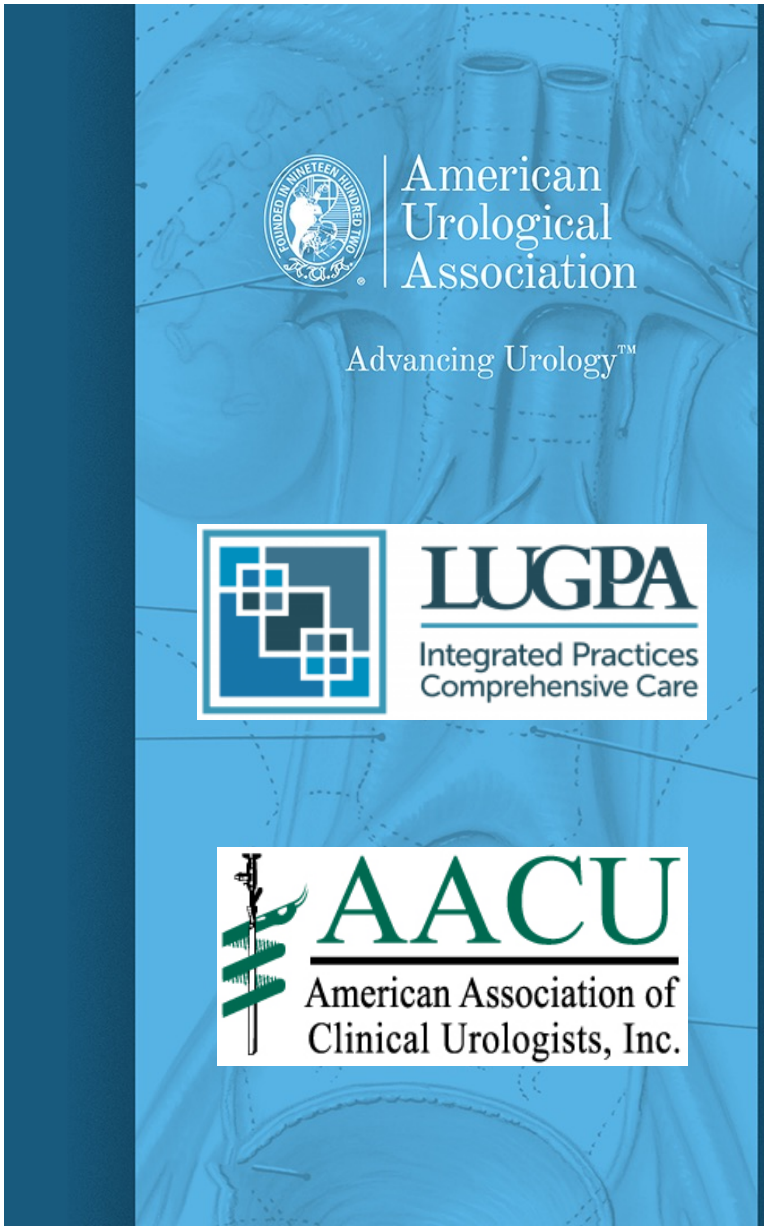

American Urological Association (AUA)
Large Urology Group Practice Association (LUGPA)
American Association of Clinical Urologists (AACU)

Joint Response
to Proposed LCD DL39367
“Genetic Testing for Oncology”

American Urological Association

Who We Are

- AUA's membership includes over 18,000 urologists, urology physician assistants and advanced practice providers in the United States. Its members play a crucial role in providing urologic care to Medicare beneficiaries. Through education, research, and health policy formulation, the AUA ensures the highest standards of urologic care, making it an invaluable support to the urologic community

- LUGPA membership consists of over 150 urology group practices in the United States, representing more than 2,100 physicians. Together, these practices deliver approximately 35% of the nation's Medicare urology services, with a particular focus on GU (genitourinary) care in independent physician office settings.

- The AACU is dedicated to addressing socio-economic and political matters within the field of urology. Their primary objective is to offer insights into issues impacting the urology profession, with a focus on influencing the resolution of these matters.

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BACKGROUND - BLADDER CANCER

- ACS: 82,290 new diagnoses and 16,710 deaths in 2023 in the US
  - 4th most common cancer men
- 70% Non-muscle invasive at initial diagnosis (“NMIBC”)
  - 50-70% recurrence
  - 10-15% progression
- 40-50% 5-year Mortality for Muscle-invasive bladder cancer (MIBC)

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CLINICAL MANAGEMENT OF BLADDER CANCER

- Protracted clinical course requiring ongoing management and (often) frequent intervention

- Surveillance protocols are intensive which includes cystoscopy and urine cytology as frequently as every 3 to 6 months.
  - Challenges:
    - Compliance with rigorous follow up
    - Invasiveness and operator dependency of cystoscopy, difficulty in clearly discriminating between benign and malignant tumors and identifying carcinoma in-situ (“CIS”)
    - Patient access and process for adjudication of suspicious findings

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URINE TUMOR MARKERS

- Currently play a crucial role in diagnosis and management and surveillance of bladder cancer

- Currently incorporated into screening and management paradigms:
  - Enhance detection of CIS and tumors not visible on cystoscopy
  - Identify tumors in the upper urinary tract (ureter, renal pelvis)
  - Predict recurrence
  - Monitor responses to intravesical therapy.

In a comprehensive analysis of 2783 manuscripts, Zhu et. al. concluded that the addition of urine markers to either cystoscopy or cytology provided the optimum sensitivity and specificity to ensure proper diagnosis and evaluation of bladder tumors

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Proposed LCD DL39367

- UroVysion: FDA approved for bladder cancer diagnosis and surveillance.
  - Uses fluorescence in-situ hybridization (“FISH”) to detect aneuploidy of chromosomes 3, 7, or 17 or loss of the 9p21 locus of exfoliated urothelial cells
  - 68 to 87% sensitive, 89 and 96% specific.
  - 83 and 100% sensitive for CIS and high grade tumors.
  - As an adjunct to cytology, FISH maintains specificity while increasing sensitivity (from approximately 45.8% to 72.2%).
- CxBladder Detect and CxBladder Triage: measure the expression of five mRNAs associated with bladder cancer (CDK1, CXCR2, HOXA12, IGFBP5, and MDK) across two distinct assays:
  - CxBladder 82% sensitivity/85% specific for bladder cancer
  - CxBladder Triage incorporates clinical factors: 95% sensitive and has 97% negative prediction value in patients with hematuria.

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Proposed LCD DL39367

- “The scope of this LCD is DNA and RNA genetic testing in the practice of oncology in the Medicare population.”
- Replaces L36975

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Concerns about Proposed LCD DL39367

- Bladder markers are not “genetic tests” so beyond scope of LCD
- These would not be evaluated by the ClinGen or OncoKB registry
- Ignores actual clinical utility of these tests
- Conclusions unsupported by clinical evidence
- May lead to worse patient outcomes and higher costs
- Inhibits innovation
- In conflict AUA Guidelines
- May exacerbate existing disparities in bladder cancer care

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Proposed LCD DL39367

- Reference to the positive predictive value (PPV) of bladder markers
  - Actual clinical practice relies more on negative predictive value (NPV).
- Ignores clinical utilization of these markers
  - Confirm presence/absence of cancer
  - Used judiciously in specific situations to improve patient outcomes and to limit the frequency and intensity of more invasive interventions.

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Markers currently covered

- Novitas (prior LCD L35396):
  - UroVysion™ Bladder Cancer Kit (UroVysion™ Kit) will be considered medically reasonable and necessary only when performed according to the FDA label (https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030052b.pdf) as follows:

    “intended for use, in conjunction with and not in lieu of current standard diagnostic procedures, as an aid for initial diagnosis of bladder carcinoma in patients with hematuria and subsequent monitoring for tumor recurrence in patients previously diagnosed with bladder cancer.”

- Maryland Physicians Care (MP.052.MPC – Bladder Cancer Biomarker Tests) considers Bladder Cancer Biomarker Tests medically necessary for the following indications:
  - UroVysion™ is considered medically necessary when performed in conjunction with current standard diagnostic procedures (i.e. cystoscopy and cytology) for either of the following conditions:
    - a. Diagnosis of person with hematuria suspected of having bladder carcinoma
    - b. Subsequent monitoring for tumor recurrence
  - Limitations
    - 1) UroVysion™ is considered not medically necessary when cystoscopy/cytology results are diagnostic for bladder cancer.
    - 2) Bladder tumor marker testing is considered experimental/investigational for population-based screening of asymptomatic patients for bladder cancer

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Markers are currently included in existing guidelines

1. AUA: Non-Muscle Invasive Guideline for Bladder cancer

   "In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™)"

2. National Comprehensive Cancer Network guidelines: IIB recommendation.

   - NCCN Bladder Cancer Guidelines do not address hematuria evaluation and is a guideline for those patients with an established diagnosis of Bladder Cancer.

   - NCCN does to want to identify the "best" tumor marker nor was the guideline designed to adjudicate for those with atypical cytology, equivocal imaging etc.

Potential to exacerbate disparities in access and outcomes

- 2/3 of counties in the United States do not have a single urologist (Medicare data).
  - Bladder cancer survival dependent on timely diagnosis and follow-up
  - Access to cystoscopy not uniform and impacted by gender, race and socio-economic factors
  - Ability to use non-invasive means to diagnosis and monitor bladder cancer is crucial.
  - Need for testing that obviated the need for patient travel shown during COVID-19 pandemic
- Disparities further exacerbated as significantly lower disease-specific survival seen in African-American, lower socio-economic status
- Bladder markers may allow patients with less access or comorbidities/surgical risks to be monitored more effectively.
- These disparities would be exacerbated under Novitas jurisdictions as these coverage restrictions are not at present at other MACs.

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Potential to Increase Costs & Liability Exposure

- Urinary markers may reduce morbidity and potentially reduce expenditures
  - Adjudicate specific situations, avoid more expensive and invasive testing (imaging, bladder biopsy, ureteroscopy, etc.)
    - 30% patients can avoid further testing with tumor markers[1]
    - Save $1740 for avoiding unnecessary biopsies[2]
- Within urology practice, the largest liability awards result from the delay in diagnosis of cancer, particularly bladder cancer
  - Removing markers may lead to greater defensive practices and more invasive procedures performed

[1]*Konety B, Shore N, Kader AK, et al. Evaluation of Cxbladder and Adjudication of Atypical Cytology and Equivocal Cystoscopy. Eur Urol. Aug 2019;76(2):238-243. doi:10.1016/j.eururo.2019.04.035*

[2]*Gomella LG, Mann MJ, Cleary RC, et al. Fluorescence in situ hybridization (FISH) in the diagnosis of bladder and upper tract urothelial carcinoma: The largest single-institution experience to date. Can J Urol. 2017;24(1):8620-8626*

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Conclusion

- Urinary markers play a crucial role in bladder cancer diagnosis and management
- Scope of LCD DL 39367 should not include these markers
  - Not a “genetic test”
  - Sources (NCCN/ClinGen/ OncoKB) do not address the proper usage of these tumor markers
  - AUA/SUO Guidelines support the use of tumor markers in the proper clinical scenarios
- Novitas would be unique in non-coverage, potentially leading to increased costs, invasive testing and health disparities

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Conclusion

- Novitas should continue to cover these tumor marker that enable proper resource utilization in a challenging patient population and care environment

- If bladder tumor markers are to included in an LCD, should be covered with appropriate use criteria
  - Stakeholder/expert input
  - Prior LCD as guidance