HHS Public Access

Author manuscript

Curr Opin Urol. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Curr Opin Urol. 2016 September ; 26(5): 447–458. doi:10.1097/MOU.0000000000000321.

What's new in screening in 2015?

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Abstract

Purpose of review—The aim of this review was to highlight important articles in the field of prostate cancer (PC) screening published during 2015 and early 2016. Four major areas were identified: 1. screening strategies; 2. post USPSTF 2011–2012; 3. screening trends/patterns; and 4. shared decision making (SDM).

Recent findings—Several studies furthered the evidence that screening reduces the risk of metastasis and death from PC. Multiplex screening strategies are of proven benefit; genetics and MRI need further evaluation. PSA screening rates declined in men above age 50 as did the overall PC incidence following the USPSTF 2011–2012 recommendation against PSA. The consequences of declining screening rates will become apparent in the next few years. More research is needed to identify the most optimal approach to engage in, and implement, effective SDM in clinical practice.

Summary—Data emerging in 2015 provided evidence on the question of how best to screen and brought more steps in the right direction of "next-generation PC screening". Screening is ongoing in all men regardless of whether they might benefit from early detection and treatment or not. After the USPSTF 2011–2012 recommendation the rates of PSA testing are declining, however this decline is observed in all men and not solely in those who will not benefit. The long-term effect of this recommendation might not be as anticipated. More studies are needed on how to implement the best available evidence on who, and when, to screen into clinical practice.

Keywords

prostate cancer; screening; 2015

Introduction

Prostate cancer (PC) screening using the prostate-specific antigen (PSA) is controversial. First, should one screen – at all? And if so – who, when and how often? We summarized the currently available guideline recommendations of who, when and how often to screen men

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in the general population for prostate cancer, and when prostate biopsy is indicated. While there is much common ground, guideline groups and experts diverge on several pivotal points, for instance ages to start and stop. The USPSTF recommended against PSA-screening for all men in 2011–2012[1], whereas most other guideline groups and experts agree that screening should start in midlife and end before age 75 and take place after shared decision-making (SDM) between an individual man and a his provider.[1–14](Table 1)

Over the past few years, the “one-size-fits-all” concept for PSA-screening appears to have been abandoned in favor of more risk-stratified approaches with the aim to optimize the balance between benefits and harm. Such approaches includes better stratifying baseline risk and adapting re-screening intervals according to a man’s age, general health and PSA level[7] as well as using multivariable approaches to help biopsy decision-making including reflex biomarkers[6] or risk calculators[15]. MRI is also emerging as a potentially promising tool in the pre-diagnostic setting as well as to guide targeted biopsies.[16] We reviewed the literature to search for any major advances during 2015, above and beyond what is already known, that would increase our understanding of who, when and how often to screen for PC.

Methods

We searched PubMed during Jan 1, 2015 – April, 30 2016 for English articles using the search words “prostate cancer” and “screening”. Both authors screened and selected the articles by title and abstract, and grouped them into the following categories based on content from full-text screen: 1. screening strategies – new data on risk-stratified screening, biomarkers, genetics and costs; 2. consequences of the USPSTF 2011–2012 recommendation; 3. screening patterns; and 4. SDM.

1. Screening strategies – new data on risk-stratified screening, biomarkers, genetics and costs

Results from ERSPC—The ERSPC consists of 8 European countries, several of which have separately reported the outcomes of screening on PC mortality. Several centers independently published their results.[17–24] The Finnish section of the ERSPC specifically studied screening failures, that is, those who died from PC despite being invited to screening. While being the largest component of the ERSPC, there was no evidence of a reduction in PC mortality between the randomized arms – something that puzzled the scientific community. Possible explanations to an ineffective screening included non-participation, interval cancers and the PSA cut-off. Correcting for non-participation indeed lead to a significant reduction in PC mortality with a hazard ratio of 0.78 (95% CI 0.64–0.96). Removing interval cancers and lowering the PSA threshold had a less pronounced and non-statistically significant effect on PC mortality.[17] This was confirmed by analyses on the entire ERSPC where it was found that the number needed to invite (NNI) and a novel metric – the number needed to overdiagnose (NNO) to prevent one PC death – varied greatly between ERSPC centers mainly due to differences in background risk and screening protocols; NNI varied between 200 to 7,000 and NNO between 16 to 69.[18] Further, the previously found reduction of metastatic PC both at diagnosis and during follow-up[19] was confirmed and was found to precede the reduction in PC mortality by about 3 years.[20]

Additionally, even though few support population-based screening, the current alternative, i.e. opportunistic screening, might result in an even less beneficial harm-benefit ratio as compared to a purely PSA based organized screening approach.[21, 23, 25]

The randomized PC screening trials mainly included men of Caucasian race and were population based; i.e. men of African ancestry or men with a positive family history or e.g. BRCA carriers were not included or under represented. It is however suggested that e.g. men of African ancestry are at higher risk of dying from PC and should be screened earlier or more intense[26]. However, a higher lifetime risk of PC death is not automatically a license to start screening. The potential benefit of avoiding PC death should still be weighed against the potential risk of over diagnosis. In case of ethnicity, this harm-to-benefit ratio does not differ from e.g. Caucasian men[27]. A strategy where men are stratified based on a baseline PSA value, and actively offered screening within the highest 10% of PSA was shown to produce a better risk-to-benefit ratio as compared to stratifying men based on race or family history of PC[28]. Once screening starts, optimizing the harm-to-benefit ratio is crucial and this could be done using a multivariable approach, including all available relevant information. [20, 29–34]

Monetary costs and costs for the individual and populations—Over the past decade, we have seen plenty of novel biomarkers for PC emerge and many of them are now being proposed to be used in combination with one another and/or with clinical examination and imaging. However, the cost of screening, diagnosis and treatment for PC can reach astronomical levels. In an editorial with the title “Prostate Cancer Screening Biomarkers: An Emerging Embarrassment of ‘Riches’?” Dr. Eggener reflects on the challenge of choosing which biomarker to order and points out that comparative effectiveness evaluations are critically important but lacking.. In addition, the author points out that nowadays urologists have the availability of a large amount of tests and interventions but that they are hardly aware of cost-effectiveness when ordering these tests.[35]

In a systematic review on the economics of PC screening, Lao et al argue that "the decision-making for PC screening should be based on the cost per quality-adjusted life year rather than the cost per life year saved" and conclude that screening is not cost-effective [36] This conclusion is contrary to the cost-effectiveness analysis based on the ERSPC data, where it is shown that PC screening can indeed be cost-effective, for instance when limited to two or three screens between ages 55 to 59.[37] However, correctly noted in[24],focusing on cost-effectiveness should not lead to losing sight on the effectiveness of screening itself.[38]

Reviews on screening strategies—Several reviews on PC screening strategies[39–42] agreed on the fact that PSA based screening, based on the evidence from population-based PSA screening trials reduces PC mortality, and also proposed that a more “tailored” screening is needed in order to maximize early diagnosis of potentially aggressive but curable PC, while minimizing overdiagnosis and overtreatment of indolent PC. As such, screening should only be started after the process of SDM and while there are many promising biomarkers the strength will be in combining those into risk prediction models including outcomes of multiparametric MRI.[16, 40]

It is emphasized that active surveillance (AS) can serve as a well-tolerated solution to avoid overtreatment for men with low-risk PC, while radical prostatectomy (RP) and radiotherapy (RP) both offer cancer control in young/fit patients when indicated. [42] In this context it is worth mentioning that two of the largest AS series published intermediate to long-term results in 2015. The Toronto series, with 993 men, median age 68 years, followed for a median of 6.4 years, used inclusive criteria and included men with very low-low-intermediate risk (T1c-T2a, PSA≤10, age ≤70, ≤GS 6, or age >70, GS ≤7) which embraced about 40–50% of eligible patients and the PC-specific survival was 98.1% at 10 years and 94.3% at 15 years.[43] The Hopkins series, with 1,298 men, median age 66 years, followed for a median of 5 years, used more restrictive criteria and included men with very low risk (T1c, GS6, PSAD < 0.15 ng/mL/cm^3, ≤2 pos cores, max 50% core involvement) which embraced about 10–20% of eligible patients and the PC-specific survival was 99.9% at 10 years and 99.9% at 15 years.[44]

Biomarkers: PSA isoforms—Numerous novel biomarkers for PC detection are now available and consist of serum-, urine-, and tissue-based assays that may supplement PSA testing, or even replace it These are covered more extensively in another paper in this issue. For the decision to perform a prostate biopsy for the first time, PSA-based assays such as the Prostate Health Index (PHI), percent free PSA (%f PSA) and the 4 kallikrein panel (or the 4Kscore which is a combination of 4 kallikreins and clinical data) test can be used[6]. For the decision to repeat biopsy PHI, %fPSA and the 4Kscore, and the urine based PCA3[6] and TMPRSS2:ERG could be considered, as well as the tissue based tests Confirm MDX, PCMT and PTEN. In addition, these tests can be combined with clinical data into so-called nomograms.[45] For instance, the Mi-Prostate Score (MiPS) combines PSA, PCA3 and TMPRSS2:ERG with the PCPT risk calculator.[46]

Evidence is accumulating regarding the role of assessing a baseline PSA test to stratify future risk of life-threatening PC[47, 48]. A large study based on a multiethnic cohort of 2,923 men, median age 58 years, were followed for 7.5 years for subsequent of high-grade PC (GS 7 or higher) it was shown that men with PSA ≤ 1 ng/mL were at 3.4% (95% CI 2.1, 4.5) 10-year risk of PC and 90% of these cancers were low risk; whereas risk was 39% in the highest PSA stratum (3–10 ng/mL). The authors therefore suggested that the re-screening interval could be up to 10 years for men with PSA < 1 ng/mL.[47]

On a similar theme, Boniol and colleagues assessed the value of variation in PSA levels between two screening visits within 2 years in 31,286 men in the PLCO trial with an initial value <4 ng/mL. The data showed that the risk of PC increased linearly with increasing PSA level at the second test. However, the variation in PSA was not associated with a higher Gleason score at time of detection.[49] This finding corroborates prior knowledge. It has previously been consistently shown that PSA rises (e.g. PSAV or PSA kinetics) do not increase the predictive accuracy above and beyond PSA alone[50, 51], and it has been proposed that men with high PSAV should not be biopsied, in the absence of other indications[52].

Among the varying guidelines for PSA testing worldwide (Table 1), there is no uniform consensus regarding the age to stop PSA testing and/or prostate biopsy. Many guidelines

propose stopping routine PSA at age 70 or 75 and discuss the upper age limit in the context of general health and life expectancy, recommending no further screening for men with a life expectancy < 10–15 years. Follow-up data from the BLSA suggests that men aged 75–80 years who have a PSA level below 3 ng/mL are unlikely to be diagnosed with a high-risk PC.[53] Long-term data from the Malmö Preventive Project suggests that men aged 60 with a PSA level < 1.0 ng/ml can possibly refrain from further testing.[7, 54, 55]

Biomarkers: PCA3 and genetics—For the urine based marker PCA3 more data became available but contradictory results on its diagnostic potential remain. Birnbaum and colleagues reported that use of PCA3 added to the PSA test can reduce adverse screening outcomes. Referring men with PCA3 scores >35 for biopsy among men with PSA between 4–10 ng/mL retained 85% of lives saved while reducing false positives by almost 50% and overdiagnoses by 25%.[56]

Yet, another study, part of the so-called IMPACT study, evaluated PCA3 in addition to PSA as a screening tool among BRCA1/2 carriers. However, the results did not provide evidence of additive predictive value of PCA3 in helping the decision to biopsy.[57]

The genetic epidemiology of PC is becoming better understood, including various mutational processes (such as ETS gene fusions; e.g. TMPRSS2:ERG or chromosomal rearrangements; e.g. PTEN loss) and germline variants[32]. Heritable BRCA2 and 1 mutations predispose to PC risk[29], as do single nucleotide polymorphisms[30]. A long-term prospective cohort study of Nordic twins showed a heritability for PC of 57%.[31]

Welch and colleagues discussed cancer biology and screening methods by making inference from incidence data from SEER for PC and breast cancer. The authors speculated in whether the difference in incidence of metastatic disease at presentation is explained by different cancer dynamics – with PC fitting the Halstedian paradigm (with cancer arising at a single location, grows and later metastasizes) or the Fisher paradigm (with cancer being a systemic disease already by the time it is detectable) – or the efficacy of two different screening strategies (a tumor marker versus anatomic imaging).[33] If PC fits the Halstedian paradigm it is particularly amenable to screening that allows for a stage shift, as shown in the ERSPC[20, 34], and thus detection at earlier stages.

GWAS studies are performed to screen the genome for genetic variants, so called single nucleotide polymorphisms (SNPs). There are now almost 100 SNPs that have been found to be associated with the risk of developing PC. Despite evidence suggesting that these genetic variants can be used for improved risk stratification, they have not yet been routinely incorporated into routine clinical practice. Next to several original publications[58, 59], Helfand et al. 60] reviewed their potential utility in PC screening and claim that it is possible that SNPs analyses can help risk stratify men who have increased susceptibility and target PSA based screening only to those men who are at increased risk. Same holds for SNPs that are strongly associated with PSA levels (so-called PSA-SNPs).[60]

Multiplex screening—Multivariable approaches to reduce the negative aspects of PSA-based screening have been proposed for many years. In a systematic review of 127

multivariable risk prediction models for PSA screening, also known as "risk calculators", 6 met inclusion criteria: Prostataclass, Finne, Karakiewcz, PCPT, Chun, and the ERSPC-RC-3. A meta-analysis of these 6 RCs showed that they all improve the predictive accuracy of PSA testing, in terms of discrimination.[61] However, calibrations measures were poorly reported.[62] Smaller studies confirmed performance of multivariate prediction over a PSA and DRE based algorithms. [63, 64]

An interesting study on the theme multiplex screening published this year was the Stockholm-3 (STHLM3) trial from Sweden, in which Grönberg and colleagues invited close to 150,000 men to participate in PC screening, comparing a multivariable model (STHLM3 model test) with PSA alone and a cut-off for biopsy of 3 ng/mL, designed as a paired non-inferiority study.[65] The model comprised protein biomarkers including PSA isoforms including some of those in the PHI[66] and the 4Kscore[67, 68], as well as MSMB, MIC1, 232 SNPs and clinical variables (age, family history, DRE, previous biopsy). Similar to the ERSPC and PCPT risk calculators[61], the PHI[66] and 4Kscore[68] as well as PSA followed by MRI in the Göteborg trial[16], the STHLM3 test improved the specificity, increased the predictive accuracy of finding GS 7 or higher (AUC 0.56, 95% CI 0.55–0.60 for PSA vs. 0.74, 95% CI 0.55–0.60 for the STHLM3 test) and reduced the number of unnecessary biopsies (by 32%, 95% CI 23–39).[65] While the authors are to be congratulated for carrying out a major screening study, which is certainly a step in the right direction, it is currently unknown whether the STHLM3 test really provides the so-needed major change in the balance of harms and benefit of PC screening. There is yet no data on repeat STHLM3 testing or on outcomes such as PC mortality. In addition, it is difficult to grasp whether the addition of the SNPs is mandatory.[69, 70] As Lamb and Bratt correctly point out [69], there are two kallikrein-based tests that are also capable in reducing unnecessary biopsies and selectively detecting high grade disease, the PHI[66] and the 4Kscore[68], which may potentially be more cost-effective[69, 71].

Regarding the role of DRE as a screening tool, DRE has long been used to diagnose PC and it was shown in early screening studies that PSA outperforms DRE in terms of detecting organ-confined disease[72]. The major limitation with DRE is its subjective nature and its domain is limited to men with low PSA levels. Here the data are conflicting. Using data from the ERSPC Rotterdam study, Gosselaar et al showed that in men with PSA levels between 2.0 – 4.0 ng/ml DRE was of no additional value, it potentially could avoid unnecessary biopsies but equally missed diagnoses of high risk PC.[73] Okotie et al confirmed this finding, but stated that delaying these diagnoses when only applying a PSA based cut-off to trigger biopsy will delay diagnoses and threaten potential cure.[74] As a result, guidelines disagree on whether to use the PSA test with or without DRE (Table 1). However, when considering population-based screening, DRE is not considered suitable, due to its subjective nature.

2. Consequences of the USPSTF 2011–2012 recommendation

Prior to 2008, USPSTF gave PC screening a grade "I" recommendation, i.e. “insufficient evidence to recommend either for or against”. In 2008, this was changed to a grade "D" recommending against screening men aged 75+, and in 2011 (draft recommendation) and

2012 they recommended against PSA for men of all ages[1]. This is in line with the Canadian Task Force[75], but in contrast to e.g. the AUA guidelines which recommends SDM[2,76]. The rationale for discouraging screening altogether is the USPSTF's concern that the harms of screening, i.e. mainly overdiagnosis and overtreatment, may not outweigh the benefits, i.e. reduced risk of metastasis and PC mortality.[1]

There have been several publications post the USPSTF 2011–2012 recommendation reporting on observed patterns of screening practices and incidence.[77–80] Two survey studies showed that there was awareness on the screening controversy yet the majority of men still believed that screening saved lives and should be used despite the USPSTF recommendation.[81, 82] Jemal et al examined the recent changes in stage specific incidence and PSA testing rates. The authors used SEER data on invasive PC incidence data from 2005 to 2012 and had the availability of 2013 incidence data from one registry (Georgia). Analyses showed that PC incidence rates started to decrease in 2008 and had the largest decrease between 2011 and 2012. Declines in incidence were only seen in local/regional stage disease. PSA testing decreased from 40.6% in 2008 to 30.8% in 2013 and were similar in men aged 50–74 and 75 years and older. Although these data cannot assess the full effect of the 2012 USPSTF recommendation, there is a decreasing trend in both incidence of low-risk PC and PSA testing.[77] Sammon et al similarly used NHIS data from 2000,2005,2010 and 2013 and found that the 2008 recommendation against PSA in men over 75 was not associated with a change in screening practices but a decrease in PSA screening after 2012, particularly in men < 75.[78] Drazer and colleagues similarly used the NHIS and found that PC screening rates declined significantly among men older than age 50 years after USPSTF 2012. However, a significant proportion of men continues to be screened despite a high risk of 9-year mortality, including one third of men age 75 years and older, suggesting that physicians may overestimate benefits and underestimate harms of screening in older men. [79] Barocas and colleagues found a 28% decrease in PC incidence in the year after the 2011 USPSTF draft guideline. Diagnoses of low, intermediate and high risk PC decreased significantly but new diagnoses of nonlocalized disease did not change.[83] Banerji et al analyzed the prospective database of 1726 patients undergoing prostate needle biopsies at Virginia Mason from 2004 to 2014 and found that patients in the post-USPSTF group had higher PSA levels ($p < 0.001$) and were more likely to be diagnosed with higher clinical stage and D'Amico high risk PC ($p = 0.036$).[84] Bhindi et al analyzed data of 3,408 prostate biopsies performed at University Health Network (Toronto) and observed a decrease in detection of low risk PC but find the sudden decrease in the detection rate of Gleason scores 7–10 concerning.[80]

Whether or not this will affect PC mortality rates remains to be seen. Do we already have solid evidence that more patients are actually starting to present with more high-risk and/or advanced PC since the USPSTF 2012? Well, there are opposing views. In a pro and con statement editorial, Dr. Barry argues that the only way to assess the effect of the USPSTF recommendation is to look at PC mortality, which will take time, and furthermore, determining cause of death among men with PC can be difficult.[85] Dr. Nelson supports his pro statement by the observation that in the population prostate carcinogenesis is constant, as is progression of PC and instead the diagnosis of PC is now being delayed. Allowing a disease to progress before diagnosis means that it will be more advanced compared to earlier

detection. This is a central tenet supporting all disease detection strategies and not just those for PC. Hence, stopping screening practices will undoubtedly affect rates of advanced disease at diagnosis and as such mortality.[85]

Prasad similarly notes in an editorial that the pendulum has swung[86] and Penson argues that it might already have swung too far[87] and that there is reason to be concerned. Instead of "all or none" Penson proposes that we focus on accelerating the development of more individualized PSA screening strategies, for instance by quantifying baseline risk for high-risk using PSA in midlife or risk calculators.[87] Castle says in an editorial that PC screening is “far from perfect but that giving up PSA screening would be taking a 20-year step backwards in the prevention of PC deaths and might deny or scare off high-risk men who would clearly benefit”, and similarly calls for implementation of more targeted risk-based strategies.[88]

The USPSTF 2011–2012 recommendation was largely informed by data from the ERSPC and PLCO trials. However, the power of the PLCO trial to detect any difference in PC mortality between trial arms was limited, because PSA testing was already widespread in the U.S. during the course of the study.[89] Just recently, a reanalysis of PLCO data by independent investigators showed that men in the control group reported having had more cumulative PSA testing than men in the intervention group; the proportion of control participants who reported having undergone at least one PSA test before or during the trial was close to 90%.[90]

3. Screening patterns, ethnicity, socioeconomic factors, family history

Worldwide, several papers studied screening trends and patterns in the community and in relation to ethnicity, socioeconomic factors and disparity.[26, 27, 91–99] They all came to the conclusion that uptake of PSA screening is strongly related to ethnicity, socioeconomic status and level of education. This brings up the issue of what actually defines “high risk” and data are conflicting. The role of family history of PC was examined within the PLCO trial (predominantly white men) whereby the authors suggest that men with a positive family history should be screened yearly with both DRE and PSA.[100] However, accumulating evidence, including data from the Korean heart study[101], BLSA and Malmö studies, now suggests that the baseline PSA level in midlife is a stronger predictor of a future diagnosis of lethal PC than both family history[28, 102] and race[28], which begs the question: why not obtain a baseline PSA to stratify risk in all men early in life? Vertosick and Vickers argue that “if a recommendation is made to screen early in men at high risk, a baseline PSA measurement at age 45 years would be a better method to identify men at high risk than family history or race”.[28] Drs. Carter and Albertsen do not disagree with the authors, but argue that taking a history and informing a man who is black and/or has a positive family history about the pros and cons of PSA screening might be very different, than just ordering a PSA test on everyone at age 45. They also speculate in that physicians will adapt the re-screening intervals to the PSA-levels with closer monitoring of higher PSA levels and more spaced out measurements in those below the age median, but that starting screening at age 45 might results in unnecessary biopsies and treatment.[103] On this point, Vickers do not believe that physicians would screen all men regularly at age 45 to 55 years, and notes that

the recommendation is to have the same conversation with all men at age 45, rather than for instance recommending screening black men or those with a family history starting at age 45 and everyone else at age 55.[28]

4. Shared decision-making

SDM is a process in which an individual learns about the disease, the harms and benefits, alternatives and uncertainty of options, weighs his own values and preferences and actively participates in the decision-making together with the clinician.[104] Most guidelines for PC screening emphasizes SDM[14], however, the “how to” needs further study. How should we best engage in pre-screening discussions[105], what information should be given and how should it be implemented in clinical practice?[13] The extent to which it is practiced in the real world is highly variable. Some authors propose that SDM for PSA screening should cover communication of four essential areas; the experts’ opinions about the test; accuracy of the test; the need for treatment; and side-effects of treatment. However, this may be unrealistic to achieve in real life, as one study found less than 10% of respondents reporting that the patient-provider communication covered all four domains.[106] Further, pre-screening discussions correlate with PSA uptake[105], either increasing or decreasing PSA screening rates depending on how the discussion about advantages and disadvantages go or how the decision-aid is framed; typically decision-aids for PC screening reduces men's interest in PSA and makes them lean away from having the test[107]. The format can also play a role and based on several publications it is obvious that there is no one size fits all[108–111] and that when confronted with the question to screen or not to screen, men want to know their risk and express acceptance to risk-stratified screening approaches such as more frequent screening if high risk and less frequent screening if low risk[112].

Conclusion

In conclusion, the debate on PC screening has shifted from “does PSA do any good?” to “does PSA do more good than harm?”. Data emerging in 2015 and early 2016 has provided evidence on the question of how best to screen. New biomarkers, multiplex screening, and PSA-based risk stratification at early age can shift the ratio of benefits and harms. However, it is crucial that guidelines and readily available risk stratification tools are implemented into daily practice, in order to stop the *misuse* of the PSA test.[113]

Acknowledgments

Dr. Sigrid Carlsson’s work on this paper was supported in part by a Cancer Center Support Grant from the National Cancer Institute made to Memorial Sloan Kettering Cancer Center (P30-CA008748). Dr. Carlsson is also supported by a post-doctoral grant from AFA Insurance.

Conflict of interest in the past 36 months

S.V.C. has received travel support (no lecture fee or honorarium) from Sanofi-Aventis.

M.J.R. is on the advisory board of Opko Health.

List of abbreviations

AA African-American

ACP	American College of Physicians
ACS	American Cancer Society
AS	Active Surveillance
ASCO	American Society for Clinical Oncology
AUA	American Urological Association
BLSA	Baltimore Longitudinal Study of Aging
BRCA	Breast Cancer Gene
DRE	Digital Rectal Examination
EAU	European Association of Urology
ERSPC	European Randomized Study of Screening for Prostate Cancer
ESMO	European School of Medical Oncology
GS	Gleason Score
GWAS	Genome-wide association study
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Data Base
NHIS	National Health Interview Survey
NND	Number needed to diagnose to prevent one death from PC
NNI	Number needed to invite to screening to prevent one death from PC
NNO	Number needed to overdiagnose to prevent one death from PC
PC	Prostate Cancer
PCA3	Prostate cancer antigen 3
PCPT	Prostate Cancer Prevention Trial
PHI	Prostate Health Index
PLCO	Prostate Lung Colorectal and Ovarian cancer screening trial
PSA	Prostate-Specific Antigen
PSAV	PSA velocity
RCT	Randomized Controlled Trial

RP	Radical Prostatectomy
RT	Radiotherapy
RC	Risk Calculators
SNP	single nucleotide polymorphism
USPSTF	United States Preventive Services Task Force
LE	life expectancy
N/A	not applicable
TRUS	transrectal ultrasound
MDX	Molecular Diagnostics
PCMT	Prostate Core Mitomic Test
PTEN	Phosphatase and Tensin Homolog
ETS	E26 Transformatin-Specific
MSMB	Microseminoprotein Beta
MIC1	Macrophage Inhibitory Cytokine 1

References

Papers of particular interest, published within the last year (Jan 1, 2015 – Dec 31, 2015), have been highlighted as:

* of special interest

** of outstanding interest

1. Moyer VA, Force USPST. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine. 2012; 157:120–134. [PubMed: 22801674]
2. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. The Journal of urology. 2013; 190:419–426. [PubMed: 23659877]
3. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline (unabridged version). American Urological Association. 2013 Available at: https://www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Cancer-Detection.pdf.
4. Heidenreich A, Abrahamsson PA, Artibani W, et al. Early detection of prostate cancer: European Association of Urology recommendation. European urology. 2013; 64:347–354. [PubMed: 23856038]
5. Mottet N, Bellmunt J, Briers E, et al. EAU Guidelines (Full Text Guidelines) Prostate Cancer. European Association of Urology. 2014 Available at: https://uroweb.org/guideline/prostate-cancer/.
6. Carroll PR, Parsons JK, Andriole G, et al. NCCN Guidelines Insights: Prostate Cancer Early Detection, Version 2.2016. J Natl Compr Canc Netw. 2016; 14:509–519. [PubMed: 27160230]
7. Vickers AJ, Eastham JA, Scardino PT, Lilja H. The Memorial Sloan Kettering Cancer Center Recommendations for Prostate Cancer Screening. Urology. 2016; 91:12–18. [PubMed: 26850815]
8. Smith RA, Manassaram-Baptiste D, Brooks D, et al. Cancer screening in the United States, 2015: a review of current American cancer society guidelines and current issues in cancer screening. CA: a cancer journal for clinicians. 2015; 65:30–54. [PubMed: 25581023]

9. Qaseem A, Barry MJ, Denberg TD, et al. Screening for prostate cancer: a guidance statement from the Clinical Guidelines Committee of the American College of Physicians. Annals of internal medicine. 2013; 158:761–769. [PubMed: 23567643]

10. Basch E, Oliver TK, Vickers A, et al. Screening for prostate cancer with prostate-specific antigen testing: American Society of Clinical Oncology Provisional Clinical Opinion. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012; 30:3020–3025. [PubMed: 22802323]

11. Murphy DG, Ahlering T, Catalona WJ, et al. The Melbourne Consensus Statement on the early detection of prostate cancer. BJU international. 2014; 113:186–188. [PubMed: 24206066]

12. Parker C, Gillessen S, Heidenreich A, et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2015; 26(Suppl 5):v69–v77.

13. Carlsson S, Leapman M, Carroll P, et al. Who and when should we screen for prostate cancer? Interviews with key opinion leaders. BMC medicine. 2015; 13:288. [PubMed: 26612204]

14. Loeb S. Guideline of guidelines: prostate cancer screening. BJU international. 2014; 114:323–325. [PubMed: 24981126]

15. Roobol MJ. Prostate cancer: Rescreening policies and risk calculators. Nature reviews. Urology. 2014; 11:429–430. [PubMed: 24980199]

16. Grenabo Bergdahl A, Wilderang U, Aus G, et al. Role of Magnetic Resonance Imaging in Prostate Cancer Screening: A Pilot Study Within the Goteborg Randomised Screening Trial. European urology. 2015

17. Kilpelainen TP, Tammela TL, Malila N, et al. The Finnish prostate cancer screening trial: analyses on the screening failures. International journal of cancer. Journal international du cancer. 2015; 136:2437–2443. [PubMed: 25359457]

18. Auvinen A, Moss SM, Tammela TL, et al. Absolute Effect of Prostate Cancer Screening: Balance of Benefits and Harms by Center within the European Randomized Study of Prostate Cancer Screening. Clinical cancer research : an official journal of the American Association for Cancer Research. 2015

19. Schroder FH, Hugosson J, Carlsson S, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). European urology. 2012; 62:745–752. [PubMed: 22704366]

20. Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic Prostate Cancer Incidence and Prostate-specific Antigen Testing: New Insights from the European Randomized Study of Screening for Prostate Cancer. European urology. 2015; 68:885–890. [PubMed: 25791513] ** This paper based on the ERSPC data shows that screening works through a stage shift. There is a decrease in metastatic disease at time of detection in favor of screening and this reduction precedes the observed mortality reduction with 3 years.

21. Arnsrud Godtman R, Holmberg E, Lilja H, et al. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Goteborg randomized population-based prostate cancer screening trial. European urology. 2015; 68:354–360. [PubMed: 25556937] * Based on the Göteborg screening trial and registry data it is shown that organized screening results in over diagnosis and a reduction of disease specific mortality reduction while opportunistic screening also results in over diagnosis but not in a reduction of pc mortality.

22. Lujan M, Paez A, Angulo JC, et al. Update of the results of the Spanish branch of the European Randomized Study on Screening for Prostate Cancer (ERSPC). Actas urologicas espanolas. 2015; 39:405–413. [PubMed: 25777669]

23. Godtman RA, Carlsson S, Holmberg E, et al. The effect of start and stop age at screening on the risk of being diagnosed with prostate cancer. The Journal of urology. 2015

24. de Carvalho TM, Heijnsdijk EA, de Koning HJ. Screening for prostate cancer in the US? Reduce the harms and keep the benefit. International journal of cancer. Journal international du cancer. 2015; 136:1600–1607. [PubMed: 25123412] * Based on statistical modeling (MISCAN) using a US population of 10 million men and US screening practices the authors projected the outcomes (PC mortality reduction and rate of overdiagnosis) of 83 screening policies, with different start and stop ages, screening frequencies and PSA cut-off values. They concluded that stopping screening

at age 70 can reduce harms and keep the benefit. It is more effective than reducing e.g. screening frequency.

25. Bill-Axelson A, Bratt O. Words of wisdom. Re: Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. European urology. 2015; 67:175. [PubMed: 25528396]
26. Lloyd T, Hounsome L, Mehay A, et al. Lifetime risk of being diagnosed with, or dying from, prostate cancer by major ethnic group in England 2008–2010. BMC medicine. 2015; 13:171. [PubMed: 26224061]
27. Bokhorst LP, Roobol MJ. Ethnicity and prostate cancer: the way to solve the screening problem? BMC medicine. 2015; 13:179. [PubMed: 26239718] * An editorial reflecting on whether a higher life time risk of PC death in some ethnic groups is a license to start screening. The authors point out the decision to screen lies in the harm (overdiagnosis) and benefit (lower PC mortality) ratio and in case of ethnicity, this harm-to-benefit ratio does not differ between groups.
28. Vertosick EA, Poon BY, Vickers AJ. Relative value of race, family history and prostate specific antigen as indications for early initiation of prostate cancer screening. The Journal of urology. 2014; 192:724–728. [PubMed: 24641912]
29. Eeles R, Goh C, Castro E, et al. The genetic epidemiology of prostate cancer and its clinical implications. Nature reviews. Urology. 2014; 11:18–31. [PubMed: 24296704]
30. Al Olama AA, Kote-Jarai Z, Berndt SI, et al. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. Nature genetics. 2014; 46:1103–1109. [PubMed: 25217961]
31. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. Jama. 2016; 315:68–76. [PubMed: 26746459]
32. Mitchell T, Neal DE. The genomic evolution of human prostate cancer. British journal of cancer. 2015; 113:193–198. [PubMed: 26125442]
33. Welch HG, Gorski DH, Albertsen PC. Trends in Metastatic Breast and Prostate Cancer--Lessons in Cancer Dynamics. The New England journal of medicine. 2015; 373:1685–1687. [PubMed: 26510017]
34. Bokhorst LP, Zappa M, Carlsson SV, et al. Correlation between stage shift and differences in mortality in the European Randomized study of Screening for Prostate Cancer (ERSPC). BJU international. 2016
35. Eggener S. Prostate Cancer Screening Biomarkers: An Emerging Embarrassment of 'Riches'? European urology. 2015 ** Interesting and timely view on the development and availability of PC screening biomarkers. It addresses the fact that of all new biomarkers available head to head comparisons and cost -effectiveness analyses are virtually lacking making it difficult to choose which biomarker to use if any next to PSA.
36. Lao C, Brown C, Rouse P, et al. Economic evaluation of prostate cancer screening: a systematic review. Future oncology (London, England). 2015; 11:467–477.
37. Heijnsdijk EA, de Carvalho TM, Auvinen A, et al. Cost-effectiveness of prostate cancer screening: a simulation study based on ERSPC data. Journal of the National Cancer Institute. 2015; 107:366. [PubMed: 25505238] * As stated in the title, this a simulation study to investigate which PSA based screening algorithm can be considered cost-effective. Conclusion is contrary to the paper of Lao et al and this paper concludes that PC screening can be cost-effective when it is limited to two or three screens between ages 55 to 59 years.
38. Noordzij MA, Blanker MH. Re: Cost-effectiveness of prostate cancer screening: a simulation study based on ERSPC data. Journal of the National Cancer Institute. 2015; 107:djv110. [PubMed: 25888716]
39. McDonald ML, Parsons JK. The Case for Tailored Prostate Cancer Screening: An NCCN Perspective. Journal of the National Comprehensive Cancer Network : JNCCN. 2015; 13:1576–1583. [PubMed: 26656524]
40. Alberts AR, Schoots IG, Roobol MJ. Prostate-specific antigen-based prostate cancer screening: Past and future. International journal of urology : official journal of the Japanese Urological Association. 2015; 22:524–532. [PubMed: 25847604]

41. Morgan T, Palapattu G, Wei J. Screening for Prostate Cancer-Beyond Total PSA, Utilization of Novel Biomarkers. Current urology reports. 2015; 16:63. [PubMed: 26169584]

42. Pini G, Collins J, Ghadjar P, Wiklund P. Guidance on patient consultation. Current evidence for prostate-specific antigen screening in healthy men and treatment options for men with proven localised prostate cancer. Current urology reports. 2015; 16:28. [PubMed: 25773347]

43. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015; 33:272–277. [PubMed: 25512465] ** A report of an active surveillance cohort with a median follow-up of 6.8 years, ranging from 0.2 to 19.8 years. The authors conclude that active surveillance for favorable-risk PC seems safe in a 15-year time frame; 2.8% of men developed metastatic disease while 1.5% died of PC. The note that the observed mortality rate is consistent with expected mortality in favorable-risk patients managed with initial definitive intervention.

44. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and Longer-Term Outcomes From a Prospective Active-Surveillance Program for Favorable-Risk Prostate Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015; 33:3379–3385. [PubMed: 26324359]

45. Crawford ED, Ventii K, Shore ND. New biomarkers in prostate cancer. Oncology. 2014; 28:135–142. [PubMed: 24701701]

46. Tomlins SA, Day JR, Lonigro RJ, et al. Urine TMPRSS2:ERG Plus PCA3 for Individualized Prostate Cancer Risk Assessment. European urology. 2015

47. Gelfond J, Choate K, Ankerst DP, et al. Intermediate-Term Risk of Prostate Cancer is Directly Related to Baseline Prostate Specific Antigen: Implications for Reducing the Burden of Prostate Specific Antigen Screening. The Journal of urology. 2015; 194:46–51. [PubMed: 25686543]

48. Kitagawa Y, Urata S, Mizokami A, et al. Simple Risk Stratification to Detect Prostate Cancer with High Gleason Score in Repeat Biopsies in a Population Screening Follow-up Study. Anticancer research. 2015; 35:5031–5036. [PubMed: 26254404]

49. Boniol M, Autier P, Perrin P, Boyle P. Variation of Prostate-specific Antigen Value in Men and Risk of High-grade Prostate Cancer: Analysis of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Study. Urology. 2015; 85:1117–1122. [PubMed: 25917734]

50. O'Brien MF, Cronin AM, Fearn PA, et al. Pretreatment prostate-specific antigen (PSA) velocity and doubling time are associated with outcome but neither improves prediction of outcome beyond pretreatment PSA alone in patients treated with radical prostatectomy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009; 27:3591–3597. [PubMed: 19506163]

51. Vickers AJ, Till C, Tangen CM, et al. An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. Journal of the National Cancer Institute. 2011; 103:462–469. [PubMed: 21350221]

52. Vickers AJ, Thompson IM, Klein E, et al. A commentary on PSA velocity and doubling time for clinical decisions in prostate cancer. Urology. 2014; 83:592–596. [PubMed: 24581521]

53. Schaeffer EM, Carter HB, Kettermann A, et al. Prostate specific antigen testing among the elderly--when to stop? The Journal of urology. 2009; 181:1606–1614. discussion 1613–1604. [PubMed: 19246059]

54. Carlsson S, Assel M, Sjoberg D, et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. Bmj. 2014; 348:g2296. [PubMed: 24682399]

55. Vickers AJ, Cronin AM, Bjork T, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. Bmj. 2010; 341:c4521. [PubMed: 20843935]

56. Birnbaum JK, Feng Z, Gulati R, et al. Projecting Benefits and Harms of Novel Cancer Screening Biomarkers: A Study of PCA3 and Prostate Cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2015; 24:677–682.

57. Cremers RG, Eeles RA, Bancroft EK, et al. The role of the prostate cancer gene 3 urine test in addition to serum prostate-specific antigen level in prostate cancer screening among breast cancer, early-onset gene mutation carriers. Urologic oncology. 2015; 33:202.e219–202.e228.
58. Pashayan N, Duffy SW, Neal DE. Implications of polygenic risk-stratified screening for prostate cancer on overdiagnosis. 2015; 17:789–795.
59. Kim S, Shin C, Jee SH. Genetic variants at 1q32.1, 10q11.2 and 19q13.41 are associated with prostate-specific antigen for prostate cancer screening in two Korean population-based cohort studies. Gene. 2015; 556:199–205. [PubMed: 25434496]
60. Helfand BT, Catalona WJ, Xu J. A genetic-based approach to personalized prostate cancer screening and treatment. Current opinion in urology. 2015; 25:53–58. [PubMed: 25405931]
61. Louie KS, Seigneurin A, Cathcart P, Sasieni P. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2015; 26:848–864. ** Louie et al performed a meta-analysis to identify PC risk models and to assess the model's performance to predict PC as compared to PSA alone. The authors identified 127 unique PC prediction models but only six models met study criteria for meta-analysis for predicting PC and concluded that risk prediction models improve the predictive accuracy of PSA testing but noted that calibration measures were poorly reported.
62. Carlsson S, Assel M, Vickers A. Letter to the editor concerning 'Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis'. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2015; 26:1031.
63. Borque-Fernando A, Esteban-Escano LM, Rubio-Briones J, et al. A Preliminary Study of the Ability of the 4Kscore test, the Prostate Cancer Prevention Trial-Risk Calculator and the European Research Screening Prostate-Risk Calculator for Predicting High-Grade Prostate Cancer. Actas urologicas espanolas. 2015
64. Poyet C, Nieboer D, Bhindi B, et al. Prostate cancer risk prediction using the novel versions of the European Randomised Study for Screening of Prostate Cancer (ERSPC) and Prostate Cancer Prevention Trial (PCPT) risk calculators: independent validation and comparison in a contemporary European cohort. BJU international. 2015
65. Gronberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50–69 years (STHLM3): a prospective population-based diagnostic study. The Lancet. Oncology. 2015 ** A report from a very large population based prostate cancer screening trial in Sweden where a predefined STHLM3 model (a combination of plasma protein biomarkers [PSA, free PSA, intact PSA, hK2, MSMB, MIC1], genetic polymorphisms [232 SNPs], and clinical variables [age, family, history, previous prostate biopsy, prostate exam]), was compared with a purely PSA based algorithm for the detection of high grade (Gleason ≥ 7) PC. The data showed that the STHLM3 model could detect a similar number of Gleason ≥ 7 PCs and reduced the percentage unnecessary biopsies with 32%. A multivariate approach like the STHLM3 model could be a step towards personalized risk-based PC diagnostic programs.
66. Loeb S, Sokoll LJ, Broyles DL, et al. Prospective multicenter evaluation of the Beckman Coulter Prostate Health Index using WHO calibration. The Journal of urology. 2013; 189:1702–1706. [PubMed: 23206426]
67. Bryant RJ, Sjoberg DD, Vickers AJ, et al. Predicting high-grade cancer at ten-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT study. Journal of the National Cancer Institute. 2015; 107 * A large study showing superior performance of the 4K panel as compared to PSA and age in detecting any and high grade PC.
68. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. European urology. 2015; 68:464–470. [PubMed: 25454615]
69. Lamb AD, Bratt O. Towards "next-generation" prostate cancer screening. The Lancet. Oncology. 2015
70. Carlsson SV, Kattan MW. Prostate cancer: Personalized risk - stratified screening or abandoning it altogether? Nature reviews. Clinical oncology. 2016; 13:140–142.

71. Heijnsdijk EA, Denham D, de Koning HJ. The Cost-Effectiveness of Prostate Cancer Detection with the Use of Prostate Health Index. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2016; 19:153–157. [PubMed: 27021748]

72. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. Jama. 1993; 270:948–954. [PubMed: 7688438]

73. Gosselaar C, Roobol MJ, Roemeling S, et al. Screening for prostate cancer at low PSA range: the impact of digital rectal examination on tumor incidence and tumor characteristics. The Prostate. 2007; 67:154–161. [PubMed: 17044079]

74. Okotie OT, Roehl KA, Han M, et al. Characteristics of prostate cancer detected by digital rectal examination only. Urology. 2007; 70:1117–1120. [PubMed: 18158030]

75. Bell N, Connor Gorber S, et al. Canadian Task Force on Preventive Health C. Recommendations on screening for prostate cancer with the prostate-specific antigen test. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2014; 186:1225–1234.

76. Eggener SE, Cifu AS, Nabhan C. Prostate Cancer Screening. Jama. 2015; 314:825–826. [PubMed: 26305653]

77. Jemal A, Fedewa SA, Ma J, et al. Prostate Cancer Incidence and PSA Testing Patterns in Relation to USPSTF Screening Recommendations. Jama. 2015; 314:2054–2061. [PubMed: 26575061] * Ecologic study with the aim to study the effect of the 2008 and 2012 USPSTF recommendations on PSA testing using SEER and NHIS data. The authors conclude that the incidence of early-stage PC and rates of PSA screening have declined, but that it is too early to draw any conclusions on the effect of the recommendations on disease specific mortality.

78. Sammon JD, Abdollah F, Choueiri TK, et al. Prostate-Specific Antigen Screening After 2012 US Preventive Services Task Force Recommendations. Jama. 2015; 314:2077–2079. [PubMed: 26575066]

79. Drazer MW, Huo D, Eggener SE. National Prostate Cancer Screening Rates After the 2012 US Preventive Services Task Force Recommendation Discouraging Prostate-Specific Antigen-Based Screening. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015; 33:2416–2423. [PubMed: 26056181] * A trend analysis based on NHIS data comparing PSA screening rates in 2005, 2010, and 2013. Simliar to the Jemal paper, the conclusion is that PSA screening significantly declined among men older than age 50 years after the 2012 USPSTF recommendation. However, still a significant proportion of men aged 75 years and older are being screened.

80. Bhindi B, Mamdani M, Kulkarni GS, et al. Impact of the U.S. Preventive Services Task Force recommendations against prostate specific antigen screening on prostate biopsy and cancer detection rates. The Journal of urology. 2015; 193:1519–1524. [PubMed: 25481037]

81. Orom H, Underwood W 3rd, Homish DL, et al. Prostate cancer survivors' beliefs about screening and treatment decision-making experiences in an era of controversy. Psycho-oncology. 2015; 24:1073–1079. [PubMed: 25382436]

82. Hunter JC, Vines AI, Carlisle V. African Americans' Perceptions of Prostate-Specific Antigen Prostate Cancer Screening. Health education & behavior : the official publication of the Society for Public Health Education. 2015; 42:539–544. [PubMed: 25616411]

83. Barocas DA, Mallin K, Graves AJ, et al. Effect of the USPSTF Grade D Recommendation against Screening for Prostate Cancer on Incident Prostate Cancer Diagnoses in the United States. J Urol. 2015; 194:1587–1593. [PubMed: 26087383]

84. Banerji JS, Wolff EM, Massman JD 3rd, et al. Prostate Needle Biopsy Outcomes in the Era of the U.S. Preventive Services Task Force Recommendation against Prostate Specific Antigen Based Screening. The Journal of urology. 2016; 195:66–73. [PubMed: 26254722]

85. Barry MJ, Nelson JB. Patients Present with More Advanced Prostate Cancer since the USPSTF Screening Recommendations. J Urol. 2015; 194:1534–1536. [PubMed: 26384450] ** An interesting analysis suggesting that the USPSTF recommendations already have an effect on the characteristics of PC at time of diagnosis.

86. Prasad V. Prostate Cancer Screening: The Pendulum has Swung, and the Burden of Proof Is with Proponents. American family physician. 2015; 92:678–680. [PubMed: 26554407]

87. Penson DF. The Pendulum of Prostate Cancer Screening. Jama. 2015; 314:2031–2033. [PubMed: 26575059]

88. Castle PE. PSA testing for prostate cancer screening. The Lancet. Oncology. 2015; 16:e2–e3. [PubMed: 25638549]

89. Carlsson S, Vickers AJ, Roobol M, et al. Prostate cancer screening: facts, statistics, and interpretation in response to the US Preventive Services Task Force Review. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012; 30:2581–2584. [PubMed: 22711853]

90. Shoag JE, Mittal S, Hu JC. Reevaluating PSA Testing Rates in the PLCO Trial. The New England journal of medicine. 2016; 374:1795–1796. [PubMed: 27144870]

91. Obana M, O'Lawrence H. Prostate Cancer Screening: PSA Test Awareness Among Adult Males. Journal of health and human services administration. 2015; 38:17–43. [PubMed: 26369233]

92. Moss J, Heidel E, Johnson J, et al. Ability of community-based prostate cancer screening to target an appropriate and underserved population. World journal of methodology. 2015; 5:10–12. [PubMed: 26140266]

93. Halbert CH, Gattoni-Celli S, Savage S, et al. Ever and Annual Use of Prostate Cancer Screening in African American Men. American journal of men's health. 2015

94. Abuadas MH, Petro-Nustas W, Albikawi ZF. Predictors of Participation in Prostate Cancer Screening among Older Men in Jordan. Asian Pacific journal of cancer prevention : APJCP. 2015; 16:5377–5383. [PubMed: 26225681]

95. Patrick AL, Bunker CH, Nelson JB, et al. Argument for prostate cancer screening in populations of African-Caribbean origin. BJU international. 2015; 116:507–508. [PubMed: 25046681]

96. Ogundele SO, Ikuerowo SO. A Survey of the Awareness of Prostate Cancer and its Screening among Men Attending the Outpatient Clinics of a Tertiary Health Center in Lagos, Nigeria. Nigerian journal of surgery : official publication of the Nigerian Surgical Research Society. 2015; 21:115–118. [PubMed: 26425064]

97. Goins RT, Schure MB, Noonan C, Buchwald D. Prostate Cancer Screening Among American Indians and Alaska Natives: The Health and Retirement Survey, 1996–2008. Preventing chronic disease. 2015; 12:E123. [PubMed: 26247423]

98. Eisinger F, Morere JF, Touboul C, et al. Prostate cancer screening: contrasting trends. Cancer causes & control : CCC. 2015; 26:949–952. [PubMed: 25822574]

99. Jeihooni AK, Kashfi SM, Kashfi SH, et al. Factors associated with prostate cancer screening behavior among men over 50 in Fasa, Iran, based on the PRECEDE model. Electronic physician. 2015; 7:1054–1062. [PubMed: 26120414]

100. Liss MA, Chen H, Hemal S, et al. Impact of family history on prostate cancer mortality in white men undergoing prostate specific antigen based screening. The Journal of urology. 2015; 193:75–79. [PubMed: 25066872]

101. Mok Y, Kimm H, Shin SY, et al. Screening Prostate-specific Antigen Concentration and Prostate Cancer Mortality: The Korean Heart Study. Urology. 2015; 85:1111–1116. [PubMed: 25917733]

102. Fang J, Metter EJ, Landis P, et al. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. Urology. 2001; 58:411–416. [PubMed: 11549490]

103. Carter HB, Albertsen PC. Re: Relative value of race, family history and prostate specific antigen as indications for early initiation of prostate cancer screening. The Journal of urology. 2015; 193:1063–1064. discussion 1064. [PubMed: 25476113]

104. Sheridan SL, Golin C, Bunton A, et al. Shared decision making for prostate cancer screening: the results of a combined analysis of two practice-based randomized controlled trials. BMC medical informatics and decision making. 2012; 12:130. [PubMed: 23148458]

105. Li J, Zhao G, Hall IJ. Pre-screening Discussions and Prostate-Specific Antigen Testing for Prostate Cancer Screening. American journal of preventive medicine. 2015; 49:259–263. [PubMed: 25997905]

106. Bhuyan SS, Chandak A, Gupta N, et al. Patient-Provider Communication About Prostate Cancer Screening and Treatment: New Evidence From the Health Information National Trends Survey. American journal of men's health. 2015

107. Barry MJ, Wexler RM, Brackett CD, et al. Responses to a Decision Aid on Prostate Cancer Screening in Primary Care Practices. American journal of preventive medicine. 2015; 49:520–525. [PubMed: 25960395]

108. Tomko C, Davis KM, Luta G, et al. A comparison of web-based versus print-based decision AIDS for prostate cancer screening: participants' evaluation and utilization. Journal of general internal medicine. 2015; 30:33–42. [PubMed: 25183475]

109. Kessler E. Capsule commentary on Tomko et al., A comparison of web- versus print-based decision AIDS for prostate cancer screening: participants' evaluation and utilization. Journal of general internal medicine. 2015; 30:94. [PubMed: 25266409]

110. Howard K, Salkeld GP, Patel MI, et al. Men's preferences and trade-offs for prostate cancer screening: a discrete choice experiment. Health expectations : an international journal of public participation in health care and health policy. 2015; 18:3123–3135. [PubMed: 25382490]

111. Gwede CK, Davis SN, Wilson S, et al. Perceptions of Prostate Cancer Screening Controversy and Informed Decision Making: Implications for Development of a Targeted Decision Aid for Unaffected Male First-Degree Relatives. American journal of health promotion : AJHP. 2015; 29:393–401. [PubMed: 24968183]

112. Koitsalu M, Sprangers MA, Eklund M, et al. Public interest in and acceptability of the prospect of risk-stratified screening for breast and prostate cancer. Acta oncologica (Stockholm, Sweden). 2015:1–7.

113. Roobol MJ. Unorganized prostate-specific antigen-based screening for prostate cancer: more harm than benefit. When will we finally start to implement guidelines and risk assessment tools in clinical practice? European urology. 2015; 68:363–364. [PubMed: 25769985]

Key points

- Screening reduces the risk of metastasis and death from prostate cancer
- Multiplex screening strategies are of proven benefit; genetics and MRI need further evaluation
- More research is needed to implement the current knowledge and identify the most optimal approach to engage in effective shared decision-making about PSA in clinical practice
- Rates of PSA screening and overall prostate cancer incidence have declined following the USPSTF 2011–2012 recommendation against PSA

Table 1

Summary of current guideline recommendations for who, when and how often to screen for prostate cancer in the general population

Guideline group (year)	Who should be screened?	Starting when? (screening tool)	Ending when?	How often?	Critieria for prostate biopsy	Reference
USPSTF (2012)	"Recommends against PSA screening; this recommendation applies to men in the general U.S. population regardless of age." (p.120 in [1])	N/A	N/A	N/A	N/A	[1]
AUA (2013)	SDM; >10–15 yr LE	55 (PSA)	"The Panel does not recommend routine PSA screening in men age 70 yr or more, or any man with a less than 10 to 15 yr LE" (p.423 in [2])	"A routine screening interval of two yr or more may be preferred over annual screening" (p.423 in [2])	"Urologists 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." (p.16 in [3])	[2, 3]
EAU (2013, 2014)	"Well-informed men"; SDM; ≥10 yr LE	40–45 (baseline PSA)	>70 yrs of age or men with a LE < 10–15 yrs	"Intervals should be adapted to the baseline PSA serum concentration." "Screening intervals should be 2–4 yr for men with PSA >1.0 ng/mL at age 45–59, whereas it could be up to 8 yr in men with PSA levels below this value." (p.351 in [4])	"The need for prostate biopsy is based on PSA level and/or suspicious DRE. Age, potential comorbidity, and therapeutic consequences should also be considered and discussed beforehand." (p.19 in [5]) "In the future, multivariable clinical risk-prediction tools need to be integrated into the decision-making process." (p.352 in [4])	[4, 5]
NCCN (v2.2016)	SDM	45 (baseline PSA, consider DRE)	"Testing >75 yr should be done with caution and only in very healthy men with little or no comorbidity" (p.511 in [6])	"PSA < 1 ng/mL, DRE normal (if done) --> repeat testing at 2–4 yr intervals; PSA 1–3 ng/mL, DRE normal (if done) --> repeat testing at 1–2 yr intervals." (p.511 in [6])	"PSA > 3 ng/mL or very suspicious DRE --> repeat PSA, DRE, workup for benign disease --> TRUS-guided biopsy or follow-up in 6–12 months with PSA/DRE or percent free PSA, 4Kscore, or PHI" (p.512 in [6])	[6]
MSKCC (2016)	Good health SDM	45 (baseline PSA without DRE)	"PSA testing should end at age 60 for men with PSA ≤ 1 ng/mL; at 70, unless a man is very healthy and has a	"If PSA ≥ 3 ng/mL: consider prostate biopsy; if PSA ≥ 1 but < 3 ng/mL: return for PSA testing every 2–4 yr; if PSA < 1 ng/mL: return for PSA testing at 6–10 yr." (p.12 in [7])	"The decision to biopsy a man with a PSA > 3 ng/mL should be based on a variety of factors including repeat blood draw for confirmatory testing of the PSA level, DRE results, and workup for benign disease. "Additional reflex tests in blood such as a free-to-total PSA ratio, the Prostate Health Index, or 4Kscore, or urinary testing of PCA3, can also be informative in some patients." (p.12 in [7])	[7]

Guideline group (year)	Who should be screened?	Starting when? (screening tool)	Ending when?	How often?	Critieria for prostate biopsy	Reference
			higher than average PSA; at 75 for all men." (p.12 in [7])			
ACS (2015)	SDM; At least at 10 yr LE	≥ 50 (PSA with or without DRE)	<10 yr LE	"Yearly for men whose PSA level is ≥ 2.5 ng/mL." "If PSA <2.5 ng/mL, screening intervals can be extended to every 2 yr" (p.42 in [8])	"PSA ≥4.0 ng/mL" "For PSA levels between 2.5 – 4.0 ng/mL, health care providers should consider an individualized risk assessment that incorporates other risk factors for PC, particularly for high-grade cancer, which may be used for a referral recommendation." (p.42 in [8])	[8]
ACP (2013)	SDM	50 (PSA and DRE)	Men over the age of 69 yr, or men with a LE < than 10 to 15 yr	"No clear evidence guides the periodicity or frequency of screening" "No clear evidence that PSA screening more frequently than every 4 yr produces any additional benefit" "PSA levels of ≥ 2.5 ng/mL may warrant yearly evaluation" (p.767 in [9])	≥4.0 ng/mL "DRE can be helpful in deciding whether to do a biopsy in men with PSA levels between 2.5 and 4.0 ng/mL." (p.765 in [9])	[9]
ASCO (2012)	SDM	LE > 10 yr (PSA)	LE ≤ 10 yr	Not specified	Not specified	[10]
Melbourne (2013) (expert panel)	Good health; SDM	40's (baseline PSA)	"Older men in good health with a >10-yr LE should not be denied PSA testing based on their age" (p.187 in [11])	Not specified	"PSA is a weak predictor of current risk and additional variables, e.g. age, ethnicity, family history, medical history, DRE findings, prostate volume, risk prediction models and new tools, such as the Prostate Health Index (phi) test and prostate cancer antigen 3 (PCA3) test, can help to better risk stratify men. " (p.187 in [11]) "PSA testing should not be considered on its own, but rather as part of a multivariable approach" (p.187 in [11])	[11]
ESMO (2015) (expert panel)	Not specified; population-based PSA screening is not recommended	Not specified (PSA)	70	Not specified	"A single elevated PSA level should not prompt a prostate biopsy, and should be verified by a second value " "The decision whether or not to have a prostate biopsy should Be made in the light of DRE findings, ethnicity, age, co-morbidities, PSA values, free/total (f/t) PSA, history of previous biopsy and patient values." (p.v69 in [12])	[12]