November 8, 2023

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Dear Dr. Barry

The Large Urology Group Practice Group Association (LUGPA) is honored to submit comments to the U.S. Preventive Services Task Force (USPSTF) "Draft Research Plan Prostate Cancer: Screening." LUGPA represents 150 urology group practices in the United States, with more than 2,100 physicians who, collectively, provide more than one-third of the nation's urology services. Our providers and practices are engaged in prostate cancer diagnosis, treatment, education, and research and have been at the forefront of implementing care models incorporating the ever-evolving understanding of this disease process as well as the risks and morbidities associated with various treatment options. We have also watched with dismay the increasing incidence of patients who present to our clinics and hospitals with clinically advanced prostate cancer at initial presentation in the 11 years since the modification by USPSTF of the PSA screening recommendations.

There is an emerging consensus in the prostate cancer community that prostate-specific antigen (PSA) screening can lead to lower prostate cancer mortality without a concomitant increase in unnecessary risks to patients. Screening men should be an individual patient's decision with continued efforts to focus on the identification of patients that are most likely to benefit from prostate cancer treatments, particularly for those with increased risk of prostate cancer, namely African American men and men with a family history of prostate cancer. . We appreciate the opportunity to be a resource for USPTF as this issue is examined and reconsidered and look forward to contributing to a policy that minimizes adverse consequences associated with care and optimizes patient outcomes.

Background

Prostate cancer is the leading cause of cancer death in men in the U.S., with 1 in 41 men dying from prostate cancer.[1] In 2023, an estimated 288,300 new cases of prostate cancer will be diagnosed in the U.S., and 34,700 men will die from prostate cancer.[2]

The survival rate for prostate cancer diagnosed as early stage is close to 100%, while later stage disease has a survival rate of only 30%.[3,4] There are few, if any, clinically evident symptoms prior to the spread of this malignancy to more advanced disease, which makes screening absolutely critical.

[1] American Cancer Society. "Key Statistics for Prostate Cancer."
[2] Ibid.
[3] American Cancer Society. Cancer Facts & Figures 2023. Atlanta, Ga: American Cancer Society; 2023. https://www.cancer.org/cancer/types/prostate-cancer/detection-diagnosis-staging/survival-rates.html
[4] Siegel DA, et al.. Prostate Cancer Incidence and Survival, by Stage and Race/Ethnicity - United States, 2001-2017. MMWR Morb Mortal Wkly Rep. 2020 Oct 16;69(41):1473-1480. doi: 10.15585/mmwr.mm6941a1. PMID: 33056955; PMCID: PMC7561091.

While the predominance of all cancers occurs in patients with no known family risk factor, prostate cancer is nonetheless highly associated with race and family history: The incidence of African-American men with prostate cancer is 64% higher than that among white men[5]; and men with a father or brother with prostate cancer are more than twice as likely to be diagnosed with prostate cancer than those without a family history.[6]

Despite the well-established correlation between an elevated PSA level, an easily obtained blood test assay performed broadly in labs and offices across the country, and the presence (or absence) of prostate cancer, prostate cancer rates in the United States have shown a recent and concerning increase over the last ten years, reversing decades of declining rates. While multiple factors certainly have contributed to this trend, one public policy change stands out as a significant contributor—the 2012 decision by the U.S. Preventive Services Task Force (USPSTF) to recommend against PSA testing for prostate cancer (Grade D) for men of all ages. The recommendation cited concerns about false positives, unnecessary procedures with undesirable side effects for slow-growing cancers, and an assessment that the harms outweighed the benefits.

Unfortunately, the Grade D rating and the subsequent discontinuation of PSA testing by primary care doctors appears to have resulted in fewer men being screened and diagnosed with treatable early-stage prostate cancer and, years later, increased diagnoses of more advanced cancers at a later stage. A recent study published in the Canadian Journal of Urology examined prostate biopsy and prostate cancer rates in the United States following the 2012 USPSTF decision. The study analyzed two groups of patients who underwent a prostate biopsy between 2010 and 2021: one before the USPSTF recommendation update and the other after the update. The study found that after the recommendation against screening, the annual prostate biopsy rate decreased by 41 percent between the two groups. Additionally, the study revealed an increase in high-grade prostate cancer rates from 51.5 percent in the first group to 59 percent in the second.[7]

In 2018, the USPSTF issued a new recommendation, changing the grade for prostate cancer screening from Grade D to Grade C for men 55 to 69. Grade C recommends that clinicians engage in a nuanced discussion of the risks and benefits of PSA screening, selectively offering or providing the service based on professional judgment and with consideration of patient preference and priorities. However, this falls short of the full endorsement of PSA testing recommended by urologists and has had little impact on increasing the number of screenings provided to patients.

LUGPA believes the USPTF may be conflating diagnosis with treatment, particularly the historical treatment of indolent prostate cancer, which can be properly monitored where treatment is delayed or not provided. Improved diagnostic techniques, more sophisticated risk assessment regarding the likelihood of poor outcomes, and an ever-growing body of predictive data have enabled urologists to assess better which patients should be surveilled and which treated. Many more men with low-risk prostate cancer are now receiving active surveillance, with the percentage increasing from 26.5% in 2014 to 59.6% in 2021. [8] While there are certainly risks to various treatment

[5] Hinata N, Fujisawa M. Racial Differences in Prostate Cancer Characteristics and Cancer-Specific Mortality: An Overview. World J Mens Health. 2022 Apr;40(2):217-227. doi: 10.5534/wjmh.210070. Epub 2022 Jan 1. PMID: 35021294; PMCID: PMC8987139.
[6] Barber L, Gerke T, Markt SC, Peisch SF, Wilson KM, Ahearn T, Giovannucci E, Parmigiani G, Mucci LA. Family History of Breast or Prostate Cancer and Prostate Cancer Risk. Clin Cancer Res. 2018 Dec 1;24(23):5910-5917. doi: 10.1158/1078-0432.CCR-18-0370. Epub 2018 Aug 6. PMID: 30082473; PMCID: PMC6279573.
[7] Shah N, Ioffe V, Chang JC. Increasing aggressive prostate cancer. Can J Urol. 2022 Dec;29(6):11384-11390. PMID: 36495581; PMCID: PMC10026730.
[8] Abstract MP43-02, American Urology Association 2022 annual meeting cancer.gov

options, it is clear that urologists have been properly limiting treatment to those most at risk of cancer progression and morbidity. Furthermore, it is paramount to invest the risks of not screening patients with as much weight as those risks ascribed to overtreatment. Those risks, unfortunately, redound to the African American community, which is already more prone to avoid the health care system for historical reasons. USPTF should no longer assume a patient diagnosed with low-risk prostate cancer typically receives treatment. Additionally, it is worth noting that there is little or no risk in patients receiving the PSA blood test; at issue are subsequent treatment options for particular patients.

Response to Specific Questions Raised by USPTF Proposed Analytical Framework

LUGPA Response:

First, we are concerned with the definition of asymptomatic men, which, in turn, is the control group and the outcome data in the proposed analytic framework. These concerns are based on the previous large trials. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which enrolled 76,774 males ages 55 to 74 years, did not report a mortality benefit; however, the negative results have been largely discounted because over 40 percent of study subjects had undergone PSA testing within three years before enrolling in the trial,[9] and a subgroup analysis estimated that more than 80 percent of control subjects underwent PSA testing during the study.[10] Over 80 percent of patients randomized to the control group had screening as part of usual care.[9,10,11]

The ERSPC trial found a small absolute survival benefit with PSA screening at nine years of follow-up, with an absolute risk reduction of 0.51 per 1000 males. By 16 years, the prostate cancer mortality rate in the screening group was 0.53 per 1000 person-years compared with 0.66 per 1000 person-years in the control group.[12,13] The absolute risk reduction of prostate cancer death was 1.76 per 1000 males. While this trial was assessed to have the lowest risk of bias, the risk of bias was unclear due to allocation concealment and completeness of outcome data.

1. **What are the benefits of prostate cancer–specific antigen (PSA)-based screening for prostate cancer vs. no screening or usual care on short- or long-term prostate cancer mortality, incidence of metastatic prostate cancer, all-cause mortality, quality of life, and function?**

   a. Do the benefits of PSA-based screening vary in populations defined by age, race, ethnicity, or family history?

[9] Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360:1310.
[10] Shoag JE, Mittal S, Hu JC. Reevaluating PSA Testing Rates in the PLCO Trial. N Engl J Med 2016; 374:1795.
[11] Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 2017; 123:592.
[12] Hugosson J, Roobol MJ, Månsson M, et al. A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. Eur Urol 2019; 76:43.
[13] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014; 384:2027.

LUGPA Response:

PSA is a proven test that can save men's lives by finding prostate cancer early. The adoption of prostate-specific antigen (PSA) screening in the United States beginning around 1987 has profoundly changed the epidemiology of prostate cancer, with a rapid doubling of incidence and, by 2015, a 50% decrease in annual prostate cancer mortality.[14] Randomized trial data support a significant mortality benefit to PSA screening.[15]

Current national prostate cancer screening recommendations do not accurately reflect the benefits of PSA screening. As a result of these recommendations, we are seeing many men diagnosed with more aggressive, advanced-stage prostate cancer because they were not screened earlier. In a recent study of 836 282 patients with prostate cancer from the Surveillance, Epidemiology, and End Results (SEER) database, before the change in USPSTF recommendations, the incidence rate of metastatic prostate cancer was stable among men aged 45 to 74 years and decreasing among men older than 75 years. After the changed USPSTF recommendations, the incidence rate of metastasis increased in men of all ages.[16] Other studies have shown a recent rise in incidence rates[17] of higher grade and stage at diagnosis, coincident with USPSTF recommendations.

Interestingly, trends like the US have been reported from other countries that followed USPSTF recommendations. In an Australian study,[18] the incidence of newly diagnosed metastatic prostate cancer before and after USPSTF recommendations was 17.7% and 31.5%, respectively ($P < .05$). However, opposite trends were reported in countries where USPSTF recommendations have not been followed. The European Randomized Study of Screening for Prostate Cancer reported a 1.6-fold increase in prostate cancer incidence and a 21% reduction in prostate cancer mortality in a PSA screening-based program.[19] Comparing metastatic incidence rate ratios for screening vs. control groups by risk category showed a reduction in metastatic disease at diagnosis in the screening arm (incidence rate ratio, 0.60; 95% CI, 0.52-0.70), preceding mortality reduction by three years.

The benefits of PSA screening do vary by race. The net benefit of PSA screening is greater for Black men than the general population.[20] Black men have a higher incidence of and mortality from prostate cancer compared with men of other races.[21] This finding is particularly important if we take into consideration that, once a man is diagnosed with prostate cancer, Black race does not appear to be associated with inferior long-term outcomes if there is equal access to care and standardized treatment.[22]

[14] National Cancer Institute. *Surveillance Epidemiology and End Results SEER data and software*. 2020
[15] Hugosson, Roobol, and Mansson (n 12).
[16] Desai MM, Cacciamani GE, Gill K, et al. Trends in Incidence of Metastatic Prostate Cancer in the US. *JAMA Netw Open.* 2022;5(3):e222246.
[17] Iyer HS, Gomez SL, Chen JT, Trinh QD, Rebbeck TR. Trends in mortality among Black and White men with prostate cancer in Massachusetts and Pennsylvania: race and neighborhood socioeconomic position. *Cancer*. 2021;127(14):2525-2534.
[18] Smith S, Wolanski P. Metastatic prostate cancer incidence in Australia after amendment to prostate-specific antigen screening guidelines. *ANZ J Surg*. 2018;88(7-8):E589-E593
[19] Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic prostate cancer incidence and prostate-specific antigen testing: new insights from the European randomized study of screening for prostate cancer. *Eur Urol*. 2015;68(5):885-890.
[20] Basourakos SP, Gulati MS Vince RA, et al. Harm-to-Benefit of Three Decades of Prostate Cancer Screening in Black Men *NEJM Evidence*.2022;1(6)
[21] DeSantis CE, Miller KD, Goding Sauer A, Jemal A, Siegel RL. Cancer statistics for African Americans, 2019. *CA Cancer J Clin* 2019;69:211-233
[22] Dess RT, Hartman HE, Mahal BA, et al. Association of Black race with prostate cancer-specific and other-cause mortality. *JAMA Oncol* 2019;5:975-983.

2. What are the harms of PSA-based screening for prostate cancer vs. no screening or usual care, including the harms of associated diagnostic follow-up?

2a. Do the harms of PSA-based screening for prostate cancer vary in populations defined by age, race, ethnicity, or family history?

LUGPA Response:

PSA screening itself has little risk. It is a simple blood test, no different than testing for cholesterol, thyroid function, anemia, and blood counts. At issue is subsequent follow-up, including prostate biopsies and treatment options considered, depending on the grade of the cancer and other various patient factors.

The potential for overdiagnosis and overtreatment remains, although these harms are mitigated significantly by contemporary protocols incorporating management of disease by *active surveillance* for men with low-risk and favorable intermediate disease. Prostate cancer is increasingly managed with this modality in which curative treatment is deferred indefinitely, and the patient is monitored for evidence of progression utilizing clinical protocols, which include periodic physical examination, PSA–based testing, as well as repeat biopsy in certain cases. Many more men with low-risk prostate cancer are now receiving active surveillance, with the percentage more than doubling from 26.5% in 2014 to 59.6% in 2021.

Biopsy complications are quite rare and typically are not associated with long-term complications. In large metanalyses, in available cohorts (n = 15.136), complications requiring hospitalization occurred in 0.5% to 1.6% of men undergoing biopsy after abnormal screening findings.[23] Overdiagnosis is also being mitigated by the use of adjuvant testing in patients with abnormal PSA testing[24,25]

3. What is the diagnostic accuracy of PSA-based screening using free PSA, PSA velocity, and use of age-specific PSA thresholds for identification of prostate cancer?

LUGPA Response:

The use of adjunctive tests can improve the balance of benefits and harms of PSA-based prostate cancer screening. Biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA but are being used to varying degrees across the country, often sadly dependent on insurance coverage or lack thereof. The probability of high-grade cancer (Gleason score ≥3+4, Grade Group 2 or higher) may be further defined utilizing the Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA.[26]

[23] Fenton JJ, Weyrich MS, Durbin S, Liu Y, Bang H, Melnikow J. Prostate-Specific Antigen–Based Screening for Prostate Cancer: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*.2018;319(18):1914–1931.
[24] Wei JT, Barocas D, Carlsson S, et al. Early detection of prostate cancer: AUA/SUO guideline part I: prostate cancer screening. J Urol. 2023;210(1):45-53.
[25] Wei JT, Barocas D, Carlsson S, et al. Early detection of prostate cancer: AUA/SUO guideline part II: considerations for a prostate biopsy. J Urol. 2023;210(1):54-63.
[26] National Comprehensive Cancer Network® (NCCN®), Prostate Cancer Early Detection Version 2.2023

5. **What are the benefits of curative treatment approaches for screen-detected or early-stage prostate cancer vs. active surveillance or watchful waiting on prostate cancer mortality, incidence of metastatic prostate cancer, all-cause mortality, quality of life, and function?**

   5a. Do the benefits of treatment vary in populations defined by age, race, ethnicity, or family history?

LUGPA Response:

Given the long natural history of prostate cancer diagnosis and evolving treatment and surveillance methodologies, we have improved substantially on the harm-benefit tradeoffs compared to those that were observed years ago, particularly in the higher-risk screened patients with localized disease. Compared with conservative management, radical prostatectomy and radiation therapy are associated with reduced prostate cancer mortality and all-cause mortality in several fair- to good-quality cohort studies. However, closer inspection of these trials shows the benefit of various treatment approaches for early-stage or screen-detected prostate cancer is predominately seen in the cohort of patients with higher-risk disease.

Approximately 17–31% of men present with high-risk localized or locally advanced disease and thus should be offered curative treatment at the primary presentation.[27] Curative treatment provides a survival benefit in this population. In the Scandinavian Prostate Cancer Group Trial-4 (SPCG-4), which included men with clinically diagnosed, predominately palpable cancers (higher stage disease), radical prostatectomy was associated with statistically significantly reduced prostate cancer mortality (RR, 0.56 [95% CI, 0.41-0.77]) and all-cause mortality (RR, 0.71 [95% CI, 0.59-0.86]), compared with watchful waiting. [28]

In a large international multisystemic review, both radical prostatectomy as part of multimodal treatment and external beam radiation therapy were very effective as primary treatment in high-risk and locally advanced prostate cancer.[29] Alternatively, the Protect trial randomized men with localized, screen-detected prostate cancer to radical prostatectomy, radiation therapy, or active surveillance with no statistically significant differences in prostate cancer mortality or all-cause mortality.[30] This study was predominantly low-risk localized prostate cancer and supports the use

[27] Rider JR, Sandin F, Andrén O, Wiklund P, Hugosson J, Stattin P. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. Eur Urol. 2013 Jan;63(1):88-96.
[28] Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med*. 2014;370(10):932-942.
[29] Moris L, Cumberbatch MG, Van den Broeck T, Gandaglia G, Fossati N, Kelly B, Pal R, Briers E, Cornford P, De Santis M, Fanti S, Gillessen S, Grummet JP, Henry AM, Lam TBL, Lardas M, Liew M, Mason MD, Omar MI, Rouvière O, Schoots IG, Tilki D, van den Bergh RCN, van Der Kwast TH, van Der Poel HG, Willemse PM, Yuan CY, Konety B, Dorff T, Jain S, Mottet N, Wiegel T. Benefits and Risks of Primary Treatments for High-risk Localized and Locally Advanced Prostate Cancer: An International Multidisciplinary Systematic Review. Eur Urol. 2020 May;77(5):614-627.
[30] Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):1415-1424

of active surveillance in this patient population.

It seems clear that aggressive management—including both screening and treatment— of aggressive prostate cancers has saved thousands of lives in the past decade. However, even with standard clinical data readily available and applied carefully, low-risk prostate cancer can be identified with reasonable consistency. These low-risk malignancies are estimated to have a protracted natural history and pose little threat to patients during their lifetime, but unfortunately, to find aggressive tumors, we must screen large populations, which often produce a diagnosis of indolent cancer. More work is needed to identify biomarkers or imaging tests predictive of occult aggressive disease and to identify early those who are likely to need intervention. Future work should focus on finding the aggressive tumors and not treating the low-risk patients rather than narrowing screening protocols.

In the subset of African American men diagnosed with prostate cancer, a number of particularly troubling trends have been observed, including a presentation at a younger age [34] (an average of 2 years earlier) [35] diagnosis with more aggressive disease and/or diagnosis at later stages, and higher morbidity and mortality rates.[36,37] Studies, however, have demonstrated that, when detected at an equivalent stage, outcomes for these patients are equivalent to those of white men, amplifying the benefits of earlier detection and thus a benefit relative to harm ratio of even greater magnitude for screening and consequent identification while curative therapy is still possible in this patient group.[38,39]

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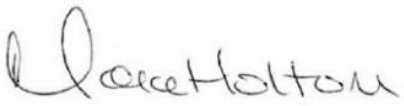
Respectfully submitted,



Evan R. Goldfischer, MD
President

Mara Holton, MD
Chair, Health Policy

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34. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection. Version 2. 2021.
Accessed September 15, 2021.
https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf
35 Pietro GD, Chornokur G, Kumar NB, Davis C, Park JY. Racial differences in the diagnosis and treatment of prostate cancer. *Int Neurourol J*. 2016;20(suppl 2): S112-S119. [PMC free article] [PubMed] [Google Scholar]
36. Rawla P. Epidemiology of prostate cancer. *World J Oncol*. 2019;10:63-89. [PMC free article] [PubMed] [Google Scholar]
37. Das H, Rodriguez R. Health care disparities in urologic oncology: a systematic review. *Urology*. 2020;136:9-18. [PubMed] [Google Scholar]
38. Dess RT, Hartman HE, Mahal BA, et al. Association of Black race with prostate cancer-specific and other-cause mortality. *JAMA Oncol* 2019;5:975-983
39. Basourakos, SP, Gulati, R, et al. NEJM Evidence
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