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Implications of the new AUA guidelines on prostate cancer detection in the US

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Abstract

In 2012 the US 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, the American Urological Association (AUA) published a new, methodologically rigorous guideline in 2013. This guideline recommended that men aged 55-69 be offered biannual screening in the setting of shared decision-making, that men under 40 or over 69 should not be screened routinely, and that evidence was insufficient to recommend screening for men 40-54. The AUA guideline has been criticized regarding the age-based recommendations, but 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 over-treatment 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

Introduction

With 238,590 new diagnoses expected in 2013, and 29,720 deaths expected, prostate cancer remains by far the most common non-cutaneous malignancy diagnosed—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 fallen inexorably, now down over 40% since their peak in the early 1990s.¹ The only other

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cancer with a comparable velocity of mortality rate decline is lung cancer, in which case the trend is explicable largely by declining prevalence of smoking. No comparable epidemiologic trend can account for the observed trends in prostate cancer. In fact, a substantial majority of the prostate cancer trend 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 ongoing (<http://globocan.iarc.fr/factsheet.asp>).

Yet last year the US 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, too, have been pulling back from previous recommendations, generally calling for a more measured and/or individualized approach to screening—though the USPSTF is unique in rejecting the concept that men and their physicians should evaluate the risks and benefits of screening together through a process of shared decision making.^{4,5}

What explains the disconnect between favorable trends in mortality and a rising tide of anti-screening sentiment? The answer is multifactorial. The USPSTF evidence review⁶ and recommendation³ 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 or accountability.⁷ However, the USPSTF review was also 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 overdiagnosed⁸ and 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 overtreatment problem and the recommendation to solve the problem 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 review the new 2013 American Urological Association (AUA) guideline on prostate cancer early detection.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 men¹³—at least in part because benign hyperplasia and other conditions are more likely to cause false positive PSA elevations among older men. Most

guidelines, moreover, recommend starting screening at age 50 or 55. Population-based data, however, indicate that only 24% of men are screened between ages 50-54, and screening rates in fact peak at 45% for men aged 70-74. Men over age 85 are equally likely to be screened as those 50-54.¹⁴ Data from the Veteran Administration system paint a similar picture: in 2003 over 60% of men 70-74 were screened, and over 30% of those 85. Furthermore, comorbidity and life expectancy had little bearing on screening rates: men with 4 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. Multiple studies have shown, moreover, that treatment practices reflect high rates of both overtreatment of low-risk prostate cancer and undertreatment 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 these problems will tend to dilute the benefits of screening compared to an optimized paradigm in which healthy men would be screened at young ages, 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 which 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 (ERPSC),^{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, however, is based incorrect interpretations of the actual trial data.

The PLCO trial randomized nearly 77,000 men at 10 U.S. centers between 1993 and 2001 to annual screening for 6 years vs. “usual care.” The critical problem with the study lies in what constituted “usual care” in the U.S. in the 1990s and 2000s: i.e., a rapid uptake and very wide prevalence of PSA testing. As a pragmatic measure, the investigators allowed those randomized were allowed 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 before 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 in the first place. 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, and, naturally, mortality rates did not differ.¹⁸ A letter to the editor following primary publication of the PLCO noted that in fact the PLCO was not ultimately a trial of screening vs. no screening, but rather a trial of annual screening vs. ad

hoc, or “opportunistic” screening forming part of usual primary care in this country.²⁵ In two subsequent publications, the PLCO authors have stated the same conclusion: 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 vs. 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 ERPSC, 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 on every 4 year intervals and most 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 it was in the U.S., resulting in a substantially lower rate of PSA “contamination” in the control arm. There were much more substantial differences in the risk profiles of the screening arm vs. control arm tumors in the ERSPC compared to the PLCO.²⁰

The ERPSC reported a 21% relative risk reduction in prostate cancer specific mortality with median 9 year followup, with the mortality curves just starting to diverge around 7 years. The primary analysis was performed as intent-to-screen; in a per protocol analysis adjusting for what contamination was present in the ERPSC 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 followup was low: 7 lives saved per 10,000 screened, balanced against 34 overdiagnoses per 10,000 screened. The ratio of these numbers yield the “number needed to treat” (NNT) of 48—that 48 men would need to be treated to save one life.²⁰

The NNT calculation assumes incorrectly that all men diagnosed are treated, and since has been rephrased as the number needed to diagnose (NND) in subsequent reports. The NND naturally falls with longer followup, to 37 in the most recent report at 11 years median followup.²¹ Even 11 years is hardly adequate to inform clinical practice: men in their 50s make screening decisions to avoid progressive disease 20 or 30 years in the future. Modeling the impact of screening with a lifetime horizon yields estimates of NND ranging between 2 and 9²⁶—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 ERPSC. 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 understand that Göteborg would be reported as a separate trial. With a median age of 56, the Göteborg men were younger on average than those 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 biannual 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 followup, the relative risk

reduction for cancer mortality was 44%, and the NND 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 depends 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%—though they did cite the same study as the only source of data regarding open vs. robot-assisted surgery.²⁹ A more recent review including large academic series as well as Medicare patients reported rates still lower, from 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 more subtle question is the potential direct harm of screening relating to anxiety, false-positive PSA tests, and the risks of biopsy. The most important biopsy risks involve infection rates which are rising in the setting of fluoroquinolone resistant Gram-negative bacteria.³¹ There is likewise no question that some men experience anxiety around PSA screening and subsequent investigations. Reflecting 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 the state of unknown status without screening, even if they had to go through a negative prostate biopsy to gain this information.³⁴ In short, men positively value the reassurance the majority gain through screening,³⁵ and neglecting this quality of life gain in a decision analysis will unfairly reduce the overall benefit associated with screening.

The 2013 AUA Guideline

In April 2013 the AUA issued guideline on prostate cancer early detection in April 2013.⁵ This document reflected a significantly higher degree of methodological rigor than the document it succeeded, the 2009 best practice statement on PSA.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 accounting

for men's values and preferences. The guideline states that men under 40 or over 69 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 the statement that for men aged 40-54 the guideline does not recommend routine screening. Unlike the USPSTF statement, the AUA allows for individualization of screening decisions for younger men with risk factors like African-American race or strong family history. The details of the guideline text also notes 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"—though in practice the guideline was widely interpreted as an explicit recommendation against screening younger men.³⁷ Finally, the AUA guideline recommends biannual 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, included leading experts in biostatistics, internal medicine, medical oncology, and radiation oncology. The guideline 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 ages 40-54. As noted above this was not a recommendation *against* screening in this age group, but was widely reported as such. The principal rationale given 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 hypothesized explanation for the improved results of the Göteborg trial compared to the ERSPC was its younger median age at randomization (56 vs 60). Another recent expert consensus statement, by contrast, recognized the unique perspective of the Göteborg trial in its recommendation to offer PSA testing between ages 50 and 69.³⁹

The principle study the AUA panel cited regarding age for first screening was a modeling study which found that screening men in their 40s would have a trivially small marginal benefit in terms of cancer deaths prevented within 10 years.⁴⁰ As noted previously, though, 10 years is not a relevant time frame for a younger man facing a screening decision. The panel did also 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, the results could not necessarily be translated to decision-making.⁵

The question of screening men over age 69 is less contentious, though 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 stopping 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 in excellent health may wish to be screened over 70, 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 different if he has had multiple, low and/or stable PSA results over the preceding decades than if he has never been screened before. Furthermore, as noted above, older men diagnosed with prostate cancer bear a high burden of both overtreatment and undertreatment¹⁶, 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 rigorously prepared guideline on this topic 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 what is overall a fair and balanced interpretation of a complex literature. Unfortunately, however, the guideline may ultimately not be highly impactful. Most men make their prostate cancer screening decisions not with urologists but rather with primary care providers, who for the most part do not look to the AUA for guidance on this question. In one survey of internal medicine and family medicine physicians, 69% of respondents stated that the guideline most influential in their screening decisions was the USPSTF; 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 age 50—and none is likely to be completed any time soon—other lines of evidence suggest that PSA testing should start earlier, and should be much less frequent for the majority of men. 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 between ages 45-49 or 51-55 is highly predictive of mortality likelihood 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 improving risk stratification further, 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 for men even with low-risk prostate cancer. Anecdotal reports have suggested that this situation may be changing in the past year or two, but no published data yet can provide confirmation. The principles of considering PSA in 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 primary care providers' practices, it seems unlikely that a smarter screening paradigm can be broadly implemented in the U.S. unless currently pending legislation is passed to force the USPSTF to include multidisciplinary expert opinion in its cancer guidelines.⁷ However, the onus is ultimately on our specialty to evolve: if urologists and other treating clinicians do not address the overtreatment problem and begin to collect data systematically 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

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* Of importance

** Of outstanding importance

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