



November 25, 2015

Albert L. Siu, MD, MSPH
Chair, U.S. Preventive Services Task Force
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RE: USPSTF DRAFT RESEARCH PLAN FOR PROSTATE CANCER: SCREENING

Dear Dr. Siu:

Thank you for the opportunity to provide comments in response to the "U.S. Preventive Services Task Force's (USPSTF) Draft Research Plan for Prostate Cancer: Screening." The Prostate Cancer Foundation (PCF) appreciates the USPSTF's effort to prioritize transparency to promote better outcomes for patients, clinicians, and the public at large by seeking input at this time.

By way of introduction, PCF is the world's leading philanthropic organization funding and accelerating prostate cancer research. The goal of the Foundation has always been to end death and suffering from prostate cancer. Founded in 1993, PCF has raised more than \$615 million and provided funding to more than 2,000 research programs at nearly 200 cancer centers and universities in 19 countries.

As you are aware, prostate cancer poses a substantial public health burden in the United States. This disease severely impacts the well-being of our citizens. Nearly 3 million U.S. men are living with prostate cancer today. Furthermore, although many strides have been made in treating prostate cancer successfully, too many men are still dying—more than 27,000 this year—and the physical, emotional, and financial costs of this disease are profound.

We are proud of our role in driving forward precision oncology to help address the complexities of prostate cancer early detection. We are pleased to see that much of this science will be considered in the current USPSTF research plan framework, and we have a number of additional recommendations that we believe will help ensure a balanced and comprehensive assessment of the current state of the art.

Proposed Analytic Framework:

The box listing "Treatment" should also include clinical trials participation. Clinical trials in prostate cancer "interception" for men at high risk for transformation of disease to lethal variants are a high priority in prostate cancer control. These are envisaged already with novel agents such as sulforaphane and "field cancerization inhibitors" for patients with positive investigational biomarkers; precision oncology chemoprevention trials based on genomic biomarkers will offer patients clinical trials options in the future.

Key Question 1:

As currently stated in the research plan, it appears that only randomized controlled trials (and systematic reviews/meta-analyses of these trials) will be included. Given the well-documented issues surrounding contamination in the National Cancer Institute sponsored Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, we would urge the following:

- Careful consideration of The Göteborg randomized prostate cancer screening trial as separate from the ERSPC is critical. Although some patients were included in the ERSPC, the Göteborg study was initiated before and independent of the ERSPC.
- Consideration of PLCO results as a trial of annual compared to opportunistic screening in the U.S., which is inherently and permanently flawed as an observation for health policy making.
- Inclusion of simulation modeling studies evaluating the impact of “true” screening vs. no-screening policies as well as the impact of screening at intervals longer than one year.¹⁻⁴
- Inclusion of outcomes beyond mortality and bone-related morbidity. This should include consequences of locally advanced and metastatic disease (e.g. androgen deprivation therapy), consequences of incurable disease and its therapy, and quality-of-life metrics.
- Consideration of the **time-dependent nature of the mortality** findings reported in the randomized trials, with changes in numbers needed to diagnose/treat to prevent a prostate cancer related death occurring as follow-up time increases.⁵
- Review of the differences in long-term outcomes according to key risk factors such as race and family history, as high-risk populations likely warrant distinct prostate cancer detection policies and disease management.

Key Question 2:

For evaluation of the harms of PSA-based screening, we strongly recommend consideration of the changing treatment trends in localized prostate cancer—in particular the changes in utilization of active surveillance in men with low risk prostate cancer. Over the past year, two large studies have reported rates of surveillance in this population of 40-50%, which differ substantially from the historical literature.^{6,7} Additionally, the validation and increasing use of prostate MRI and tissue-based molecular signatures to differentiate clinically indolent from aggressive disease warrants evaluation in the context of the potential harms related to overtreatment of men with indolent disease.⁸⁻¹⁰

Key Question 3:

In order to assess the impact of treatment for localized prostate cancer on prostate-cancer related mortality, we recommend consideration of overall trends in prostate cancer stage at presentation compared to that of other malignancies (e.g. breast cancer) during the PSA screening era as well as the overall trends in prostate cancer-specific mortality during the past 25 years.¹¹ In addition, data from the ProtecT trial (which randomized patients to surveillance, prostatectomy, or radiotherapy) will be forthcoming in 2016. Importantly, if PIVOT data are evaluated they should be stratified according to risk category given the significant differences in the impact of treatment for distinct risk strata.

Key Question 4:

Regarding the potential harms of treatment for early stage prostate cancer, we would underscore the importance of using the most current data in light of the changes in surgical approach and delivery of radiotherapy that have occurred over the past 10-15 years. The data on harms of treatment utilized in the previous version of these recommendations were largely historical and not reflective of current practices. It will also be important to separate out the benefits and harms for each distinct management modality being evaluated.

Key Question 5:

In addition to assessing the impact of prostate cancer risk calculators for increasing the positive predictive value of prostate biopsy, we urge the panel to consider the increasing availability and

utilization of blood and urine-based prostate cancer biomarkers as well as MRI to reduce false positives from PSA testing. Reducing false positives reduces unnecessary treatment and associated risks. Examples of current biomarkers include the urine-based PCA3 test, approved by the FDA validated in a recent EDRN study, and the blood-based 4Kscore, which is validated for the detection of Gleason 7 or greater prostate cancer on biopsy.¹²⁻¹⁶

Proposed Contextual Questions

The contextual studies proposed will be critical in the final USPSTF Research Plan; however, we are uncertain how these studies will be integrated into the review at his time. PCF seeks further clarification from the Task Force on this issue. Insights into patient preferences, including shared-decision making models, and practice patterns are important variables that may inform better health policy for U.S. men facing prostate cancer. In today's edition of The New York Times, an editorial referenced the "screen smarter" approach to reducing prostate cancer deaths and unnecessary treatment. A strategy to "screen smarter" would take into account new genomics-based tests in blood, urine, saliva and biopsy material. Improved positive and negative predictive values (PPV and NPV respectively) will be essential for accurately distinguishing lethal clones with metastatic potential in a patient versus clones that are indolent and do not need immediate intervention.

The Draft Research Plan, in heightening awareness around these issues of prostate cancer screening, creates an important opportunity to build upon and leverage philanthropic and federal research efforts to help reduce the prostate cancer death rate. We view this scheduled review of the USPSTF recommendations as an important inflection point in charting a path forward for delivering much needed and long awaited precision diagnostics, treatments, and cures. Therefore, PCF is convening an action-oriented Screening & Detection Research Summit in early 2016 focused on developing a consensus approach for the detection of lethal prostate cancer and surveillance of men unlikely to experience disease-related morbidity or mortality. We would be thrilled to welcome USPSTF members to this multidisciplinary meeting.

Thank you for your consideration of our comments. We look forward to working with the Task Force and reviewing the updated Research Plan.

Sincerely,



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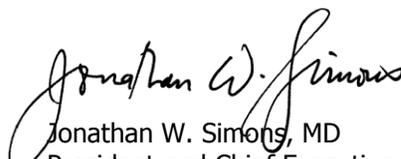
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