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Author

Cooperberg, Matthew R

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Platinum Opinion

The New US Preventive Services Task Force "C" Draft Recommendation for Prostate Cancer Screening

Matthew R. Cooperberg *

Departments of Urology and Epidemiology & Biostatistics, UCSF Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco San Francisco, CA, USA

In 2011, the US Preventive Services Task Force (USPSTF), the guideline panel with the greatest influence among US primary care providers [1], issued a "D" recommendation regarding prostate-specific antigen (PSA)–based prostate cancer screening—asserting, in effect, that no men should ever be offered screening [2]. This decision, finalized in 2012, reflected both critical misinterpretations of the evidence available at the time, and growing impatience with the intractable pervasiveness of overtreatment for low-risk prostate cancer in the USA [3].

The "D" recommendation had an immediate and significant suppressive effect on rates of both PSA screening and prostate cancer diagnosis across the country [4,5]. Perhaps predictably, the decline in low-risk cancer diagnoses (ie, less overdiagnosis) was matched evenly by a decline in high-risk diagnoses, strongly suggestive of more underdiagnosis of potentially lethal disease [5]. Age-adjusted prostate cancer incidence rates are now at the lowest level since the 1980s, and this was the first year since the dawn of the PSA era that reported prostate cancer mortality rates have not declined [6]. The 2012 USPSTF recommendation was inconsistent with most other guidelines—which predominantly advise some variation on shared decision making—and was highly controversial, leading, in part, to a bill submitted to Congress to mandate that the USPSTF include specialist expertise in its deliberations [7].

Last month, in a major reversal, the USPSTF issued a new draft guideline, with a "C" recommendation that men aged 55–69 yr should be informed about the benefits and harms of screening, and offered PSA testing if they choose it [8]. For men aged ≥70 yr, the recommendation remains "D", or "do not screen." This change is obviously a big step in the right direction. Whether "C" is the correct conclusion, however, depends heavily on the evidence included to characterize both the benefits and harms of screening, and multiple important errors and limitations remain in this regard.

In terms of benefits, the new guideline and its underlying evidence review [9] state that screening men between the ages of 55 and 69 yr will save one to two lives per 1000 men screened within 13 yr. This conclusion is based primarily on the most recent report from the ERSPC trial [10]. While the guideline continues to insist that the quality of the ERSPC and the PLCO trials were both "fair", the new update finally acknowledges that the latter, in which more than 90% of the "control" participants received at least one PSA test [11], was in fact a trial of opportunistic vs. ad hoc screening rather than screening vs. no screening, and does not attempt to adjust down the survival benefit based on the PLCO.

The decision to exclude the Göteborg screening trial [12], for which only the older subset was included in the ERSPC, was a decision shared with the American Urology Association guideline [13], had the result of reducing the overall mortality benefit observed across trials and, more importantly, prevented a level 1 evidence–based recommendation for screening men aged 50–55 yr. In fact, a growing body of evidence from nonrandomized but very well-characterized—and, in one case, completely uncontaminated—cohorts indicates that the use of PSA at earlier ages, when benign prostatic hyperplasia and related processes are less likely to drive false-positive PSA elevation, could effectively stratify men to early detection, repeat PSA testing, or extended deferral of further testing. Under such a strategy, the majority of men tested once at 45 or 50 yr could defer any further consideration of prostate cancer risk for a decade or more [14,15].

* UCSF Helen Diller Family Comprehensive Cancer Center, University of California, Box 1695, 550 16th Street, San Francisco, CA 94143-1695, USA. Tel. +1 415 8853660; Fax: +1 415 8857443.
E-mail address: mcooperberg@urology.ucsf.edu.

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Inclusion of these cohort studies would also make clear that the 13-yr horizon to which the USPSTF guideline refers is far too short. For a 55-yr-old man, the question is outcomes at 30 yr and more. While the guideline reflects the latest follow-up reported to date for the ERSPC trial, the evidence is abundantly clear that mortality risk increases sharply with longer follow-up, and that, by extension, the number of lives saved rises and the numbers needed to screen and treat fall accordingly [14–17]. Randomized trials yield valuable insights, but a new trial randomizing men younger than 50 yr is extremely unlikely at this stage, and avoiding contamination in a control arm in any developed country would be pragmatically impossible. Ignoring all nonrandomized evidence on principle yields an incomplete picture of the knowledge base on PSA screening, and does a large disservice to at-risk men.

This problem is particularly salient for African-Americans, men with a positive family history, and other groups with a higher risk of lethal prostate cancer. While acknowledging higher rates of cancer and lethal disease in these populations, the guideline cites no screening research outside the PLCO or ERSPC trials, both of which involved overwhelmingly Caucasian cohorts. The call for more research in these groups is of course appropriate, but randomized trials will not provide the answers in any foreseeable future, and better consideration must be paid to cohort studies, modeling [18], and other complementary sources of information, most of which would support earlier screening in high-risk groups.

Despite explicitly excluding nonrandomized evidence in defining benefits, the USPSTF opted to include both trials and cohorts in measuring harms. Their choice of cohorts to include, moreover, was far from inclusive and overemphasized outdated studies, thus leading to overestimation of the harms. The inadequacy of the literature review on this question is evident, for example, in the selection of references for the PCOS and CaPSURE cohorts which were over a decade out of date relative to more recent papers [19,20]. Cohorts such as PROST-QA [21] were excluded entirely, as were large meta-analyses [22–25] and other data sources. While there is no argument that surgery and radiation can adversely affect urinary, bowel, and sexual functions, the statements that one in five men need diapers in the long term after surgery, two in three suffer long-term sexual dysfunction, and one in six men suffer long-term bowel complications after radiation are simply not defensible in light of more contemporary data.

The new guideline reiterates a "D" recommendation against any screening for men aged $\geq$70 yr. While the ratio of benefits and harms may be different for older men—and certainly a somewhat elevated PSA can be more difficult to interpret in this age group—life expectancy for healthy men at age 70 is now quite protracted, and there is a big difference between a man who has had prior reassuring PSA results in his 50s and 60s and one who has never been screened before. Older men who are not treated effectively for high-grade prostate cancer face an approximately 25% risk of prostate cancer mortality [26], and conversations with healthy men in their 70s should be more individualized and nuanced than the new guideline suggests.

Finally, the USPSTF has again missed a major opportunity to advocate that screening efforts should focus on identification of higher-risk cancers. The statement that we cannot distinguish aggressive, potentially lethal cancer from more indolent disease ignores decades of research and progress. In fact, prostate cancer can be risk-stratified with approximately 80% accuracy using clinical parameters alone [27], accuracy that can be further improved with emerging imaging, genomic, and other tests.

The evidence review stated that a single investigator abstracted all the study data [9]. Given the massive volume of prostate cancer research published in the past 5 yr, this may have been an insurmountable challenge for any individual, especially one without prior experience in prostate cancer research. In fact, the evidence review and guideline miss many critical studies directly addressing the priority questions identified in the *Research Needs and Gaps* section. In contrast to the 2012 guideline, this time the USPSTF actively sought informal input from four urologic oncology experts, although none of these contributed directly to the evidence review or final guideline.

The draft recommendation closed for formal comment on May 8, 2017, but readers can certainly continue to voice their opinions to the USPSTF leadership, and should continue to engage with their local primary care communities. Following the draft and final "D" recommendations in 2011 and 2012, Twitter proved to be an active forum for debate on the subject [28], one monitored by many patients and policymakers. Those with opinions on this subject are encouraged to make their thoughts heard on Twitter and other social media platforms using the hashtags #pcsm and #uspstf.

The new "C" recommendation represents substantial progress in the right direction towards offering men a fair opportunity to discuss the risks and benefits of screening with their primary care providers. Hope springs eternal the finalized recommendation will reflect a fairer and more comprehensive consideration of the available evidence base. The USPSTF should, like other guidelines panels, formally engage stakeholders and experts with both breadth and depth of knowledge and experience in order to give men and their physicians the best possible guidance on the perennially complex questions surrounding early detection of prostate cancer.

Conflicts of interest: The author has nothing to disclose.

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