April 25th, 2025

Office of the Contractor Medical Director
Novitas Solutions
Medical Affairs Department
2020 Technology Parkway, Suite 100
Mechanicsburg, PA 17050

RE: LCD Reconsideration Request – Local Coverage Determination, Genetic Testing In Oncology: Specific Tests (L39365). Removal of existing non-coverage language of Cxbladder Triage (0363U) and determination of positive coverage language for Cxbladder Triage based on the evidence provided.

On behalf of Pacific Edge Diagnostics USA LTD we formally request the removal of the non-coverage language for Cxbladder Triage through a reconsideration of Local Coverage Determination, Genetic Testing in Oncology: Specific Tests (L39365). Cxbladder Triage is a molecular diagnostic test used to assist in the risk stratification of patients presenting with microhematuria that are being evaluated for suspected bladder cancer. Cxbladder Triage is recommended by the American Urological Association (AUA) for use in patients presenting with microhematuria considered to be at intermediate risk of developing bladder cancer[1], which is new information for the contractor to consider.

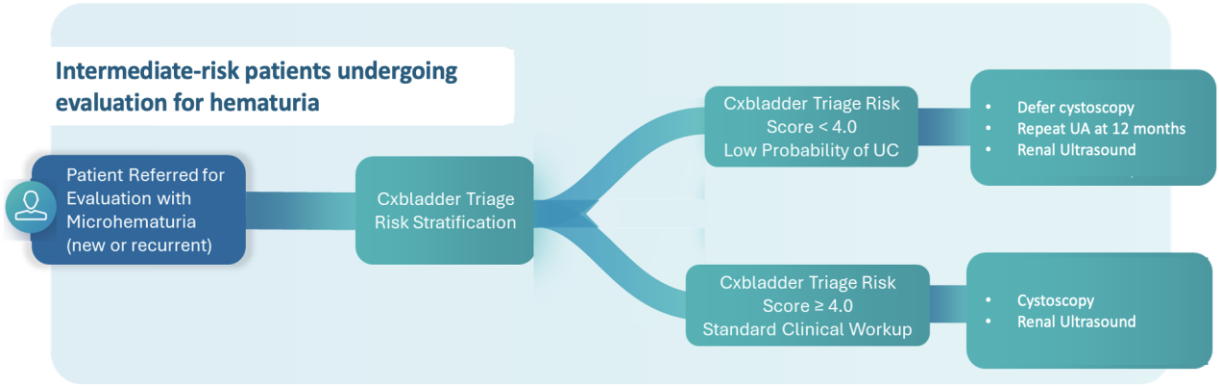
Cxbladder Triage can assist clinicians in risk-stratifying microhematuria patients who need a complete clinical workup versus those patients that can avoid unnecessary procedures. Pacific Edge has demonstrated through published analytical validity, clinical validity, and clinical utility data that Cxbladder Triage results can be used to reduce the burden of unnecessary cystoscopy and imaging procedures without missing tumors for Medicare beneficiaries.

This is a formal LCD reconsideration request that meets the requirements set forth in chapter 13, section 13.3.2 of the Medicare Program Integrity Manual and the instructions set forth on the Novitas "The local coverage determination (LCD) reconsideration process" website (www.novitas-solutions.com/webcenter/portal/MedicareJH/pagebyid?contentId=00007706).

First, the request is submitted by a health care professional doing business in Novitas Solutions' jurisdiction (Pacific Edge). Second, the request is submitted in writing and is being sent to Novitas/FCSO by email. and identifies the language Pacific Edge wants added to or deleted from the LCD (see section VIII of this letter). Fourth, there is an extensive body of peer-reviewed evidence in support the proposed change along with guideline inclusion from the American Urological Association; many of these documents have been published in the last 1.5 years and were not considered when Novitas drafted its current review of the evidence for Cxbladder Triage in L39365. We have provided copies of these articles/guidelines for your consideration. Fifth, the letter demonstrates the impact on patient management for clinicians using molecular diagnostic testing. In addition, we have included language that the requestor wants added to or deleted from an LCD along with a justification for the proposed language supported by the new

evidence. This request contains all the same evidence submitted on March 21, 2025 under L35396 'Biomarkers for Oncology' and deemed valid on March 26, 2025, and is submitted on L35396 to specifically request removal of non-coverage language and/or positive coverage language on this LCD as deemed appropriate by the Contractor.

Under section 1862(a)(l)(A) of the Social Security Act, an item or service may be covered by Medicare if it is "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Pursuant to chapter 13, section 13.5.4 of the Medicare Program Integrity Manual, "reasonable and necessary" is defined to mean the item or service is (i) safe and effective, (ii) not experimental or investigational, and (iii) appropriate, including the duration and frequency that is considered appropriate for the item or service. With respect to the third requirement in section 13.5.4, appropriateness is based on whether the item or service is (i) furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member, (ii) furnished in a setting appropriate to the patient's medical needs and condition; (iii) ordered and furnished by qualified personnel, (iv) one that meets, but does not exceed, the patient's medical need, and (v) at least as beneficial as an existing and available medically appropriate alternative. Evidence of analytical validity, clinical validity, and clinical utility is used to demonstrate that a test is reasonable and necessary. Clinical utility studies with leading academic health systems demonstrate that using Cxbladder Triage modifies physician management of patients based on the risk stratification information provided as highlighted in the clinical pathway figure below.



I. Justification for this LCD reconsideration

Microscopic hematuria (MH) is an early indicator of urothelial carcinoma (UC). However, in addition to urothelial carcinoma (bladder and upper tract, i.e. ureters and renal pelvis), there are also various benign causes of hematuria (e.g. idiopathic, infection, calculi, renal disease, trauma, or recent urological procedure),[2] 95–98% of those with microhematuria, do not have bladder cancer.[3]

Previously, the main laboratory support to physicians who are evaluating patients for bladder cancer (hematuria) has been cytology and fluorescence *in situ* hybridization (FISH), both of which have significant performance limitations, particularly poor sensitivity. For example, cytology has sensitivity ranging from 11% for low-grade tumors to 54% for high-grade tumors.[4] This technique relies on intact cells being sloughed from the bladder and preserved in the urine, as well as microscopic evaluation by a board-certified cytopathologist. Cytology results are subject to very high institutional variability regarding the quality of pathology, with poor inter-pathologist concordance that leads to high rates of atypical and suspicious findings.[5] The main strength of cytology is its use as an adjunct to identify some high-grade tumors. FISH on the other hand is usually used as a reflex test when cytology is inconclusive, but it also has poor sensitivity with high variability.[6] Due to high false-negative rates, neither test can be used to rule out disease safely.

Diagnostic Cystoscopy (examination of the urinary tract by insertion of a camera into the urethra to inspect the health of the bladder) is considered the standard of care recommended by AUA guidelines for evaluation of microhematuria. It may produce both false-negative and false-positive results and has high operator-dependent variability in its performance and accuracy. A systematic review in 2010 highlighted a number of these issues and found that white-light cystoscopy had sensitivity of 33–88% and specificity of 43–100% across five studies.[7] While blue-light cystoscopy enhances the sensitivity for sessile lesions, the high false-positive rate means that the patient may require an additional and unnecessary biopsy. Urine cytology has high specificity and can be used to provide clinical resolution for samples with equivocal or false-negative cystoscopy findings; however, as cytology has low sensitivity,[8] some high-grade or muscle-invasive tumors may be missed. Therefore, there is an unmet need for non-invasive tests with high sensitivity and specificity to help rule out bladder cancer in patients presenting with microhematuria where no benign causes of the condition have been identified.

II. New Evidence Summary

Pacific Edge has developed AV, CV and CU evidence for Cxbladder Triage in microhematuria populations and AV and CV evidence in gross hematuria populations. The evidence Table is organized by evidence type from top to bottom CU, then CV, then AV. Within each evidence type, it is organized by date of publication. New evidence not previously reviewed by the contractor has been highlighted in bold.

Study	Evidence type	Population types	Performance characteristics (%)			Comments
			Sn	NPV	Sp	
Lotan et al., 2024[9]	CU–RCT	135 LR MH 255 NLR (MH or GH)	90	99	56	CU evidence from a prospectively enrolled, randomized controlled trial for Triage. When compared to SOC, the test arm showed a statistically significant relative reduction in cystoscopies of 59% (27% vs 67%).

						No tumors were found in patients with a negative result after 12 months of follow up. Study also confirmed prior CV for MH and GH as statistically similar. **This information has not been previously reviewed by the contractor**
Davidson et al., 2020[10]	CU-RWE	MH or GH (N = 884)	89.4[e]	98.9	59	CU-RWE from MH and GH patients for Triage combined with imaging. Sn of 98.1%, NPV of 99.9%, and Sp of 98.4%; test-negative rate was 53%. Not sponsored by Pacific Edge. Note that imaging is used to detect upper tract disease.
Lough et al., 2018[11]	CU-Case Study	MH (n=33 reviewed by 12 clinicians = 396 clinician decisions)	N/A	N/A	N/A	CU evidence based on 396 clinical decisions in a retrospective case study. 55.0% reduction in invasive procedures from baseline for patients with a Triage result, 40.4% reduction in flexible cystoscopies and 46.5% reduction in contrast CT scans
Lotan et al., 2023[12]	CV	MH or GH (N = 804)	89	99	63	CV evidence on an independent cohort in MH and GH patients from US and Singapore cohorts; CV is statistically similar to prior CV, while also compared to other Cxbladder tests, including enhanced versions.
Davidson et al., 2019[13]	CV - RWE	MH or GH (N = 551)	95.5	98.6	34.3	CV evidence on independent cohort of MH and GH patients. When combined with imaging, the pathway including Cxbladder Triage had a Sn of 97.7% and NPV of 99.8%. An independent real world clinical validation not sponsored by Pacific Edge. Note that imaging is used to detect upper tract disease.
		GH (N = 366) [b]	95.1	98	32.8	
		MH (N = 185) [c]	100	100	42.6	
Raman et al., 2021[14]	CV	MH or GH (N = 548)	92.6	99.6	–	CV evidence on independent cohort of MH and GH patients. Test-negative rate was 52% in patients from Southern California Permanente Medical Group.
Harvey et al., 2024[15]	AV	Manufactured analytes in urine samples	N/A	N/A	N/A	AV evidence for Cxbladder Triage (and other Cxbladder products), including analytical sensitivity, analytical specificity, limit of detection, linearity, analytical precision, stability and assay thresholds**. This information has not been previously reviewed by the contractor.**
Kavalieris et al., 2015[16]	AV	MH or GH (N = 587)	95	98	45	AV evidence for Cxbladder Triage in MH and GH populations. Combined AV with bootstrapped CV.

[a]Referred patients.
[b]Tumor confirmed (N = 41).
[c]Tumor confirmed (N = 3).
[d]Included CxbT and CxbM.
[e]Sn was 92% (N = 23/25) for HG tumors and 86% (N = 18/21) for LG tumors.

AV = analytical validity; CU = clinical utility; CV = clinical validity; CxbM = Cxbladder Monitor; CxbT = Cxbladder Triage; GH = gross hematuria; HG = high-grade; LG = low-grade; MH = microhematuria; NPV = negative predictive

value; PPV = positive predictive value; Sn = sensitivity; Sp = specificity; UC = urothelial carcinoma; US = United States; RWE = Real World Evidence; LR = Low Risk; NLR = Not Low Risk.

III. American Urological Associations Guideline Recommendations

In 2024 the AUA initiated a review of the published evidence for urine-based biomarkers for use in hematuria patients. Having reviewed the evidence, including key publications from Pacific Edge regarding Cxbladder products, the AUA Microhematuria Guidelines were updated in Feb 2025 with the following language:

- "In appropriately counselled intermediate-risk patients who want to avoid cystoscopy and accept the risk of forgoing direct visual inspection of the bladder urothelium, clinicians may offer urine cytology or validated urine-based tumor markers[1]. This recommendation is included in the patient flow chart below in the box titled "Cystoscopy and Ultrasound" with the reference to Urine Based Tumor Markers (UBTM)
- Cxbladder Triage was the only validated urine-based tumor marker to receive an "AUA Strength of Evidence - **A**" (See Table 5 below) for microhematuria evaluation, based on STRATA – the only identified randomized clinical trial to evaluate the use of a urine-based biomarker to guide patient evaluation, with an observed negative predictive value (NPV) of 99%[1].

Figure 1: AUA Microhematuria Guidelines 2025. Cxbladder Triage is appropriate for use in Intermediate-Risk patients as a the only "validated UBTM" with Grade A Evidence[1]

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AUA/SUFU Microhematuria Diagnostic Algorithm

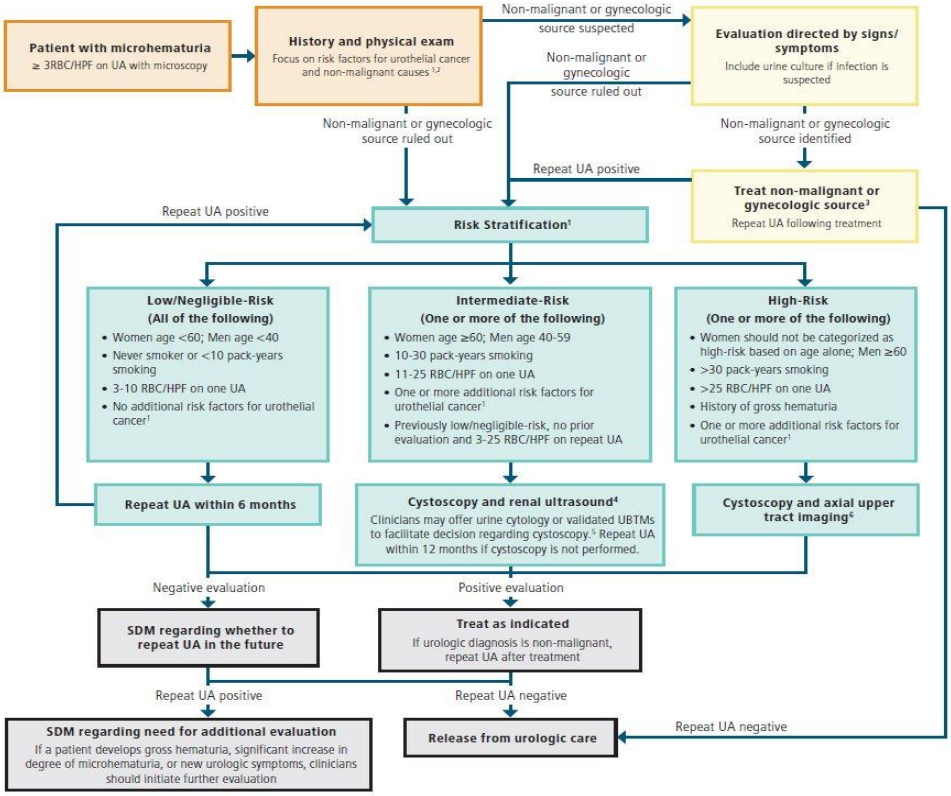

Table 5: Reported Negative Predictive Values for the Detection of Bladder Cancer Using the Available Cytology and Urine-Based Biomarkers

Assay[A]	Hematuria Population	Total Patients (n)	Reported Negative Predictive Value	AUA Strength of Evidence[B]
CxBladder Resolve	MH and GH	Total n=548; MH n=289	99.8%[98]	B
CxBladder Triage	MH[C]	n=390	99%;[97] 95%CI: 95 to 100%[D]	A
	MH and GH	Total n=571; MH n=185	100%;[99] 95%CI: 94 to 100%[E]	C
NMP22 BladderChek (qualitative)	MH	n=876	95% - 100%[100-102]	C
Urine cytology	MH	n=513	95.0% - 98.7%[100, 103, 104]	C
	MH and GH	Total n=4,497; MH n=1,743	89.5%[F] - 96.0%[77, 105-107]	C
UroVysion	MH and GH	Total n=828; MH n=384	97%[105]	C
Xpert	MH and GH	Total n=1,152; MH n=597	98.0% - 99.6%[105, 106]	C

A. To be included in the table, NPV for the assay was reported in a purely MH population or MH patients comprised ≥25% of total hematuria population. All studies included ≥100 microhematuria patients.
B. Strength of evidence in relation to reported NPV. Refer to Table 1 for strength of evidence definition and methodology.
C. The RCT[97] is the only identified study designed to evaluate use of a urine-based biomarker to guide evaluation.
D. NPV for detection of high-grade disease[97], 100%; 95%CI: 97 to 100%. NPV for lower risk patients, 100%; 95%CI: 94 to 100%.
E. NPV reported for MH subgroup.[99]
F. NPV of 89.5%[107] reported for detection of bladder cancer and UTUC.

IV. Clinical Utility of Cxbladder Triage in Microhematuria

The clinical utility of a test refers to its ability to impact decisions in disease management and improve patient outcomes.[17] Evidence consistently demonstrates the ability of Cxbladder Triage to aid clinicians in treatment decision-making, reducing the need for unnecessary invasive testing and improving outcomes among patients with hematuria.

In a newly published randomized trial using the Cxbladder Triage test (STRATA), 390 eligible patients were enrolled into the study. Of those, 135 were stratified as lower-risk (LR) microhematuria (MH) patients and were randomized into a test arm and a control arm (81 and 54 patients respectively). The other 255 patients were stratified as not lower risk (NLR) and were included to determine the performance of the assay. The study's primary objective was to assess the reduction in cystoscopic procedures using a Cxbladder Triage-based approach compared to the SOC (standard of care). In the study, patients randomized into the Cxbladder Triage arm received a lower number of cystoscopic procedures compared to the SOC group (27% and 67%

respectively) with relative reduction of 59%. Per study protocols, clinicians in both arms were given the choice to order cystoscopy if warranted. Cxbladder was also demonstrated to be safe, because no tumors were found in patients with a negative result within the 12-month follow up of the protocol. All patients were included in the performance of the assay and showed a sensitivity of 90%, NPV of 99%, Specificity of 56% and a PPV of 15% across all hematuria patients (MH and GH). High NPV allows physicians to confidently manage patients with a negative test result as low risk. Low PPV is not used in clinical decision making for these patients, and patients with a positive result continue to be managed by standard of care with a full examination. The performance characteristics of the assay are statistically similar to previously published studies confirming the reproducibility of the assay performance across multiple patient populations[9].

One real world study evaluated the clinical utility of Cxbladder Triage in 884 hematuria patients in New Zealand. The demographics of this study population are similar to the Medicare population with a median age of 65 years, with 66% male (bladder cancer is more prevalent in males than females) and with 81% identifying as of European descent. Given the similarities of these hematuria populations and similarities in the clinical pathways for managing those patients, the findings from this New Zealand-based study are applicable to US clinical practice. Of fifty-one cases of bladder cancer, Cxbladder Triage gave five false-negative results (two high-grade and three low-grade tumors). Cxbladder Triage had a sensitivity of 98.1% (95% CI: 89.6–99.9), an NPV of 99.9% (95% CI: 99.2–99.9), and a specificity of 98.4% (95% CI: 97.3–99.2).[10] These findings indicate that Cxbladder Triage can reliably identify patients with hematuria who can be safely managed without the need for cystoscopy.

A retrospective case-based study (Lough et al 2018)[11] was conducted in the United States, evaluating thirty-three patients who presented with asymptomatic microscopic hematuria (AMH). A total of 396 physician–patient decision assessments were generated from twelve participating physicians by reviewing real-world case notes from these AMH patients. The study demonstrated significant changes in physicians' behavior after incorporating Cxbladder Triage results. For patients identified as having a low probability of urothelial carcinoma (UC), there was a reduction in the number of cystoscopy procedures performed. Conversely, for patients classified as not being low risk of UC by Cxbladder Triage, physicians intensified their diagnostic approach by increasing the number of procedures, including cystoscopy.

Notably, among Cxbladder Triage-negative patients, fewer diagnostic procedures were performed in 79 (43.4%) of 182 clinical decisions compared to baseline. Additionally, physicians reduced the use of invasive procedures in 93 (55.0%) of 169 clinical decisions. This included the cancellation of 67 (40.4%) of 166 scheduled flexible cystoscopies and 40 (46.5%) of eighty-six contrast-enhanced CT scans.

These findings highlight the clinical utility in a decision-impact study of Cxbladder Triage in optimizing patient management by reducing unnecessary and invasive procedures for Cxbladder Triage defined low risk patients while ensuring appropriate diagnostic escalation for high-risk cases.

V. Clinical validation of Cxbladder Triage

Four studies have evaluated the clinical validity of Cxbladder Triage in patients with hematuria. In these studies, Cxbladder Triage had a sensitivity of 89–96% and an NPV of 98.0–99.6% with over one thousand samples from patients presenting with hematuria being evaluated. When reviewing the individual studies, the 2019 study by Davidson et al.[13], should stand out, as this was an independently performed validation study of 571 hematuria patients from Canterbury, New Zealand in a population similar to the Medicare population with a median age for referred patients of 66 that is 69% male and while the publication does not state ethnicity, in the 2018 NZ census, Caucasians made up ~70% of the NZ population. The study showed an overall sensitivity of Cxbladder Triage that was higher than that of urine cytology (96% vs 50%), with 42 of 44 UC cases being detected [13]. The test sensitivity was 100% (95% CI: 29.2–100) in MH patients and 95.1% (95% CI: 83.5–99.4) in GH patients (the false negatives were both TaLG). Davidson et al. determined a clear utility for the test in their hospital and the entire New Zealand healthcare system that when clinicians are provided with Cxbladder Triage results in combination with imaging they can reliably identify patients in whom cystoscopy can be avoided with negligible risk.

A 2021 study that included 548 patients with MH or GH from the US, Australia, and New Zealand that showed Cxbladder Triage had a sensitivity of 92.6% and an NPV of 99.6%, with one false-negative result (low-grade tumor)[14]. More recently, a study of 804 patients with hematuria from the US (100% GH) and Singapore (70% MH, 30% GH) by Lotan et al[12] , found that Cxbladder Triage had a sensitivity of 89%, an NPV of 99%, and a specificity of 63%, with three false-negative results (two low-grade Ta tumors and one PUNLMP). And finally, a 2024 study[9] was an RCT study that established clinical utility of the test; however, the performance of Cxbladder Triage was also calculated in all patients included (390). The study showed a sensitivity of 90% with a NPV of 99% and a specificity of 56% with only one missed low-grade tumor. All positive Triage results would progress through standard of care hematuria work up for cystoscopy, while Triage negative results could be evaluated by non-invasive methods with minimal risk with the false negatives being defined as low grade disease. It is worth mentioning here that these studies include a large patient population from different ethnicities and origins though most are US Caucasian.

VI. Analytical Validity of Cxbladder Triage

The original Cxbladder Triage publication by Kavalieris et al., 2015[16] described the development of Cxbladder Triage using urine from those presenting with blood in their urine, with a focus on safely ruling out those that are at low risk of having UC with a high sensitivity and negative predictive value. In response to comments from Novitas' prior evidentiary review, Harvey et al (2024)[15] published an updated analytical validation of Cxbladder Detect, Triage and Monitor products that included a full analytical validation of Cxbladder Triage. This data showed the level of reproducibility the assay has at the analyte level, and its performance against potential interfering substances that might be found in the process or in patients' samples. The AV publication describes the Cxbladder Triage assay and associated analytical performance according to accepted validation criteria and showed that the assay was accurate and reproducible and was able to tolerate clinically meaningful levels of contaminants from patients' urine sample without affecting the performance of the assay, and where the contaminants did start to affect the assay, there were controls to identify the effect.

VII. Other Considerations

By definition, a screening test is used to find disease in patients who do not have symptoms. Microscopic hematuria (MH) is a symptom of urothelial carcinoma (UC) with incidence of UC ranging from 3-5%.[3] Cxbladder Triage is indicated for patients presenting with microhematuria and used as part of the differential diagnosis to help identify and rule out bladder cancer. For this reason, Cxbladder Triage should not be considered a screening test. The clinical utility of Cxbladder Triage is to identify the patients that present with a risk factor, microhematuria, that have significantly lower risk of currently having UC so that they can be managed according to the low risk AUA guidelines recommendation rather than given a full workup that is unnecessary for those patients. The value to the Medicare population of adopting Cxbladder Triage prior to cystoscopy is reduction of unnecessary cystoscopy and imaging procedures for patients at intermediate risk, while simultaneously improving the yield of cancer diagnoses within the patients that do receive the full workup. This indication was reinforced in the 2025 update to the AUA guideline for microhematuria.

VIII. Coverage Medical Necessity Indications, and/or Limitations of Coverage

By integrating Cxbladder Triage into the patient management pathway, clinicians can make more informed decisions and potentially reduce the burden of unnecessary invasive procedures. This approach aligns with the goals of personalized medicine, ensuring that each patient receives the most appropriate care based on their specific risk profile and clinical presentation. Moreover,

utilizing tests with high negative predictive value helps to streamline the diagnostic process, minimizing patient anxiety and healthcare costs associated with unnecessary procedures. As healthcare continues to evolve, the integration of advanced diagnostics like Cxbladder Triage in clinical practice not only demonstrates adherence to high standards of medical care but also highlights the commitment to improving patient outcomes through innovative and evidence-based strategies.

We request that Novitas remove the language from L39365 that identifies Cxbladder Triage as a non-covered service and provide coverage via reconsideration of L35396 Biomarkers for Oncology (**JL LCDR 2025-0321-100).**

Thank you for your consideration in this matter.

Respectfully submitted.

David Levison

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