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BY ELECTRONIC SUBMISSION

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Re: Non - Recommended PSA - Based Screening

Dear Drs. Conway and Goodrich,

On behalf of LUGPA, we thank you for the opportunity to comment on the draft electronic clinical quality measure (ECQM) developed by Mathematica Policy Research on "unnecessary screening for prostate cancer using prostate - specific antigen (PSA)." LUGPA has significant clinical concerns regarding how the implementation of this policy as written will affect patient care; these concerns are based on several factors:

1. LUGPA (and other organizations representing physicians who care for or represent the interests of patients with prostate cancer) fundamentally disagrees with the scientific methodology on which the United States Preventative Services Task Force (USPSTF) based its Grade "D" recommendation regarding PSA-based prostate cancer screening;
2. Data regarding prostate cancer diagnosis suggest that the medical communities response to the USPSTF recommendation may already have resulted in reduced detection of biologically significant cancer with resultant missed opportunity for curative intervention; and
3. The timing of the proposal is premature given the fact that the USPSTF itself is revisiting the issue of PSA-based prostate cancer screening.

I. LUGPA

In 2008, when physician leaders of large urology group practices began to recognize the need for a formal association to help meet the challenges of the future, LUGPA was initially established with the purpose of enhancing communication between large groups, allowing for benchmarking of operations, promoting quality clinical outcomes, developing new business opportunities, and improving advocacy and communication in the legislative and regulatory arenas. Since that time, LUGPA has expanded its mission to include smaller group practices that are equally committed to providing integrated, comprehensive services to patients suffering from genitourinary disease. LUGPA currently represents 121 urology group practices in the United States, with more than 2,000 physicians who collectively provide approximately 30% of the nation's Urology services.[1]

Integrated urology practices are able to monitor health care outcomes and seek out medical "best practice" in an era increasingly focused on medical quality and the cost-effective delivery of medical services, as well as better meet the economic and administrative obstacles to successful practice. LUGPA's mission is to provide urological surgeons committed to providing integrated, comprehensive care the means to access resources, technology, and management tools that will enable them to provide all services needed to care for patients with acute and chronic illnesses of the genitourinary system, including men with prostate cancer, in an efficient, cost-effective, and clinically superior manner, while using data collection to create parameters that demonstrate quality and value to patients, vendors, third party payors, and regulatory agencies and legislative bodies.

Over the past several years, LUGPA has taken an active role in providing CMS and other governmental agencies, including the Medicare Payment Advisory Commission (MedPAC) and the Government Accountability Office (GAO), critical data and other information regarding diagnostic and therapeutic modalities used in providing prostate cancer care to Medicare beneficiaries. On numerous occasions, LUGPA representatives have met with senior leaders in all of these agencies, as well as with members of Congress, to discuss peer-reviewed and other empirical studies of the utilization of various modalities for diagnosing and treating prostate cancer in Medicare beneficiaries. In addition, LUGPA has provided comments to CMS on the Medicare Shared Savings Program/Accountable Care Organizations proposed rule and continues to take a leadership role with respect to proposed bundled payment systems for prostate biopsy services.

[1] Centers for Medicare and Medicaid Services, *Medicare Provider Utilization and Payment Data: Physician and Other Supplier*, available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Physician-and-Other-Supplier.html.

We hope to continue the relationship we have established with CMS, MedPAC, GAO, and others by providing meaningful commentary to agency reports, inquiries, and proposals. Thus, we respectfully provide the following comments on the proposed ECQM regarding non-recommended PSA-based prostate cancer screening.

II. The Scientific Underpinning of the USPSTF Recommendation is Flawed

We do not believe that USPSTF reached a correct conclusion regarding the clinical value of PSA screening. In fact, we believe that the task force decision is based on incomplete data, an inappropriate superimposition of the risks of therapy onto the risks of screening and a misunderstanding for clinical changes that are occurring presently in the real world management of PSA screening in conjunction with the shared decision making being offered to patients with newly diagnosed prostate cancer in the United States today. At the time of the recommendation we expressed concern that great harm will ensue for patients with intermediate and high risk localized prostate cancer as well as those already with advanced, asymptomatic metastatic disease, unintended victims of collateral damage as a consequence of the USPSTF recommendation to avoid the overtreatment of prostate cancer patients with low risk disease.

The authors of the supporting review article in the Annals of Internal Medicine (Chou et al.) and members of the USPSTF shared a number of distinct characteristics that are troublesome: a void of urology, urologic oncology, radiation oncology or medical oncology inclusion; some authors are not physicians and it is unclear for those who are physicians if they are in active practice. Hence, the review authors and the USPSTF together may lack certain clinical insights that would assist them to understand: 1) the significant clinical concerns and consequences of their recent f PSA screening recommendations in this country and worldwide, 2) the educated and appropriate use for PSA screening, 3) PSA utilization in conjunction with the rapidly advancing field of compendium and complimentary biomarkers and how the screening efficiency has rapidly changed in the last 2 years and 4) ultimately, best practices for the future.

It is critical to the discussion of screening to differentiate risks of screening from risks of treatment. Unfortunately, the section of the draft document on Harms of Screening and Treatment virtually ignores the physical risks of screening, focusing entirely on risks of biopsy and treatment. Actual physical risks of the screening process itself are minimal: PLCO reports a combined incidence of 26.3 events per 10,000 men screened, or 0.26%. It is not common clinical practice to automatically biopsy every patient detected on PSA screening; there are many factors that influence this decision including free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity, prior biopsy history and other comorbidities.

In making its recommendation, the USPSTF acknowledged that the existing studies on prostate cancer screening had very significant methodological flaws, as agreed upon by the authors of the manuscript as well; in fact, two studies were characterized as "fair." However, it was unclear as to the method by which these two studies (the Prostate, Lung, Colorectal and, Ovarian Cancer Screening Trial (PLCO)2 and the European Randomised Screening for Prostate Cancer (ERSPC)3 trial) were weighted. It was clear that the panel gives enormous weight to the PLCO study and virtually disregards the findings of the ERSPC; however, the flaws in the PLCO study appear much deeper than those in the ERSPC. Please consider the following:

1. The panel states that overall mortality is the goal studied by all trials reviewed. This is simply untrue. The ERSPC and Göteburg[4] trials were specifically statistically powered to evaluate prostate cancer specific mortality (PCSM), not all cause mortality. Overall mortality provided a parameter for assessing randomization rather than serving as an end point in itself.[5] Dismissing the importance of a statistically significant 20% reduction in the overall PCSM for ERSPC and 44% reduction of PCSM in the Göteburg component as "small to none" misses the clear clinical benefit to these patients and their families.
2. The PLCO study recruited 40% of men with a history of prior screening into their control arm. Furthermore, as the control arm was defined as "usual care," and not "no screening," patients were continued to be allowed to receive PSA testing during the study interval, resulting in screening being performed in >50% of the "control" arm, thus diluting the differential impact of PSA screening. Other than a statement that the authors attempted to correct for this, the USPSTF does not discuss their appreciation of this obvious error.
3. Although the major randomization error in (2) above is mentioned in passing, the following significant flaws in the PLCO do not appear to have been considered by the panel:
    a. Only approximately 40% of patients in the screening population who screened positive actually underwent prostate biopsy.

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[2] Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360:1310-9

[3] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360:1320-8.

[4] Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010;11:725-32

[5] Schröder FH . Stratifying Risk — The U.S. Preventive Services Task Force and Prostate-Cancer Screening. N Engl J Med. 2011; doi 10.1056/NEJMp1112140, published October 26, 2011.

   b. The overall follow-up with 98% mortality data in the PLCO trial was only 7 years.

4. These errors in the PLCO, not mentioned in the USPSTF recommendations, reveal that the PLCO report is inconsistent with the characteristics of a screening trial. Although the percentage of cancers in screened patients (7.4%) was higher than seen in "usual care" men (6.1%), this difference is far less than would be expected in a screened vs. unscreened population. Consider that in the ERSPC, the reported figures were 8.2% vs. 4.8%, respectively. Additionally, in PLCO, the presence of stage III/IV disease was nearly the same (122 in screened vs. 133 in "usual care") compared to what is consistent with screened vs. unscreened studies like ERSPC where unscreened men were much more likely to have higher stage disease and, indeed, they did, with 41% more positive bone scans compared to screened men at diagnosis. There exist today multiple unmet needs in caring for men with prostate cancer. Curing men with localized high risk disease is tantamount to reducing the approximate 28,000 annual cause specific mortality within the US; furthermore, while ~5% of the newly diagnosed prostate cancer patients within the US present with metastatic disease, the urologic oncology community goals are not to increase that percentage population but rather to identify them as early as possible in order to initiate our many recently approved therapies and thus avoid the sequelae of this disease.
5. There is no mention of 2 sub-group analysis in the PLCO trial showing survival benefits:
   a. About 10% of both controls and usual care men had undergone 2 or more PSA tests before randomization; their PCSM was 25% lower than men not tested and
   b. A later study of a healthier sub-group of PLCO men by Crawford showed a 44% survival benefit.[6]

This discounting of the then-available data from the ERSPC study was subsequently shown as erroneous. In its 2012 update, the ERSPC data demonstrated a 21% survival advantage to PSA screening for all patients, and furthermore, for those with the longest follow-up (over 10 years) this increased to 38%. As such, the screening efficiency of PSA testing in this study is similar to that reported for breast or colo-rectal cancer;[7] CMS is not proposing elimination of screening for these diseases.

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[6] Crawford, ED, Grubb III, R, Black, A, et al. Co-morbidity and Mortality Results From a Randomized Prostate Cancer Screening Trial. J Clin Onc 2011; 29(4): 355-361

[7] Schröder FH, Hugosson J, Roobol MJ et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; 366:981-990).

II. CMS Must Consider the Impact of the USPSTF Recommendation on Trends in Prostate Cancer Diagnosis

Before any further policy change is suggested in PSA testing in the United States, particularly one that proposes to encourage physicians and EPs with remunerative gain who do not order PSA tests in any men, it is appropriate to regard the changes that have already occurred in the prostate cancer field since the controversy surrounding the USPSTF Grade D recommendation against PSA testing began in 2011, culminating in its publication in 2012.

In a relatively short period of time, we have already seen a number of studies reflecting a significant and concerning change not only in the number of prostate cancers diagnosed, but also the stage and grade of newly diagnosed patients. Even if a causal link has yet to be definitively established, it is clear that a temporally related effect of the USPSTF Grade D recommendation has been associated with a decrease in the incidence of prostate cancer screening in the US. Originally these studies emanated from individual hospitals or health care systems; they clearly indicated significant reductions in PSA testing, referrals for elevated PSA, performance of prostate biopsies and lower detection rates of prostate cancer. [8,9,10]

More recent studies have reflected similar changes nationally. One study based on the National Health Interview Survey (NHIS) showed significant declines in PSA based screening in men over age 50: the decline was from 33.2% to 24.8% in men ages 50- 59 and from 51.2% to 43.6% in men ages 60 -74.[11] A review of the National Cancer Database (NCBD) and revealed a national decrease of 28% in incident diagnoses of prostate cancer in the single year after the USPSTF draft recommendation. [12] Similarly, a review of SEER data was recently shown to show a

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[8] Greene R, Tausch T, Deo Perez D et al. An Examination of PSA Utilization and Referral Patterns in a Large Integrated Health Care System Following the US Preventative Services Task Force Recommendations. J Urol 2013; 189(4S): e513

[9] Aslani A, Minnillo BJ, Johnson B, et al. The Impact of Recent Screening Recommendations on Prostate Cancer Screening in a Large Health Care System. J Urol 2013; 191(6):1737

[10] Bhindi B, Mamdani M, Kulkarni GS, et al.Impact of the U.S. Preventive Services Task Force Recommendations against Prostate Specific Antigen Screening on Prostate Biopsy and Cancer Detection Rates. J Urol 2015; 193: 1519

[11] Drazer M, Huo D, Eggene, S. National prostate cancer screening rates after the 2012 US Preventive Services Task Force recommendations discouraging prostate-cancer-specific antigen-based screening. J Clin Oncol. 2015; 33: 2416

[12] Barocas DA, Mallin K, Graves AJ et al. The effect of the U. S. Preventive Services Task Force grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the United States. J Urol. 2015; 194: 1587

precipitous decrease in prostate cancer detection in men over 50, from 213,562 men in 2011 to 180,043 men in 2012: a drop of 33,519 cancers detected in a single year![13] A recent review, again examining the NHIS, studying responses from >20,000 men before and after the USPSTF decision, found that the largest declines in men reporting PSA screening occurred between 2010 and 2013 and the declines were greatest in men between the ages of 50-54 (from 23% to 18%) and men ages 60-64 (from 45% to 35%). These declines were greater than observed in the elderly population - exactly the population with the most potential for benefit.[14]

In addition to the incidence of PSA screening and actual detection of prostate cancer falling after the USPSTF publication, there is also mounting evidence that the cancers being found are of higher risk. An analysis of National Oncology Data Alliance records of men with newly diagnosed prostate cancers in the US, reported that the number of men whose PSA levels were > 10 at diagnosis gradually dropped between 2005-2010; however, the number of men whose PSA levels were > 10 at the time of diagnosis rose 3% annually between 2011-2013, suggesting that cancers were being detected later. [15]

Further, in another single institutional study, there was reported a 31% reduction in prostate biopsies two and a half years after the USPSTF recommendation. These authors also reported a statistically higher PSA level at diagnosis, as well as significantly higher clinical stages detected, along with higher D'Amico risk scores at the time of diagnosis. These findings caused the authors to conclude that the reduction of prostate biopsies occurred concomitantly with a decrease in the detection of potentially curable prostate cancer and to suggest that repeat efforts at screening might be needed to prevent the reversal of decades of improvement in the prostate cancer mortality rate. [16]

III. The USPSTF is in the Process of Reviewing the Issue of Prostate Screening

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[13] Jemal A, Fedewa SA, Ma J, et al. Prostate Cancer Incidence and PSA Testing Patterns in Relation to USPSTF Screening Recommendations. JAMA. 2015 Nov 7;314(19):2054-2061.

[14] Sammon JD, Abdollah F, Choueiri TK, et al. Prostate-Specific Antigen Screening After 2012 US Preventive Services Task Force Recommendations. JAMA. 2015 Nov 17;314(19):2077-2079.

[15] Hall MD, Schultheiss TE, Farino G, et al.: Increase in higher risk prostate cancer cases following new screening recommendation by the US Preventive Services Task Force (USPSTF). J Clin Oncol 33, 2015 (suppl 7; abstr 143)

[16] Banerji JS, Wolff EM, Massman JD III et al: Prostate needle biopsy outcomes in the era of the U.S. Preventive Services Task Force recommendations against PSA based screening. J Urol 2015.

Despite the objections of those most intimately involved in prostate cancer diagnosis and treatment, the USPSTF opted to finalize its grade "D" recommendation on prostate cancer screening. This decision (among others), and the relative lack of transparency associated with the USPSTF process, has prompted legislators to act in a bipartisan, bicameral manner to propose changes in the manner in which the USPSTF conducts its reviews. The USPSTF Transparency and Accountability Act of 2015, introduced by Reps. Marsha Blackburn (R-TN-7) and Bobby Rush (D-IL-1) is the vehicle to reform the USPSTF process. This legislation aims to reform the process by which the U.S. Preventive Services Task Force (USPSTF) reviews and develops recommendations for clinical preventive services; a process that is currently exempt from transparency provisions such as the Federal Advisory Committee Act (FACA) and the Administrative Procedures Act (APA).

The bill includes a critically important mandate to ensure that a "balanced representation of primary and specialty care providers" and other key stakeholders in the healthcare community are involved in development and review of USPSTF recommendations. Other changes include publishing a draft research plan to guide the systematic evidence review process; considering findings and research by federal agencies and departments; and making the evidence review available for public comment.

Whether in response to potential legislative reforms or due to a recognition that its original one-size-fits-all recommendation disadvantaged patients at higher risk for developing prostate cancer, the USPSTF is planning to update their 2012 decision and has already issued a "Draft Research Plan for Prostate Cancer: Screening" with opportunities for comment by interested parties by November 26, 2015.These new guidelines might be available as soon as 2017.[17]

IV. Summary

Given the aforementioned detrimental trends that have already occurred since the USPSTF decision, LUGPA is deeply concerned that we now will compound these changes by promising a financial benefit to doctors and other EPs who decide against PSA testing. LUGPA believes is it time to review and revise the potential harm caused by recommending against prostate cancer screening in its entirety; of note, given the natural history of prostate cancer diagnosis to death, whether initially localized or metastatic upon presentation, it is imperative that we utilize the

[17] Draft Research Plan for Prostate Cancer: Screening. Accessed at: http://www.uspreventiveservicestaskforce.org/Page/Document/draft-research-plan/prostate-cancer-screening

most current literature available to make policy decisions to avoid escalating prostate cancer as the 2nd leading cause of male US cancer mortality. LUGPA is committed to contemporaneous review of the current literature and evidenced based medicine evidence regarding screening, diagnosis, and management of this disease. As such, we are concerned that the literature cited by CMS simply does not reflect the current state of knowledge regarding either prostate cancer screening processes or the potential impact of the USPSTF recommendations on stage and grade migration. A brief review of the framing document produced by this entity reveals a lack of familiarity and depth in preparing for this task, with not a single reference cited beyond 2013.

On behalf of LUGPA, we would like to thank CMS for providing us with this opportunity to comment on the proposed ECQM. Please feel free to contact Dr. Kapoor at (516) 342-8170 or dkapoor@impplc.com if you have any questions or if LUGPA can provide additional information to assist CMS as it considers this issue.

Respectfully submitted,

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