Dear Dr. Siu,

Speaking on behalf of the American Urological Association (AUA) as current Chair of the Science & Quality Council and former Chair of the Practice Guidelines Committee, I commend the US Preventive Services Task Force (USPSTF) for seeking public comment on such an important topic. The AUA and its members strongly believe that blanket statements regarding PSA testing directed at the entire male population disregard the published benefits associated with such testing in men who may be at higher risk than the average male; as such, we applaud USPSTF in its efforts to incorporate risk stratification into its recommendations regarding PSA testing.

Following extensive discussions with expert urologists who specialize in the detection and treatment of prostate cancer, I am pleased to submit the following comments on the USPSTF Draft Research Plan for Prostate Cancer: Screening on behalf of the AUA and its members:

**Proposed Analytic Framework**

- The box listing “Early detection of prostate cancer” should be amended to “Detection of prostate cancer” given that not all diagnoses result in the detection of an early-stage cancer.
- Under Treatments, “Ultrasonography” should be amended to “High-intensity focused ultrasound (HIFU).”

**Proposed Key Questions to Be Systematically Reviewed**

**Key Question 1:** In looking at a “single threshold test,” is this intended to provide a potential basis for risk stratification? The AUA would support the investigation of the utility of a baseline PSA in a man, prior to the potential onset of other conditions that may affect PSA such as benign prostatic hyperplasia, as a strategy for risk stratification. Modeling data has shown that such a baseline can be used to guide alternative screening strategies for prostate cancer and lead to reductions in false positive tests and overdiagnosis.1

In discussing morbidity, this definition should be expanded to include the side effects associated with the use of androgen deprivation therapy. Reviewers are encouraged to evaluate SPCG-4 data, which showed that timely treatment can lead to decreased morbidity that may be present in patients following alternative pathways.2

**Key Question 3:** Again, the definition of morbidity should be expanded to include those side-effects associated with the use of androgen deprivation therapy.

**Key Question 5:** This question should take into account not only the positive predictive value of PSA, but the negative predictive value as well. Both positive and negative values need to be considered together in reference to the screening test itself and not just the potential biopsy. Moreover, the screening process can be viewed as more than just a PSA test, and might be viewed instead as an algorithm that may include PSA testing, biopsy, and appropriate imaging to improve diagnostic accuracy.

1. In discussing morbidity, this definition should be expanded to include the side effects associated with the use of androgen deprivation therapy. Reviewers are encouraged to evaluate SPCG-4 data, which showed that timely treatment can lead to decreased morbidity that may be present in patients following alternative pathways.

2. Key Question 3: Again, the definition of morbidity should be expanded to include those side-effects associated with the use of androgen deprivation therapy.
This is an important question that can help shape appropriate use of PSA testing; however, sufficient information is unlikely to be found if search results are limited to randomized controlled trials. Given that prostate cancer is a chronic disease that can potentially extend 10- to 15-years (or more) from the time of initial diagnosis, diagnostic and treatment modeling data must be included in a comprehensive review. The primary model utilized in the creation of the AUA Guideline on Early Detection of Prostate Cancer, for example, has been validated against both prostate cancer incidence trends in the US population before and after the advent of screening and against prostate cancer diagnosis patterns in the PLCO trial. Modeling studies are increasingly being used to guide screening policies, including those by the USPSTF on breast and colorectal cancer.

**Proposed Contextual Questions**

- The contextual studies are essential in the framing of the final USPSTF report; however, it remains unclear how these will be incorporated into the final USPSTF report and subsequent recommendations.
- Question 1 should be amended to include active surveillance, which is an important option for men following diagnosis, as reflected in question 2.
- Question 3 should be amended to include current imaging tools, such as multiparametric MRI, which has been shown to provide the detailed information regarding disease state necessary to make an informed treatment decision.

**Proposed Research Approach**

- The population of interest for KQs 3 and 4 is currently limited to men diagnosed at stage 1 or 2; however, stage 3 would include those men who are potentially asymptomatic and diagnosed with locally advanced prostate cancer—published data, such as that of the EORTC study have shown that this disease state is still possibly curable through radiation and/or surgical approaches. As such, the benefit of earlier detection through PSA could be quite large for these men and should not be excluded from review.
- In looking at interventions for KQs 3 and 4, subgroup analysis should be conducted to include severity of disease (via Gleason or D'Amico classification) at time of diagnosis given the large benefit differential between disease stages.
- The current comparison for KQs 3 and 4 is “no treatment.” It is suggested that this be amended to include surveillance or active monitoring to differentiate this from lack of action following diagnosis.
- The outcomes for KQ 1 should be amended to include side effects from use of ADT in the definition of morbidity.
- The outcomes for KQs 3 and 4 will need to be broken down and benefits/harms reviewed for each specific treatment modality in question.
- The current timeframe is limited to those studies published since the last release of the USPSTF statement on PSA testing; however, there are important publications that pre-date this cutoff, such as those by R. Etzioni et al., regarding modeling data that would fit with the expanded scope of this 2015 effort that should be considered for inclusion.

**Overall comments**

- Active surveillance is an increasingly important option following diagnosis of prostate cancer. This form of treatment relies heavily on imaging. Much of the harm associated with PSA is over-diagnosis and the next steps following testing, which most often include biopsy. Imaging is an important tool that should be reviewed for utility in conjunction with PSA testing to reduce those over-diagnosis-related harms while maintaining the benefit to men at higher risk.

Once again, AUA is encouraged by the USPSTF inclusion of the contextual questions addressing the nuances of screening, and it is the hope and recommendation of the AUA that these findings be used in the assessment of the key questions as well. As treating physicians, it is our duty to present the best available data on the benefits/harms associated with PSA testing, and this can only be presented through appropriate risk stratification. Ultimately, the final decision to undergo PSA testing is left to the patient and his own interpretation of the balance between risks and benefits. As such, the USPSTF is encouraged to pursue additional research into how a patient assesses that risk/benefit trade off and, ultimately, makes a decision as to whether or not he should be tested.
While the USPSTF panel is composed of independent, national experts in prevention and evidence-based medicine, urology representation is noticeably absent. As the primary treating specialty for prostate cancer, it is essential that urology is represented to ensure appropriate interpretation of currently available literature and expert input into diagnosis and treatment of this disease. It would be a disservice to patients to release guidance information on the primary method used to diagnose prostate cancer without consulting with those physicians who work with such patients every day. As such, we urge the USPSTF to seek further input from the urology community as guidance statements are developed. This request is in line with American Medical Association House of Delegates Resolution 225 adopted November 16, 2015, which advocates for the inclusion of relevant specialty societies and their members in guideline and performance measure development, including in technical expert panels.

Again, I thank you for your consideration of our feedback. Should you have any questions regarding these comments, I welcome an open discussion on this topic and look forward to reviewing the updated USPSTF framework.

Respectfully,

J. Stuart Wolf, Jr., MD, FACS
Chair
Science & Quality Council

REFERENCES: