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Implications of the New AUA Guidelines on Prostate Cancer Detection in the U.S.

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Abstract In 2012, the U.S. Preventive Services Task Force (USPSTF) issued a blanket "D" recommendation against all prostate-specific antigen (PSA)-based early detection efforts for prostate cancer, reflecting critical misinterpretations of the major evidence regarding benefits and harms of such testing. Against the backdrop of the ensuing controversy, in 2013 the American Urological Association (AUA) published a new, methodologically rigorous guideline. This guideline recommended that men aged 55–69 be offered biennial screening in the setting of shared decision-making, that men under 40 or over 69 years of age should not be screened routinely, and that evidence was insufficient to recommend screening for men aged 40–54 years. While it has received criticism with regard to the age-based recommendations, the AUA guideline reflects a far better and more balanced presentation of the available evidence than the USPSTF statement. However, because the USPSTF is far more influential than the AUA among primary care providers, the ultimate impact of the new AUA guideline on practice patterns may be limited. Optimizing early detection practices should involve consensus-building incorporating both primary care and specialist input, with the goals of minimizing overtreatment of low-risk disease while continuing to reduce prostate cancer mortality rates through early detection and aggressive management of high-risk disease.

Keywords Prostate cancer · AUA guidelines · Prostate-specific antigen

This article is part of the Topical Collection on *Prostate Cancer*

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Introduction

With 238,590 new diagnoses and 29,720 deaths having been forecast for 2013, prostate cancer remains by far the most commonly diagnosed non-cutaneous malignancy—and the second leading cause of cancer mortality—among men in the United States [1]. Since prostate-specific antigen (PSA)-based screening began, age-adjusted prostate cancer mortality rates have plummeted, now down over 40 % since their peak in the early 1990s [1]. The only other cancer with a comparable velocity of decline in mortality rate is lung cancer, in which case the trend is largely explicable by the declining prevalence of smoking. No comparable epidemiologic trend can account for the observed trends in prostate cancer. In fact, a substantial majority can be attributed to a combination of early detection and improved management of high-grade disease [2••], a significant public health victory. The age-standardized prostate cancer mortality decline achieved in the U.S. has been the steepest in the world, and appears to be continuing. (http://globocan.iarc.fr/factsheet.asp).

Last year, however, the U.S. Preventive Services Task Force (USPSTF), the Federal panel commissioned by the Agency for Healthcare Research and Quality (AHRQ) to make policy recommendations regarding preventive health interventions, issued a "D" recommendation against PSA-based screening, concluding that the harms of screening outweigh the benefits and that routine screening should not be offered to any men [3•]. Other guidelines have also been pulling back from previous recommendations, generally calling for a more measured and/or individualized approach to screening, although the USPSTF is unique in rejecting the concept that men and their physicians should evaluate the risks and benefits of screening through a process of shared decision-making [4, 5•].

What is the reason for the disconnect between favorable trends in mortality and the rising tide of anti-screening

sentiment? The answer is multifactorial. The USPSTF evidence review [6] and recommendation [3•] are deeply flawed documents, reflecting critical misinterpretations of key evidence regarding benefits of screening, together with selective citations leading to an overstatement of the harms. The USPSTF process for cancer recommendations has also become an increasingly politicized one, marked by a notable lack of transparency and accountability [7•]. Moreover, the USPSTF review was conducted and published in the context of a rising backlash against overdiagnosis and subsequent overtreatment of low-risk prostate cancer, with estimates that 23–42 % of prostate cancers are overdiagnosed [8] and that the vast majority of these are managed with immediate treatment rather than active surveillance or other conservative strategies [9, 10].

At their roots, both the issue of overtreatment and the recommendation to resolve the issue through blanket cessation of screening reflect similar failures to recognize the profound biologic heterogeneity of prostate cancer [11]. Many—perhaps most—prostate cancers identified through screening are indolent, and would never cause symptoms or loss of life had they never been detected. Higher-risk prostate cancers, on the other hand, are a major source of suffering and early death in the United States, outcomes that can frequently be averted through early detection and aggressive management [12•]. This article will describe the current state of screening and the evidence for and against it, and in this context will review the new 2013 American Urological Association (AUA) guideline on early detection of prostate cancer [5•].

Who is Screened? Who is Treated?

Without question, PSA-based screening has not been implemented optimally in the U.S. over the years. Multiple lines of evidence suggest that PSA-based early detection efforts are more effective for younger men [13•], at least in part because benign hyperplasia and other conditions are more likely to cause false-positive PSA elevations among older men. Most guidelines recommend starting screening at age 50 or 55. Population-based data, however, indicate that only 24 % of men are screened between the ages of 50 and 54, and in fact, screening rates peak at 45 % for men aged 70–74. Men over the age of 85 are equally likely to be screened as men aged 50–54 [14]. Data from the Veteran's Administration health system paint a similar picture: in 2003, over 60 % of men aged 70–74 were screened and over 30 % of men over the age of 85. Furthermore, comorbidity and life expectancy had little bearing on screening rates: men with more than four major comorbidities were no less likely to be screened than the healthiest older men [15].

In practice, then, screening rates are too low among young healthy men and too high among older men with limited life expectancy. In addition, multiple studies have shown that treatment practices reflect high rates of both overtreatment of low-risk prostate cancer and under-treatment of high-risk disease, problems which are particularly salient among older men [9, 10, 16]. Furthermore, much treatment in the U.S. is administered by relatively low-volume providers [17], whose outcomes may not be equal to those achievable by higher-volume practitioners. All of these factors will tend to dilute the benefits of screening, compared to an optimized paradigm, in which healthy men would be screened at a young age, and treated by high-quality providers only if higher-risk cancer were identified.

What Do the Randomized Trials Really Tell Us?

There are three major randomized controlled trials of PSA screening reported in the contemporary era that inform the USPSTF and other guidelines: the prostate arm of the Prostate, Lung, Cancer, and Ovarian (PLCO) screening trial [18, 19•], the European Randomized Study of Screening for Prostate Cancer (ERSPC) [20, 21•], and the Göteborg screening trial [22••]. The evidence from these trials is often described by the USPSTF and others as contradictory [3•]. This claim is inaccurate, however, and is based upon misinterpretation of the actual trial data.

Between 1993 and 2001, the PLCO trial randomized nearly 77,000 men at 10 U.S. centers to annual screening for six years versus "usual care." The critical problem with the study lies in what constituted "usual care" in the U.S. in the 1990s and 2000s: a rapid uptake and very wide prevalence of PSA testing. As a pragmatic measure, the investigators allowed those who were randomized to have been screened before the study, and in fact, 44 % of the enrollees had had at least one prior PSA. Moreover, screening was quite common in the "usual care" arm, even after randomization, ranging from 40 % to 52 % per year [18]. Overall, *only 21 %* of the men in the "usual care" arm never received a PSA test prior to or during the PLCO trial [23•]. Of course, men who had already been found to have an elevated PSA through routine care were never even approached for the study. Finally, the rates of prostate biopsy among men with elevated PSAs were very low, falling from 40 % in the first study year to 30 % by the third year [24].

Thus, unsurprisingly, even the rates of prostate cancer incidence were minimally different between the two study arms. The stage distribution was virtually identical. Stage I and II tumors (by definition, screen-detected) accounted for 96 % and 94 % of the screening and "usual care" groups, respectively. Naturally, mortality rates did not differ [18]. A letter to the editor following primary publication of the PLCO noted that, ultimately, it was not a trial of screening versus no screening, but rather a trial of annual screening versus ad hoc or "opportunistic" screening constituting a part of usual

primary care in this country [25]. The PLCO authors have stated the same conclusion in two subsequent publications, that the PLCO informs us that annual screening is no better than opportunistic screening, but *does not* allow conclusions to be drawn about the benefits of screening versus no screening [19•, 23•]. The PLCO should not be included in meta-analyses of screening trials, and the failure of the USPSTF to recognize this fundamental truth indicates a critical gap in the members' understanding of the evidence.

The ERSPC, an even larger trial than the PLCO, randomized over 182,000 men at seven centers in Europe between 1991 and 2003. Each center had slightly different protocols for screening and biopsy referral—most screening at four-year intervals and the majority referred for biopsy at a PSA threshold lower than 4.0 ng/ml. PSA screening was much less prevalent in general practice in Europe during the study period than in the U.S., resulting in a substantially lower rate of PSA "contamination" in the control arm, and consequently much more substantial differences in the risk profiles of the screening arm-versus control-arm tumors in the ERSPC compared to the PLCO [20].

The ERSPC reported a 21 % relative risk reduction in prostate cancer-specific mortality at a median nine-year follow-up, with the mortality curves just starting to diverge around seven years. The primary analysis was performed as intent-to-screen. In a per-protocol analysis, adjusting for contamination that was present in the ERSPC and for nonattendance (failure of men in the screening arm to actually have a PSA drawn), the relative risk reduction was higher, at 29 %. The absolute risk reduction at this length of follow-up was low: 7 lives saved per 10,000 screened, balanced against 34 overdiagnoses per 10,000 screened. The ratio of these numbers yields a "number needed to treat" (NNT) of 48, meaning that 48 men would need to be treated to save one life [20].

The NNT calculation incorrectly assumes that all men diagnosed are treated, and has been rephrased as the number needed to diagnose (NND) in subsequent reports. The NND naturally decreases with longer follow-up, to 37 in the most recent report at a median 11 years of follow-up [21•]. Even 11 years is hardly adequate to inform clinical practice, with men in their 50s make screening decisions to avoid progressive disease 20 or 30 years into the future. Modeling the impact of screening with a lifetime horizon yields estimates of NND ranging between 2 and 9 [26]—rates that compare favorably to just about every other intervention in preventive medicine.

The Göteborg trial is frequently incorrectly described as a subset analysis of the ERSPC. It was conceived and launched before the ERSPC; 60 % of the Göteborg patients (those over age 54) were included in the ERSPC analysis, with the prior understanding that Göteborg would be reported as a separate trial. At a median age of 56, the Göteborg men were younger on average than those in either PLCO or ERSPC, and it was the younger men in the Göteborg trial who were not included with the ERSPC. The Göteborg trial screening protocol entailed biennial screening until age 69. The control group was characterized by very low rates of contamination. Substantial differences were noted in disease characteristics at diagnosis and in treatment patterns: 44 % of the men in the screening arm were managed, at least initially, with active surveillance. With 14-year median follow-up, the relative risk reduction for cancer mortality was 44 % and the NND was 12. The mortality curves were continuing to diverge substantially beyond 14 years [22••].

What Are the Harms of Screening?

As noted above, the USPSTF methodology relies on an assessment of the relative benefits and harms of screening. In mischaracterizing the PLCO conclusions, and essentially ignoring the Göteborg trial, the recommendation substantially underestimates the benefits of screening. Furthermore, its assessment of the harms of screening—which focuses on the harms of *treatment* rather than of screening per se—overstates these harms through selective literature review. As one example, the guideline makes repeated reference to a perioperative mortality rate for radical prostatectomy of 0.5 % [3•, 6]. The citations for this figure are papers reporting the experience in Medicare (thus limited to older patients and generally representing low-volume surgeons) for open surgery in the mid-1990s [27, 28].

The USPSTF ignored data in a more recent study (again, restricted to the Medicare population), reporting much lower rates of 0.1–0.2 %, although they did cite the same study as the only source of data regarding open versus robot-assisted surgery [29]. A more recent review that included large academic series as well as Medicare patients reported still lower rates, 0.04-0.1 % [30]. The USPSTF likewise selected for consideration papers presenting high rates of quality-of-life impairment after treatment, ignoring multiple series and meta-analyses reporting more favorable outcomes [6].

A subtler question is the potential direct harm of screening relating to anxiety, false-positive PSA tests, and the risks of biopsy. The most significant biopsy risks involve infection, rates of which are rising in the setting of fluoroquinolone-resistant Gram-negative bacteria [31]. Likewise, there is no question that some men experience anxiety around PSA screening and subsequent investigations. Recognizing this impact to psychological quality of life, one recent decision analysis assigned all men a small quality-of-life decrement for three weeks following screening [32]. While this is not an unreasonable assumption, the further postulation that men start at perfect health *before* screening, and that their quality of life can only decline with screening, is problematic.

The majority of men screened are found to have a very low PSA [33], and therefore a very low risk of prostate cancer

mortality. In a survey of men without cancer, the overwhelming majority prefer the state of being "normal by screening" to that of unknown status without screening, even if they have to go through a negative prostate biopsy to acquire this information [34]. In short, men positively value the reassurance that the majority gain through screening [35•], and neglecting this quality-of-life benefit in a decision analysis will unfairly reduce the overall benefit associated with screening.

The 2013 AUA Guideline

In April 2013, the AUA issued a new clinical guideline on early detection of prostate cancer [5•]. This document reflected a significantly higher degree of methodological rigor than the document it succeeded, the 2009 PSA Best Practice Statement [36]. The core recommendation in the new guideline is that men aged 55–69 be offered PSA-based screening for prostate cancer through a shared decision-making (SDM) process that accounts for their values and preferences. The guideline states than men under 40 or over 69 years of age should not be screened, with the caveat that some men in their 70s with excellent life expectancy may benefit. The most significant reversal from the 2009 best practice statement is that the guideline does not recommend routine screening for men aged 40–54,. Unlike the USPSTF statement, the AUA allows for individualization of screening decisions for younger men with risk factors such as African-American race or strong family history. The details of the guideline text also note that the AUA does not explicitly *discourage* screening in this age range, citing the principle that "absence of evidence does not constitute evidence of absence." In practice, however, the guideline was widely interpreted as an explicit recommendation against screening younger men [37]. Finally, the AUA guideline recommends biennial screening for most men [5•].

Compared to the USPSTF, the AUA guideline panel represented a vastly greater collective experience and expertise with the prostate cancer literature, and in addition to academic urologic oncologists, the panel included leading experts in biostatistics, internal medicine, medical oncology, and radiation oncology. The panel followed a rigorous published methodological approach in developing its recommendations, and in general, the guideline reflects a deeper understanding and more appropriate interpretation of the available evidence than the USPSTF statement.

However, the AUA guideline has not been without its own controversy since its release [37, 38]. At particular issue was the statement that the panel does not recommend screening between the ages of 40 and 54. As noted above, while this was not a recommendation *against* screening in this age group, it was widely reported as such. The principal rationale for this recommendation was the fact that the PLCO and ERSPC trials did not include men under 55. The AUA did not consider the 40 % of men in the Göteborg trial who were 50–55 at time of screening and were not included in ERSPC [21•, 22••]. One hypothesis for the improved results of the Göteborg trial compared to the ERSPC is its younger median age at randomization (56 vs. 60). In contract, another recent expert consensus statement recognized the unique perspective of the Göteborg trial in its recommendation to offer PSA testing between ages 50 and 69 [39•].

The principle study cited by the AUA panel regarding age for first screening was a modeling study that found that screening men in their 40s would have a negligible marginal benefit in terms of cancer deaths prevented within 10 years [40]. As noted previously, however, 10 years is not a relevant time frame for a younger man making a screening decision. The panel did cite a study from Malmö, Sweden (discussed in further detail below) [13•, 33] suggesting that an early baseline PSA is highly predictive of subsequent cancer diagnosis and progression, but felt that without evidence that this information would change management approach, the results could not necessarily be translated to decision-making [5•].

The question of screening men over age 69, while less contentious, is still not entirely straightforward. The basis for AUA's recommendation against screening was the finding in the ERSPC that men over 70 did not enjoy a reduction in cancer mortality with screening [5•]. A recent modeling study comparing various screening strategies found that ceasing screening at age 70 would reduce overdiagnosis by 50 %, but would also reduce the probability of saving a life by 27 % [41]. The AUA does allow that men over 70 in excellent health may wish to be screened, suggesting that in this age group, a PSA threshold for biopsy as high as 10 ng/ml might be most appropriate, and that those with a PSA <3 ng/ml should discontinue further screening [5•].

On this question, the AUA panel did not expressly consider prior screening history. A screening decision for a healthy man in his 70s who has had multiple low and/or stable PSA results over the preceding decades will be different from one who has never been screened before. Furthermore, as noted above, older men diagnosed with prostate cancer bear a high burden of both overtreatment and under-treatment [16], and men diagnosed with *high-grade* cancer, even in their 80s, face up to a 25 % risk of prostate cancer death within 10 years in the absence of local treatment [42•].

Overall, the AUA early detection guideline reflects perhaps the most rigorous analysis from a methodological standpoint. The age-based recommendations are not without some degree of controversy, and in all likelihood, do not reflect an optimal screening schedule. Nonetheless, the document does present an overall fair and balanced interpretation of a complex body of literature. Unfortunately, however, the guideline ultimately may not be highly impactful. Most men make their prostate

cancer screening decisions not with urologists, but with primary care providers, who for the most part do not look to the AUA for guidance. In one survey of internal medicine and family physicians, 69 % of respondents stated that the most influential guideline in their screening decisions was the USPSTF, and only 4 % identified the AUA as most influential [43].

Where Do We Go from Here?

The pre-2012 status quo—characterized by infrequent screening of young men, intensive screening of older men, indiscriminate treatment of low-risk disease, and inadequate focus on quality of care and the quality-of-life impacts of treatment—clearly cannot continue. There are two paths forward. One path, advocated by the USPSTF and others, is to abandon PSA screening altogether, even if the baby is thrown out with the bathwater and mortality rates return to pre-screening-era levels [44]. The second path is to screen—and treat—smarter.

Although there are no randomized screening trials including men under the age of 50, and none is likely to be completed anytime soon, other lines of evidence suggest that PSA testing for the majority of men should start earlier and should be much less frequent. As noted above, a population-based Swedish study has provided fascinating, unique insights. The Malmö Preventive Project banked blood on over 70 % of the entire population of the city of Malmö between 1974 and 1984, years before PSA was available for clinical use. PSA testing has never been highly prevalent in the city, allowing for a revealing natural history study. Some men developed prostate cancers detected through clinical means and treated per local standards. Years later, PSAs were assayed retrospectively on the banked blood.

A single PSA assessment for men aged 45–49 or 51–55 is highly predictive of likelihood of mortality over the next 25 years [13•]. A single PSA <1.0 ng/ml at age 60 is associated with a negative predictive value for prostate cancer mortality of 99.8 %. Conversely, 90 % of cancer deaths occurred among men with a PSA >2.0 ng/ml at age 60 [33]. Thus, a rational screening strategy might involve a baseline PSA at age 45 or 50. The majority of men with PSAs below the median can avoid further testing for the next 5 or 10 years at least, and those with higher values can choose between immediate biopsy and closer PSA monitoring. Certainly, a consensus is emerging that most men opting for screening do not need annual testing [5•, 21•, 41].

However, perhaps the most important component of a smarter screening strategy is the recognition that the purpose of screening is to detect *high-risk* prostate cancer early, within the window of opportunity for cure. Indeed, one of the significant flaws in the AUA guideline was the absence of any specific statement that prostate cancer needs to be risk-stratified, and that diagnosis must be uncoupled from immediate treatment for men with low-risk disease [5•]. Men should be advised before biopsy—and ideally even before a PSA is drawn—that while high-risk cancer, if detected, may be amenable to immediate treatment, low-risk prostate cancer is most commonly suitable for active surveillance, at least as initial management [45, 46]. One of the more egregious statements in the USPSTF recommendation refers to our "inability to reliably distinguish tumors that will remain indolent from those destined to be lethal" [3•]. The truth is that prostate cancers can be risk-stratified with up to 80 % accuracy with respect to likelihood of progression to metastasis and mortality, using a wide range of scores, nomograms, and other instruments [47–49].

While a number of emerging biomarkers hold promise for further improving risk stratification, screening need not wait for their availability. Avoiding overtreatment of cancers identified as low-risk, even by contemporary clinical standards, would preserve most of the survival benefits realized by screening. However, as noted previously, rates of active surveillance have historically been very low even for men with low-risk prostate cancer. Anecdotal reports have suggested that this situation may have begun changing in the past year or two, but there is no published data as of yet to provide confirmation. The principles of considering PSA in the context of other patient characteristics and of focusing diagnosis and treatment efforts on high-risk cancers form the basis of the recently released Melbourne Consensus Statement, offering an additional perspective on the screening controversy [39•].

Given the unique credibility of the USPSTF, deserved or otherwise, in guiding practices of primary care providers, it seems unlikely that a smarter screening paradigm can be broadly implemented in the U.S. unless currently pending legislation is passed to compel the USPSTF to include multidisciplinary expert opinion in its cancer guidelines [7•]. However, the onus to evolve is ultimately on our specialty. Unless urologists and other treating clinicians address the issue of overtreatment, and begin to systematically collect data on prostate cancer management trends and outcomes, we will lose PSA-based screening, to the detriment of untold thousands of men who will suffer avoidable progressive disease and early mortality [44].

Compliance with Ethics Guidelines

Conflict of Interest Dr. Matthew R. Cooperberg declares no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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