions. While some data suggest use of these secondary screening tools may reduce unnecessary biopsies (i.e. reduce harms) while maintaining the ability to detect aggressive prostate cancer (i.e. maintain the benefits of PSA screening), more research is needed to confirm this. However, the likelihood of a future population-level screening study using these secondary screening approaches is highly unlikely at least in the near future. Therefore, this document focuses only on the efficacy of PSA screening for the early detection of prostate cancer with the specific intent to reduce prostate cancer mortality and not secondary tests often used after screening to determine the need for a prostate biopsy or a repeat prostate biopsy (e.g., PSA isoforms, PCA3, imaging).

The framework for this guideline follows that of the Institute of Medicine (IOM) recommendations for guideline development, including a systematic review of the evidence by a multidisciplinary panel.[2] While the evidence that guideline panels evaluate may be the same, the weighting of the evidence and the Panel's perspective can be very different (e.g., public health versus individual perspectives) leading to differing interpretations of evidence and policy implications (Figure 1). It is important to note that the guideline statements listed in this document target men at average risk, defined as a man without risk factors, such as a family history of prostate cancer in multiple generations and/or family history of early onset below age 55 years, or African American race. Because the harm-benefit profile of PSA-based prostate cancer screening is highly age dependent, guideline statements included in this document target four index patients; these age ranges were chosen to correspond to age ranges tested in randomized trials and data from population and simulation studies.

Four Index Patients

1. Men <40 years of age
2. Men age 40-54 years
3. Men age 55-69 years
4. Men age 70+ years

Figure 1: Influence of evidence and interpretation on policy creation



METHODOLOGY

Consistent with AUA published guideline methodology,[3] the process started by conducting a comprehensive systematic review. The AUA commissioned an independent group to conduct a systematic review and meta-analysis of the published literature on prostate cancer detection and screening. The protocol of the systematic review was developed *a priori* by the expert panel. The search strategy was developed and executed by reference librarians and methodologists and spanned across multiple databases including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials and Scopus. Controlled vocabulary supplemented with keywords was used to search for the relevant concepts of prostate cancer, screening and detection. The search focused on DRE, serum biomarkers (PSA, PSA Isoforms, PSA kinetics, free PSA, complexed PSA, proPSA, prostate health index, PSA velocity, PSA doubling time), urine biomarkers (PCA3, TMPRSS2:ERG fusion), imaging (TRUS, MRI, MRS, MR-TRUS fusion), genetics (SNPs), shared-decision making and prostate biopsy. The expert panel manually identified additional references that met the same search criteria to supplement the electronic search.

The outcomes of interest were also *a priori* determined by the Panel and included prostate cancer incidence, mortality, quality of life, the diagnostic performance of each of the tests and the harms of testing (premature death and complications from testing and biopsy). Modeling studies were included when original studies were limited by follow-up time and screening protocols. The methodology team independently rated the methodological quality of the studies and provided an overall judgment of the whole body of evidence based on their confidence in the available estimates of effect.

The framework for rating the quality of evidence is an adaptation and modification[3] of the GRADE framework (Grading of Recommendations, Assessment, Development and Evaluation).[4] In this adaptation, the AUA rates the quality of evidence as high, moderate or low (A, B or C). The strength of a statement was rated according to AUA guideline methodology as further described below. The confidence in the estimates of effect (quality of the evidence) was determined based on study quality, imprecision, indirectness, inconsistency and the likelihood of reporting and publication bias.[5]

The methodology team summarized the data with an explicit description of study characteristics, methodological quality, main findings and the quality of the evidence (confidence in the estimates). The methodology team attended panel meetings and facilitated incorporation of the evidence into the guideline.

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens (see Table 1).[3] ***Standards*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence. ***Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C evidence. ***Options*** are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; ***Options*** may be supported by Grade A, B or C evidence.[3] For some clinical issues, little or no evidence may exist from which evidence-based statements can be constructed. In such instances, the Panel may provide guidance in the form of *Clinical Principles* or *Expert Opinions* with consensus achieved using a modified Delphi technique if differences of opinion exist among panel members.[6] A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge and judgment and for which there is no evidence. In the case of this guideline, such statement types were not included. The completed evidence report may be requested through the AUA by emailing guidelines@auanet.org.

Table 1: AUA Nomenclature

Linking Statement Type to Evidence Strength

Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence
Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C evidence
Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B or C evidence
Clinical Principle: a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature
Expert Opinion: a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

Quality of Individual Studies and Determination of Evidence Strength.

The 2013 systematic review included over 300 eligible studies that addressed the questions of interest. In brief, six well known randomized trials addressed the question of mortality benefit of prostate cancer screening. Considering various methodological limitations and biases, the estimate for the effect of screening (versus no screening) on prostate cancer-specific mortality was obtained from the European Randomized Study of screening for Prostate Cancer (ERSPC).[7] The quality of the evidence was moderate for benefits and high for harms in men aged 55 to 69 (see later discussion of randomized controlled trials [RCTs]). Follow-up was quite limited, and quality of evidence was low on screening benefits in men outside of this age range, population subgroups with greater than average risk of the disease and screening protocols different from those used in the ERSPC.

Modeling studies were considered by the Panel to address these issues. A modeling study considers disease progression as a process of clinical or prognostic states and aims to estimate the rates of progression through these states in the absence of screening. Given the rate estimates, different screening protocols can be superimposed and their tradeoffs projected via computer simulation. To validate the models, specific screening protocols used in published studies can be considered and the model-projected

incidence patterns compared with those observed in these studies. The primary model considered by the Panel[8] has been validated against prostate cancer incidence trends in the US population before and after the advent of screening[9] and against prostate cancer diagnosis patterns in the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial.[10]

Modeling studies are increasingly being used to guide screening policies. The US Preventive Services Task Force (USPSTF) previously used modeling in developing breast[11] and colorectal cancer[12] screening recommendations. In 2018, USPSTF used modeling studies in the development of the most recent grade C recommendation for PSA-based prostate cancer screening.[13]

The evidence concerning harms and adverse effects of screening was high quality, and fairly robust estimates of the incidence of these complications were obtained from randomized and non-randomized studies.

Ample evidence was available to support the use of various shared-decision making processes that increased men's knowledge scores, reduced their decisional conflict and promoted greater involvement in decision making.

Unfortunately, the literature supporting the efficacy of DRE and biomarkers other than PSA for screening average risk men provided minimal evidence to draw conclusions. For the most part, this evidence had low to moderate quality and was more relevant to cancer detection in higher risk men than true average risk population screening. The outcomes of these studies were often reported as diagnostic accuracy estimates rather than patient important outcomes such as mortality or quality of life.

Limitations of the Literature. The systematic review and guideline process identified clear gaps in the available evidence base. Data are needed to clarify the harm/benefit balance of screening in men younger and older than those enrolled in the available randomized trials. Even for the age groups enrolled, critical outcomes, such as overdiagnosis and the additional number needed to treat, are not easily estimated from empirical trial data. Data on the harm-benefit balance are needed in men with varying spectra of family history of prostate cancer and men from various ethnicities and with other known risk factors of developing the disease. Outcomes of newer screening tests used in combination with PSA need to be determined. Men contemplating screening will need outcome data based on follow-up that exceeds the 10 year horizon currently available in the literature.

Extrapolating results from one population to another must be done cautiously since the benefits of screening are dependent on the baseline incidence of and mortality from cancer without screening, the specific screening protocol, biopsy referral criteria and compliance with biopsy recommendations. The mortality from prostate cancer in the absence of screening is higher in the Netherlands and Sweden as compared to the US[14] and these were the only two countries of the seven participating in the ERSPC trial where a mortality benefit was observed. Thus, the benefits of PSA-based screening seen in these two countries may not be generalizable to the US population. Further, the screening protocol, criteria for biopsy referral and compliance with biopsy recommendations differed considerably in the US population and ERSPC trial settings.

The available evidence base permitted the Panel to recommend screening with limited confidence in the target group age 55 to 69 years. This age range represents the group with the highest quality evidence of benefit. However, the Panel recognizes the potential for harm, and for this reason recommends shared decision making prior to screening decisions.

Guideline Review. The guideline was first reviewed for currency in 2015. This update review utilized search dates from the initial publication of the guideline through March 2015. This search identified 2,916 articles, of which 39 were included for further review following initial scope and abstract review. The 2018 review searched 2015 through November 2017. This search included review of the initial key questions reviewed for the guideline as well as one additional key questions related to the effects of PSA testing on the rate of metastatic prostate cancer diagnosis. This new key question utilized the initial search date of the original eight key questions (1995) through November 2017. The search identified 4,587 citations, of which 24 were found to be relevant and included in the final update review.

***Panel Selection and Peer Review Process*.** The Panel was created by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair and Vice Chair who in turn appointed a multidisciplinary panel with expertise in the guideline subject. All panel members were subject to and remain subject to the AUA conflict of interest disclosure criteria for guideline panel members and chairs. Panel members were predominantly urologists, and the target users of the guideline are urologists.

The AUA conducted an extensive peer review process. The initial draft of this guideline was distributed to 52 peer reviewers; 25 responded with comments. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the PGC. It was then submitted to the AUA Board of Directors for final approval. Funding of the Panel was provided by the AUA. Panel members received no remuneration for their work.

BACKGROUND

Evidence Base

RCT's

Characteristics of trials

Trials. Previous meta-analyses[15,16] and the AUA panel

literature search identified six trials: Stockholm, Norrkoping, Quebec, ERSPC, Goteborg and PLCO. The first three trials provided limited evidence since, among other design problems, the Stockholm trial screened with only one test and a high cut-off of PSA for biopsy; the Stockholm, Norrkoping and Quebec trials lacked allocation concealment; and the Quebec trial did not report according to intention to screen. The Goteborg study is part of the ERSPC, but was independently designed, initiated and reported separately from ERSPC. Sixty percent of participants were included in ERSPC.[17,18]

Age groups. The trials included men age 45 to 80 years, but only the Quebec trial informs about men below age 50 and above age 74 years. Evidence from studies with little bias comes only from the PLCO trial for men age 55 to 74 years[19] and only from the Goteborg trial for men age 50 to 55 years.[17] The ERSPC main report[18] focuses on men age 55 to 69 years. Thus the bulk of evidence is for men age 55 to 69 years included in the ERSPC, Goteborg and PLCO trials.[17-19] None of the studies has power to analyze by ethnicity.

Screening algorithms. The trials with least risk of bias used different screening algorithms, varying between annual PSA screening and DRE with a biopsy threshold of PSA 4.0 ng/mL (PLCO) to a range of algorithms in the ERSPC with threshold as high as 10.0 ng/mL in one center and a four year interval (in six of seven centers) to a two year interval with a threshold of 3.0 ng/mL in Goteborg.

***Contamination/Bias*.** The ERSPC and the PLCO trials have reported the extent of contamination in detail.[20,21] The contamination was 20-25% in the ERSPC trial,[18,20] and 77% with a PSA screen after five years in the PLCO trial[21] with a high exposure to PSA screening and DRE also at inclusion into the trial (prescreening). This likely contributed to the lower-than-expected number of deaths on both arms in the trial. Also, in PLCO there was a lack of adherence to diagnostic biopsies.[21] There was a potential treatment bias in ERSPC; as compared with men in the control arm, men in the screened arm were more likely to be treated at a university center and more likely to receive aggressive treatment for localized cancers.[7] However, differences in treatment received were not significant after adjustment for differences in disease stage and other patient/clinical characteristics in the screening and treatment arms.[22]

Results

Mortality. None of the studies were designed to estimate if PSA screening influences overall mortality. Meta-analyses of the trials[15,16] do not show any statistically significant prostate cancer mortality reductions (risk ratios [RR] varying between 0.88 and 0.95). The estimates are not impacted by the inclusion or exclusion of studies with high risk of bias (Stockholm, Norrkoping, Quebec) or how the Goteborg study is handled in relation to ERSPC. The results of ERSPC and PLCO differ: the studies show an RR for prostate cancer mortality (with 95% confidence interval) of 0.79 (0.68-0.91) and 1.09 (0.87-1.36), respectively, with a corresponding estimate in the Goteborg study of 0.56 (0.39-0.82). The effect size in PLCO was reduced by contamination, prescreening, and lack of adherence with diagnostic biopsies.[10] The evidence profile for mortality outcomes can be found in Table 2.

Numbers needed to screen and to diagnose. At the initial publication of this guideline, numbers needed to invite to screen and additional number needed to diagnose to avoid one prostate cancer death in the ERSPC (11 years of follow-up) and the Goteborg (14 years of follow-up) studies are as follows: 1,055 to invite and 37 to diagnose, 293 to invite and 12 to diagnose, respectively. However, these estimates are extremely sensitive to follow-up duration and are likely to be much lower over the long term; for example, it has been estimated that the additional number to diagnose is less than 10 over the long term.[23,24] Longer term follow up now shows that benefits accrue with time, with additional details provided in guideline statement discussion.

Incidence of cancer and overdiagnosis. The occurrence of prostate cancer has been higher in the group invited to be screened in studies that estimated incidence (Norrkoping, ERSPC, Goteborg, PLCO: pooled estimate of RR=1.46), but with heterogeneity between studies.[15] The RR was highest in the ERSPC and Goteborg studies. Modeling shows a range of estimates of lead times, and overdiagnosis estimates corresponding to US incidence lie between 23% and 42%,[25] but are as high as 66% in data from the Rotterdam section of the ERSPC and increase with age.[26] Overdiagnosis is defined in this document as the detection of a prostate cancer that would have remained undetected during life in the absence of screening.

Other outcomes. Side effects of screening other than overdiagnosis have not been reported in a form that allows for summary estimates in meta-analyses. Fatal complications of biopsies are very rare,[27] but the positive predictive value following an elevated PSA is low, reported to be less than 30%[15,16] and complications requiring hospitalization within 30 days after biopsy occur in approximately 4% of cases, of which three in four are for infections.[28,29] Reports hitherto report low levels of anxiety following screening,[27,30,31] but studies assessing long-term effects of radical prostatectomy indicate that side effects of radical treatment are prevalent and long lasting.[32] The evidence profile for additional harm outcomes can be found in Table 3.

Population data

It is noteworthy that the introduction of PSA-based prostate cancer screening was followed by subsequent dramatic reductions in prostate cancer mortality. For example, in the US following the introduction of widespread PSA screening in the late 1980's, there ensued a ~70% increase in prostate cancer incidence.[35] Despite steadily rising prostate cancer mortality throughout the 1970s and 1980s, several years after the introduction of PSA screening, mortality rates began to decline. By 2008, mortality rates had fallen

nearly 40% relative to their highs in the early 1990s. As of 2018, an estimated 164,000 men will be newly diagnosed with prostate cancer, and nearly 30,000 men will die from the disease.[36]

Outside the US, similar patterns have been noted. In an analysis of prostate cancer incidence and mortality rates across the world, Center et al.[37] noted that incidence rates have been rising steadily in the past 10 years. However, over this same time period, prostate cancer mortality rates have been falling.

It is helpful to compare and contrast two different populations that had very different uptakes of prostate cancer screening: the US and the UK.[38] In the US PSA screening became widespread in the late 1980s and early 1990s. In contrast, PSA screening was rarely performed in the UK and to this day remains lower than 10% of the population.[39] Prostate cancer death rates in the US began to decline in the early 1990s and by 2009 had dropped by more than 40% since their peak in the early 1990s.[40]The peak in incidence in the US was followed by a decline (36%) in mortality starting several years later. Though mortality rates also declined in the UK, the decline was much more modest (only 12%). Indeed, since 1994 prostate cancer mortality rates have declined four times faster in the US compared to the UK.[41] However, other ecological studies within the US fail to support the relationship between PSA screening and prostate cancer mortality reductions,[42] and the differences in the UK and US may be partly due to more aggressive treatment after diagnosis in the US when compared to the UK and differences in attribution of cause of death.[38]

Modeling Studies

Modeling studies are used to supplement observed data on cancer outcomes by filling in the latent process of disease progression based on observed data on disease incidence under screening. By virtue of the fact that models address the latent process of disease progression they can provide information on unobservable aspects of the process. Thus, for example, models have provided estimates of the time by which screening advances prostate cancer diagnosis and of the frequency of overdiagnosis associated with PSA screening.[26,43] Models have also been used to quantify the role of PSA screening in explaining population declines in prostate cancer mortality[44] thereby providing indirect evidence about screening benefit that is complementary to that obtained from randomized trials. Finally, models have been used to interrogate the vast array of potential PSA-based screening policies to identify those that are most likely to preserve benefit while reducing adverse outcomes

Table 2: Evidence profile for mortality outcomes

Outcome	Source & setting*	Relative risk	Absolute effect	Quality of evidence
Prostate cancer-specific mortality	1 RCT (ERSPC)[18] 162,243 men Age 55-69, PSA every four years	0.80(0.65–0.98)±	1 death fewer per 1,000 men screened	Moderate
	1 RCT (PLCO)[19] 76,693 men Age 55-74, annual PSA screening for six years and DRE annually for four years	1.14 (0.76, 1.70)	From 1 death fewer to 1 death more per 1,000 men screened	Low*

*The quality of evidence regarding prostate cancer-specific mortality derived from PLCO is low due to methodological limitations relating to the degree of contamination in the control arm. Therefore, PLCO does not provide a direct comparison of screening v. not screening. Rates of screening in the control group increased from 40% in the first year to 52% in the sixth year for PSA testing and ranged from 41% to 46% for DRE.

± After a median follow-up of 11 years in the core age group, relative risk reduction 21% (RR, 0.79; 0.68 to 0.91), and 29% after adjustment for contamination and noncompliance. Absolute risk reduction 1.07/ 1,000 screened.

Table 3: Harm outcomes

Adverse event	Estimate	Definition (data source)	Quality of evidence supporting association*
False positive tests	75.9%	Proportion of men with PSA >3.0 ng/mL and no cancer on subsequent biopsy (ERSPC)[18]	Moderate to High
	12%	Cumulative risk of at least 1 false-positive test (PSA> 4.0 µg/L) after 3 rounds of testing every four years (Finnish center, ERSPC)[18]	
	13%	Cumulative risk of at least 1 false-positive test (PSA> 4.0 µg/L) after 4 rounds of annual testing (PLCO)[19]	
	5.5%	Risk for undergoing at least 1 biopsy due to a false-positive test (PLCO)[19]	
Overdiagnosis	66%	Cases overdiagnosed as a fraction of screen-detected cases (ERSPC (Rotterdam) age 55-67 years, four year screening interval)[33]	Moderate
	23-42%	Cases overdiagnosed as a fraction of screen-detected cases (SEER-9, 1987-2000)[26]	
Lead time	5.4-6.9 years	Average time by which screening advances diagnosis among cases who would have been diagnosed during their lifetimes in the absence of screening (SEER-9, 1987-2000)[26]	Moderate
Minor (hematuria/ hematospermia)	20-50%	20-50% (first time sextant biopsy, Netherland site, ERSPC)[18] 24-45% (ERSPC, Rotterdam)[28]	High
Composite medical complications (infection, bleeding, urinary difficulties)	68/10,000	PLCO[34]	High
Fever post biopsy	3.5-4.2%	3.5% (ERSPC)[18] 4.2% (ERSPC, Rotterdam)[28]	High
Hospitalization post biopsy	4%	Loeb et al. and Nam et al.[28,29]	High

The core age group, 136,689 screening tests were performed (average, 2.27 per subject). Of these tests, 16.6% were positive, and 85.9% of the men with positive tests underwent prostate biopsy.

*The quality of evidence means how much confidence we have in the reported quantitative estimate. It does not mean the methodological quality of the study(s) although the latter is one factor that affects confidence in the estimate.

and costs.[8]

First, models of prostate cancer natural history and progression have been used to estimate the lead time, which is the time by which screening advances diagnosis. The lead time is not directly observable because once a case has been detected by screening, the time at which a patient would have presented clinically is unknown. However, the distribution of the lead time can be deduced from data on disease incidence before and after the adoption of screening via appropriate models. Three models[26] have been used to estimate the average lead time corresponding to US incidence trends based on data from the Surveillance, Epidemiology and End Results (SEER) registry[40] from 1985 to 2000. The average lead time estimates range from 5.4 to 6.9 years across the models. The same models have also been used to estimate the frequency of overdiagnosis among men age 50 to 84 years during this same calendar interval.

Estimates of the fraction of screen-detected cases that are overdiagnosed range from 23% to 42%. The estimate of 23% is the same as the estimate obtained in a different study[43] that used a very different model, but the same SEER incidence data to estimate the frequency of overdiagnosis in the US. The estimate of 42% is based on a model[45] initially derived using data from the Rotterdam section of ERSPC. In that study, the frequency of overdiagnosis among screen-detected cases was 50%, but the likelihood that a screen-detected case has been overdiagnosed can vary from less than 5% to more than 75% depending on the age at diagnosis, the PSA level and the grade of the prostate biopsy.[46]

The second use of models has been to interpret trends in prostate cancer mortality under screening. Prostate cancer death rates in the US began to decline in the early 1990s and by 2009 had dropped by more than 40% since their peak in the early 1990s.[40] Since PSA screening disseminated into population practice before trials of screening efficacy were mature, these evolving trends in population death rates provided a natural experiment for interrogating PSA screening benefit. However, it has been difficult to disentangle the effects of screening from the effects of changes in primary treatment that have occurred since the mid-1980s. These changes have primarily included increased use of radical prostatectomy for clinically localized disease, the ability to deliver greater doses of radiation to the prostate and the advent of neoadjuvant and adjuvant hormonal therapies.

The third use of models has been as decision analysis tools,[47-50] to determine the relative benefits and harms of competing screening policies in order to facilitate decisions by policy makers and clinicians about how best to use the PSA test in practice. The development of these decision analysis models began even as the two large screening trials in the US and Europe got under way. In the absence of observed results concerning PSA screening efficacy, the models typically relied on plausible mechanisms of screening benefit, most commonly a version of the stage-shift assumption. A recent article found this assumption to yield benefits consistent with that observed in the ERSPC trial.[50] The models have generally produced consistent findings indicating that screening every other year provides benefit that is similar to annual screening while reducing costs, false positive tests and overdiagnosis. Screening men between age 40 and 50 years provides small increments in lives saved with little cost in terms of overdiagnosis but with high numbers of tests required. Screening men over age 70 years results in a high frequency of overdiagnosis and potential overtreatment but this can be mitigated by more conservative biopsy-referral criteria, less frequent screening of men whose PSA levels are low, or referral of low-risk cases to active surveillance.[10]

In conclusion, modeling studies have yielded the following inferences that are particularly pertinent for screening policy development. First, PSA screening yields survival benefits that have contributed, to some extent, to the dramatic and sustained drop in prostate cancer death rates in this country. Second, PSA screening advances prostate cancer diagnosis by five to six years on average. Approximately one in four screen-detected cases reflects overdiagnosis. Strategies that screen less frequently than every year, and even less frequently for men with low PSA levels, are likely to be of value in reducing costs and harms while preserving most of the potential benefit of PSA-based screening.

Interpretation of the Evidence

The AUA guideline panel interpretation of the evidence differs from that of a public health perspective. The AUA guideline panel interpreted the evidence from the perspective of the individual with emphasis on the information (both benefit and harm) that an asymptomatic man would need to make an informed decision about prostate cancer screening. The Panel evaluated the best evidence from randomized trials of screening, but did not assume that all trials were of equal relevance. For example, the PLCO and ERSPC randomized trials ultimately addressed different questions (see section on RCT's) screening versus no or little screening in ERSPC as compared to annual screening versus usual care in the PLCO trial. By the time the PLCO trial began, usual care was opportunistic screening in the US and was, on average, every other year. Furthermore, the Panel utilized population data as supporting evidence for a beneficial effect of screening, and used modeling studies to fill gaps in knowledge. This use of modeling was felt to be important given the short time horizon of a decade provided by current randomized trial results, and the paucity of data regarding the benefits of screening outside the age range of 55 to 69 years. The evidence reviewed by the Panel clearly shows that the current practice of prostate cancer screening in asymptomatic men with comorbidities that limit life expectancy, and treatment of virtually all men after diagnosis –even those with non-aggressive features and limited life expectancy- results in substantial harm. Thus, the Panel focused on both shared decision making in the face of uncertainty[51] and approaches to early detection of prostate cancer that would reduce harms while maintaining the

benefits.

A major difference in interpretation of the evidence is whether or not the ERSPC and PLCO should be considered equally relevant with respect to the benefits of screening. The trials tested two different hypotheses as noted above; screening versus no or little screening in the ERSPC and organized versus opportunistic screening in the PLCO. The latter interpretation of the PLCO trial is in line with statements in the PLCO publications.[19,21] A modest effect of PSA screening versus none implies that a substantially larger study than PLCO is needed to meaningfully test more versus less frequent screening. Thus the PLCO was underpowered to address the question of organized versus opportunistic screening. The Panel interprets the randomized evidence to indicate that the ERSPC trial reflects the effect of PSA screening in a situation with low background screening.

The bulk of the information comes from screening men age 55 to 69 years. The evidence from screening men under age 50 or over 69 years is very scarce; additionally, there is no evidence concerning the benefits of screening men of differing ethnicity. There is no data from head to head comparisons of the effect of screening interval length. The main evidence is from the ERSPC four-year interval and the Goteborg two-year interval, but these are not really comparable. There is substantial evidence for overdiagnosis of prostate cancer following PSA screening, but it is likely that this has been overestimated by the trials. If overdiagnosis is also followed by active treatment, both the psychological burden of cancer diagnosis and the risk of serious side effects that compromise quality of life also ensue in a group of men with no benefit. A further dilemma is that conservative approaches to management such as active surveillance have been only sparsely tested in randomized trials to establish treatment protocols and/or safety.

Benefits of PSA screening

The benefits of PSA screening merit careful consideration while developing an approach to prostate cancer screening. It is also important to emphasize that the benefits (or lack thereof) of PSA-based screening for prostate cancer may not be representative of prostate cancer screening in general. While there are several potential tests that could be applied in screening for prostate cancer, almost all currently available data pertain to the use of PSA with or without DRE. As a primary screening test, there is no evidence that DRE is beneficial, but DRE in men referred for an elevated PSA may be a useful secondary test.

Almost all of the randomized studies that have evaluated PSA-based screening for prostate cancer have demonstrated a benefit in terms of lower stage and grade of cancer at diagnosis.[52-54] Several studies have also revealed a significant reduction in prostate cancer specific mortality rates attributable to PSA-based screening for prostate cancer.[7,34,55-56] At least two of the older studies have been criticized for methodological issues and are not considered as robust.[55,56] ERSPC and PLCO Cancer Screening trials are more recent and accepted as more well conducted studies; albeit addressing different questions as noted elsewhere (see section Interpretation of the Evidence). These studies have been the focus of much of the analysis and interpretations. In the ERSPC study, which to-date includes the largest randomized cohort of greater than 182,000 men, prostate cancer specific mortality was significantly lower in men who underwent screening compared to unscreened men.[7] The difference in mortality rates between screened and unscreened men also increased with time and when accounting for compliance.[18] However in the PLCO study that was conducted in the US and enrolled over 76,000 men, there was no significant difference in the prostate cancer specific or overall mortality between the screened and the unscreened men.[19,34] There have been well documented criticisms of the PLCO study mainly relating to the high rates of screening in the control group (3 in 4 men underwent at least one test) as well as the level of PSA screening prior to trial enrollment (up to 40%).[21] These factors could have led to the null result of the trial even in the presence of a screening benefit.[10] The rates of biopsy in men with an abnormal PSA at baseline or at subsequent screening were also lower in the PLCO study at 64% and 50% respectively.[57] This can be compared to the nearly 86% rate of biopsy compliance in the ERSPC study.[7]

Prostate cancer specific mortality was the primary endpoint for both the ERSPC and the PLCO trials. However, one cannot ignore the benefits of earlier detection through screening in decreasing the risk of metastatic disease.[54] The incidence of metastatic disease at presentation has declined by approximately three-fourths in the US since the advent of PSA screening. Further, in data from the ERSPC, the cumulative risk of metastatic disease at 9 to 11 years of follow-up was 31% to 33% lower in the screened arm compared to the control arm.[7,18] The Goteborg arm of the trial demonstrated a 56% reduction in risk of metastatic disease.[17] Most of this reduction in metastatic disease was seen in cancers detected at the time of diagnosis in the screened arm and not following diagnosis. This reduction is more pronounced with longer follow up.

An alternative data source to RCTs is population level data. While population level data are considered a lower level of evidence, this does not mean they are without merit. Indeed, key strengths include large sample sizes and the use of "real world" data as opposed to an "idealized world" that occurs within a clinical trial setting.

Since the advent of PSA screening, the incidence of patients presenting with advanced prostate cancer has declined remarkably, and death rates from prostate cancer as reported in the National Cancer Database have declined at the rate of 1% per year since 1990.[58] Other data indicate similar declines in prostate cancer related mortality in the US. The degree to which this is attributable to PSA screening is highly controversial even though it is temporally linked with the introduction of PSA-based screening.

As previously discussed, in addition to seeing a decline

in mortality, there is also an increase in disease incidence. This could reflect either greater screening practices or greater prevalence of true risk factors for prostate cancer in the population (e.g., changing dietary habits, increasing obesity rates, environmental toxins) or the advent of extended biopsy protocols that sample twice or more the number of cores that were being sampled in the early to mid- 1990's. Given the paradox of rising incidence but falling mortality, it is highly unlikely that the rising prevalence of a factor that truly increases prostate cancer risk could account for these findings.

We recognize that population level data cannot establish causality. That being said, there is ecological data that provides supporting evidence that the introduction of PSA-based screening is generally followed by a decline in rates of advanced disease and, in some cases, by a fall in prostate cancer mortality. The degree to which the mortality decline is attributable to PSA-based screening is unclear and ultimately unknowable from empirical observation. Modeling studies have been employed to link declines in mortality to changes in prostate cancer screening and treatment. They have concluded that primary treatment explains up to one third of the mortality decline leaving two thirds to be explained by other factors, primarily PSA.[44] Similar modeling studies have been conducted to partition declines in breast cancer mortality into those plausibly due to mammography screening and advances in adjuvant chemotherapy.[59,60]

The benefits of prostate cancer screening may extend beyond improving survival and could accrue from limiting disease morbidity arising from bladder outlet obstruction, hematuria, bone pain etc. Benefits from screening will also need to be considered from the man's viewpoint. Relevant endpoints considered in clinical trials and advantages in survival or lack thereof may not be valued similarly by every man.[61] The time horizon that is optimal to detect a benefit from PSA-based prostate cancer screening has also not been defined. Data from the ERSPC suggest that the benefit of screening increases with time.[17,18] Time horizons that are important to individual men will obviously vary according to age. A younger male will have a longer time horizon and may be more likely to risk the potential harms of screening in order to gain the potential benefits; however, he will also have to live with harms, if they occur, for a longer period. The tradeoff may not be as attractive for an older man with a shorter time horizon. Currently available data do not allow us to extrapolate in an empirical way beyond 10 to 14 years, which make it hard to forecast outcomes beyond that time frame. These studies will continue to accrue follow-up data, which may indicate a greater benefit with time.

Models of primary treatment changes in the population have been combined with projections of treatment impact on disease-specific survival based on published trials and comparative effectiveness studies. Results indicate that less than half of the drop in disease-specific deaths can be explained by treatment changes alone.[56] While this does not prove that screening is efficacious, it is highly suggestive that screening has played some role in the mortality decline. A previous modeling study[34] translated the decline in the incidence of distant stage disease into deaths prevented each year through 1999 and concluded that a substantial fraction of the drop in deaths could be attributed to the shift in disease stage with screening followed by earlier treatment. This finding is consistent with another study that modeled the impact of population screening on disease-specific deaths in the US under a similar assumption, namely that cases that would have been diagnosed with distant-stage disease in the absence of screening but that were detected at an earlier stage by screening receive a corresponding disease-specific survival benefit.[18]

In summary, an approach to PSA-based prostate cancer screening has to take into account the controversies surrounding available data and the fact that over a decade the benefits are modest in terms of prostate cancer deaths averted; 1 death per 1,000 men screened in the ERSPC.[7] However, the relative benefit (20% reduction in disease-specific deaths) could be very meaningful at the population level. The potential benefits of screening could extend beyond survival as a primary outcome, and will depend on the relevant time horizon for an individual. Further, disconnecting screening from automatic treatment will significantly impact the risk benefit ratio.

Harms

Prostate cancer screening itself is associated with a number of potential harms, both psychological and physical. The transrectal or transperineal prostate biopsy has risks of hematuria, hematochezia, hematospermia, dysuria and retention, pain and infection.[62] Hematuria and hematospermia are the most frequently observed side effects with wide variation in observed rates. Hematospermia after biopsy occurs in 10% to 70% of patients while hematuria is seen 14% to 50% of the time.[62,63] While the risk of hospitalization due to bleeding complications remains low, infectious complications are increasing steadily over time, possibly due to fluoroquinolone resistance.[64,65] The 30 day risk of hospitalization after biopsy for any cause has been estimated to be approximately 4%, of which three in four are for infections.[28,29] The use of routine fecal culture and sensitivity tailored antibiotic prophylaxis may be one approach to reduce infection rates.[66,67]

The American Urological Association has published a white paper to provide some guidance regarding periprocedural prophylaxis.[68] The harms inherent to the biopsy process were used as one justification for the USPSTF recommendation against prostate cancer screening. Since prostate biopsies are also an important part of some active surveillance programs, understanding these risks and communicating them to patients is not only integral to informed consent for prostate cancer screening but also for consideration of treatment options.

Once diagnosed with prostate cancer, a man is faced with the risk of overtreatment of indolent disease due to the assumption that diagnosis with a malignancy

must necessarily result in treatment of this malignancy. Estimates of overdiagnosis vary widely from less than 5% to more than 75%[26,33] depending upon the population used with lead times of 5 to 15 years.[26] In general, overdiagnosis estimates are not portable across geographic settings because they depend not only on the screening and biopsy protocol, and compliance with biopsy referral under screening, but also on practice patterns and disease incidence in the absence of screening. Our best estimates[18,43] for the fraction of screen-detected cases overdiagnosed in the US in the 1990's is approximately one in four, but the likelihood of overdiagnosis is highly age dependent. Subsequent analyses taking nonattendance and contamination into account have lowered these numbers closer to that seen with breast and colon cancer screening,[69-71] but the risk of overtreatment remains a valid concern due to the impact of treatment on quality of life.[49] Although prostate cancer specific mortality and the need for related palliative care is decreased by screening, quality of life may be impaired as a result due to lasting impairment in urinary, bowel and sexual function.[72] Thus, personal preferences should play a large role in both a decision to screen and in prostate cancer management if diagnosed.[49,73,74]

Lastly, the psychological impact of prostate cancer screening must be considered and viewed as a potential harm. There is considerable distress involved in the decision making process, the biopsy and deciding among treatment options. Along with the stress due to PSA screening and unnecessary biopsies, the diagnosis of prostate cancer alone may incite severe psychological stress with one study showing an increased rate of suicide and cardiovascular events in newly diagnosed men. [75] Even when men select active surveillance rather than curative therapy, anxiety may continue and trigger intervention in men who would never have needed treatment in their lifetime;[76] although it would appear that anxiety remains low for most men on surveillance in the short term. All of these potential harms must be carefully discussed with a man prior to embarking on a screening program and at each step of screening- whether this is the decision to have a PSA blood test or biopsy- the man should be given the information and the option of stopping based on his individual quality of life and longevity goals.

Policy Implications

When medical interventions have both possible benefits and risks, then expected net benefit of the intervention for an individual will depend on how a man (in the PSA context) values the possible outcomes. For one man, the benefits may outweigh the risks, but for another, even with the same outcome probabilities, the risks may outweigh the benefits. In these "close call" situations, a shared decision making approach can be used to make the best possible decision about the intervention at the individual level.

Shared decision making. Shared decision making between clinicians and men is a strategy for making health care decisions when there is more than one medically reasonable option. Each choice has different patterns of outcomes, and the values a man places on those outcomes need to be considered in order to make an optimal decision. Such decisions are said to be "preference sensitive."[77] The characteristics of a shared decision making process include involvement, at minimum, of a clinician and man in the decision making process (although others may be invited in by either party), bilateral sharing of information, joint participation in the decision-making process and then reaching agreement on a management strategy to implement.[78] Men should be able to invite others, such as a spouse, friend or family member into the process; however, it should not simply be assumed the man wants anyone else to participate. The bilateral information sharing involves the clinician helping the man understand their options and the risks and benefits of each option, while the man helps the clinician understand what matters to them in the context of the decision. From the clinicians' perspective, understanding a man's values and preferences can be seen as a diagnostic task,[79] as important as the diagnosis of disease in a man presenting with symptoms. Shared decision making contrasts with a more paternalistic style of decision-making, where clinicians tell men what they should do, often based on their own values and preferences. A number of authors have proposed steps for shared decision-making in the office setting.[80,81]

Shared decision making can be facilitated with patient decision aids (PDAs). A number of guideline groups have recommended a shared decision-making process for helping individual men decide whether or not to have a PSA test for prostate cancer screening.[82,83] According to the International Patient Decision Aids Standards Collaboration, PDAs are, "…designed to help people participate in decision making about health care options. They provide information on the options and help patients clarify and communicate the personal value they associate with different features of the options."[84] Patient decision aids are not shared decision making in and of themselves; rather, they are tools to make shared decision making practical in the busy world of medical practice.

The most recent Cochrane Collaboration systematic review of randomized trials of PDAs for preference sensitive conditions identified 86 trials published through 2009 involving over 20,000 participants and addressing 35 different decisions.[82] A meta-analysis of these trials showed that using decision aids compared to usual care resulted in greater patient knowledge, more accurate risk perceptions (when decision aids included probabilities), decisions more consistent with values (when explicit values clarification was included), lower decision conflict related to feeling uninformed and unclear about personal values, fewer people who were passive in decision making, and fewer people who remained undecided. Thus, there is strong evidence that a shared decision making process facilitated by PDAs improves the quality of preference-sensitive medical decisions.[85]

In the Cochrane review, 11 trials addressing PSA screening found a significant 15% reduction in PSA screening among men exposed to a PSA decision aid compared to usual care.[82] However, these trials used

decision aids that were produced before the evidence from the two large PSA screening trials became available. More information is needed on how men will decide about PSA screening when presented with the most recent evidence, but most likely some fully informed men will want to be screened, while others won't.

The AUA systematic review summarized the evidence supporting decision making. High quality evidence indicated that shared decision making increased men's knowledge scores, reduced decisional conflict and promoted greater involvement in decision making. The comparative evidence regarding the best delivery method of shared decision making was considered to be of low quality.

Information elements presented to men across the summarized shared decision making studies included the following:

More commonly described

1. Putative mortality benefit of screening in absolute terms
2. Description of options after abnormal PSA is detected
3. The likelihood of false-positive and false-negative results
4. Description of subsequent tests needed for follow up on abnormal screening results
5. Harms of screening (additional procedures, hospitalization, sepsis)

Less commonly described

1. Information about prostate gland anatomy and function
2. Prostate cancer incidence and mortality
3. Treatment options for early and late prostate cancer
4. Complications of treatment options for early and late prostate cancer

The Panel concluded that PSA-based screening should not be performed in the absence of shared-decision making. Thus, we recommend against organized screening in settings where shared-decision making is not part of routine practice (e.g., health fares, health system promotions, community organizations).

What a man needs to know prior to making a decision about testing. Men considering a screening test for prostate cancer should be aware of several facts that may influence their decision whether to obtain a PSA test or not. First, they should be aware that their risk of dying of prostate cancer is about 3% over a lifetime on average. Although many men may be diagnosed with prostate cancer, only a minority will ever progress to advanced disease and even fewer will have a fatal prostate cancer. From 1977 to 2005 the life time risk of being diagnosed with prostate cancer rose 2.3 fold from 7.3% to 17%. During this same period the life time risk of death from this disease decreased by 20% from 3% to 2.4%.[86] Men should consider the threat posed by prostate cancer and weigh this against other potential life-threatening conditions.

Second, no screening test is perfect. Some tests like the DRE are not very sensitive and will miss many early prostate cancers. Other tests, like the PSA test can generate a significant number of false positive results due to low specificity. The performance of a screening test is determined in part by the cut point utilized. This is the value that separates positive tests from negative tests and therefore predicts whether a cancer is present or absent. For PSA, a cut point of 4.0 ng/mL has been the historic threshold.[87] When lower cut points such as 2.5 – 4.0 ng/mL are utilized approximately 80% of PSA tests will yield false positive results.[7] Estimates from ERSPC (using a cutpoint of 3.0ng/mL) suggest that PSA screening will correctly predict the presence of prostate cancer in about one of every four biopsies.[7]

Third, PSA values can be elevated for many reasons. Normal physiologic variation often occurs and as many as 20% of elevated values will return to normal within one year.[88] Serum PSA levels also vary with age, race, BMI and prostate volume. They can increase as a result of benign prostate hypertrophy, prostatitis and any prostate manipulation such as prostate massage and biopsy. Finasteride and other 5α reductase inhibitors can decrease PSA values by approximately 50%.[89]

Fourth, prostate biopsies and treatments targeting localized prostate cancer carry risks. For every 1,000 men tested, approximately 100 to 120 will have an elevated PSA value.[90] Most of these men will undergo a prostate biopsy, and approximately one third will experience some type of mild to severe symptom including pain, fever, bleeding, infection or problems urinating. Approximately 4% will be hospitalized within 30 days after biopsy.[28,29] Among those men who are diagnosed with prostate cancer approximately 90% will undergo treatment,[91] although over treatment rates may decrease with greater acceptance of active surveillance in the US. Treated men will experience one of three outcomes: 1) recurrent cancer that will progress despite their treatment, 2) no evidence of disease recurrence, but no benefit from treatment either because their cancer was never destined to progress and 3) no evidence of disease recurrence because their cancer was cured. While only some men benefit from treatment, all who are treated are exposed to the complications of treatment. For every 1,000 men screened, 2 will develop serious cardiovascular events, one will develop deep venous thrombosis or pulmonary embolus, 29 will develop erectile dysfunction, 18 will develop incontinence and less than 1% will die from treatment.[90] The reader is reminded that these are estimates for men deciding on screening, not men deciding on treatment after diagnosis.

Unfortunately, no data are available that provide

estimates extending to 15 to 25 years. Data from randomized trials allow us to estimate how many men might benefit from PSA screening over a time horizon of about 10 years. Estimates from the ERSPC trial suggest that approximately 60 men of every 1,000 between the ages of 55 to 69 years will develop clinical evidence of prostate cancer within 10 to 14 years if they choose NOT to be screened; while approximately 96 of every 1,000 men will be diagnosed with prostate cancer if they choose to be screened.[90] Of the 1,000 men who choose NOT to have screening, 5 will die of their disease within 10 to 14 years. Of the 1,000 men who choose screening, 4 will die of their disease within 10 to 14 years. This amounts to 1 life saved by screening for every 1,000 men screened; however, models have projected that over a man's lifetime, the number of lives saved by screening could be as many as 6 per 1,000 men screened.[25,92]

Increasing the Ratio of Benefit to Harm

Screening for cancer in asymptomatic individuals, including prostate cancer, involves a tradeoff of benefit and harm. Through a decade, the absolute benefits of prostate cancer screening are modest for men age 55 to 69 years, and the harms are substantial.[90] Over a lifetime horizon the benefits increase but so do the harms. The ratio of benefit to harm can be improved by taking into account the age and health state of the individual,[93] and a man's personal preferences. Furthermore, baseline PSA results can be used to guide alternative screening strategies that screen less frequently than every year; and using more conservative criteria (e.g. higher PSA thresholds) to refer older men to biopsy, may lead to reductions in false positive tests and overdiagnosis.[8] The Panel encourages the use of tools that account for age and health state to estimate life expectancy for older men.[93]

Target Population

The strongest evidence of benefit for PSA screening for early diagnosis of prostate cancer is in the age group 55 to 69 years[18] since this is the group studied in randomized trials. Thus, targeting of men age 55 to 69 years, after a risk benefit discussion, represents one approach to screening that is based on best evidence.

For men below age 40 years, the Panel recommends against PSA-based screening. The low prevalence of disease in men below age 40 years means that even in the best case of screening benefit in this age group, the incremental number of lives save by screening this age group is likely to be very small.

Men age 40 to 54 years often undergo PSA-based screening. However, as compared to initiating screening at age 50 years, it was estimated that screening beginning at age 40 years would result in the prevention of fewer than 1 prostate cancer death per 1,000 men.[94] Given that 99% of deaths from prostate cancer occur above age 54 years, the Panel believes that screening average risk men below age 55 years should not be routine. For men younger than age 55 years at higher risk (e.g., positive family history, African American race), decisions regarding prostate cancer screening should be individualized based on personal preferences and an informed discussion regarding the uncertainty of benefit and the associated harms of screening. The reader is reminded that the likelihood of prostate cancer in an individual with a family history of the disease increases directly with the number of affected first degree relatives, and is higher if the disease occurred in multiple generations and/or was diagnosed at an early age (below age 55 years) as compared to a diagnosis in a single generation at an older age.[95]

Men over age 70 years have a high prevalence of prostate cancer but also have a greater risk of competing diseases and overdiagnosis when compared to younger men.[96] In the ERSPC randomized trial of screening, there was no indication for a mortality reduction among men age 70 years or older;[18] however, the trial was not powered to detect a benefit in this age group. In addition, there is strong evidence for a lack of treatment benefit for men in this age group, especially those with a life expectancy below 10-15 years.[97,98] Therefore, given the lack of direct evidence for a benefit of screening beyond age 70 years, and especially beyond age 74 years, the Panel discourages routine screening in this age group.

Some men with high risk aggressive prostate cancers with a life expectancy less than a decade, may benefit from the diagnosis and treatment of their disease.[98] Thus, the goal should be to identify these men while avoiding the associated overdiagnosis and over treatment of those with lower risk disease that occurs with opportunistic screening.

Several approaches, including higher PSA thresholds to recommend prostate biopsies for older men and discontinuing PSA testing among older men with lower PSA levels, could help achieve the goal of reducing overdiagnosis. In the PIVOT trial where the mean age at enrollment was 67 years,[98] those with a PSA above 10ng/mL had a significant reduction in all-cause mortality after a decade following surgery when compared to observation; surgery provided no reduction in mortality among those with a PSA of 10ng/mL or below. In an observational study of men who had a PSA below 3ng/mL at age 70 to 75 years, the probability of death from prostate cancer during the remaining years of life was similar to the lifetime probability of death from prostate cancer in the general population (1% to 3%), and continued to decline with age. For those men with a PSA of 3.0ng/mL or more, their life time probability of prostate cancer death was approximately 7% and continued to increase with age.[99] Thus, the Panel encourages several considerations for older men who choose to be tested beyond age 70 years that could increase the ratio of benefit to harm. First, increasing the trigger for a prostate biopsy (e.g. to 10ng/mL) based on the evidence that these men have the most to gain from a diagnosis and treatment of prostate cancer over a decade.[98] Second, discontinuing PSA screening among older men age 70 to 75 years who have PSA levels below 3ng/mL.[99]

Testing Frequency

There is evidence to suggest that annual screening is not likely to produce significant incremental benefits when compared with an inter-screening interval of two years. The PLCO trial compared annual screening with opportunistic screening in the US population, which corresponded to screening on average every two years.[21] Prostate cancer mortality rates were similar in the two groups through 13 years of follow-up.

Modeling studies have projected that screening intervals of two years will preserve most of the benefits of screening and reduce the harms (i.e., false positive tests and overdiagnosis)[8] when compared with screening every year.

Intervals for rescreening can be individualized by a baseline PSA level that is predictive of the risk of prostate cancer detection and the risk of development of an aggressive prostate cancer.[100] A number of studies suggest that screening intervals of two to four years are unlikely to miss a curable prostate cancer.[101-103] For example, in a population based screening study (Goteborg) with seven-year follow-up and a PSA biopsy prompt of 3ng/mL, only 3 cancers (detection rate 0.07%) were detected within three years among those men with a baseline PSA below 1.5ng/mL. Furthermore, in a study of men age 60 years whose serum was stored and later assayed for PSA, there was a 0.5% risk of developing metastatic disease and a 0.2% risk of prostate cancer death at 25 years after a baseline PSA level of 1.0ng/mL.[101]

Based on these data, the Panel believes that annual PSA screening as a routine should be discouraged for those who choose to be screened, that two year PSA intervals are a reasonable approach and will be unlikely to miss a curable prostate cancer in most men, and that for men over 60 with PSA levels below 1.0ng/mL, longer PSA screening intervals (e.g., of four years) could be considered. The reader is reminded that for men with a PSA below 3ng/mL at age 70 to 75 years, PSA screening could be safely discontinued if a man at this age is still being screened.[100]

Biopsy Trigger

There is no PSA level below which a man can be informed that prostate cancer does not exist. Rather, the risk of prostate cancer, and that of high grade disease, is continuous as PSA increases.[104]

In the intervention (screened) arm of the ERSPC randomized screening trial, a PSA trigger of 3ng/mL was associated with a reduction in prostate cancer mortality for men age 55 to 69 years when compared to the control arm (not screened).[18] However, the Panel believes that the urologist should consider factors that lead to an increased PSA including prostate volume, age, and inflammation rather than using an absolute level to determine the need for a prostate biopsy – keeping in mind that PSA is not a dichotomous test but rather a test that indicates the risk of a harmful cancer over a continuum. The Panel believes that postponing and/or avoiding a prostate biopsy 1) in a man with a large prostate, 2) in the older male especially if in less than excellent health, and 3) in the setting of a suspicion of prostatic inflammation, would be acceptable even at PSA levels exceeding 3-4ng/mL. We could find no evidence to support the use of antibiotics to reduce PSA levels in otherwise asymptomatic men, and this practice could lead to an increased risk of post biopsy sepsis.

Additionally, for those men over age 70 years and especially above age 74 years where there is no direct evidence for a benefit of screening, if screening is chosen, a higher PSA trigger could reduce the harms of screening by subjecting only those men to biopsy who are more likely to harbor a lethal phenotype and benefit most from treatment.[96]

Much effort has been invested in the discovery of methods for improving the ability of PSA to predict the presence of prostate cancer. At this point, the use of DRE, PSA derivatives (PSA density and age specific reference ranges) and PSA kinetics (velocity and doubling time), PSA molecular forms (percent free PSA and proPSA), novel urinary markers (PCA3), and prostate imaging should be considered secondary tests (not primary screening tests) with potential utility for determining the need for a prostate biopsy, but with unproven benefit as primary screening tests. The Panel recognizes that these tests can be used as adjuncts for informing decisions about the need for a prostate biopsy –or repeat biopsy- after PSA screening, but emphasizes the lack of evidence that these tests will increase the ratio of benefit to harm. Further, risk calculators that include multiple variables (in addition to PSA) as an aid to predicting the risk of prostate cancer have not been proven to increase the benefit to harm ratio, and their value in predicting cancer on biopsy is not necessarily generalizable to a population that differs from that in which the tool was developed.

Downstream Consequences of Testing

As outlined previously, PSA screening can lead to psychological harm and biopsy related complications. However, the greatest harm associated with prostate cancer screening is the detection of cancers that would otherwise have remained undetected without screening (overdiagnosis), subsequent treatment of these cancers (over treatment) and the associated side effects from a treatment that does not improve survival. For screening to be an acceptable population intervention, these harms must be reduced. Thus the Panel discourages the use of PSA screening for early diagnosis of prostate cancer in older men, especially those that have associated comorbidities that limit life expectancy to 10 to 15 years or less for whom diagnosis and treatment is unlikely to improve health outcomes.[97,98]

STATEMENTS/DISCUSSION

Age <40 years

Guideline Statement 1.

The Panel recommends against PSA screening in men under age 40 years. (Recommendation;

Evidence Strength Grade C)

Discussion. The prevalence of prostate cancer in men under age 40 years is extremely low. Population based studies reveal the prevalence of prostate cancer in men below age 40 years to be about 0.1% with numbers as low as 700 cases being reported to the SEER registry between 2001 and 2007.[105] Prior autopsy studies have been able to identify clinically undetected cases of prostate cancer in men as young as 20 years of age but the prevalence has been low even in these retrospective studies of small cohorts of men.[106] US studies reveal a higher prevalence of 2% to 29% of undiagnosed cancer at autopsy even in men under age 40 years, particularly African-Americans, compared to studies from Europe and Asia.[106] The prevalence among European men in their twenties is <5% while it rises to 5% to 10% in men in their thirties.[107] Even in men under age 40 years who are found to have prostate cancer at autopsy, the disease tends to be of low volume and low Gleason grade.

None of the prospective randomized studies evaluating the benefits of PSA-based screening for prostate cancer included men under age 40 years. Hence there are no data available to estimate the benefit of prostate cancer screening in this population. However, the harms that can accrue from screening, which include the side effects of diagnostic biopsies and perhaps subsequent treatment will certainly apply to men in this age group who would be subject to screening. Therefore, due to the relatively low prevalence of clinically detectable prostate cancer in men below age 40 years, the absence of any evidence demonstrating benefits of screening and the known harms, screening is discouraged for men under age 40 years of age.

Age 40 to 54

Guideline Statement 2.

The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C)

Discussion. The Panel recommends that screening, as routine practice, not be encouraged in men age 40 to 54 years who are not at increased risk for the disease based on family history and race, for example. There is no high-quality evidence to support this practice in the general population. Specifically, the two large randomized clinical trials (PLCO[34] and ERSPC[7]) did not include men under age 55 years and, therefore, do not inform the decision. While there is some lower-quality evidence (quality rating=c) that an absolute reduction in prostate-cancer mortality rate may be associated with population-wide screening of men in their 40's at average risk, the benefit is relatively small. Howard et al.[94] noted that annual PSA screening of men in their 40's is associated with a 10-year prostate cancer-specific mortality rate of 0.037 deaths/1,000 men compared to 0.041 deaths/1,000 men if no screening was performed. While the evidence of benefit of screening of men age 40 to 55 years indicates that the effect size is marginal at best, at least in terms of prostate-cancer specific mortality, the weight and quality of the evidence demonstrating the harms of screening remains high. Effectively, the Panel concluded that the harms of screening in this population were at least equal to the benefits, if not higher and, to this end, recommends that screening should not be routine practice.

In making this recommendation, the Panel recognizes that there may be other benefits associated with screening that we either did not consider or have not been demonstrated by the current literature. Effectively, we acknowledge that the "absence of evidence does not constitute evidence of absence" and, as such, we are not explicitly stating that screening should be actively discouraged in this group of men. The literature in this area is quite dynamic and future studies may document additional benefits in this younger population. For example, Lilja et al.[108] have documented in a large study of 21,277 men from Malmo, Sweden, that a single PSA measurement taken between age 33 to 50 years is highly predictive of subsequent prostate cancer diagnosis and advanced stage at diagnosis. Additionally, Carlsson et al.[109] noted that in a prospective cohort study of men with screening starting at age 50-54 years (3,479 screened, 4,060 unscreened), PSA-screened men carried a 2.56 fold increased risk for prostate cancer diagnosis, but also a decreased risk for metastatic diagnosis and prostate cancer related death.

The Panel recognizes that certain subgroups of men age 40 to 54 years may realize added benefit from earlier screening. Such men who may be at higher risk include men of African American race and those with a family history of metastatic or lethal adenocarcinomas (e.g., prostate, male and female breast cancer, ovarian, pancreatic) spanning multiple generations, affecting multiple first-degree relatives, and that developed at younger ages.[110,111] For such men, decisions regarding prostate cancer screening should be individualized.[112] These men should be informed of both the known harms and the potential benefits of screening at an earlier age and shared decision making should ensue with an understanding that there are no comparative data to demonstrate that men at higher than average risk for prostate cancer will benefit more from screening when compared to those at average risk. In the future it is possible that individuals at high risk of developing a lethal prostate cancer phenotype may be identifiable at an early age through genetic testing and/or new biomarkers. These individuals could then be targeted for more intense screening even at a young age.

In summary, given the Panel's interpretation of the evidence concerning the benefits and harms of annual screening in men age 40 to 55 years who are not at an increased risk for prostate cancer and the rarity of fatal prostate cancers arising in this age group, the Panel does not recommend this practice as a routine. The reader is advised to remember that this does not imply that there is absolutely no benefit to screening this age group, rather that there are significant enough harms associated with screening that the benefits likely are not great enough to outweigh the harms.

Age 55 to 69

Guideline Statement 3.

For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of reducing the rate of metastatic prostate cancer and prevention of prostate cancer death against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on men's values and preferences. (Standard; Evidence Strength Grade B)

Discussion. Although there are considerable harms associated with screening and the quality of evidence supporting this statement is high (A), the Panel felt that in men age 55 to 69 years, there was sufficient certainty that the benefits of screening could outweigh the harms that a recommendation of shared decision-making in this age group was justified. This recommendation is in line with the updated 2018 USPSTF grade C recommendation, which states that the decision to undergo periodic PSA-based screening for prostate cancer should be an individual one for men aged 55 to 69 years.[13] The Panel believes that the test should not be offered in a setting where this is not practical, for example community-based screening by health systems or other organizations.

Evidence for screening benefit in this setting is moderate and is derived from large RCTs. Specifically, results from ERSPC document a relative risk reduction of prostate cancer-specific death of 21% at a median follow-up of 11 years.[18] While the absolute reduction in prostate cancer-specific mortality was relatively small on earlier analysis (0.10 deaths per 1,000 person-years or 1.07 deaths per 1,000 men randomized), this may represent an underestimate of benefit given the length of follow-up of the study and the degree of non-compliance in the intervention arm. Longer follow up in the ERSPC study population shows that the benefits of screening accrue with time, with a reduction in deaths from prostate cancer increasing from 7 per 10,000 men screened to 13 per 10,000 men screened at an increased follow up of 13 years.[113] Additional estimates of benefit from mathematical modeling suggest that the absolute reduction in mortality will continue to decline further with longer follow up.[24] Further analysis of individual sites within the ERSPC cohort also point to a potential reduction in metastatic disease for screened populations preceding a reduction in mortality on average by three years,[114] with an absolute reduction in the cumulative incidence of metastatic disease of 31 cases per 10,000 men at a median of 12 years of follow-up.[54]

The Panel acknowledges that the prostate component of PLCO failed to show a benefit to screening with a median follow-up of 13 years,[19] but attributes this finding to high rates of screening in the control arm biasing the study to the null. After accounting for differences in the PLCO and ERSPC trials, including protocol adherence and contamination, there was a consistent 25%-30% relative reduction in deaths from prostate cancer.[115]

Any discussion of the benefits and harms of prostate cancer screening in men age 55 to 69 years should consider the man's individual life expectancy. Prior studies have documented that men with less than a 10 to 15 year life expectancy are unlikely to realize a benefit from aggressive treatment for localized prostate cancer[98] and as such, it follows that the earlier disease detection associated with screening in these men likely will be less beneficial, if beneficial at all. To this end, shared decision making should include a discussion of the man's baseline mortality risk from other co-morbid conditions, their individual risk for prostate cancer, given their race/ethnicity and family history, and the degree to which screening might influence their overall life expectancy and chance of experiencing morbidity from prostate cancer or its treatment.

It should also be noted that multiple approaches subsequent to a PSA test (urinary and serum biomarkers, imaging) are available for identifying men more likely to harbor a prostate cancer and/or one with an aggressive phenotype. The use of novel markers, imaging, and/or risk calculators can be considered for prostate biopsy decisions in men with a suspicious PSA level to inform biopsy decisions.

Guideline Statement 4.

To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. As compared to annual screening, it is expected that screening intervals of two years preserve the majority of the benefits and reduce overdiagnosis and false positives. (Option; Evidence Strength Grade C)

Discussion. While RCT's have used both two- and four-year screening intervals, there is no direct evidence supporting a specific screening interval. The available evidence is mostly based on modeling, and some evidence may be gleaned from randomized trials, although none of these trials actually randomized men to different intervals as a primary objective. Modeling studies[8, 47] have projected that screening men every two years preserves the majority (at least 80%) of lives saved compared with annual screening while materially reducing the number of tests, the chance of a false positive test and overdiagnosis.

The two largest screening trials have provided some indirect evidence about the likely benefits of more versus less frequent screening. In the ERSPC, a comparison between the Rotterdam section (interscreening interval four years) and the Swedish section (interscreening interval two years) suggested that a two year screening interval significantly reduced the incidence of advanced disease.[116] Evidence on the comparison of a two-year screening interval with annual screening was provided by the PLCO trial. This trial compared annual screening with a control group

that had screening rates similar to those in the US population which corresponded to screening on average every two years.[21] Prostate cancer mortality rates were similar in the two groups through 13 years of follow-up, suggesting little benefit from screening more frequently than every two years. In addition, data from a randomized trial (Goteborg) and a case-control study suggest that a rescreening interval of four years is not likely to miss a curable prostate cancer among men with a PSA below 1.0ng/mL.[101,103]

In reviewing the effects of a single PSA screening on prostate cancer detection and median 10-year prostate cancer mortality, Martin et al. found that while there was a higher proportion of men diagnosed with prostate cancer in the intervention group (4.3%) compared to the non-screened control group (3.6%), there was no significant difference in prostate cancer mortality after a median follow-up of 10 years (0.30 per 1,000 person-years for the intervention group versus 0.31 for the control group).[117]

Age 70+

Guideline Statement 5.

The Panel does not recommend routine PSA screening in men over age 70 years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C)

Discussion. The Panel recognizes that men over age 70 years can have a life-expectancy over 10 to 15 years , and that a small subgroup of men over age 70 years who are in excellent health may benefit from PSA screening, but evidence to support the magnitude of benefit in this age group is extremely limited. Men in this age group who choose to be screened should recognize that there is strong evidence that the ratio of harm to benefit increases with age and that the likelihood of overdiagnosis is extremely high particularly among men with low-risk disease.

Evidence for screening benefit in this setting is unclear and indirect. An absolute reduction in mortality is possible but likely small with a quality rating of C. The quality of the evidence for harm remains high or at least higher than benefit (A). The certainty in the balance of harm and benefit is moderate justifying a recommendation against routine PSA-based screening.

The rationale for this recommendation is based on the absence of evidence of a screening benefit in this population with clear evidence of harms. In the ERSPC randomized trial of screening, there was no reduction in mortality among men age 70 years or older.[18] Although men in this age group have a higher prevalence of prostate cancer and a higher incidence of fatal tumors, they also have increased competing mortality compared to younger men,[96] and no compelling evidence of a treatment benefit, especially in men with a limited life expectancy below 10 to 15 years.[97,98] Therefore, given the lack of direct evidence for benefit of screening beyond age 70 years, and especially beyond age 74 years, as well as higher quality data regarding harms, the Panel discourages *routine* screening in this age group.

Men over age 70 years who wish to be screened should do so after an understanding that the ratio of benefit to harm declines with age, although there is evidence that men with high risk disease in this age range may benefit from early diagnosis and treatment over a decade or less.[98] In order to identify the older man more likely to benefit from treatment if screening takes place, the Panel recommends two approaches. First, increasing the prostate biopsy threshold based on evidence that men with a PSA level above 10ng/mL are more likely to benefit from treatment of prostate cancer when compared to those with a PSA below 10ng/mL.[96] Second, discontinuation of PSA screening among men with a PSA below 3ng/mL, given evidence that these men have a significantly lower likelihood of being diagnosed with a lethal prostate cancer during the remaining years of life when compared to men with a PSA above 3ng/mL.[99]

The likelihood of overdiagnosis increases as men age, and is particularly high for older men with low-risk disease. Modeling studies of overdiagnosis in the US population have estimated that among men aged 70 to 79 years, half or more of cases detected by PSA screening with PSA less than 10 and Gleason score 6 or below are overdiagnosed. Among men over age 80 years, three-fourths or more of cases detected by PSA screening with PSA less than 10 and Gleason score 6 or below are overdiagnosed.[118] Because of the harms of biopsy, overtreatment, and overdiagnosis in this population, shared decision making and consideration of individual values, preferences, and quality of life goals are paramount.

RESEARCH NEEDS AND FUTURE DIRECTIONS

From a public health perspective, the current strategy of PSA-based prostate cancer screening is not acceptable due to the high rates of overdiagnosis and over treatment. Estimates suggest that 1 in 4 US men diagnosed with prostate cancer harbor indolent disease[43] and that 90% of all men diagnosed with prostate cancer are treated. However, a recommendation against use of PSA screening for the early detection of prostate cancer ignores the proven benefits that accrue with time for some of the men who are screened[18] and does not account for an individual man's preferences, age and family history. Thus, the Panel recognizes the limitations of the current literature to inform men regarding the balance of benefit and harm of prostate cancer screening, and the need for further research in this area.

Knowledge Gaps. To be successful, the benefits of prostate cancer screening must outweigh the harms. Reductions in prostate cancer mortality and the burden of advanced disease must exceed any loss of quality of life associated with screening and treatment. The Panel identified four major areas where knowledge gaps prevented a precise assessment of the magnitude of screening benefits and the harms. First, the outcomes from randomized trials of prostate cancer screening are limited to one decade. Any benefits accruing beyond this point have yet to be assessed. Public health advocates have highlighted the substantial quality of life decrements that are immediate and prolonged that are associated with the treatment of prostate cancer,[90] however these harms may be balanced by future reductions in prostate cancer mortality. Second, the absence of evidence for any benefit of screening outside the age range of 55 to 69 years does not necessarily mean that there is no benefit. This does, however, preclude recommendations for the starting age for PSA screening and the age at which PSA screening should be discontinued. While recommendations for screening men age 40 to 50 years are often made under the assumption that these men have the most to gain because of a longer life expectancy; a low prevalence of disease, longer lead times, and a prolonged time living with the side effects of treatment, make assessments of benefits and harms difficult. Competing causes of death reduce the benefits of screening older men above age 70 years. Thus, the Panel was unable to recommend routine PSA screening for the average risk man for whom direct evidence of benefit for screening is absent (i.e., men below age 55 years and above age 70 years). Third, the ideal approach to serial PSA screening once initiated is unknown. There is no evidence that annual screening will improve the ratio of benefit to harm when compared to testing at intervals of two to four years – intervals that have been associated with a reduction in prostate cancer specific death for men between the age of 55 to 69 years.[18] There have been no direct comparisons of various screening intervals or comparative studies that base screening intervals on baseline PSA levels. Fourth, direct evidence for any additional benefit of using DRE, PSA derivatives (PSA density, PSA kinetics, age adjusted PSA levels), PSA molecular forms (proPSA, freePSA, complexed PSA), novel urinary biomarkers (PCA3), or imaging as primary screening tests is absent. Although DRE has been considered a mainstay of screening together with PSA, the Panel could find no evidence to support the continued use of DRE as a first line screening test. For men who have undergone PSA-based screening and present for evaluation, the interventions above including DRE and risk assessment tools using the results of multiple tests, could be useful in determining the need for a prostate biopsy, or the chance that cancer has been missed on a prior biopsy.

Communicating these uncertainties to men, identifying the men most likely to benefit from screening, and identifying the men once diagnosed who are more likely to benefit from treatment, are research priorities.

Communication. Unlike many interventions in which the ratio of benefit to harm is high and the choice clear cut, prostate cancer screening is a preference sensitive intervention for which there are reasonable choices to screen or not. For this reason, the Panel emphasized the importance of shared decision making as a prerequisite to screening. Shared decision making implies that physicians and men have informative data regarding benefit and harm prior to a decision. Decision support tools that help provide this information have been developed, but optimal methods (pictograms, text, computerized) that best communicate uncertainty to men and that allows individualized decisions regarding screening are needed. Further, improved tools for estimating life expectancy would help identify those more likely to benefit from screening.

Clinical Research. The lack of comparative effectiveness studies of screening and no screening with follow-up beyond a decade was problematic in developing a guideline for PSA-based prostate cancer screening. The absolute benefits of PSA-based prostate cancer screening relative to the rates of overdiagnosis and overtreatment of disease among different populations is an important area for future research. Further, evaluation of the optimal management of screen detected cancers and the cost effectiveness of these options will be important to understand before making broad policy decisions regarding prostate cancer screening.

The ERSPC investigators continue to follow men in the intervention and control arms of the largest screening trial reported to date.[18] Longer follow up will provide further evidence to help assess the benefits and harms of screening.[49] In addition, longer follow-up in ERSPC will provide insights into the optimal approaches to screening in terms of testing intervals and age cut points to discontinue screening. Because men age 40 to 50 years have not been enrolled in randomized trials of screening, modeled outcomes will be an important research priority to help inform decisions in this age group, and clarify optimal screening strategies.[119] In addition, the ProtecT trial,[120] an intervention trial comparing active surveillance, radiation, and prostatectomy among men in a large PSA-based screening study will further define the benefits of screening among men age 50 to 69 years, and the most appropriate management options after diagnosis.

Basic Research. Identification of those men at greatest risk for prostate cancer development and progression would provide a means of targeted screening, thereby reducing unnecessary testing, false positive tests, and the burden of overdiagnosis and over treatment. Current collaborative efforts using germ line DNA to identify risk alleles are ongoing.[121] An improved understanding of the interaction between inherited risk alleles and the environment (lifestyle choices) could provide a potential means of prevention. Future studies of the genetic and epigenetic basis of disease development and progression may provide biomarkers and/or panels of biomarkers with improved specificity when compared to PSA. When available, risk assessment tools combining multiple predictors will need to be evaluated in carefully designed trials to be generalizable to the population in which they would be used.

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Early Detection of Prostate Cancer Panel, Consultants and Staff

H. Ballentine Carter, MD, Chair
Johns Hopkins Hospital
Baltimore, MD

Peter C. Albertsen, MD, Vice Chair
University of Connecticut Health Center
Farmington, CT

Ruth Etzioni, PhD
Fred Hutchinson Cancer Research Center
Seattle, WA

Stephen J. Freedland, MD
Duke University
Durham, NC

Kirsten Lynn Greene, MD
University of California, San Francisco
San Francisco, CA

Lars Holmberg, MD
King's College of London Medical School
London, UK

Philip Kantoff, MD
Harvard Medical School
Boston, MA

Badrinath R. Konety, MD
University of Minnesota
Minneapolis, MN

David F. Penson, MD
Vanderbilt University,
Nashville, TN

Anthony L. Zietman, MD
Massachusetts General Hospital
Salem, MA

Consultants
Mohammad Hassan Murad, MD, MPH
Osama Altayar, MD
Mohammed Nabhan, MD

Staff
Heddy Hubbard, PhD., MPH, RN, FAAN
Michael Folmer
Abid Khan, MHS
Carla Foster, MPH
Erin Kirkby, MS
Patricia Lapera, MPH
Del'Rhea Godwin-Brent

CONFLICT OF INTEREST DISCLOSURES

All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

Board Member, Officer, Trustee: Philip Kantoff, BIND Biosciences (C) (Expired)

Consultant/Advisor: Peter C. Albertsen, Blue Cross/Blue Shield (C), Dendreon Corporation (C), ; Glaxo Smith Kline (C)(Expired), Johnson & Johnson (C) (Expired); **Stephen J. Freedland,** Amgen (C), Medivation (C), Bayer (C), Mitomics (C), Astellas (C), AstraZeneca (C), Dendreon (C), Janssen (C), Glaxo Smith Kline (C) (Expired); **Philip Kantoff**, Bellicum (C), BIND Biosciences (C), Blend (C), BN-IT (C), Dendreon (C), Dendreon (C), Johnson and Johnson (C), Metamark (C), Oncocellmdx (C), Sanofi (C), Sotio (C), Tokai (C), Amgen (C)(Expired), Genentech (C)(Expired); **Badrinath R. Konety,** Allergan(C), Axogen Inc.(U), Dendreon (C), Endo Pharmaceuticals (C), Spectrum Pharmaceuticals (C), Centocor Ortho Biotech (C) (Expired)

Investigator: Peter C. Albertsen, Agency Health Care Quality (C) (Expired), National Cancer Institute (C) (Expired), Sanofi (C)(Expired)

Leadership Position: Anthony L. Zietman, American Board of Radiology (U), American Society for Radiation Oncology (U), National Cancer Institute, GU Steering Committee (C)

Meeting Participant or Lecturer: Peter C. Albertsen, Ferring Pharmaceuticals**, (C), Stephen J. Freedland,** Amgen (C)(Expired), AstraZeneca (C)(Expired), Centocor Ortho Biotech (C)(Expired); **Badrinath R. Konety,** Amgen (C)

Scientific Study or Trial: Peter C. Albertsen, Agency Health Care Quality (C); **Stephen J. Freedland,** Glaxo Smith Kline

Peer Reviewers

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William W. Bohnert, MD
Peter R. Carroll, MD
William J. Catalona, MD
Philipp Dahm, MD, MHSc
James A. Eastham, MD, GVC
John B. Forrest, MD
Marc B. Garnick, MD
Christopher Gonzalez, MD
C. D. Anthony Herndon, MD
Richard M. Hoffman, MD
Jeff Holzbeierlein, MD
Adam Stuart Kibel, MD
W. Robert Lee, MD
Stacy Loeb, MD
Malcolm Mason, MD
Viraj A. Master, MD, PhD
David Edgar Neal, MD
Kevin Pranikoff, MD
Hassan Razvi, MD
Joseph Smith, MD
Pramod C. Sogani, MD
J. Brantley Thrasher, MD
Dennis D. Venable, MD
Timothy J Wilt, MD
J. Stuart Wolf, Jr., MD

DISCLAIMER
This document was written by the Detection of Prostate Cancer Guidelines Panel of the American Urological Association Education and Research, Inc., which was created in 2011. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the committee included urologists, primary care physicians, radiation and medical oncologists and epidemiologists. The mission of the committee was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the detection of prostate cancer**.**

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (‘off label‘) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.