PacificEdge
CANCER DIAGNOSTICS

‘Genetic Testing In Oncology: Specific Tests’
Our Response

The Local Coverage Determination ‘Genetic Testing in Oncology: Specific Tests’ (L39365)[1] released on 9 January 2025, if unchallenged, is expected to end Medicare coverage of Cxbladder by 24 April 2025.

Novitas, the Medicare Administrative Contractor with jurisdiction for Pacific Edge’s Laboratory Operations in Hershey, PA, has finalized L39365 with a non-coverage determination for Cxbladder products.

While Novitas may have violated procedure and withdrawn their assurances to review all Pacific Edge’s evidence, this document will focus on the scientific and medical issues in the evidentiary review associated with the LCD.

The evidentiary review is particularly disappointing because it questions Pacific Edge’s steadfast commitment to generating the compelling clinical evidence required to drive behavior change in physicians. Specifically, we seek to produce evidence that is founded on the frameworks of Analytical Validity (AV), Clinical Validity (CV), and Clinical Utility (CU)[2], with the endpoints and sample sizes required for coverage decisions and guideline inclusion.

“We are determined that the view put forward in the LCD does not go publicly unchallenged.”

We are determined that the view put forward in the LCD does not go publicly unchallenged.

We have therefore produced this point-by-point rebuttal of the LCD’s evidentiary review. Our goal is to ensure all our stakeholders – patients, clinicians, medical policy makers, healthcare payers, and our investors and our own people – clearly understand our position and the justification for our confidence in the clinical value of Cxbladder.

Dr Peter Meintjes
Chief Executive Officer

Dr Tamer Aboushwareb
Chief Medical Officer

Dr Justin Harvey
Chief Technology Officer

[1] The ‘Genetic Testing in Oncology: Specific Tests’ (L39365) LCD and the associated Local Coverage Article ‘Response to Comments: Genetic Testing in Oncology: Specific Tests’ (A59856) can be downloaded from the following link www.cms.gov/medicare-coverage-database/search.aspx.

[2] For definitions of AV, CV and CU please refer to the appendix of this document on page 17.

Executive Summary

The 'Genetic Testing in Oncology: Specific Tests' Local Coverage Determination (L39365) relies on a flawed review of the high-quality peer-reviewed evidence supporting the use of our tests and a flawed process.

The flaws in process and the evidentiary review of L39365 have led to the finalization of the LCD and have prejudiced Pacific Edge. However, this document focuses on a rebuttal of the evidentiary review of Cxbladder because the review questions Pacific Edge's steadfast commitment to generating the compelling clinical evidence required to drive behavior change in physicians.

Our objection to the evidentiary review can be broadly summarized as follows:

1. Novitas conflates biomarker discovery and feasibility testing with test development. Its review focuses heavily on a single manuscript covering the original discovery and feasibility study conducted by Holyoake et al (2008) that sought only to demonstrate that the biomarkers discovered in tissue can be detected at levels in urine sufficient for the purposes of subsequent test development.

   It fails to recognize that the limitations of the Holyoake et al (2008)[1] study were addressed by the subsequent test development paper (O'Sullivan et al (2012))[2]. It also fails to acknowledge the multiple papers since these two foundational studies were published that have demonstrated the AV, CV and CU of Cxbladder Triage, Detect and Monitor.

   Cxbladder has been validated in the relevant patient populations at statistically significant sample sizes. It has been designed appropriately for its purpose of ruling out Transitional Cell Carcinoma (TCC) / Urothelial Cancer (UC[3]) in patients presenting with hematuria and patients under regular surveillance for previous diagnosis of Non-Muscle Invasive Bladder Cancer (NMIBC).

   (Sections: 1 to 7)

2. Novitas misinterprets evidence for Cxbladder (Triage and Detect) by framing them as screening tests for an asymptomatic population, rather than tests to support clinical decision making. Its suggestion[4] that patients must have histologic, cytologic, and/or flow cytometric test results to justify a suspicion of cancer and therefore the use of diagnostic tests runs contrary to Medicare's longstanding definition of screening (i.e., tests where the intended use is in patients *without signs or symptoms of the underlying disease*).

   Screening tests – under the Medicare definition - are well understood as not covered by the Medicare Program. However, genetic tests covered by Medicare, where the patient population is symptomatic, but no diagnosis for cancer has been established and no histologic, cytologic, and/or flow cytometric testing has been performed, are common and clinically useful.

   (Sections: 3, 5, 7, 8, 10, 11, 13)

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[1] Holyoake A, O'Sullivan P, Pollock R, et al. Development of a multiplex RNA urine test for the detection and stratification of transitional cell carcinoma of the bladder. Clin Cancer Res 2008;14:742–9.

[2] O'Sullivan P, Sharples K, Dalphin M, et al. A multigene urine test for the detection and stratification of bladder cancer in patients presenting with hematuria. J Urol 2012;188:741–7

[3] TCC (Novitas' preferred terminology) and UC (Pacific Edge's preferred terminology) are synonyms. We have used TCC in direct quotes from the LCD and TC/UCC in our responses.

[4] See section 11 of this document.

3. Novitas misinterprets evidence for Cxbladder Detect and Triage because it misunderstands the patient population targeted by the tests (patients presenting with hematuria). In addition to bladder cancer, hematuria has a number of more benign causes including benign prostate hyperplasia (BPH) Cystitis, Calculi etc. The study focused on patients who already had hematuria because the test was meant to detect TCC/UC in those cases. It was not meant for people without symptoms, especially when there could be multiple other potential causes influencing the results.

   (Sections: 1, 2, 3, 5, 7, 8, 10, 11, 13)

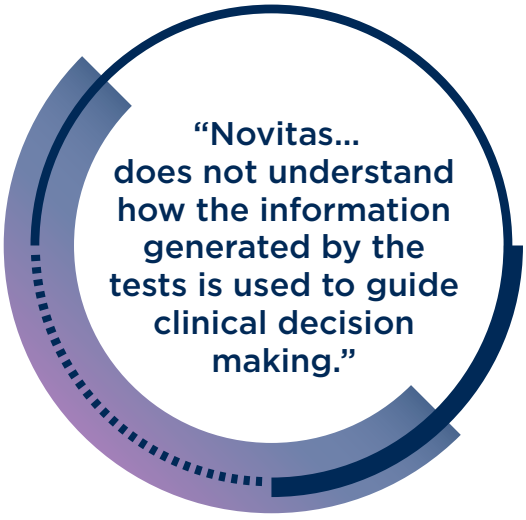
4. Novitas misinterprets evidence for Cxbladder because it does not understand how the information generated by the tests is used to guide clinical decision making. The review is unnecessarily focused on the tests' Positive Predictive Value (PPV) and the anxiety patients face with a False Positive test. Instead, it should have focused on Cxbladder's high Negative Predictive Value (NPV) and False Negatives, which are the relevant considerations when stratifying the risks of cancer in hematuria patients. All patients that test positive are subject to standard of care that includes cystoscopy, while those who return a negative test may be able to avoid the invasive examination.

   (Sections: 2, 3, 5, 7, 8, 10, 11, 13)

5. Novitas has based its evidentiary review on a preliminary version of the Cxbladder test, referred to as uRNA-D, which is not the test offered to Medicare patients. Biomarker discovery and feasibility testing of such a predecessor product is not appropriate for this review.

   (Sections: 1 to 7)

Pacific Edge believes these issues are serious and should be sufficient evidence for Novitas to retire Genetic Testing in Oncology: Specific Tests' Local Coverage Determination (L39365).

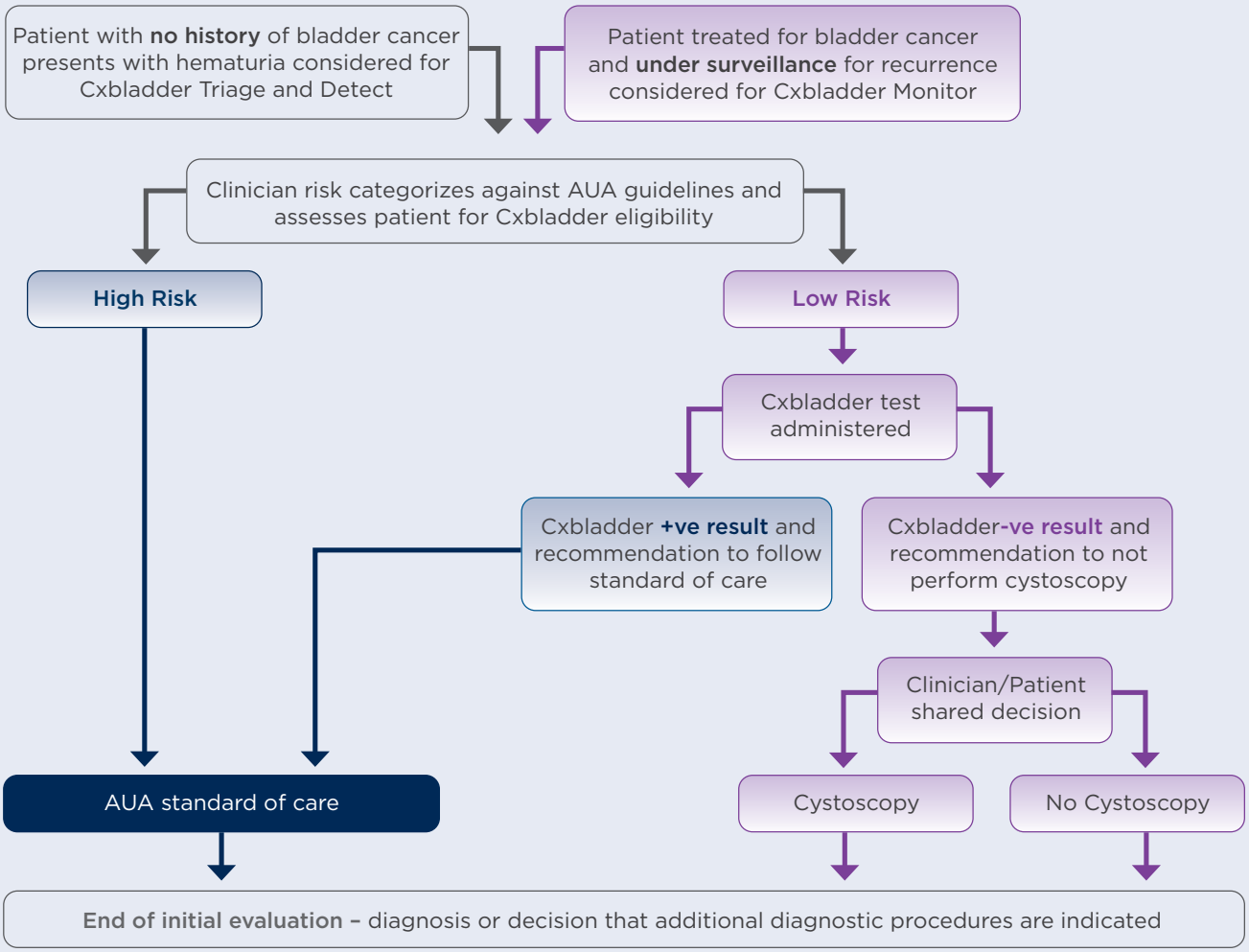


[5] Lotan Y, Daneshmand S, Shore N, Black P, Scarpato KP, Patel A, Lough T, Shoskes DA, Raman JD. A Multicenter Prospective Randomized Controlled Trial Comparing Cxbladder Triage to Cystoscopy in Patients With Microhematuria. The Safe Testing of Risk for Asymptomatic Microhematuria Trial. J Urol 2024.

How Cxbladder Is Used In Clinical Practice

Novitas' misunderstanding of how Cxbladder is used in clinical practice undermines both its review of the clinical evidence supporting the use of our tests and the logic behind the non-coverage determination. A clear and accurate grasp of how clinicians incorporate our tests into practice is therefore essential to understanding our objections to the evidentiary review and the 'Genetic Testing in Oncology: Specific Tests' LCD itself. We set out the use case below and the clinical and economic benefits on page 10.

CXBLADDER USE IN CLINICAL PRACTICE



PATIENTS PRESENTING WITH HEMATURIA

In patients with no history of bladder cancer presenting with hematuria a negative Cxbladder Triage and Cxbadder Detect result is used to help clinicians rule out the presence of bladder cancer and avoid an unnecessary cystoscopy. A positive Cxbladder Detect result can assist clinicians to resolve diagnostic dilemmas and prioritize patients for a more intensive workup.

SURVEILLANCE FOR BLADDER CANCER RECURRENCE

In patients treated for bladder cancer and under surveillance for recurrence a negative Cxbladder Monitor result is used help clinicians rule out the presence of bladder cancer and reduce the burden of surveillance examinations.

‘Genetic Testing In Oncology: Specific Tests’ – A Point-by-Point Rebuttal

The full ‘Genetic Testing in Oncology: Specific Tests’ (L393365) Local Coverage Determination can be found on the Medicare Coverage Database at the following link www.cms.gov/medicare-coverage-database/search.aspx. In the following pages, we have highlighted key excerpts from the LCD alongside our responses. Each section heading reflects the central themes of these excerpts for clarity and ease of reference.

1. Goals of the Holyoake et al (2008) study

Novitas: “Cxbladder tests are founded on the premise that differences in gene expression between urothelial cancer and non-urothelial cancer (including non-neoplastic tissue) can be measured in urine to determine if urothelial cancer is present or not present.”

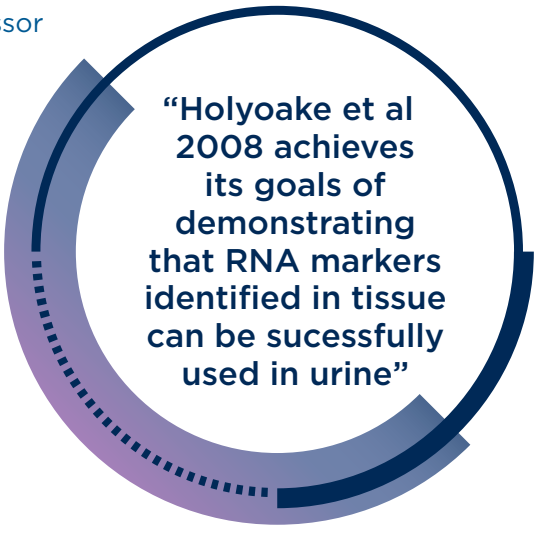
“A well-designed test would be able to not only discriminate between patients with urothelial cancer (as a specific abnormal pattern of mRNA transcriptional activity) and healthy unaffected patients (normal pattern), but also between patients with urothelial cancer and patients affected by other diseases (other distinct abnormal patterns) whether non-malignant (e.g. urinary tract infection) or malignant (e.g. renal cell carcinoma, RCC)”.

Our Response: Novitas’ first statement is correct. However, the second statement is not. The goal of the Holyoake et al (2008) study that Novitas uses to justify this statement was a feasibility study to show that RNA markers identified in tissue can be used to identify TCC/UC in patients from a urine sample.

Holyoake et al (2008) never asserted that the test (a predecessor test to Cxbladder referred to as uRNA-D) can provide discrimination between TCC/UC tumors and other urological conditions such as urinary tract infections or other malignancies and it achieved its goal.

The test in Holyoake et al (2008) was not optimized to identify each different condition, but specifically to identify the presence or absence of TCC/UC in patients presenting with hematuria, not in asymptomatic individuals.

Holyoake et al (2008) achieved its goals of demonstrating that RNA markers identified in tissue can successfully be used in urine.



2. Normal Cell Comparatives in the Holyoake study

Novitas: "The methodology [of Holyoake et al 2008] presumed that the ureter epithelium (tissue) taken from patients with kidney cancer would supply an mRNA expression profile comparable to urine from a patient without bladder cancer. This approach discounted the differences between tissue from a single cell type (urothelium) and urine, which contains both cell-free mRNA and cell-bound mRNA, all from a variety of urothelial and non-urothelial sources (e.g., kidney and prostate gland).

A more accurate approach, if using tissue to design the test, would be to compare mRNA profiles between urothelial cancer and normal bladder urothelium from the same patient to minimize the confounding differences. After test design with tissue, there would need to be confirmation that mRNA expression profiling of tissue translated to urine testing, which could be best characterized by comparing tissue profiles with urine profiles of the same patient."

Our Response: Novitas asserts that Holyoake et al (2008) was a flawed design to use tissue from TCC/UC tumors and normal urothelium from patients that had Renal Cell Carcinoma (RCC) to identify the appropriate markers for our test. This is incorrect, and we strongly disagree with the reviewers.

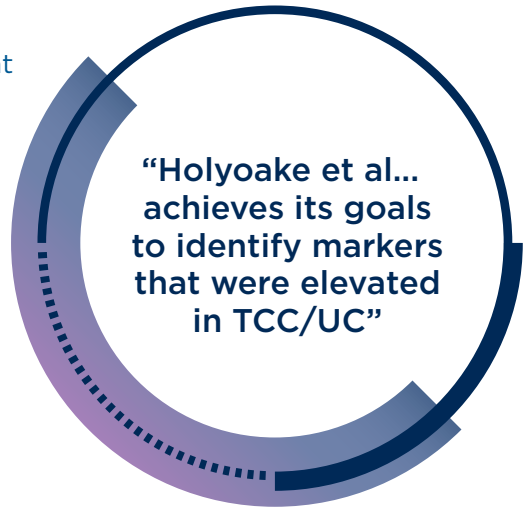
The goal of the study was to identify the markers that were specifically elevated in TCC/UC tissues as compared to normal tissue whether that tissue is from completely normal patients or patients with RCC. The key biological reason is that RCC has a completely different underlying molecular pathology when compared to TCC/UC and that the associated epithelium from the ureter obtained during nephrectomy is non-malignant and considered normal tissue.

Novitas' suggested approach is also incorrect. They suggest that it would have been better to use normal bladder tissue from the same patients with TCC/UC does not take into account "field effects", where the surrounding tissue may harbor many of the same underlying molecular alterations as the tumor itself and be in the early stages of tumorigenesis from the same underlying genetic origins.

Field effects are well-documented and prevalent in bladder cancer due to its association with widespread urothelial changes caused by carcinogenic exposures, such as smoking and chemical exposure.

If we had used normal tissue from the same patient, we would have not been able to differentiate between the presence or absence of the marker expression. If we had used completely healthy people, there would be an ethical problem getting urothelial biopsies to confirm their normal status.

Holyoake et al (2008) achieves its goals to identify markers that were elevated in TCC/UC tissue vs Normal urothelial tissue and uses appropriate control patients with RCC.



3. Comparison with Healthy Patients

Novitas: "...in the test finalization phase, urine from patients with TCC was compared to urine from patients with other diseases affecting the urologic tract, both malignant and non-malignant. No urine from healthy patients was used to design the final test. Moreover, the non-TCC malignancies were not identified in this paper (e.g., no diagnoses of prostate cancer or kidney cancer).

"Therefore, potential genes for an mRNA profile were discovered by comparing TCC tissue to benign ureter tissue and then subsequently honed to a final test design by comparing urine from patients with bladder cancer to urine from patients with other diseases (both malignant and non-malignant) without comparing to urine from healthy patients."

Our Response: Novitas claims that it would have been essential to compare urine from healthy patients to those of the TCC/UC and other urological conditions to confirm that our test can indeed identify TCC/UC.

This assertion demonstrates a misunderstanding of the indication of the test. Our test is NOT a screening test. It is NOT indicated for or used in people that have no signs of urological problems. Our test is indicated in patients presenting with hematuria for evaluation at the urology office or for those who have been previously diagnosed with bladder cancer and are under surveillance.

Attempts to optimize our tests using urine from completely healthy individuals would NOT have provided the appropriate discrimination needed to differentiate between those patients.

In the real world, our test is used in a patient population that is most likely to have another urological condition that may also cause hematuria (for example, urinary tract infection (UTI), benign prostate hyperplasia (BPH), prostate cancer, etc. It is therefore imperative that our tests can differentiate between those conditions and TCC/UC, which is the malignancy it is intended to exclude.

Fundamentally, the reviewers conflate biomarker discovery with diagnostic test development. While the biomarkers were selected on tissue and tested on urine (this is normal practice), the Cxbladder Detect assay was developed on 485 urine samples from patients that were obtained from every consenting patient presenting with gross hematuria from nine independent urology clinics (as described in O'Sullivan et al (2012)).

This yielded a patient population for test development (primarily the bioinformatic algorithm) of 419 non-TCC/UC samples and 66 TCC/UC samples. The non-TCC/UC samples appropriately comprised the expected patient population of hematuria patients that included BPH, Cystitis, Calculi, and other cancers.

Cxbladder has been designed appropriately to segregate TCC/UC from non-TCC/UC in hematuria patients and minimize those patients that would be worked up un-necessarily with cystoscopies.

Cxbladder is not a screening test. It is used in hematuria patients to identify patients that do not need further evaluation. It does not need to be validated in healthy people. Cxbladder was validated in the relevant patient populations at statistically significant sample sizes (O'Sullivan et al 2012). It has been designed appropriately for its purpose.

4. Biomarker Selection

Novitas: "Thirdly, of the over 26,000 genes investigated [in the Holyoake et al (2008) publication], ultimately only four genes (CDC2, MDK, IGFBP5, and HOXA13) were selected. In isolation, the selected genes were not considered unique to the development of urothelial carcinoma. For instance, the authors stated "TOP2A and CDC2, which are involved in DNA synthesis and cell cycle control, showed very high overexpression across the majority of tumors examined".

"In fact, when selecting genes, the [Holyoake et al (2008)] most frequently focused on the power of a gene to discriminate in 1 or more aspects of their test (e.g., HOXA13 and IGFBP5 were the best genes for discriminating between Ta tumors and T1-T4 tumors), but they often failed to adequately discuss the significance of the gene itself in the development of urothelial carcinoma.

"In the paper's discussion, each of the 4 selected genes were described briefly. A single literature citation each was provided for 3 of the 4 genes stating that there were no assertions CDC2, IGFBP5, and MDK were unique to urothelial carcinogenesis. Altogether, this demonstrates that the test is based on correlation not causation and is thus an indirect assessment of the presence of TCC."

Our Response: Here the reviewer appears to misunderstand the description from the authors of Holyoake et al (2008). When Holyoake et al (2008) say that "those two markers (TOP2A and CDC2) were highly overexpressed across the majority of the tumors examined", they mean *all TCC/UC tumors*. This is precisely why these markers were selected as the genes most representative of all TCC/UC tumors. The same approach was repeated for all other selected genes.

Novitas... appears to have ignored the true Cxbladder test development in O'Sullivan et al (2012).

The combination of the four (and later five) gene expression profiles were the genes/markers that provided the most accurate prognosis of the presence of disease as well as the severity (Ta-T4) which made them the best combination for this intended use.

Importantly, Holyoake et al (2008) make no claim that those individual markers are unique to urothelial carcinogenesis. In fact, we would argue that no currently available genomic marker component (i.e., individual gene) could be identified as unique to a single cancer.

Similarly, it is important to note that gene expression is quantitative and not binary. So while the genes may be present in multiple cancers and/or tests, the ratios of the expression levels between them will drive the specificity of the test, not merely the presence and/or combination of the genetic markers.

Every development study for a biomarker uses exactly this same methodology to identify the most frequently expressed markers for a certain application and then endeavors to develop an expression profile algorithm that can identify the probability of having the disease.

It is our view Novitas misunderstands the Holyoake et al (2008) publication and appears to have ignored the true Cxbladder test development in O'Sullivan et al (2012).

This yielded a patient population for test development (primarily the bioinformatic algorithm) of 419 non-UC samples and 66 UC samples. The non-UC samples appropriately comprised the expected patient population of hematuria patients that included BPH, Cystitis, Calculi and other cancers. Consequently, Cxbladder has been designed to segregate UC from non-UC and minimize those patients that would be worked up un-necessarily with cystoscopies.

5. The Absence of Asymptomatic Patients

Novitas: "Patients included in the test finalization portion of the [Holyoake et al (2008)] study all received flexible cystoscopy and all presented with symptoms concerning for urinary tract disease. No asymptomatic patients were included. This selection process demonstrates potential bias in excluding baseline, "normal," asymptomatic controls and selecting against patients with diseases that did not rise to a level of concern requiring cystoscopy.

Our Response: Here Novitas repeats the claim that it was flawed to not include normal patients in the finalization of the test result. Again, we maintain Novitas does not appear to understand that the Cxbladder algorithm was developed using "normal" urine samples (from hematuria patients that did NOT have TCC/UC) against "bladder cancer" urine samples (from hematuria patients that did have TCC/UC). Nor does Novitas appear to understand the intended use of the test in a hematuria population to rule out TCC/UC and thereby spare patients from an unnecessary and invasive cystoscopy.

The test is not a screening test. It is NEVER administered to "normal individuals" (asymptomatic and/or healthy individuals), it is only administered to patients presenting with hematuria or on surveillance for bladder cancer. Including asymptomatic people in the development of a test that is never meant to be administered to normal people would be medically inappropriate and a waste of resources.

For the benefit of clarity, we repeat that our test is NOT a screening test administered to try to detect urothelial cancers in the normal population. Cxbladder is intended for use in hematuria patients (Triage and Detect) or bladder cancer patients under surveillance for recurrence (Monitor) with the primary goal to reduce the burden of unnecessary invasive diagnostic procedures and the associated comorbidities on patients presenting with signs of disease, but who would benefit from de-escalation.

6. Homogenous population used in biomarker discovery

Novitas: "Also, note that the patients were selected from a Japanese population at a single institution in Kyoto, potentially limiting the relevance and applicability of the test in other dissimilar populations, such as the predominantly Caucasian but still highly diverse population of USA Medicare patients. The generalizability of results from a Japanese patient population to more heterogenous populations is questionable, thereby reducing the certainty of translating these results to the United States."

Our Response: Underlying diversity of the samples in a biomarker discovery publication like Holyoake et al (2008) is not required, and Novitas is incorrect to point this out.

Underlying sample diversity is critical in the subsequent test development publications for AV, CV and CU, and we note that this is addressed for Cxbladder Detect in O'Sullivan et al (2012) and multiple subsequent test-specific publications for analytical validity, clinical validity, and clinical utility.

The studies, subsequent to Holyoake et al (2008), show that Cxbladder offers clinicians and patients significant clinical value in Caucasian and US populations specifically. Additionally, peer reviewed modelling by Pacific Edge shows Cxbladder also offers healthcare payers significant economic benefits[1].

Cxbladder was developed on relevant patient populations (O'Sullivan et al (2012)) and validated in subsequent publications. It has been designed appropriately for its purpose.

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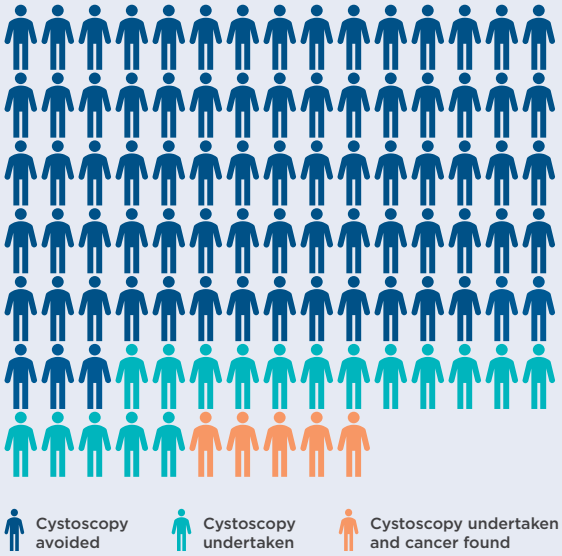
[1] Tyson MD, Abouassaly R, Durant, A, Bosworth Smith, A, Seemann, D, Shoskes, D. Budgetary Impact of Including the Urinary Genomic Marker Cxbladder Detect in the Evaluation of Microhematuria Patients. Urol Pract. 2023 Nov

Cxbladder's Clinical, Economic And Patient Value

Pacific Edge's budget impact modelling shows Cxbladder offers better care, avoids unnecessary procedures and improves workflow when used to intensify or de-intensify hematuria evaluation or in the surveillance for the recurrence of bladder cancer. For healthcare payers Cxbladder offers substantial total cost savings per patient.[1,2]

CXBLADDER DETECT VS AUA GUIDELINES



HEMATURIA EVALUATION[1]

Cxbladder Detect rules out 78 of the 95[3] patients without cancer and requires only 22 cystoscopies to find the five patients with cancer.

This results in savings of **>US$500** per patient presenting with hematuria.

CXBLADDER MONITOR VS AUA GUIDELINES

CANCER RECURRENCE SURVEILLANCE[2]

Cxbladder Monitor alternated with cystoscopy for surveillance of bladder cancer after nine months of treatment.

This results in 12.4% reduction in cystoscopies over a five-year surveillance period.

Savings estimated at as much as **US$680** per patient over the five-years.

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[1] Budgetary Impact of Including the Urinary Genomic Marker Cxbladder Detect in the Evaluation of Microhematuria Patients - PubMed (PMID: 37914255).

[2] Tyson et al (2024). Modelling the impact of incorporating Cxbladder Monitor in the surveillance of patients after non-muscle invasive bladder cancer in the US. abstract presented to the WSAUA in Kauai, Hawaii.

[3] Pacific Edge's model assumes a 5% incidence of bladder cancer in patients presenting with hematuria and referred to a specialist for a urological work up.

7. Follow Up Investigations and Cancer Heterogeneity

Novitas: "A third source of bias was found in the selection and interpretation of the reference standards (cystoscopic and histologic results). Very few of the patient workups for TCC and other diseases were detailed in the study. While it is very likely that other diagnostic modalities, such as radiology, were employed to diagnose non-TCC disease, the study failed to detail these workups. In fact, the types of non-TCC malignancies were not classified in this paper.

"Moreover, TCC itself is not a monolithic disease but rather a heterogenous cancer with many different origins that can include environmental and/or genetic etiologies. Thus, different subtypes of TCC would have different behaviors such as increased aggressiveness or increased likelihood of metastasis. This paper primarily focused on the stage and grade of disease without consideration of the other complexities within the category of TCC. Thus, the study's selection of reference standards could have introduced bias into the accuracy, performance, and applicability of the uRNA-D test."

Our Response: Here Novitas appears to repeat a foundational misunderstanding of the intended use of the test, the appropriate patient population, and its clinical utility. We have NEVER asserted that our test should replace any other diagnostic modalities for those patients.

We refer Novitas to the presentation we provided in January 2024, the presentation we provided on July 26, 2023, and the public comments associated with the draft determination 'Genetic Testing for Oncology' (DL39365).

Notwithstanding these representations and addressing the reviewer's views on the heterogeneity of TCC/UC, Novitas' statement is largely untrue. The likelihood of metastasis and the clinical staging are determined solely on the progression of the disease, not on the heterogeneity of the tumor.

Among cancers more generally, urothelial carcinoma is not as heterogeneous as Novitas suggests, and tumor heterogeneity doesn't influence clinical practice according to the AUA guidelines. Specifically, the guidelines refer to low-grade or high-grade TCC/UC and make no mention of the cancer heterogeneity.

In all Pacific Edge studies, low grade and high grade were clearly identified. The selection of the individual genes was based on the ability to, where possible, identify both. The tests, however, are optimized for the identification of high-grade disease.

To address Novitas' comments regarding other patient workups, we refer Novitas to the Cxbladder Detect publication O'Sullivan et al (2012), and the Cxbladder Triage publication Kavalieris et al (2015)[1], which describe cystoscopic and histopathology diagnosis methods. Furthermore, the Cxbladder Monitor publication, Kavalieiris et al (2017)[2] describes cystoscopy with or without a computerized tomography scan with urographic phase, with cancer or other abnormalities confirmed during local histopathological examination of resected tissue.

Cxbladder does not have the biases claimed by Novitas and uses the relevant clinical staging in the practice of urology. Cxbladder was validated in the relevant patient populations at statistically significant sample sizes (O'Sullivan et al (2012)). It has been designed appropriately for its purpose.

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[1] Kavalieris L, O'Sullivan PJ, Suttie JM, et al. A segregation index combining phenotypic (clinical characteristics) and genotypic (gene expression) biomarkers from a urine sample to triage out patients presenting with hematuria who have a low probability of urothelial carcinoma. BMC Urol 2015;15:23

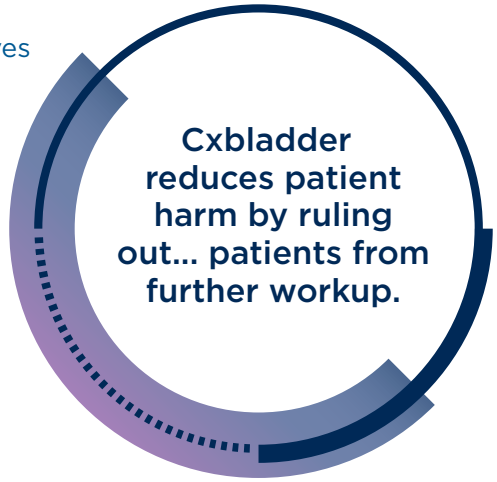
[2] Kavalieris L, O'Sullivan PJ, Frampton C, et al. Performance Characteristics of a Multigene Urine Biomarker Test for Monitoring for Recurrent Urothelial Carcinoma in a Multicenter Study. J Urol 2017;197:6,1419-1426.

8. Positive Predictive Value and False Positives

Novitas: "When a line of tests fails to truly discriminate between the disease of interest and all other conditions, normal or pathophysiologic, there is increased concern that the tests could cause patient harm. Unsurprisingly, Cxbladder tests generally have low PPVs (down to 15-16% as seen in Konety, et al (2019) and Lotan, et al (2023)) and high numbers of false positives (in Konety's paper there were 464 false positive results as compared to 86 true positive results and in Lotan's paper there were 110 false positive results as compared to 19 true positive results).

"In fact, the majority of Cxbladder papers avoid disclosing the PPV and number of false positives of their tests. Yet, these statistics are significant in that false test results, particularly false positives, can lead to patient anxiety and distress among other procedural issues related to follow up for an inaccurate result. If numerous false positive results in Cxbladder are accepted as an inherent trait of the test, providers may not be as vigilant in closely following patients with a positive Cxbladder result after a negative cystoscopy."

Our Response: We agree with Novitas that significant false positives in healthy patients could create unnecessary anxiety for patients. However, Cxbladder tests are not used in healthy patients, they are used in patients presenting with hematuria.



Although incidence of bladder cancer in these patients is low (particularly microhematuria patients), they are already suspected of having bladder cancer according to the AUA Guidelines and face the prospect of invasive, costly procedures with comorbidities. Cxbladder reduces patient harm by ruling out up to 75% of those patients from further workup, and importantly, those with a Cxbladder positive result (false or true) continue to receive the standard of care suggested by AUA guidelines.

Novitas' final point does not apply when Cxbladder Triage or Detect are used as indicated, because they are intended for use prior to a cystoscopy to inform the decision to perform a cystoscopy. If Cxbladder is positive, and a cystoscopy is negative, this should not dissuade a physician from vigilance but rather focus on that physician to consider the standard of care by AUA Guidelines.

Lastly, noting that PPV is low in tests that have been optimized for NPV and for a role in ruling out patients is not meaningful. The utility of Cxbladder tests is determined by the NPV of the tests. They have been appropriately validated for this purpose.

9. Biomarkers and Precision Medicine

Novitas: "Biomarker testing is a part of precision medicine (also known as personalized laboratory medicine). Precision medicine is a tailored approach to medical care and treatment. Because each patient has a unique combination of genetic heritage and somatic changes, and therefore, a unique pattern of biomarkers, precision medicine for oncology involves the use of biomarker testing to pinpoint the disease management needs of individual patients and avoid the use of treatments which are unlikely to be successful.

"Much of this testing involves direct evaluation of the genetics of the malignancy through various testing methodologies. These methodologies can include high level genetic evaluations such as karyotyping (analysis of chromosomes) to more detailed evaluations such as identifying specific pathogenic point variations (analysis of specific nucleotide changes)."

Our Response: Biomarker testing is part of precision medicine, but it is not ONLY part of precision medicine. Novitas' own definitions section for Biomarkers recognizes that Biomarkers are a "biological or molecular compound found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or a condition or disease."

This is accurate, and clearly different from the application of biomarkers to precision medicine. Novitas is limiting the use of Biomarkers in this LCD to precision medicine applications without any clear justification, when Biomarkers can be used in far more varied ways that are also medically useful.

If the intent is to allow pre-diagnosis biomarkers to be covered under a different LCD, Novitas should not use that LCD as the basis for non-covering our tests and communicate in good faith for the Medicare beneficiaries we serve the appropriate path for coverage of such tests transparently.

Novitas' Response to Comments

Novitas – as part of the finalization of the LCD – is required to publish a response to comments made during the September 2023 notice and comment period on the original draft of the LCD, then called 'Genetic Testing for Oncology'.

These responses are detailed in a Local Coverage Article 'Response to Comments: Genetic Testing in Oncology: Specific Tests' (A59856). The full article can be found on the Medicare Coverage Database at the following link www.cms.gov/medicare-coverage-database/search.aspx. What follows is a point-by-point critique of key comments with subheadings in each section setting the areas of contention.

10. A Redefinition of Screening

Novitas: "Oncologic genetic testing is considered screening if it is performed before the ordering provider either establishes a diagnosis of cancer or a substantiated suspicion of cancer through histologic, cytologic, and/or flow cytometric testing.

"This limitation follows the regulation that screening tests in asymptomatic patients are generally non-covered by Medicare except under very specific circumstances, as discussed in CMS IOM [Centers for Medicare & Medicaid Services (CMS) Internet-Only Manuals] Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, Section 280 Preventive and Screening Services."

Our Response: "This statement attempts to redefine the testing of symptomatic patients without an established diagnosis as the "testing of asymptomatic or healthy patients" i.e., screening. This is not consistent with Medicare's definition of screening, as "tests and exams used to detect potential health issues before symptoms appear." It also misunderstands the utility of genetic tests. This is not consistent with Medicare's definition of screening, as "tests and exams used to detect potential health issues before symptoms appear". It also misunderstands the utility of genetic tests.

Novitas: "Oncologic genetic testing is considered screening if it is performed before the ordering provider either establishes a diagnosis of cancer or a substantiated suspicion of cancer through histologic, cytologic, and/or flow cytometric testing. This limitation follows the regulation that screening tests in asymptomatic patients are generally non-covered by Medicare except under very specific circumstances, as discussed in CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, Section 280 Preventive and Screening Services."

Our Response: Nothing in the CMS IOM and Medicare Benefit Policy Manual supports the first sentence in this paragraph. The longstanding definition by Medicare is that screening tests are defined as such when the intended use is in patients that are otherwise healthy and without symptoms and NOT prior to substantiated suspicion of disease and/or diagnosis.

[1] Lotan Y, et al (2024). A Multicenter Prospective Randomized Controlled Trial Comparing Cxbladder Triage to Cystoscopy in Patients With Microhematuria. The Safe Testing of Risk for Asymptomatic Microhematuria Trial. J Urol 2024.

[2] Harvey JC et al (2024) Analytical Validation of Cxbladder® Detect, Triage, and Monitor: Assays for Detection and Management of Urothelial Carcinoma. Diagnostics. 2024; 14(18):2061.

11. Substantiated Suspicion of Cancer

Novitas: "Establishing a diagnosis of cancer requires at baseline pathologic evidence via histology or cytology. Note that histology includes microscopic examination of tissue sections and cytology includes microscopic evaluation of fluids such as pleural effusions, blood, and bone marrow [e.g., smears] or tissue such as core biopsies [e.g., touch prep].

"Regarding concerns for patients who may not be candidates for a tissue biopsy due to high risk of complications, we did identify in the NCCN guidelines some cancers where cell-free, circulating tumor deoxyribonucleic acid was recommended as an alternative if a tissue biopsy could not be obtained.

"Also, for the purposes of this LCD, a substantiated suspicion of cancer requires direct, physical sampling of a lesion, such as needle aspiration or excision of tissue, followed by microscopic evaluation (histology or cytology). For hematologic lesions, we recognize that flow cytometry is often performed concurrently with histology and/or cytology. Given this accepted diagnostic practice, the LCD will be adjusted to include flow cytometry as sufficient for establishing a substantiated suspicion of cancer."

Our response: A substantiated suspicion of cancer should not be an exclusion requirement imposed on genetic tests. This is not supported by medical practice, misunderstands the value of molecular technologies and if accepted, would re-define Medicare's longstanding definition of screening to incorrectly include symptomatic patients without an established diagnosis as asymptomatic and healthy.

12. Indirect Laboratory Testing

Novitas: "While radiologic testing can identify lesions that are suspicious for cancer, confirmation requires a physical sampling and microscopic examination of the lesion. Indirect laboratory testing (e.g., serum tumor markers such as Prostate Specific Antigen [PSA]), even when used with other indirect diagnostic tests such as radiology can still prove misleading without direct microscopic examination of lesional cells/tissue."

Our Response: Novitas privileges physical sampling of lesions over other diagnostic tools in a way that is not consistent with the standard of care for prostate cancer early detection pathways described at NCCN and by the AUA. PSA is used routinely to screen patients and identify those more likely to need further workup. It is a known limitation of PSA that it has more false positives than are desirable, but importantly, pre-diagnosis genetic testing is one of the key innovations that is being and will be improved in this clinical pathway over time.

Alternatively, it can be argued that while Novitas' view is factually correct, it reduces the value of those evaluation methods in the reduction of potentially unnecessary invasive procedures that may harm patients. In case of prostate cancer, Medicare has recently started paying for Multiparametric MRI prior to biopsies in patients with elevated PSA precisely to reduce the potential of taking biopsies from patients that do not need it. The Cxbladder tests provide the same utility for hematuria patients that are suspected of having TCC/UC.

Novitas: "While cytogenetics, fluorescent in situ hybridization, and antigen receptor gene rearrangement assays of B- and T-lymphoid cells can all be used in the evaluation of cancer, these are not first-line tests; instead, these three tests are performed in addition to histologic or cytologic evaluations. Each of these tests require lesional tissue or cells, which when obtained, already receive histologic and/or cytologic evaluation. Moreover, to our knowledge, not one of these three tests would be sufficient alone to diagnose cancer; instead, these tests provide supportive evidence in the context of a prior histologic or cytologic result. As a result, requiring histologic or cytologic evaluation before molecular testing makes sense for these three tests."

Our response: Pacific Edge has no fundamental disagreement with this assessment, but it appears to have limited where Novitas identifies value from other genetic tests such as Cxbladder.

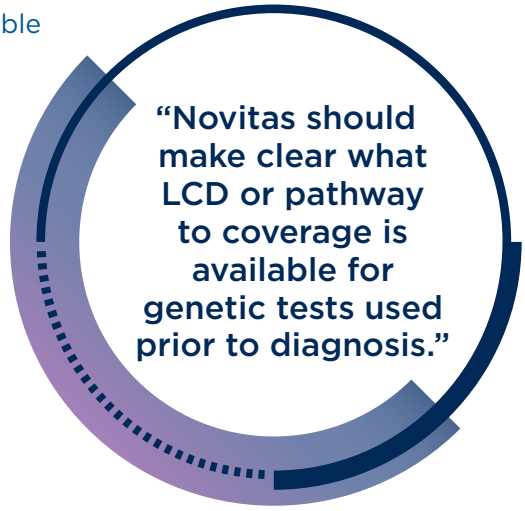
13. Overuse Of Genetic Tests or Unnecessary Testing

Novitas: "The requirement for histologic, cytologic, and/or flow cytometric evidence of cancer or a suspicion of cancer additionally addresses the pernicious issue of ordering genetic testing without full knowledge of the patients' cancer history, which includes ordering broad genetic testing for cancers only described by an organ system. For example, the term "colon cancer" is non-specific and includes multiple subsets of cancers with a variety of manifestations. If a provider does not, at minimum, have a pathology report on the histology of the "colon cancer." It cannot be expected that molecular testing, even hereditary cancer testing, would be tailored to the patient's specific needs."

Our response: This comment appears targeted at screening tests that do not aim to be specific to the symptoms of the presenting patient. This also assumes that the sole purpose of genetic testing is to guide therapy selection in the context of precision medicine, but this misunderstands the value of genetic biomarkers and is not the only purpose of genetic testing.

Novitas: "In the case of molecular testing ordered as a set of tests evaluating a concern for cancer (e.g., bone marrow biopsy submitted for morphologic, flow cytometric, and molecular evaluation all at once), tests should be performed reflexively to prevent unnecessary testing. If there is no histologic, cytologic, or flow cytometric evidence diagnosing or creating a suspicion for cancer, subsequent molecular testing would not be covered under this LCD policy.

Our response: If this LCD is not appropriate for certain tests, Novitas should make clear what LCD or pathway to coverage is available for genetic tests used prior to diagnosis and assess those for AV, CV and CU in line with Medicare's coverage policies.



Appendix: Clinical Evidence

Pacific Edge's clinical study program is focused on developing clinical evidence for Cxbladder tests in a structured framework.

- **Analytical Validity (AV):** Evidence that a test is repeatable in the lab for a given indication and population
- **Clinical Validity (CV):** Evidence a test works in the same way on an independent eligible population for a given indication
- **Clinical Utility (CU):** Evidence that a test changes clinical practice in the hands of a physician, typically in prospectively recruited RCTs
- **Real World Evidence (RWE):** CU verification of the real-world use of the test in clinical practice, usually through regular use of the test by physicians

Clinical Utility evidence obtained through randomized control trials is required to change standard of care guidelines (in addition to AV and CV evidence).

SUMMARY OF CLINICAL EVIDENCE

	Study		Pop. Type	Sensitivity (Sn)	NPV	Specificity (Sp)	Comment
Triage Plus	Proof of concept	Lotan et al., 2022	MH + GH*	97%	99.7%	90%	Pooled data from US and Singapore cohorts (*n*=804). Called Detect+ in publication.
	CV	DRIVE (unpublished) (1)	MH + GH*				*Study in progress*
		AUSSIE (unpublished) (4)	MH + GH*				*Study in progress*
		microDRIVE (unpublished) (5)	MH*				*Study in progress*
	CU	CREDIBLE (not started) (6)	MH				Protocol in final development stages, site selection starting by the end of year
Triage	AV	Kavalieris et al., 2015	MH + GH*	95.10%	98.50%	45%	**Sn, Sp, NPV** values when test-negative rate is 40%
		Harvey et al. 2024	MH + GH				
	CV	Davidson et al., 2019	MH + GH*	95.5% (1)	98.6% (1)	34.3%	GH only: **Sn** (95.1%), **NPV** (98%), **Sp** (32.8%); MH only: **Sn** (100%), **NPV** (100%), **Sp** (42.6%)
		Konety et al., 2019	(2)	100%			Cxbladder (3) correctly adjudicated all UC confirmed patients (*n*=26) with atypical urine cytology results (*n*=153, 4)
		Lotan et al., 2022	MH + GH*	89%	99%	63%	Pooled data from US and Singapore cohorts (*n*=804)
	CU	Davidson et al., 2020	MH + GH*	89.4& (5)	98.9% (5)	59% (5)	39% of patients testing negative for Cxb Triage & imaging did not get cystoscopy & were managed at primary care (6)
		Lotan et al., 2024 (7)	MH + GH*	90%	99%	56%	Showed clinicians using Triage undertook 59% fewer cystoscopies on low-risk patients presenting with hematuria
Detect	AV	O'Sullivan et al., 2012	GH*	81.8%	97%	85.1%	Cxb Detect detected 97% of HG tumors & 100% of Stage 1 or greater tumors
		Harvey et al. 2024	MH + GH				
	CV	Lotan et al., 2022	MH + GH*	74%	97%	82%	Pooled data from US and Singapore cohorts (*n*=804)
		DRIVE (unpublished) (1)	MH + GH*				*Study in progress*
	Health Economics	Tyson et al., 2023	MH				Published economic model shows significant savings for healthcare payers (median savings of $559 in direct costs per patient)
Monitor	AV	Kavalieris et al., 2017	(1)	88% (2)	97% (2)	N/A	(3)
		Harvey et al. 2024	MH + GH				
	CV	Konety et al., 2019	(4)	100%			Cxbladder (5) correctly adjudicated all UC confirmed patients (*n*=26) with atypical urine cytology results (*n*=153, 6)
	CU	Koya et al., 2020	(7)				Integration of Cxb Monitor into the surveillance schedule reduced annual cystoscopies (39%) (8,9)
		Li et al., 2023	(7)				Cxbladder Monitor safely postpones a patient's next scheduled cystoscopy, the current 'gold standard' for bladder cancer surveillance
		Guduguntla et al. 2024	(7)				Cxbladder Monitor can be safely used in an alternating schedule with Flexible Cystoscopy for patients on annual bladder cancer surveillance.

* Referred patients. Definitions - MH: Microhematuria, GH: Gross Hematuria.

FOOTNOTES FOR CLINICAL EVIDENCE SUMMARY

	Footnotes	
Triage Plus	(1)	Observational study to validate performance characteristics and clinical utility of Cxbladder tests (Cxb Triage, Cxb Detect, Cxb Triage Plus).
	(2)	Observational study to validate performance characteristics of Cxb Triage Plus in patients with UC of the upper tract.
	(3)	Patients with suspected upper tract UC (UTUC) or surveillance patients with a history of UTUC.
	(4)	Observational study to validate performance characteristics and clinical utility of Cxbladder tests (Cxb Triage, Cxb Detect, Cxb Triage Plus).
	(5)	Observational study to validate performance characteristics of Cxb Triage Plus in microhematuria (MH) patients.
	(6)	Clinical utility study comparing the reduction of cystoscopy use when implementing the new clinical pathway to SOC in a defined MH population.
Triage	(1)	Cxb Triage performance; Cxb Triage & imaging combined performance had a **Sn** of 97.7% & **NPV** of 99.8%.
	(2)	Patients included hematuria evaluation (*n*=436) or surveillance previously diagnosed with UC (*n*=416) with both Cxbladder & urine cytology results.
	(3)	Cxbladder includes Cxbladder Triage & Cxbladder Monitor.
	(4)	This included *n*=70 for patients with hematuria & *n*=83 for patients with previously diagnosed UC and overall test negative rate of 30.7%.
	(5)	Cxb Triage performance; Cxb Triage & imaging combined performance had a **Sn** of 98.1%, **NPV** of 99.9% & **Sp** of 98.4%.
	(6)	Cxb Triage negative rate was 53%; Follow-up period of 21-months showed no missed cancers, demonstrating safety.
	(7)	Cxb Triage demonstrated to have clinical utility in safely risk stratifying low risk microhematuria patients and not undertake cystoscopy.
Detect	(1)	Observational study to validate performance characteristics and clinical utility of Cxbladder tests (Cxb Triage, Cxb Detect, Cxb Detect^{+}).
Monitor	(1)	Surveillance patients previously diagnosed with primary or recurrent UC.
	(2)	Cxb Monitor performance characteristics on surveillance patients diagnosed with primary UC; Cxb Monitor had a **Sn** of 93% and **NPV** of 94% on patients with recurrent UC.
	(3)	Using Kavalieris et al., (2017) data set, Lotan et al., (2017) compared relative performance of Cxb Monitor against NMP22 ELISA, NMP22 BladderChek and urine cytology.
	(4)	Patients included hematuria evaluation (*n*=436) or previously diagnosed UC (n=416) with both Cxbladder & urine cytology results.
	(5)	Cxbladder includes Cxbladder Triage & Cxbladder Monitor.
	(6)	This included *n*=70 for patients with hematuria & *n*=83 for patients with previously diagnosed UC; test negative rate of 30.7%.
	(7)	All patients were being evaluated for recurrence of UC (*n*=309 providing 443 samples).
	(8)	Cxb Monitor identified all seven confirmed recurrence events identified on the first cystoscopy.
	(9)	Patients returning negative Cxb Monitor results (*n*=235) had no pathology-confirmed recurrence at 1st cystoscopy

REFERENCES SUMMARY OF CLINICAL EVIDENCE

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Triage Plus	Lotan et al., (2022). Urinary Analysis of FGFR3 and TERT Gene Mutations Enhances Performance of Cxbladder Tests and Improves Patient Risk Stratification[1]. The Journal of Urology, 10-1097.
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	Harvey et al. (2024)., Analytical Validation of Cxbladder® Detect, Triage, and Monitor: Assays for Detection and Management of Urothelial Carcinoma. Diagnostics. 2024; 14(18):2061.
Detect	Lotan et al., (2022). Urinary Analysis of FGFR3 and TERT Gene Mutations Enhances Performance of Cxbladder Tests and Improves Patient Risk Stratification. The Journal of Urology, 10-1097.
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Monitor	Kavalieris et al., (2017). Performance characteristics of a multigene urine biomarker test for monitoring for recurrent urothelial carcinoma in a multicenter study. The Journal of Urology, 197(6), 1419-1426.
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[1] Triage Plus was called Detect+ in this publication

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CANCER DIAGNOSTICS

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