August 8, 2016

Noridian Healthcare Solutions, LLC
JE Part B Contractor Medical Director(s)
Attention: Draft LCD Comments
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Re: Draft Local Coverage Determination Bladder Tumor Markers (DL36680)

Dear Dr. Lurvey:

Thank you for the opportunity to comment on this draft local coverage determination on Bladder Tumor Markers (DL36678). The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

The College of American Pathologists (CAP) is a national medical specialty society representing more than 18,000 physicians who practice anatomic and/or clinical pathology. College members practice their specialty in clinical laboratories, academic medical centers, research laboratories, community hospitals and federal and state health facilities.

Members of both AMP and CAP are experts in molecular pathology and the implementation of this coverage policy will directly impact their practices. We are submitting joint comments because at this time both of our organizations share the same concerns regarding this draft LCD.

Background: Bladder Tumor Diagnosis
National Comprehensive Cancer Network (NCCN) guidelines are updated on an annual basis and encompass the most current medical evidence for practice guidelines in bladder oncology (NCCN 2016). The NCCN 2016 guidelines have addressed the use of ancillary laboratory testing to aid in the diagnosis and monitoring of bladder cancer. The American Urological Association (AUA) has released updated guidelines in 2012 and 2016 for the diagnosis and monitoring of bladder cancer in patients with Asymptomatic Microhematuria (AMH) (Davis et al) and non-muscle invasive bladder cancer (AUA 2016).

For the diagnosis of bladder cancer, the AUA guidelines state that "The most common presenting symptom in patients with bladder cancer is microscopic or gross hematuria..." and "according to the AUA Guideline on the diagnosis, evaluation, and follow-up of patients with asymptomatic microhematuria (AMH), the rate of urinary tract malignancy in AMH is approximately 2.6%. " (Davis et al) NCCN guidelines state "patients presenting with these symptoms should be evaluated with office cystoscopy to determine if a lesion is present" and "urine cytology may also be obtained around the time of cystoscopy." NCCN guidelines acknowledge that traditional white-light cystoscopy (WLC) used by Urologists often miss flat high-grade lesions (carcinoma in situ, CIS) representing 5%-10% of bladder cancer. (NCCN 2016)

The AUA recommends that urine cytology and bladder tumor marker tests be reserved for patients with persistent microhematuria whose initial work-up was negative of those who are at increased risk for Urinary Cancer (David et al). "Although not indicated for routine screening and evaluation of AMH," AUA guidelines point out, "urinary cytology (voided or barbotage) may be used in the surveillance of bladder cancer for certain patients as it possesses a high sensitivity and positive predictive value for high-grade tumors and CIS." (Dimashkieh H et al) (Schroeder GL et al) AUA guidelines also note, "equivocal urine cytology can occur in as high as 21% of patients being evaluated for hematuria". (Mokhtar GA et al) "Even in patients with high-grade cancers, cytology may be read as suspicious or atypical". (Nabi, et al; Raitenan, et al) "Thus, utilization of another test to arbitrate an atypical or equivocal cytology reading may be helpful in reducing the need for unnecessary diagnostic evaluations in intermediate- and high-risk bladder cancer patients. Several studies have used ImmunoCyt™ (Odisho AY et al) and UroVysion® FISH (Lotan Y et al) (Skacel M et al) (Zhou et al) in this context." Both of these urine molecular pathology evaluations have been found to assist in the identification of patients with malignancy and require a pathologist's professional interpretation. One study showed that 91% of patients with positive FISH and equivocal cytology were found to have bladder cancer on subsequent biopsy (Kipp BR et al). **Further, this strategy has also been shown to be cost effective.** (Gayed BA et al)

Recommendations for Bladder Cancer Diagnosis

We agree with Noridian that the routine use of urinary markers for bladder cancer screening in place of cystoscopic evaluation is not recommended. For a patient's first visit to the urologist for bladder cancer evaluation, we agree testing for bladder cancer tumor markers should be done only in conjunction with cystoscopy.

The capacity of cystoscopy to detect bladder cancer is dependent on the anatomic site and the tumor morphology. In some situations cystoscopy will fail to detect bladder cancer on the first visit, yet the patient's symptoms persist (eg hematuria). The patient may have additional risk factors (eg >65 years of age, lifetime smoker). In subsequent visits, we recommend that the use of bladder tumor markers should be at the discretion of the urologist without the requirement for cystoscopy and cytology. For example, a flat high-grade lesion (CIS) is often missed by cystoscopy so additional cystoscopy may have little clinical utility for the diagnosis of bladder cancer. Cystoscopy cannot detect upper tract bladder cancer in the kidney or pelvis. In these situations bringing a patient back for a second cystoscopy in order to collect urine for bladder tumor marker testing adds an additional invasive procedure as well as unnecessary expense to patient care. **Consequently, we request that the limitation that bladder cancer tumor markers must be performed in conjunction with cystoscopy be removed from this LCD - after an initial urological evaluation and a prior atypical urine cytology result.**

Also, we are requesting clarification regarding UroVysion. UroVysion is molecular assay and not an immunoassay. Please confirm as to whether or not UroVysion is covered by the following statement: *Bladder cancer tumor markers performed by immunoassay are ONLY considered medically necessary as an adjunct in the diagnosis and monitoring of bladder cancer in conjunction with cystoscopy*?

Background: Bladder Cancer Monitoring

When a patient has been diagnosed with bladder cancer, NCCN guidelines state the following: "additional workup for all patients should include urine cytology if not already tested and evaluation of the upper tracts," with imaging technologies. NCCN guidelines state, "management of bladder cancer is based on the pathologic findings of the biopsy specimen, with attention to histology, grade, and depth of invasion. These factors are used to estimate the probability of recurrence and progression to a more advanced stage," placing the bladder cancer into low and high risk categories. "Consideration may be given to FDA-approved urinary biomarker testing by fluorescence in situ hybridization or nuclear matrix protein 22 in monitoring for recurrence." (Kamat AM et al) (Grossman HB et al)

The AUA guidelines indicate "a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™)" (2016). "The presence of significant inflammation immediately post BCG instillation can affect the accuracy of urine cytology." In contrast, the accuracy of UroVysion FISH is not affected by hematuria or other inflammatory processes, such as urinary tract infection and BCG treatment (Halling KC et al). "A persistently positive UroVysion® FISH following completion of induction BCG predicts a poor response to BCG therapy with a higher likelihood of recurrence and progression" (Kamat AM et al) (Mengual L et el) (Whitson J et al) (Kipp BR et al) (Savic S). Based on these data, AUA guidelines indicate "clinicians can use UroVysion® FISH as an early guide to predict response to intravesical BCG therapy." (2016)

Some patients may present with a positive urinary marker while the bladder appears cystoscopically tumor-free. (AUA 2016) This is sometimes known as an "anticipatory positive" finding. UroVysion® FISH has been found to yield an "anticipatory positive" test in approximately 30-40% of patients. (Sarosdy MF et al) (Yoder BJ et al) In a surveillance study of urinary cancer patients, 65% of patients who had a positive FISH but negative cytology and biopsy developed recurrent disease within 29 months (Yoder BJ et al). A 2015 study also suggests that "patients with atypical cytology and positive UroVysion® FISH may develop recurrent identifiable tumors earlier than a patient with a negative UroVysion® FISH". (Seideman C et al)

Recommendations for Bladder Cancer Monitoring

We assert that the approach used to monitor bladder cancer progression should be left to the discretion of the urologist. The diagnostic work up used to detect the bladder cancer will demonstrate if cystoscopy, cytology and/or a urinary biomarker is best suited to monitor residual disease. Following a diagnosis of bladder cancer, we agree cystoscopy and cytology may be desirable. However, these methods may produce false negative results. For example, cystoscopy may miss flat high-grade lesions (CIS) and cytology may produce equivocal results. In those instances, a cell based urinary biomarker such as UroVysion FISH or Immunocyt may be the most appropriate methodology for monitoring residual disease. If cytology produces an equivocal result, then bringing a patient back for a second cystoscopy in order to collect urine for bladder tumor marker testing (UroVysion FISH, Immuncyt) adds unnecessary expense to patient care. The unintended consequence may be to encourage overuse of cystoscopy. **Consequently, we request that the limitation that bladder cancer tumor markers must be performed in conjunction with cystoscopy be removed for patients with a history of bladder cancer.**

Recommendations: Utilization Guidelines

In rare instances, more than one bladder cancer test per date of service (eg cytology with reflex FISH) is reasonable and necessary. For example, a patient with negative cystoscopy, equivocal cytology and positive UroVysion FISH may have upper tract bladder cancer (eg renal kidney pelvis is suspected). In these instances, left and right renal/ureter washes may be collected from left and right kidneys. Cytology is performed and when equivocal can be reflexed to urinary biomarkers tests (UroVysion FISH, Immuncyt) to determine which kidney is affected. This testing is critical to therapeutic decision making since surgical removal of the affected tumor will be considered for patient management. The goal is to limit nephrectomy to a single kidney while leaving the unaffected kidney intact.

ICD-10 Coding

The proposed policy states that the ICD-10 codes, R31.2, Z78.9, Z85.51, should be used only when repeat testing is believed to be medically reasonable and necessary, and must be listed as secondary with the primary neoplastic diagnosis. We contend that the ICD-10 codes Z85.51 (Personal history of malignant neoplasm of bladder) should be sufficient without a primary neoplastic diagnosis for bladder cancer monitoring in patients with a history of bladder cancer. In this instance, the Z85.51 codes specifies the medical necessity of testing for therapeutic decision making and the absence of the primary ICD-10 code should not be reason to disallow testing.

General Comments
The references noted in the body of the draft LCD text do not match up with the reference list. For example, the LCD refers to reference 6, but no reference 6 is listed. We are requesting clarification of the appropriate references.

We respectfully ask that you consider these comments which were prepared by members of AMP and CAP who provide services to Medicare beneficiaries covered by Noridian. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever is needed to assist you with this draft LCD. Please direct your correspondence to Tara Burke, AMP Senior Policy Analyst, at tburke@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

Association for Molecular Pathology
College of American Pathologists

References:
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