PROSTATE CANCER FOUNDATION

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Sent via e-mail: Robert.Cosby@ahrq.hhs.gov

Re: OPPORTUNITY FOR PUBLIC COMMENT - SCREENING FOR PROSTATE CANCER –USPSTF RECOMMENDATION STATEMENT DRAFT

Dear Dr. Cosby:

This letter is to provide comments in response to the U.S. Preventive Services Task Force's (USPSTF) request to the Prostate Cancer Foundation to review the draft Recommendation Statement against prostate-specific antigen (PSA)-based screening for prostate cancer. Founded in 1993, PCF has raised more than $480 million to fund more than 1,500 prostate cancer research programs at nearly 200 university research centers in 20 countries. PCF has been funding research on better biomarkers for detecting, profiling, and monitoring prostate cancer activity for over 15 years.

As the world's largest source of philanthropic support for prostate cancer research, PCF has reviewed the data from the five screening trials and has assessed that the judgment that the "harms of PSA-based screening for prostate cancer outweigh the benefits" misrepresents the uncertainty surrounding the benefits of screening both on a population-wide and on an individual level. It is PCF's view that the "moderate certainty" with which the task force makes its grade D recommendation on this issue both discounts the limitations of the data regarding the benefits of screening and assumes that the Task Force's valuation of benefit versus harm is generalizable to all men.

In our opinion, there is an insufficient level of certainty to warrant replacement of the 2008 USPSTF designation of an "I Statement" (meaning "evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined") with a "grade D" recommendation (meaning "there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits") against PSA-based screening for prostate cancer in all age groups.

As is well-described in the Task Force's review, the results of the two largest and highest-quality screening studies conflict. The ERSPC demonstrated a small but significant mortality benefit to screening after 9 years of follow up in men aged 55 to 69; the PLCO showed no benefit to screening[1,2]. Many explanations have been offered to account for this discrepancy, including the longer duration of follow-up in the ERSPC trial compared to the PLCO, prescreening and overtreatment of men in the PLCO trial, and, in the ERSPC, differences in the treatment of men diagnosed in the screened arm as compared to the control arm[3]. It is noteworthy that a subgroup of the ERSPC, which is the trial better positioned to detect a difference between screening and control arms, demonstrated a larger mortality benefit than the ERSPC after 14 years of follow up, providing support for the idea that the benefit to screening in the ERSPC may increase with longer follow up[4].

PCF appreciates the USPSTF heightening awareness of the issues of severe complications and patient suffering from the overdiagnosis and overtreatment of indolent prostate cancers. Harms associated with adverse effects stemming from the PSA test itself, together with the diagnostic testing that so often follows, plus the treatment of prostate cancer received by the vast majority of those diagnosed, are a significant source of hardship. Additionally, the costs are not borne by the patient alone. Consideration needs to be given to the emotional

and physical suffering experienced by patients and their families. Furthermore, recent cost-effectiveness analysis of PSA-based screening estimated that the cost of diagnosis and treatment is over $5,227,306 per patient to prevent one U.S. prostate cancer death[5].

We believe that, taken altogether, the data have favored a small but significant benefit to screening, one that may increase with time. Again, we agree wholeheartedly with the Task Force's characterization of the harms of overdiagnosis and overtreatment. However, we feel that the "balance of benefits and harms cannot be determined." In his *New England Journal of Medicine* editorial accompanying the publication of the ERSPC and PLCO results, Dr. Michael Barry noted that, "the implications of the trade-offs reflected in these data, like beauty, will be in the eye of the beholder[6]." It is our position that the trade-off of benefit and harms is now, as it was in 2008, a personal decision that should be made by a patient in conjunction with his physician.

Just as it is inappropriate to issue a "one size fits all" pro-screening message, it is equally inappropriate, and potentially irresponsible, to issue a blanket statement against testing, because some studies have demonstrated strong benefits to prostate cancer screening. We believe that there is strong evidence that for some men—generally those younger and in good health— that testing saves lives. Men who are in good health and have more than a 10-15 year life expectancy should have the choice to be tested and not be discouraged from doing so. The USPSTF recommendation could produce a cruel form of rationing in which the well-off and well-informed would receive PSA tests while many of the underserved would not. That could disproportionately affect men at a higher risk for prostate cancer incidence and mortality such as African American men.

As a body dedicated to identifying opportunities for improving delivery of effective services and helping others provide preventive care in different populations, the USPSTF would ideally issue an unprecedented "I + R statement" with the "R" standing for the notion that, "research on superior tests for detecting lethal cancers is needed." Such a recommendation would marshal existing resources toward a solution, rather than expend resources on debate alone.

The PSA debate can become moot with intensive and accelerated research that delivers a better test. For more than a decade, PCF has been supporting research to find new and better molecular biomarkers for prostate cancer. At PCF's 2011 Scientific Retreat, data on 17 new biotechnologies that complement or have the potential to replace PSA screening were presented. Many of these biotechnologies have the potential to discern between indolent and lethal prostate cancers. Patient participation in clinical trials to evaluate these new tests will be essential. New data on urine and blood tests using genetic biomarkers also offer the promise of eliminating a large number of unneeded biopsies and subsequent unnecessary treatment.

Given the enormity of the problem of overdiagnosis and overtreatment, PCF is supporting a $5 million research project, the National Proactive Surveillance Network, to determine which patients can be maintained on proactive surveillance and which patients need to be recommended for surgery or radiation. Work supported by PCF has already demonstrated, through the use of modeling, that there is a significant and robust quality of life benefit to active surveillance as compared with initial treatment for men with low-risk disease[7]. Additional clinical trials of proactive surveillance are urgently needed to develop guidelines for men whose cancers are not life-threatening.

PCF believes that the USPSTF's position provides a teachable and actionable moment for the medical community to improve targeting of PSA screening in patients, reduce over-testing and improve processes of patient education on the risks of overtreatment from PSA screening. The debate around USPSTF's recommendation also highlights the need to channel resources toward a "whole-of-government" public-private partnership that accelerates research on a set of tests that are superior to PSA-based screening. Such an effort could be led by NCI—with its considerable resources—in alignment with HHS, CMS, NIH, AHRQ, FDA, VA, non-profit organizations, and the biotechnology industry. CRADAS offer one of several possible mechanisms for establishing such a partnership.

In summary, PCF:

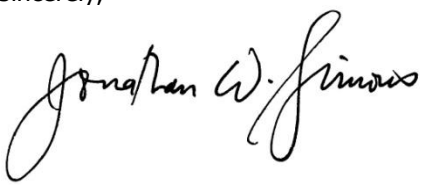
- Supports a step back from a grade D recommendation to an I statement with regard to PSA-based screening for men under the age of 75.
- Supports continued routine PSA screening of informed patients until new American Urological Association clinical guidelines on PSA screening are issued and disseminated.
- Supports a patient's choice to have a PSA test. The decision should be made between a man and his personal physician based on his individual status with respect to age, symptoms, family history, and concerns about prostate cancer.
- Supports American Cancer Society communications calling for far better processes of informed patient decision-making both prior to, and after, PSA screening in healthy men.
- Appreciates the efforts of many other prostate cancer organizations in responding the USPSTF recommendations, including the efforts of those in the Prostate Cancer Roundtable.
- Opposes the elimination of reimbursement for an informed patient requesting screening.
- Strongly recommends intensified National Cancer Institute focus and research investment in better early detection tests of lethal prostate cancers. We also recommend new public-private research partnerships. Such public-private partnerships will accelerate the discovery, testing, and validation in U.S. men of new biotechnologies for lethal cancer detection that are superior to PSA screening.
- Calls for greater patient participation in clinical studies evaluating new genomics-based prostate cancer detection tests.
- Calls for greater eligible patient participation in and physician referral of patients to ongoing new clinical trials evaluating Proactive Surveillance (watchful waiting).

Given the early success of the NCI Small Business Innovation Research Program (SBIR) Phase IIB Program in leveraging $2 of third party investment for every $1 invested, mechanisms already exist at the NCI for speeding validation of promising early stage diagnostics that can be compared head-to-head against the PSA test in an intensely NCI peer-reviewed process. The NCI, in partnership with stakeholders like the Prostate Cancer Foundation, American Urological Association, Canary Foundation, and American Cancer Society, is uniquely positioned to lead a collaborative approach to solving the problem of developing a test that can discern between lethal and indolent prostate cancers. PCF is committed to helping to fast-forward a research partnership focused on this effort.

Thank you for considering PCF's comments on this important matter at this time. Continued communication and involvement of patients, patient groups, physicians who actually take care of patients, researchers and other impacted entities is imperative for sound policy-making around the issue of PSA-based screening, and we welcome the opportunity to continue this dialogue. PCF would be pleased to provide any assistance and expertise that would further benefit this process.

If you have questions, or if we may provide you with additional information, please feel free to contact us at any time.

Sincerely,



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