

September 9, 2023

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Submitted via email to ProposedLCDComments@fcso.com and
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Dear Drs. Schaening-Perez and Stevens,

The American Urological Association (AUA), the Large Urology Group Practice Association (LUGPA), and the American Association of Clinical Urologists (AACU) extend their appreciation for the opportunity to submit joint comments in response to the proposed Local Coverage Determination (“Draft LCD”) DL39365, Genetic Testing for Oncology. The Draft LCD has a high potential to negatively impact patient care and, therefore, we advise that it be modified to provide broad coverage of these indispensable tools for the timely identification and management of bladder cancer.

The AUA, with a membership of over 18,000 medical professionals in the United States including physicians, physician assistants, and advanced practice nurses, holds an esteemed position in the landscape of urologic care in the United States. Through its commitment to education, research, and health policy development, the AUA upholds the highest standards in urologic care, benefiting the urology community and Medicare recipients alike. LUGPA unites over 150 urology group practices, accounting for than 2,100 physicians, who collectively provide approximately 35% of the nation's Medicare urology services and works in tandem with the AUA to achieve the shared vision of improved quality, expanded patient access and reduction in costs. The AACU, established in 1968, is dedicated to addressing socio-economic and political matters within the urology field, bridging the gap between urologists and legislators to ensure optimal legislative outcomes that benefit clinical patient care.

It is our belief that the proposed modifications to coverage criteria are incorrectly applied to urine-based tumor markers, and thus finalizing the draft policy as written will have adverse impacts on the provision of high-quality patient care while ultimately increasing system costs. The guidelines utilized in the Draft LCD do not adequately consider the differences between the urine-based tumor markers and genetic biomarker tests. As discussed in our presentations to Novitas and First Coast, CPT coding recognizes FISH tests as cytopathology (pathology) tests coded as 88120. This is the same coding family as a PAP smear; CPT codes 88141-88175. Genetic testing is found in the 812XX, 813XX and 814XX code families. The AUA, LUGPA and

AACU are anxious to participate in conversations regarding guidelines surrounding these tests in a separate LCD, but they do not belong in the Draft LCD and are not truly genetic tests.

Furthermore, the Draft LCD does not utilize the widely accepted standards for these tests found in guidelines promulgated by the AUA and Society of Urologic Oncology (SUO). AUA guidelines are the specialty of urology's well established and accepted governing resource and should be included when promulgating an LCD of this nature. Considering the panel's failure to incorporate the AUA/SUO guidelines: Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer and their choice to base their recommendations solely on National Comprehensive Cancer Network (NCCN) guidelines that do not address the clinical scenario in which urine-based tumor markers are most commonly deployed, urine-based tumor marker tests should be removed from the Draft LCD entirely.ⁱ

Beyond the patent miscategorization, our organizations have several significant concerns with the Draft LCD rationale.

The Draft LCD introduces a proposal that significantly limits coverage for urine-based tumor markers, citing the following key observations:

1. Insufficient Study in the Medicare Population: Concerns arise due to the markers' limited study within the Medicare population.
2. Low Positive Predictive Value (PPV): The markers exhibit a relatively low PPV, raising concerns about possible false positives.
3. Cost Considerations: The cost associated with these markers is deemed significant.

The argument that the markers' limited study within the Medicare population justifies a lack of coverage raises questions. Notably, the Medicare population largely comprises older adults, a demographic with an elevated susceptibility to bladder cancer. Research involving urine-based tumor markers has extensively included older adults. For example, In the study evaluating CxBladder Monitor, 82% of patients were over the age of 60.ⁱⁱ Furthermore, a study of 15,779 patients evaluated for hematuria found that the mean age was 60.9 (14.6) years.ⁱⁱⁱ

Similarly, the notion that the markers' low PPV should dictate non-coverage warrants further examination. The inherent question is what the purpose is of using the marker in clinical decision making. It is recognized that diagnostic tests are developed with a balance of sensitivity and specificity and that both positive and negative predictive value are driven by the prevalence of disease. In patients with a low likelihood of disease presence, the PPV is going to be low. For many urine markers the current utility is either to exclude the presence of cancer which is driven by a high negative predictive value (NPV) or to adjudicate patients with atypical cytology or equivocal cystoscopy. While these clinical questions are important to clinicians and patients, they are not addressed in many guidelines such as the NCCN. Most urine markers including Cxbladder monitor have a high NPV which helps exclude the presence of cancer in patients undergoing surveillance for bladder cancer. Studies such as Kamat et al. (2012)^{iv}, Mengual et al. (2007)^v, and Whitson et al. (2009)^{vi} provide valuable insights into the utility of

fluorescence in situ hybridization (FISH) for predicting response to Bacillus Calmette-Guerin (BCG) therapy and for surveillance of bladder cancer patients treated with BCG therapy.

For example, the European Urology Journal (2019) highlighted a study showcasing the urine-based tumor marker Cxbladder had an NPV 97% (95% confidence interval [CI] 94-98%) compared with 93% (95% CI 91-94%) for cytology; Cxbladder correctly adjudicated all patients with both atypical cytology and equivocal cystoscopy.^{vii} Additionally, studies like those by Schlomer et al.^{viii} and Lotan et al.^{ix} underscore the challenges of atypical and equivocal cytology readings and the potential of urine markers like ImmunoCyt™ and UroVysion® FISH to aid in reducing unnecessary diagnostic evaluations. In both of these studies, the Urovysion FISH assay had a much higher PPV in the setting of atypical cytology or equivocal cystoscopy which allowed detection of cancer recurrence while avoiding biopsies in all patients with these findings. This selective use of urine markers can reduce cost and morbidity by reducing unnecessary surgery while avoiding delay of diagnosis of recurrence. There are other specialized uses of markers such as predicting response to common treatments such as intravesical BCG.

Most notably, Kaiser Permanente, one of this nation's largest healthcare networks, with 12.7M covered lives, has recently evaluated and published its clinical findings for CxBladder in the hematuria screening, as well as its bladder cancer surveillance population. In Southern California, 2326 Cx Bladder home urinary tests were performed: 1932 CxBladder Triage tests were resulted on patients referred to Urology for hematuria; 394 CxBladder Monitor tests were resulted on patients with a history of bladder cancer. Of the 1932 hematuria patients tested, 1200 resulted with "low probability" and avoided cystoscopy (78%). 358 patients resulted with "high probability" (22%). 280 of the 358 patients underwent cystoscopy and 18 bladder cancers were diagnosed. Cancer detection rate in the CxBladder positive screening cohort who underwent subsequent endoscopic evaluation was 6.4%. Of the 394 bladder cancer follow up patients tested with CxBladder, 284 resulted with "low probability" and avoided cystoscopy (72%). 105 patients resulted with "high probability" and 98 underwent cystoscopy. 16 bladder cancers were detected in this group, with a cancer detection rate of 16.3%. Overall, 77% of patients evaluated with CxBladder tested as low probability and avoided cystoscopy, and of the 378 patients who tested high probability and underwent cystoscopy 34 bladder cancers were identified with an overall detection rate of 9%. Internal regional estimates of cystoscopies performed within the healthcare network number approximately 25,000 annually. The subsequent expenditures and impact to capacity from hematuria and bladder cancer monitoring have broad implications with the use of a novel urinary biomarker that addresses both types of urologic populations.^x

The cost of tumor marker testing is remarkably insignificant when considered in the context of the massive spend associated with the surveillance and treatment of bladder cancer patients. An average FISH test costs less than 1% of the \$55,267 median attributed cost after two years of bladder cancer treatment. A study published in the Journal of the American Medical Association Network (2020) underscored total median costs at 1 year were \$29 459; at 2 years, \$55 267 and at 5 years, \$117 361. Patients with progressive disease had significantly higher

median 5-year costs (\$232 729 vs \$94 879), with outpatient care, pharmacy, and surgery-related costs contributing.^{xi} A FISH test costs approximately \$500.

In conclusion, we firmly believe the implications of the Draft LCD will detrimentally impact access to urine-based tumor markers in the context of bladder cancer, thereby compromising patient care. If urine-based tumor markers are to be included in an LCD, their coverage should be determined through appropriate use criteria widely recognized by the specialty of urology and guided by expert input and stakeholders. We implore you to reconsider the inclusion of these tests in the proposed LCD and stand ready to engage in further discussions about the merits of these tools in patient care.

Thank you for your attention to this matter.

Sincerely,



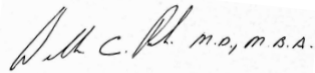
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ⁱⁱⁱ Woldu SL, Ng CK, Loo RK, Slezak JM, Jacobsen SJ, Tan WS, Kelly JD, Lough T, Darling D, van Kessel KEM, de Jong JJ, van Criekinge W, Shariat SF, Hiar A, Brown S, Boorjian SA, Barocas DA, Svatek RS, Lotan Y. Evaluation of the New American Urological Association Guidelines Risk Classification for Hematuria. *J Urol*. 2021 May;205(5):1387-1393. doi: 10.1097/JU.0000000000001550. Epub 2020 Dec 24. PMID: 33356483.

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^v Mengual L, Marin-Aguilera M, Ribal MJ et al: Clinical utility of fluorescent in situ hybridization for the surveillance of bladder cancer patients treated with bacillus Calmette-Guerin therapy. *Eur Urol* 2007; 52: 752.

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