11 September 2023

PACIFIC EDGE RELEASES SUBMISSIONS ON MEDICARE LCD

DUNEDIN, New Zealand – Cancer diagnostics company Pacific Edge (NZX, ASX: PEB) today releases details of written submissions on the draft local coverage determination (LCD) that proposes non-coverage of Cxbladder tests by Medicare, the US national health insurance provider.

The written submissions argue Cxbladder Triage, Detect and Monitor tests should retain Medicare coverage based on the clinical value they offer to patients, clinicians, and healthcare payers.

Written submissions are the second element of the notice and comment period required when proposing a new LCD. The details released today concern the draft LCD DL39365 proposed by Novitas the Medicare Administrative Contractor (MAC) with jurisdiction for Pacific Edge's US laboratory on July 27, 2023, and its sister MAC First Coast Service Options (FCSO).

Pacific Edge Chief Executive Dr Peter Meintjes said: "Pacific Edge believes there is no new information in these submissions, but they provide further context of a sensitive process and show the weight of opinion supporting the arguments for continued Medicare coverage Cxbladder."

The material released can be found attached and includes:

- A Pacific Edge letter to Novitas Medical Director Dr Patrick Mann MD summarizing the submissions on the draft LCD of which the company is aware.
- Pacific Edge's medical rebuttal of Novitas' evidentiary review of the clinical evidence supporting Cxbladder tests.
- A letter from the American Urological Association (AUA), the Large Urology Group Practice Association (LUGPA), and the American Association of Clinical Urologists (AACU) - the three most influential urological organizations in the US, covering every practicing urologist in the country. The letter includes unpublished non-peer-reviewed results from Kaiser Permanente that shows Cxbladder Triage safely excluded 78% of the patients presenting with hematuria from a cystoscopy. It also showed similarly positive results for Cxbladder Monitor for patients under surveillance for the recurrence of bladder cancer.
- A submission from the diagnostic technology industry group 'The Coalition for 21st Century Medicine' which provides a detailed critique on the structure and approach of the draft LCD.
- An open letter from long-time Pacific Edge research collaborator Dr Yair Lotan Professor of Urology at University of Texas Southwestern Medical Center, and 13 other key urologic opinion leaders supporting the use of urine bladder cancer markers. This letter has also been accepted for publication in the journal "Bladder Cancer", the official journal of the US advocacy group, the Bladder Cancer Advocacy Network.

The written submissions follow the presentations made during the open public meetings held in August. The written comments are important, because MACs are required to respond to all comments in a process that is also reviewed by the Centers for Medicare and Medicaid Services (CMS).

Written submissions closed in the US on 9 September. Novitas and FCSO may take up to 365 days from the original US publication date (27 July 2023) to withdraw or finalize the LCD including a response to written comments. When finalized, the MACs must provide a minimum of 45 days' notice before the LCD becomes effective.

For more information:

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OVERVIEW

Pacific Edge: www.pacificedgedx.com

Pacific Edge Limited (NZX/ ASX: PEB) is a global cancer diagnostics company leading the way in the development and commercialization of bladder cancer diagnostic and prognostic tests for patients presenting with hematuria or surveillance of recurrent disease. Headquartered in Dunedin, New Zealand, the company provides its suite of Cxbladder tests globally through its wholly owned, and CLIA certified, laboratories in New Zealand and the USA.

Cxbladder: www.cxbladder.com

Cxbladder is a urine-based genomic biomarker test optimized for the detection and surveillance of bladder cancer. The Cxbladder evidence portfolio developed over the past 14 years includes more than twenty peer reviewed publications for primary detection, surveillance, adjudication of atypical urine cytology and equivocal cystoscopy. Cxbladder is the focal point of numerous ongoing and planned clinical studies to generate an ever-increasing body of clinical utility evidence supporting adoption and use in the clinic to improve patient health outcomes. Cxbladder has been trusted by over 4,400 US urologists in the diagnosis and management of more than 100,000 patients, including the option for in-home sample collection. In New Zealand, Cxbladder is accessible to 75% of the population via public healthcare and all residents have the option of buying the test online.

September 9, 2023

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Submitted via email to ProposedLCDComments@fcso.com and ProposedLCDComments@novitas-solutions.com

Dear Drs. Schaening-Perez and Stevens,

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

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

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

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

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

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

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

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

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

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

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

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

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

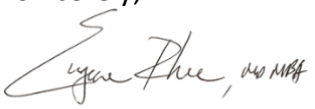
The cost of tumor marker testing is remarkably insignificant when considered in the context of the massive spend associated with the surveillance and treatment of bladder cancer patients. An average FISH test costs less than 1% of the $55,267 median attributed cost after two years of bladder cancer treatment.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

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

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

Thank you for your attention to this matter.

Sincerely,



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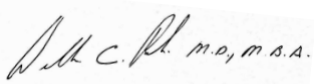

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September 7, 2023

VIA Electronic Mail to: ProposedLCDComments@novitas-solutions.com

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RE: Proposed LCD – Genetic Testing for Oncology (DL39365)

Dear Dr. Mann:

On behalf of the Coalition for 21st Century Medicine (C21), thank you for the opportunity to submit comments regarding the above-captioned proposed local coverage determination (LCD). C21 comprises many of the world's most innovative diagnostic technology companies, clinical laboratories, physicians, venture capital companies, and patient advocacy groups. C21's mission is to improve the quality of health care by encouraging research, development, and commercialization of innovative diagnostic technologies that will personalize patient care, improve patient outcomes, and substantially reduce health care costs.

For the reasons outlined below, C21 respectfully recommends that Novitas withdraw the draft LCD at the end of the comment period, and convene one or more Contractor Advisory Committee (CAC) meetings before engaging in future LCD development in genetic testing for oncology – both with respect to such tests in general, as well as the 13 specific tests evaluated in the proposed LCD. Engagement with the CAC would allow Novitas to obtain input from healthcare professionals, beneficiary representatives, and representatives of medical organizations to obtain meaningful feedback that would "ensure an unbiased and contemporary consideration of 'state of the art' technology and science" and would support the development of a clinically appropriate LCD.[1] By considering the CAC's input (as well as that from interested stakeholders, like C21), Novitas could address key clinical questions and develop an updated proposal to ensure that Medicare beneficiaries will continue to have timely access to advanced molecular diagnostic tests.

Alternatively, if Novitas elects to finalize the LCD, C21 recommends that Novitas modify the LCD to remove the presumption against coverage for tests not supported in at least one of the three listed compendia, and convene a CAC meeting before finalizing non-coverage for the 13 specifically-referenced tests.

[1] Medicare Program Integrity Manual ch. 13, § 13.2.4.3.

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1. SUPPORT FOR NOVITAS'S LONGSTANDING APPROACH TO COVERAGE OF DIAGNOSTIC TESTING SERVICES

For more than sixteen years, C21 has worked with the Centers for Medicare & Medicaid Services (CMS) and Medicare Administrative Contractors (MACs) on the development, promulgation, and implementation of policies intended to facilitate appropriate Medicare coverage and payment for high-quality clinical laboratory tests. C21 appreciates the work of Novitas over the past decade in reviewing novel advanced diagnostic tests and establishing LCD policies, including its current LCD for oncology tests, "Biomarkers for Oncology" (L35396). C21 strongly supports the current LCD, and appreciates Novitas's willingness to identify individual tests as covered services based on its assessment of the analytical validity, clinical validity, and clinical utility evidence supporting each test. As we noted in our Open Meeting presentation, we are concerned that the proposed "Genetic Testing for Oncology" LCD would, if finalized, significantly limit beneficiary access to advanced diagnostic tests, including many tests performed by C21 members with longstanding Medicare coverage following a previous test-specific evidence review by Novitas.

Historically, it has been both CMS' and Novitas' position that unless an LCD explicitly identifies a test as a non-covered service following an individualized review of the evidence for that test, such test would be eligible for Medicare coverage on a case-by-case basis. C21 strongly supports this position. Moreover, in recent years this requirement has been codified in federal law, as the 21st Century Cures Act prohibits Medicare contractors from implementing non-coverage policies unless the contractor makes an evidence-based determination that a test does not meet the statutory/regulatory criteria for Medicare coverage.[2]

2. CONCERNS WITH PROPOSED LCD FRAMEWORK

a. Novitas should not issue a final LCD that delegates coverage decisionmaking authority to external databases – particularly insofar as the the LCD does not contain a viable, timely alternative pathway to coverage.

Under the proposed LCD, a genetic test must have adequate support in one of three databases to be covered: (i) National Comprehensive Cancer Network's (NCCN) database, (ii) National Institutes of Health (NIH)-sponsored clinical genome resource, ClinGen, or (iii) Memorial Sloan Kettering's tumor mutation database, OncoKB™. All tests not supported in one or more of these compendia would be presumptively non-covered, unless/until they successfully complete the LCD reconsideration process. This proposed coverage framework raises several concerns, including:

- *While third-party guidelines/recommendations can provide useful information when deciding whether to cover a test, relying solely on such determinations is not a*

[2] Social Security Act § 1862(l)(5)(D).

permissible substitute for evidence-based, test-specific review. Under the 21st Century Cures Act, MACs must include a "a summary of evidence that was considered **by the contractor** during the development of such determination and a list of the sources of such evidence" (emphasis added) as well as "[a]n explanation of the rationale that supports such determination."[3] Furthermore, while the Medicare Program Integrity Manual allows MACs to "supplement their research… with clinical guidelines, consensus documents, or consultation by experts," the Manual does not allow the MACs use these sources as a substitute for its own review.[4] Therefore, the decision to cover or not cover a particular test must be based on evidence reviewed **by Novitas**, and Novitas must memorialize its rationale by publishing an explanation for the decision. Relying on a third-party database without itself engaging in a test-specific evaluation or offering a test-specific rationale – as proposed – would be contrary to the Act, and amount to a preemptive non-coverage determination without the requisite test-specific, evidence-based review. Such reliance is particularly problematic insofar as there is no assurance that any of the compendia will have reviewed any individual test, particularly for novel assays.

- *Novitas does not have authority to delegate coverage decisions to third parties.* Congress delegated to the HHS Secretary the authority to "enter into contracts with any eligible entity to serve as a [MAC]" and establish LCDs.[5] Congress did not, however, grant the Secretary or the MACs the authority to delegate powers to other private parties. The U.S. Court of Appeals for the District of Columbia Circuit has stated that that "subdelegations to outside parties are assumed to be improper absent an affirmative showing of congressional authorization."[6]

  The court's concern is particularly relevant here. When private entities (like NCCN or MSK) update their databases, or NIH updates ClinGen, they are not required to comply with any of the procedural controls that normally apply to the development of LCDs. Specifically, they are:

  - Not required to issue a proposed decision that explains their rationale;
  - Not required to accept public comments on those proposals;
  - Not required to hold an open meeting to collect stakeholder feedback; and
  - Not required to consider and respond to public comments when finalizing their decisions.

  As a result, the decisions made by NCCN, MSK, and/or NIH are not subject to the same procedural controls and safeguards – and may be made with a different set of substantive considerations – than those that would have been required had the government's authorized delegate (Novitas) made the decision via the process required by law.

[3] *Id.*

[4] Medicare Program Integity Manual ch. 13, § 13.2.3.

[5] 42 U.S.C. §§ 1395kk-1(a)(1), (a)(4).

[6] *U.S. Telecom Ass'n v. F.C.C.*, 359 F.3d 554, 565 (D.C. Cir. 2004).

In support of its ability to delegate coverage decisions to third parties, Novitas points to Medicare's use of third-party compendia when deciding whether to cover certain chemotherapy drugs off-label.[7] However, this precedent is distinguishable from the diagnostic testing in three key respects.

- First, the Social Security Act explicitly requires Medicare to consider certain compendia when determining coverage for off-label uses for cancer chemotherapy drugs.[8] There is no analogous instruction that allows Novitas to use the compendia in the same way for clinical laboratory tests.
- Second, in the cancer drug context, the compendia are used to expand coverage beyond FDA-approved labeling for certain drugs – not to restrict coverage.
- And lastly, even if a particular off-label use is not supported in the compendia, Medicare explicitly retains the ability to review other published literature – i.e., Medicare is not solely bound based on the compendia's decision.[9]

- *Availability of the LCD reconsideration process is not an adequate alternative pathway to coverage.* Novitas states that interested stakeholders may request coverage for a test not supported in one of the three compendia via the LCD reconsideration process. However, this framework would not give test developers and other stakeholders an opportunity for public comment prior to implementation of non-coverage based on the compendia – even if the compendia themselves have not reviewed the evidence supporting a test. Therefore, reliance on the reconsideration process alone does not satisfy the requirement that MACs may not impose a policy restricting coverage for an item or service absent an evidentiary review. Rather, Novitas must review evidence, hold a public meeting, and consider public comment before making a non-coverage decision.

  Furthermore, Novitas makes no commitments regarding the timeframe on which it will substantively consider reconsideration requests, or how often it intends to update the LCD to reflect new evidence. MACs have 60 calendar days to determine whether a reconsideration request is valid.[10] Once determined to be valid, however, CMS does not require the MACs to substantively respond to a reconsideration request within any specific period of time. As such, reconsideration requests may remain in a MAC's queue for several months, if not longer, depending on MAC workloads and priorities. Furthermore, even once a MAC decides to substantively respond to a reconsideration request issuing a proposed LCD, that MAC has up to 365 calendar days to issue a final LCD.[11] As a result, tests not meeting compendia requirements may remain non-covered for multiple years, even if they otherwise have strong evidence supporting assay performance.

[7] Article – Response to Comments: Genetic Testing for Oncology (A59417).

[8] *See* Social Security Act § 1861(t)(2)(B) (applicable to Part B drugs); 1860D-2(e)(4) (applicable to Part D drugs); 1927(g)(1)(B) (applicable to drugs delivered to Medicaid beneficiaries).

[9] *See* Medicare Benefit Policy Manual ch. 15, § 50.4.5(C).

[10] *See* Medicare Program Integrity Manual ch. 13, §13.3.3.

[11] *Id.* §13.5.1.

- *NCCN is the only pathway to coverage for multianalyte algorithmic tests to obtain coverage.* Two of the three databases referenced by Novitas in the proposed LCD – ClinGen and OncoKB – do not review multianlayte algorithmic tests that may combine these variants with an empirically derived algorithm. These databases' restriction to single gene assays is plainly stated in their public-facing materials:

    - ClinGen: "We then use this data to answer a number of key curation questions: Is **this gene** associated with a disease, and by which mechanisms do variation cause this disease? Is **this variant** causative? Will this information affect medical management?"[12] (emphasis added)
    - OncoKB: "Alteration- and tumor type-specific therapeutic implications are classified using the OncoKB™ Levels of Evidence system, which assigns clinical actionability to **individual mutational events**."[13] (emphasis added)

  (At the Open Meeting, a speaker from MSK/OncoKB explained that database does account for certain concurrent gene-gene interactions in its reporting. The speaker did not, however, refute the point that OncoKB does not include recommendations multianlyte algorithmic tests.) As a result, multianalyte tests would only be eligible for coverage if supported in NCCN.

  Reliance on NCCN is not an appropriate substitute for evidence-based, test-specific review, as NCCN guidelines are largely consensus-based and may not reflect input from certain specialties or subsets of healthcare providers.[14] Indeed, NCCN itself acknowledges the limitations of this approach:

  > *The NCCN Guidelines® are a **statement of evidence and consensus of the authors regarding their views** of currently accepted approaches to treatment. **Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.** The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding*

[12] https://clinicalgenome.org/start/.

[13] https://www.oncokb.org/about.

[14] NCCN, Development and Update of Guidelines, https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines (last visited August 2023) ("Recommendations within the NCCN Guidelines are derived from critical evaluation of evidence, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts and researchers in those situations where high-level evidence does not exist. Panels are charged with evaluating the efficacy of treatment, utility of tests or evaluations, and toxicity of the various interventions. Recommendations (or changes to existing recommendations) are agreed upon by Panel Members following review and discussion of the evidence during the Panel meetings. The Panel Members deliberate on the interpretation of the clinical evidence, and vote on how the evidence should be incorporated into the existing Guidelines. The Panel Chair and Panel Members then develop the wording to denote the specific recommendations within the Algorithms.")

> *their content, use or application and disclaims any responsibility for their application or use in any way.*[15]

Furthermore, updates to NCCN can be irregular, varying by disease state,[16] and standards for inclusion may vary significantly between different types of cancer (e.g., breast, bladder, prostate, cutaneous melanoma, and uveal melanoma). And lastly, NCCN guidelines may be challenging for providers (and Novitas itself) to faithfully translate into coverage policy, since certain guidelines are routinely updated, and the documents do not lend themselves to easy implementation of coverage policy (e.g., 84 guidelines consisting of 218 algorithms, as described by NCCN at the 2022 Open Meeting).

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Given the issues outlined above, we respectfully recommend that that Novitas withdraw the draft LCD at the end of the comment period, and convene one or more CAC meetings before engaging in future LCD development in this area. In the event that Novitas elects to finalize the draft LCD, however, we offer the following additional comments for your consideration:

- *The proposed LCD would identify tests supported by a majority of NCCN panel members as non-covered.* Novitas proposes to non-cover tests with a Category "2B" rating in NCCN. NCCN assigns a "2B" rating to tests for which there is NCCN "consensus" – i.e., 50-85% agreement – that the "intervention is appropriate" based on lower-level evidence.[17] It is unclear why Novitas believes tests supported by a majority (or potentially, a substantial majority) of NCCN panel members should be automatically non-covered. We encourage Novitas to remove the presumption against coverage for "2B" rated tests, and at minimum, review claims for such tests on a case-by-case basis consistent with longstanding Novitas practice.

- *The proposed LCD defines "screening" tests in a manner inconsistent with longstanding CMS policy.* The proposed LCD requires patients to have an "established a diagnosis of cancer or found significant evidence to create suspicion for cancer in their patient via a clinical evaluation and abnormal results (cancer or suspicious for cancer) from histologic and/or cytologic examination." In the "Response to Comments" article associated with the now-withdrawn version of L39365, Novitas takes the position that oncology tests performed prior to the availability of such evidence are "screening" tests:

> *Oncologic genetic testing is considered screening if it is performed before the ordering provider either establishes a diagnosis of cancer or a*

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[15] *See, e.g.,* NCCN Guidelines Version 3.2023: Bladder Cancer, https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf, at 3 (emphasis added).

[16] For example, the NCCN guidelines for rectal cancer have been updated 4 times since the start of 2023, while the guidelines for primary cutaneous melanoma have been updated just once (on January 5th, 2023).

[17] NCCN, Development and Update of Guidelines, https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines (last visited August 2023).

substantiated suspicion of cancer through histologic, cytologic, and/or flow cytometric testing.

Novitas's position is not consistent with CMS's longstanding definition of a "screening" test – i.e., a test for patients without "signs or symptoms" of the underlying condition.[18] Indeed, such signs or symptoms of cancer may exist without evidence from a "histologic and/or cytologic examination" – e.g., hematuria in patients suspected of bladder cancer. Therefore, if Novitas elects to finalize the LCD, we urge Novitas to remove the requirement for histologic and/or cytologic results, and permit evidence-based coverage for assays when run on patients with "signs or symptoms" of cancer.

- *Novitas's rationale for limiting coverage to these three specific databases – to the exclusion of all others – is not clear.* C21 appreciates the detailed assessment that Novitas conducted of each of the three databases, and agrees that all three databases may provide useful information to Novitas when evaluating the totality of the evidence supporting an individual test. However, dozens of other professional societies and guideline developers also make evidence-based recommendations regarding molecular diagnostic tests that reflect and/or inform the applicable standard of care, yet do not appear to have been evaluated for inclusion in the LCD. It is unclear why Novitas believes a favorable recommendation in an alternative evidence-based database or professional society guideline would not be sufficient to support a favorable coverage determination.

b. Evidentiary review of 13 specifically listed tests

In addition to our comments about the proposed LCD framework more generally, we offer the following comments in response to the test-specific evidentiary review for the 13 tests:

- *Novitas should restrict longstanding coverage only where supported by new evidence.* Several tests proposed for non-coverage in the draft LCD have been covered by Novitas for many years, including several for which Novitas initially decided to initiate coverage following a detailed review of the available evidence:

Test	Medicare Coverage Effective Date
DecisionDx-Melanoma	December 2018 (Palmetto)
DecisionDx-SCC	April 2022
Cxbladder Detect	July 2020

[18] *See, e.g.,* Screening for Colorectal Cancer – Stool DNA Testing (CAG-00440N), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=277 (last visited August 2023) ("This decision memorandum does not address the use of stool DNA testing as a diagnostic test to evaluate signs or symptoms of colorectal disease. (…) When making national coverage determinations concerning the scope of the CRC screening benefit under Medicare Part B, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that a test is appropriate for general screening in individuals with no signs or symptoms of colorectal cancer.")

Test	Medicare Coverage Effective Date
Cxbladder Monitor	July 2020
Cxbladder Triage	January 2023
PancraGEN	November 2010
UroVysion	July 2014
Colvera	January 2021

C21 agrees that Medicare coverage decisions should be made on the basis of the best available evidence, and therefore, it may be necessary to restrict or remove coverage. That being said, patients and providers alike rely on longstanding coverage determinations, particularly insofar as as such coverage was based on a review of the evidence supporting those tests. Therefore, existing test-specific coverage should be restricted only (a) if new evidence becomes available that reasonably questions whether an assay remains reasonable and necessary, (b) Novitas clearly identifies this new or updated evidence in a draft LCD, and (c) subjects any new or updated conclusions to public scrutiny via the LCD notice and comment process. Insofar as Novitas believes it has such grounds, we request that Novitas reissue the draft LCD to clarify these considerations.

- *Novitas must apply a consistent standard of review to all tests within the scope of the proposed LCD – not a different (higher) standard for specifically reviewed tests.* For compendia-supported tests, Novitas assumes that tests are analytically valid if run in a CLIA-certified laboratory, because "CLIA includes an analysis of accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference interval, and any other performance characteristics required for the test system in the laboratory that intends to use it."[19] However, this same presumption is not afforded to any of the thirteen tests that underwent Novitas's test-specific evidentiary review, even though each of these tests is also performed in a CLIA-certified laboratory. Insofar as Novitas believes performance in a CLIA laboratory is sufficient to establish analytical validity for compendia-supported tests, it should make similar assumptions when it conducts a test-specific evidentiary review.

- *Novitas must consider and substantively respond to stakeholder comments on its test-specific evidentiary review of the 13 tests.* At the Open Meeting, Novitas stated that it is particularly interested in reviewing "new evidence" not already listed in the bibliography of the LCD. C21 agrees that evidence not previously considered would be highly probative, but also believes Novitas must review and respond to all comments submitted on the LCD, including comments regarding:
    - The overarching framework for review of evidence (e.g., overall approach, level of evidence required);

[19] Article – Response to Comments: Genetic Testing for Oncology (A59417).

- Novitas's interpretation of the literature cited in the proposed LCD (e.g., if a cited article does not reflect the intended use population of the test, or has some other limitation that explains reported performance characteristics);
- Published literature not included in the LCD;
- Other clinical guidelines and consensus statements not referenced in the proposed LCD; and
- Clinician experience with such tests (even if unpublished).

Notwithstanding Novitas's prior review of certain documentation, nothing in the Program Integrity Manual allows Novitas to ignore or not respond to public comments supported by evidence, even if such evidence relates to data the MAC may have already considered.

- *Novitas must consider and respond to stakeholder feedback, even if unpublished.* While C21 agrees that published evidence is an important component of any evidentiary review for an LCD, nothing in the Program Integrity Manual explicitly prohibits MACs from considering unpublished feedback. Indeed, the Manual actually suggests that such review and response is required, as it requires MACs to respond to "all timely received public comments" in the comment/response article.[20]

c. Concerns with coding article

In the proposed coding article (DA59125), Novitas does not identify any "unspecified" laterality codes or codes for cancer of unknown origin as covered when reported for genetic testing services. Insofar as Novitas decides to finalize the LCD, we urge Novitas to add both sets of codes for the reasons set forth below.

When treating physicians are considering genetic testing for oncology patients, they are looking for specific genetic variants or signatures in the tumors in order to guide treatment. The specific location where the tumor originated is generally no longer relevant by the time patients are referred for genetic testing to guide treatment. For example, when a patient presents with advanced non-small cell lung cancer, the location of the original tumor (e.g., right upper lobe versus left lower lobe) is irrelevant to selecting an appropriate chemotherapeutic or immunotherapeutic regimen to be guided by genetic testing.

In addition, by the time a patient presents to an oncologist with advanced cancer, it may not always be clear at that point where the tumor originated. Therefore, when the treating physician refers patients for genetic testing at that point in the course of their disease, the treating physician may not specify the originating site of the tumor nor provide an ICD-10-CM code as the referring diagnosis that is specific to the laterality or location of the originating tumor. Novitas's proposal to exclude ICD-10-CM codes from the list of covered codes that describe unspecified sites (e.g., ICD-10-CM C34.00, C34.10, C34.30, C34.80, and C34.90 for malignant neoplasm of lung)[21] would negatively impact access to medically necessary genetic testing in such cases

[20] Medicare Program Integrity Manual ch. 13, §13.5.5.

[21] **C34.00** *"Malignant neoplasm of unspecified main bronchus"*
C34.10 *"Malignant neoplasm of upper lobe, unspecified bronchus or lung"*
C34.30 *"Malignant neoplasm of lower lobe, unspecified bronchus or lung"*

where the treating physician is unable to or otherwise does not provide more specific information to determine the laterality of the original tumor. And, as noted above, knowing and reporting the laterality of the original tumor is generally irrelevant to the purpose and use of genetic testing for patients with cancer. The testing is medically necessary consistent whether or not the originating site of the tumor was on the right or left or in an upper lobe or lower lobe.

Furthermore, some patients present with advanced cancer where the origin of the tumor is unknown (commonly referred to as Cancer of Unknown Primary). Under these circumstances, genetic testing can still help help guide treatment decision making. Exclusion of codes C80.0 *"Disseminated malignant neoplasm, unspecified"* and C80.1 *"Malignant (primary) neoplasm, unspecified"* would block access to genetic testing in this patient population for whom genetic testing may be critically important to guide therapy.

Consistent with our request, CMS covers both unspecified laterality codes and Cancer of Unknown Primary codes, where appropriate, for next generation sequencing tests covered under NCD 90.2.[22]

* * * *

C21 is grateful for the opportunity to comment on the proposed LCD, and would be pleased to meet with Novitas if it has any questions. Please contact me at hmurphy@c21cm.org or (916) 835-5117 should you have any questions or if we can provide you with further information.

Sincerely,

Hannah Murphy

C34.80 *"Malignant neoplasm of overlapping sites of unspecified bronchus or lung"*
C34.90 *"Malignant neoplasm of unspecified part of unspecified bronchus or lung"*

[22] *See* Transmittal 12184 (Change Request 13278) (Aug. 3, 2023), r12184otn.pdf (cms.gov), at pgs. 12-69.

Commentary on Novitas LCD

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Conflicts of Interest:
Yair Lotan: Consultant
Nanorobotics, C2I genomics, Photocure, Astra-Zeneca, Merck, Fergene, Abbvie, Nucleix, Ambu, Seattle Genetics, Hitachi, Ferring Research, verity pharmaceutics, virtuoso surgical, Stimit, Urogen, Vessi medical, CAPs medical, Xcures, BMS, Nonagen, Aura Biosciences, Inc., Convergent Genomics, Pacific Edge, Pfizer, Phinomics Inc, CG oncology, Uroviu, On target lab

Daniel Barocas: Pacific Edge, Ambu, Lantheus, Pfizer, On target labs

Sam Chang: Consultant
Astellas, Merck, Janssen, Pfizer, Virtuoso Surgical, Photocure, Tu Therapeutics, Nonagen, Pacific Edge , Urogen, Prokarium, Valar Science

Siamak Daneshmand
Consultant for: Janssen, Ferring, Photocure, Taris, Spectrum, Pacific Edge, BMS, Sesen, Protara, Pfizer, CG Oncology

Badrinath Konety: Consultant for Pacific Edge, Astrin Biosciences, Asieris Pharmaceuticals, Convergent Genomics, Illumina, Ferring Pharmaceuticals, Styx Biotechnology, Geneverify.

Joshua Meeks: Consultant: Merck, AstraZeneca, Incyte, Janssen, BMS, UroGen, Prokarium, Imvax, Pfizer, Seagen/Astellas, Research Funding: VHA, NIH, DoD, Compensation for talks/educational courses: AUA, OncLive, Olympus, UroToday, Clinical Trials: SWOG, Genentech, Merck, AstraZeneca, Incyte

Sima Porten: Research with, KDx, Nonagen and Signatera, Consultant with Pacific Edge.

Jay Raman: Education Chair for American Urological Association; Investment interest in United Medical Systems; Ongoing research with MDxHealth, Pacific Edge, Urogen Pharma, Steba Biotech

Charles Rosser: Executive team for Nonagen Bioscience Corp.

Kristen Scarpato: Photocure, CxBladder

John P Sfakianos: Natera and pacific edge.

Wade J. Sexton: Pacific Edge, Urogen Pharmaceuticals

Neal Shore: Arquer,Astra Zeneca, Aura biosciences, Diacarta, Ferring, Janssen, MDxHealth, Merck, Pacific Edge, Photocure, Protara, Roche

Robert Svatek: Consultant CG Oncology and Verity Pharma

The role of biomarkers (aka, markers) in detecting and managing cancer is an evolving field. It is crucial to develop biomarkers robustly that mirror drug development in the pharmaceutical industry. The goal for markers should be to provide a clear benefit in managing patients that is additive to both clinical and laboratory information. Markers should be developed in phases, with initial assay development and validation followed by clinical studies to evaluate the marker's performance characteristics in assessing specific clinical conditions (e.g., sensitivity, specificity, predictive value) and ability to improve a clinically meaningful outcome. Ultimately, economic validation is also

warranted, especially as we move forward with value-based healthcare. Trials should focus on answering specific clinical questions and thereby demonstrate the incremental value of the marker in predicting the benefit of a treatment or detection of a defined disease state. Additionally, the benefits of the marker need to be balanced by any harmful interpretation that can occur from false positive and false negative results, which could lead to patient anxiety, unnecessary costs, and as well as potentially incorrect clinical decision making predicated on test result.

While clinical utility is arguably the most important parameter to judge the value of a marker in managing a patient, acceptable reimbursement is a critical component for the viability of a marker. A marker with evidence-based utility which is not reimbursed will thus render it unavailable for patients and clinicians thereby forfeiting a valuable tool(s) in clinical decision making. Novitas Solutions, Inc. (Novitas) provides administrative services for government-sponsored healthcare programs and serves as a Part A/B Medicare Administrative Contractor (MAC) under multiple contracts for the Centers for Medicare and Medicaid Services (CMS). As a MAC, Novitas serves as a single point-of-contact entity processing Medicare Part A and B claims from hospitals and other institutional providers, physicians and practitioners. Novitas serves the Medicare Program in Jurisdiction L, which encompasses Delaware, New Jersey, Pennsylvania, Maryland, as well as the District of Columbia, and Jurisdiction H which includes Arkansas, Colorado, Louisiana, Mississippi, New Mexico, Oklahoma and Texas. The recent release of a draft local coverage determination (LCD Genetic Testing for Oncology) by Novitas proposes a fundamental change to the criteria Novitas would use to determine coverage for molecular diagnostic tests.

In the draft LCD, Novitas proposed a new external review model for coverage determined only by including or excluding the tests or biomarkers in one of a limited number of external databases and published guidelines (references to ClinGen, NCCN, and OncoKB). Before the draft LCD, the established determination process was for MACs to determine coverage and reimbursement through a product-specific internal review of the published literature. Such a change in the LCD would drastically impact urine-based tumor marker use and accessibility since Novitas proposes to severely limit coverage for a variety of markers.

While this draft specifically focused on a few urine markers (among other molecular tests) including the Cxbladder urinary tests (detect, triage, and monitor urine-based markers) and UroVysion fluorescence in situ hybridization (FISH), this approval process change could have a profound ripple effect with significant deleterious impact on other current and future urine marker tests. Hence, it is of paramount importance to consider the implication of such a ruling for additional biomarker accessibility, the merits of the decision and, most importantly, its implication for optimized clinical care.

When considering urine marker development for bladder cancer, there has been considerable effort to identify candidate markers or panels of markers to improve the evaluation of at-cancer risk patients, especially those with hematuria, and to enhance

surveillance of bladder cancer specifically.[1-3] It is important to delineate the specific clinical scenario which in turn can significantly impact the type of marker needed. A comprehensive marker evaluation may not always capture the specific value in answering a clinical question. For example, a marker used to help determine which patients with hematuria should undergo further evaluation would optimally have a high negative predictive value (NPV) so that cancer is not missed rather than a high positive predictive value (PPV) which limits evaluation to only a small percentage of patients. The rationale for the aforementioned approach being that if patients meet the criteria for microhematuria with current recommendations to perform cystoscopy in most cases, then excluding patients at extremely low risk for cancer could be an excellent way to improve compliance (and decrease costs) with evaluation while limiting unnecessary procedures (cystoscopy and imaging).[2,4,5]

Furthermore, any positive marker result (whether true or false) would be followed up with a cystoscopy, thereby avoiding incremental testing beyond current standard of care. In other clinical scenarios, such as patients with abnormal cystoscopy or cytology that is atypical but not conclusive for cancer, a marker with a high PPV would be valuable since the goal would be to biopsy those patients who are likely to have cancer but avoid unnecessary surgery in patients who may have inflammation or other benign changes. The American Urologic Association (AUA)/ Society of Urologic Oncology (SUO) guidelines for non-muscle invasive bladder cancer (NMIBC) already state that a clinician **may use biomarkers** to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™).[6] A recent publication also found that CxBladder Monitor could adjudicate patients with atypical cytology or equivocal cystoscopy[7], showing up to 35% of patients can avoid unnecessary further procedures.

There are several concerns with the types of criticisms raised by Novitas in the draft LCD (Genetic Testing for Oncology). The first is based on limited published guidelines (references to ClinGen, NCCN, and OncoKB). The NCCN guidelines are focused on patients with a known diagnosis of cancer, and their only statement on pre-diagnosis is a recommendation for all patients with hematuria to undergo cystoscopy. As such, they do not focus on evaluating hematuria or managing unique scenarios like atypical cystoscopy or cytology, which urologists routinely must manage. The AUA has developed guidelines for managing hematuria in conjunction with the Society of Urodynamics Female Pelvic Medicine and Urogenital Reconstruction (SUFU)[5].

Similarly, the AUA and SUO developed guidelines for the management of NMIBC[6]. These guidelines include standardized methodology and evaluation of all available data with recommendations based on robust levels of evidence. They evaluate the role of urine markers and other tests for detecting and managing bladder cancer. It would be inappropriate for Novitas to ignore the recommendations of these widely accepted guidelines in making decision regarding reimbursement/coverage.

Novitas did not specify why it was excluding the Urovysion FISH assay, which has been FDA-approved for more than two decades and whose use has been supported by the AUA guidelines to assess response to intravesical BCG and adjudicate equivocal cytology (as noted above). They had specific concerns regarding the Cxbladder line of tests. While Novitas focused on these markers, many criticisms could be applied to other urine markers.

One comment focused on the fact that the tested patient population included a strong bias towards male patients of European ancestry and that the Cxbladder tests have not been adequately investigated in the context of the Medicare population. The focus on male patients is inherent in all studies related to bladder cancer because there are more than three times as many bladder cancer cases in men relative to women. In 2023, of the 82,290 newly diagnosed bladder cancer patients, there were 62,420 men versus 19,870 women[8]. There is a significantly higher rate[9] of bladder cancer in whites relative to non-white populations. The average annual age-standardized incidence in the US was 0.49, 0.61, 0.4, and 0.46 relative to whites for black, American Indian, and Alaska Native, Asian American and Pacific Islander, and Hispanic, respectively. Moreover, it is challenging to enroll many minority patients in large bladder cancer trials since they represent a smaller percentage of the prevalence population and have a lower relative cancer rate.

It is also unclear why Novitas asserted that Cxbladder tests were not vetted in the context of Medicare patients since the average age of bladder cancer patients is over 70. In the study evaluating CxBladder Monitor, 82% of the patients were over 60[10] years of age. Thus, it seems this marker is particularly focused on the Medicare population, as is the case for most markers used for bladder cancer surveillance. Another area of concern raised by Novitas pertained to issues related to false positive tests. There is no question that most urine markers suffer from a low PPV, impacting their clinical performance, interpreting Clinical scenarios where a patient undergoes a surveillance cystoscopy with no demonstrable tumor albeit with a positive urine marker presents a clinical conundrum. In such cases, whether the white light cystoscopy "missed" cancer or the marker is falsely positive is a dilemma. The use of enhanced cystoscopy has illustrated the fact that white light cystoscopy can miss some papillary tumors and carcinoma in situ, which may result in a positive marker[11]. Multiple papers have been published on "anticipatory" positive results for many different markers[12-14], finding that patients with a positive marker are more likely to recur during an extended follow up than patients with a negative marker. The important question is the role of the marker in this setting. For example, the PPV of markers is much higher if there are equivocal findings on cystoscopy which resulted in the AUA guidelines supporting the use of markers in that setting[15]. In the case of the Cxbladder monitor test, the design of the test was to focus on NPV and not PPV. Since the marker was designed to optimize sensitivity, it is not surprising that the specificity is lower. If one tries to avoid cystoscopy in some patients, the high NPV will facilitate reducing the number of cystoscopies. Similarly, an attempt to reduce cystoscopy in patients with low-risk clinical features with microscopic hematuria would also benefit from a marker with high NPV. There is still a need for ongoing trials to support this latter use. A randomized trial

is underway to obtain the evidence needed to result in guideline recommendations for the use of a marker in the hematuria evaluation (NCT03988309). In summary, the performance characteristics of markers may vary in terms of optimizing PPV or NPV and they should be judged on their clinical utility.

Another concern raised in the Novitas draft document focuses on how the studies were funded. Novitas notes that most of the primary literature regarding Cxbladder test development and performance is funded, if not directly underwritten, by the test's parent company, Pacific Edge Diagnostics. This should be fully addressed as the development of almost all US markers, devices, and pharmaceuticals is funded by industry. Conflict of interest should indeed be considered in reviewing papers. Still, marker development is usually performed at tertiary medical centers and advanced community care centers. The company is blinded to the results of cystoscopy when analyzing markers, and the urologist is blinded to the results of the marker when performing cystoscopy. To suggest that there is a bias in testing performance suggests an incomplete understanding of prospective observational biomarker study designs. Furthermore, there is a "catch" for validating markers independent of company support early in marker development. Namely, until there is coverage for markers, it would be almost impossible to use markers in routine clinical practice given cost to individual patients. Thus, the imperative for outsourced funding, whether industry or government, to obtain data across a cohort of patients. Also, until there is payor coverage, there are only a limited number of laboratories who will perform the assay. As such, marker companies must be involved in development and validation of their assays.

This commentary is not meant to be a broad appeal for the indiscriminate coverage for all urine markers for detection and management of bladder cancer. We acknowledge that many of the authors of this commentary have consulted with Pacific Edge and other urine marker companies. However, the authors are clinical scientists who have a strong interest in improving the care of patients suspected to have or with bladder cancer and have been involved in research with urine markers and continue to evaluate new markers. While that can be perceived as a conflict, we are not intending to endorse a particular marker with this commentary. Our goal is to encourage fair evaluation of bladder cancer markers for their intended use. There should also be balanced assessment of markers across the disease spectrum. In table 1, the performance characteristics of prostate and bladder cancer-related markers are enumerated, and one can see that there are not many differences in performance characteristics between some of the covered prostate cancer markers compared to the uncovered bladder cancer markers. Future decisions on coverage should take into consideration the available marker data published in the literature, intended use of marker, expert opinion, and stated position of stakeholders such as the AUA, SUO, SUFU, etc. through their guideline and expert opinion panels.

Table 1: Performance Characteristics of Prostate and Bladder Cancer Related Markers

	Molecular marker	AUC	Sensitivity	Specificity	PPV	NPV	Medicare LCD	references
Prostate Biomarker Test								
Serum-Based Biomarkers								
Prosate-Specific Antigen	PSA	0.55[16]	60%[17]	79%[17]	22%[18]	93.8%[18]	LCD - Biomarker Testing for Prostate Cancer Diagnosis (L37733)	(16) Auprich M, et al. Eur Urol. 2011;60: 1045-1054., (17) Oto Jet al. Sci Rep. 2020; 10: 2463. (18) de la Calle C, et al., J Urol. 2015 Jul;194(1)
PHI	total PSA, Free-PSA, p2PSA isoform	0.71[19]	82%[20]	80%[20]	27%[21]	97%[21]	LCD - Biomarker Testing for Prostate Cancer Diagnosis (L37733)	(19) Nordström T, et al. Eur Urol.2015; 68: 139-146. (20) Al Saidi SS, et al. Oman Med J. 2017; 32: 275-283. (21) White J, et al. Prostate Cancer Prostatic Dis. 2018; 21: 78-84.
4KScore	total PSA, Free-PSA, intact PSA, hK2	0.8-0.9[22]	75%[19]	65%[19]			LCD - Biomarker Testing for Prostate Cancer Diagnosis (L37733)	(19) Nordström T, et al. Eur Urol.2015; 68: 139-146. 922) Zappala SM, et al. Rev Urol. 2017; 19: 149-155.
Urine-Based Biomarkers								
ExoDx Prosate IntelliSore (EPI)	Exosomal RNA - SPDEF, PCA3, ERG	0.7[23]	92%[23]	34%[23]	35%[23]	91%[23]	LCD - Biomarker Testing for Prostate Cancer Diagnosis (L37733)	(23) McKiernan J, et al. JAMA Oncol. 2016; 2: 882-889.
MiPS Michigan Prostate Score	PCA3 and TMPRS52 mRNA	0.69[24]	93%[25]	33%[25]			LCD - Biomarker Testing for Prostate Cancer Diagnosis (L37733)	(24) Tomlins SA, et al. Eur Urol. 2016;70: 45-53. (25) Gene-based tests for screening, detection, and/or management of prostate cancer. Medical Policy Manual Genetic Testing. 2020; Policy No. 17

								http://www.policy.asuris.com/geneticTesting/gt17.pdf
Progensa (PCA3)	Long Non-coding RNAs	0.73[26]	69%[26]	65%[26]	34%[27]	90 %[27]	LCD - Biomarker Testing for Prostate Cancer Diagnosis (L37733)	(26) Nicholson A, et al., Health Technol Assess. 2015; 19: 1-191. (27) Physician Brochure for the PRoGensa® PCa3 assay
SlectMDX	HoXC6 and DLX1 mRNA	0.71-0.83[28]	91%[28]	36%[28]	45%[29]	95%[29]	LCD - Biomarker Testing for Prostate Cancer Diagnosis (L37733)	(28) Van Neste L, et al. Eur Urol. 2016; 70:740-748. (29) Haese A et al., J Urol. 2019 Aug;202(2):256-263.
Tissue-Based Biomarkers								
ConfirmMDX	DNA Hypermethylation - GsTPA, APC, RASSF1	0.74[30]	68%[30]	64%[30]		96%[30]	LCD - Biomarker Testing for Prostate Cancer Diagnosis (L37733)	(30) Van Neste L, et al. Prostate. 2016; 76: 1078-1087.
Bladder Biomarker Test								
Urine-Based Biomarkers								
Cytology	Cell Phenotype		38%[31]	98%[31]	64.%[32]	88%[32]	Lab: Bladder/Urothelial Tumor Markers (L36678)	(31) Blick, C.G., et al., BJU Int. 2012, 110, 84–94. (32) Dimashkieh H, et al.,Cancer Cytopathol. 2013 Oct;121(10):591-7
UroVysion	FISH		72%[33]	83%[33]	46%[32]	92%[32]	Lab: Bladder/Urothelial Tumor Markers (L36678)	(32) Dimashkieh H, et al.,Cancer Cytopathol. 2013 Oct;121(10):591-7 (33) T.Hajdinjak, T. UroVysion FISH Test for Detecting Urothelial Cancers: Meta-Analysis of Diagnostic Accuracy and Comparison with Urinary Cytology Testing; Elsevier: Amsterdam, The Netherlands, 2008; pp. 646–651. (20)Dimashkieh H, et al., Cancer Cytopathol. 2013 Oct;121(10):591-7

CxBladder (Detect)	mRNA -IGFBP5, HOHA13, MDK, CDK1, CXCR2	0.87[34]	82%[34]	85%[34]	25%[35]	97%[35]		(34) O'Sullivan, P. et al.,J. Urol. 2012, 188, 741–747. (35) Lotan et al., J of Urology April 2023; 209:762-772
NMP-22	Nuclear matrix protein 22 ELISA	0.73[34] (17)	69%[36]	77%[36]		87%[37]	Lab: Bladder/Urothelial Tumor Markers (L36678)	(34) O'Sullivan, P. et al.,J. Urol. 2012, 188, 741–747. (36) Hu, X. et al., Cancers 2022, 14, 3181. (37) Lotan et al., 2017
NMP-22 BladderChek	point of care test		58%[36]	88%[36]		86%[37]	Lab: Bladder/Urothelial Tumor Markers (L36678)	(36) Hu, X. et al., Cancers 2022, 14, 3181. (37) Lotan et al., 2017
CxBladder (Monitor)	2 clinical features and mRNA - IGFBP5, HOHA13, MDK, CDK1 , CXCR2		91%[37]			96%[37]		(37) Lotan et al., 2017
ImmunoCyt	IHC	0.79[38]	73%[36]	66 %[36]	26–67%[39]	91–96%[39]	Lab: Bladder/Urothelial Tumor Markers (L36678)	(36) Hu, X. et al., Cancers 2022, 14, 3181. (38) He H,et al., Oncol Lett. 2016 Jul;12(1):83-88. (39) Fradet Y, Lockhard C., Can J Urol. 1997;4:400–405.

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Dear Dr. Mann,

We are writing in response to your open request for comment on DL39365. This letter also addresses the draft LCD from First Coast Service Options. We have numerous concerns regarding the LCD, but most critically, the evidentiary review associated with the non-coverage determination of Cxbladder products.

EXECUTIVE SUMMARY:

- This letter contains Pacific Edge's response to the LCD for our Cxbladder Triage (0363U) and Detect (0012M) tests which are indicated for the hematuria evaluation in patients with no prior diagnosis of urothelial carcinoma (UC) as well as the Cxbladder Monitor test (0013M) which is indicated for surveillance of patients diagnosed with non-muscle invasive bladder cancer (NMIBC).
- We maintain that our published clinical data supports the inclusion of Cxbladder Triage and Detect for specific patient populations in the clinical pathway for hematuria evaluation, and the published clinical data supports the inclusion of Cxbladder Monitor into the clinical pathway for surveillance of patients diagnosed with non-muscle invasive bladder cancer(1-4).
- The letter also references three Cxbladder tests (Cxbladder Resolve, Enhanced Detect, and Enhanced Triage) referenced in the LCD that are in development and not commercially available and therefore are not appropriate for an evidentiary review or inclusion/exclusion from coverage(5).
- We share our medical rebuttal to many of the points made in the evidentiary review on the LCD that we believe do not reflect the clinical value of the tests and the substantial clinical evidence developed to validate them.
- Pacific Edge respectfully makes the following requests for changes to the LCD.

REQUESTS

1. ***We request Cxbladder Triage, Detect, and Monitor be included as covered tests in the final LCD language for the specific patient populations outlined below. The published clinical evidence and the demonstrated real world clinical value of these tests with high negative predictive value affirms the need for continued access of these tests to the Medicare population (see appendix for specific evidence).***
2. ***If Novitas does not support the request above:***
    a. ***We request that all tests in the hematuria evaluation pathway be completely removed from this LCD as they do not fit the inclusion criteria which requires an***

established diagnosis or significant suspicion of cancer. This removal would include Cxbladder Triage and Detect.

b. ***We request that once removed from LCD DL39365, Cxbladder Triage and Detect continue to be covered per the guide and documentation requirements of LCA 58917 as currently covered when the tests are documented as medically necessary by the treating physician.***
c. ***We request that Novitas convene a Contractor Advisory Committee session to determine if urinary biomarkers should be included in an existing or new LCD.***

3. ***We request that all mentions of Enhanced Cxbladder Detect, Resolve or Enhanced Cxbladder Triage be removed from the LCD as these tests are not available for clinical use. The data supporting the analytic validity, clinical validity, and clinical utility of these tests is still under development.***

SUPPORT FOR REQUESTS:

Support for Request #1

We request Cxbladder Triage, Detect, and Monitor be included as covered tests in the final LCD language for the specific patient populations outlined below. The published clinical evidence and the demonstrated real world clinical value of these tests with high negative predictive value affirms the continued access of these tests to the Medicare population.

Rationale:

<u>Cxbladder Detect</u>

Clinical Scenario and Patient Population

Cxbladder Detect is intended for use with patients presenting with any microhematuria to risk stratify those patients into low, intermediate, and high risk of bladder cancer. This stratification can reduce the burden of investigations for the low and intermediate risk patients after shared decision making with the patient and prioritize those with high risk for full investigation. The test can also be used to adjudicate diagnostic dilemmas when cytology is equivocal, or cystoscopy is un-informative in both microscopic and gross hematuria patients.

There are approximately 7 million patients in the US that present annually with hematuria, of which 75% present with microhematuria (defined as ≥3 RBC/HPF and with no visible blood in urine).

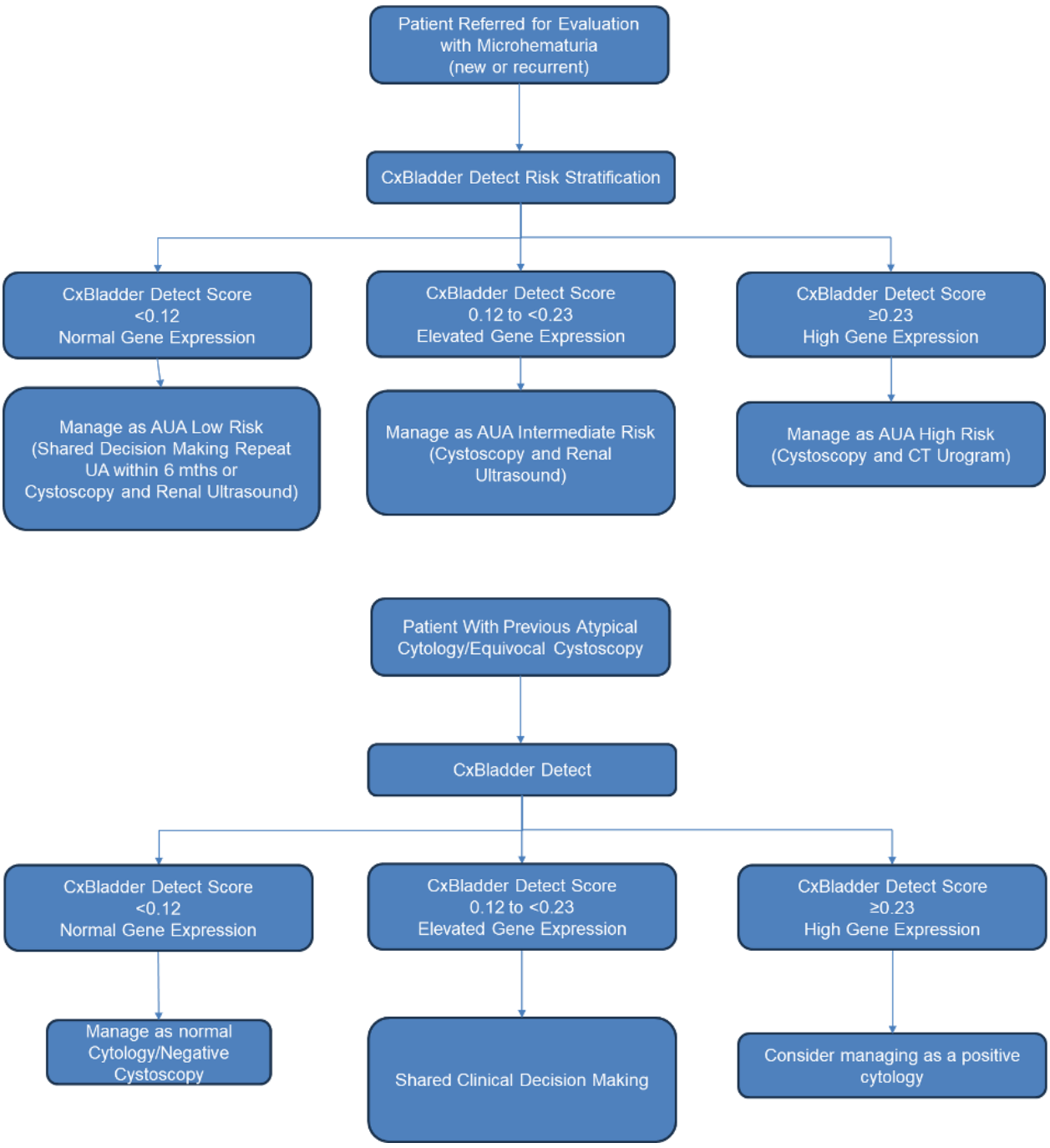
These patients are risk stratified by AUA guidelines into low, intermediate, and high risk microhematuria based on clinical and demographic factors with the approximate percentages being 5%, 12%, and 83% respectively(6).
Studies have shown that most of these patients do not have UC, with prevalence data showing approximately 5% of patients having UC(6).
The current standard of care for those patients is dependent on their risk stratification, where only low risk patients are counseled to return in 6-8 months for another urine analysis (UA) to determine if they need a full workup. Intermediate and high-risk patients on the other hand are provided a full workup, including a cystoscopy, to assess the bladder and CT (Computerized Tomography) urography to assess the upper tract. The risks associated with this standard of care are those associated with any invasive procedure including infections, urethral damage, and any allergic reactions to contrast agents used for CT urography to name a few.

The clinical utility of Detect is driven by the high negative predictive value that identifies the patients that present with microhematuria that are at significantly lower risk of currently having UC so that they can be given lower intensity diagnostic evaluations. The value to the Medicare population of adopting Detect prior to cystoscopy is the reduction of unnecessary cystoscopy and imaging procedures for patients who do not need it, while simultaneously improving the yield of cancer diagnoses within the patients that do receive the full workup.

Proposed Eligibility Criteria for Cxbladder Detect

- Microhematuria (MH) patients referred to the urology office for evaluation.
    - MH is defined as ≥3 RBC/HPF with no visible blood in urine.
    - Gross hematuria for adjudication of diagnostic dilemmas.
- Non-malignant or gynecologic causes ruled out by urologist prior to ordering the test.
    - UTI (urinary tract infections), kidney stones, etc..., ruled out.

The diagram below illustrates the two clinical pathways for Cxbladder Detect:



Conclusion

Cxbladder Detect should be a covered benefit for Medicare patients under the LCD because:

- It has demonstrated analytical validity, clinical validity, and clinical utility in published studies ***(see appendix for specific studies)***.
- The current standard of care drives significant overuse of diagnostic procedures, specifically invasive and unpleasant cystoscopy. For lower risk patients, this has a

disproportionate impact on the elderly given the higher rates of complications in patients with multiple co-morbidities.

The clinical value of expanded use of tests with high negative predictive value also benefits patients as it reduces the financial burden on the health care system by removing patients from unnecessary procedures with no impact on patient outcomes.

Cxbladder Triage

Clinical Scenario and Patient Population

Triage is indicated to risk stratify and identify lower-risk hematuria patients to reduce the burden of unnecessary investigations. It is intended for use by primary care physicians or at the urology office to prioritize patients and manage unnecessary referrals for more invasive evaluation at the urology office.
The clinical utility of Triage is to identify the patients that present with 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 Triage prior to cystoscopy is reduction of unnecessary cystoscopy and imaging procedures for patients at lower risk, while simultaneously improving the yield of cancer diagnoses within the patients that do receive the full workup.

Proposed Eligibility Criteria for Cxbladder Triage

- Microhematuria (MH) patients at the Primary care office, or low risk patients referred to the urology office.
- MH is defined as ≥3- 25 RBC/HPF with no previous incidence of gross hematuria.
- Non-malignant or gynecologic causes ruled out by urologist prior to ordering the test.
    - UTI, kidney stones, etc..., ruled out.

Conclusion
Cxbladder Triage should be a covered benefit for Medicare patients under the LCD because:

- It has demonstrated analytical validity, clinical validity, and clinical in published studies ***(see appendix for specific studies).***
- The current standard of care drives significant overuse of diagnostic procedures, specifically invasive and unpleasant cystoscopy. For lower risk patients, this has a disproportionate impact on elderly patients given the higher rates of complications in patients with multiple co-morbidities.

The clinical value of expanded use of tests with high negative predictive value also benefits patients as it reduces the financial burden on the health care system by removing patients from unnecessary procedures with no impact on patient outcomes.

Cxbladder Monitor

Clinical Scenario and Patient Population

The Cxbladder Monitor test is intended for use in patients with prior diagnosis of NMIBC that are on a surveillance protocol for follow up for recurrence of disease. The test is intended for use starting at 9 months post diagnosis of either primary or recurrent disease with no recurrence in between. The test should be used in an alternating fashion with cystoscopy to reduce the diagnostic burden on these patients. Patients with a negative test (NPV (Negative Predictive Value) 97%) can defer the cystoscopy to the next scheduled surveillance visit with no impact in identifying recurrence. Those patients with a positive test should continue with the normal surveillance protocol.

There are approximately 800,000 patients that are seen annually for UC recurrence in the U.S. Bladder cancer has a high rate of recurrence with a 1-year recurrence rate of 15-61%, and a 5-year recurrence rate of 31-78%(7). Therefore, patients are subjected to a frequent and intensive monitoring schedule. These patients generally follow a surveillance protocol that calls for cystoscopy at regular intervals depending on the risk classification of those patients (AUA guidelines table below). High and intermediate risk patients are followed up every 3 months for the first two years of surveillance, every 6 months for years 3-4, then annually afterwards with no set limit to stop surveillance. Low risk patients are recommended for follow up at 3 months post diagnosis, 9-12 months after that, then annually for the next 5 years. It is important to note that all these recommendations are restarted if recurrence of disease occurs, and cystectomy is not recommended.

The risks associated with this standard of care are similar to those described above for the hematuria evaluation, with the added risk of repeat incidence of the same problems over a prolonged period of surveillance.

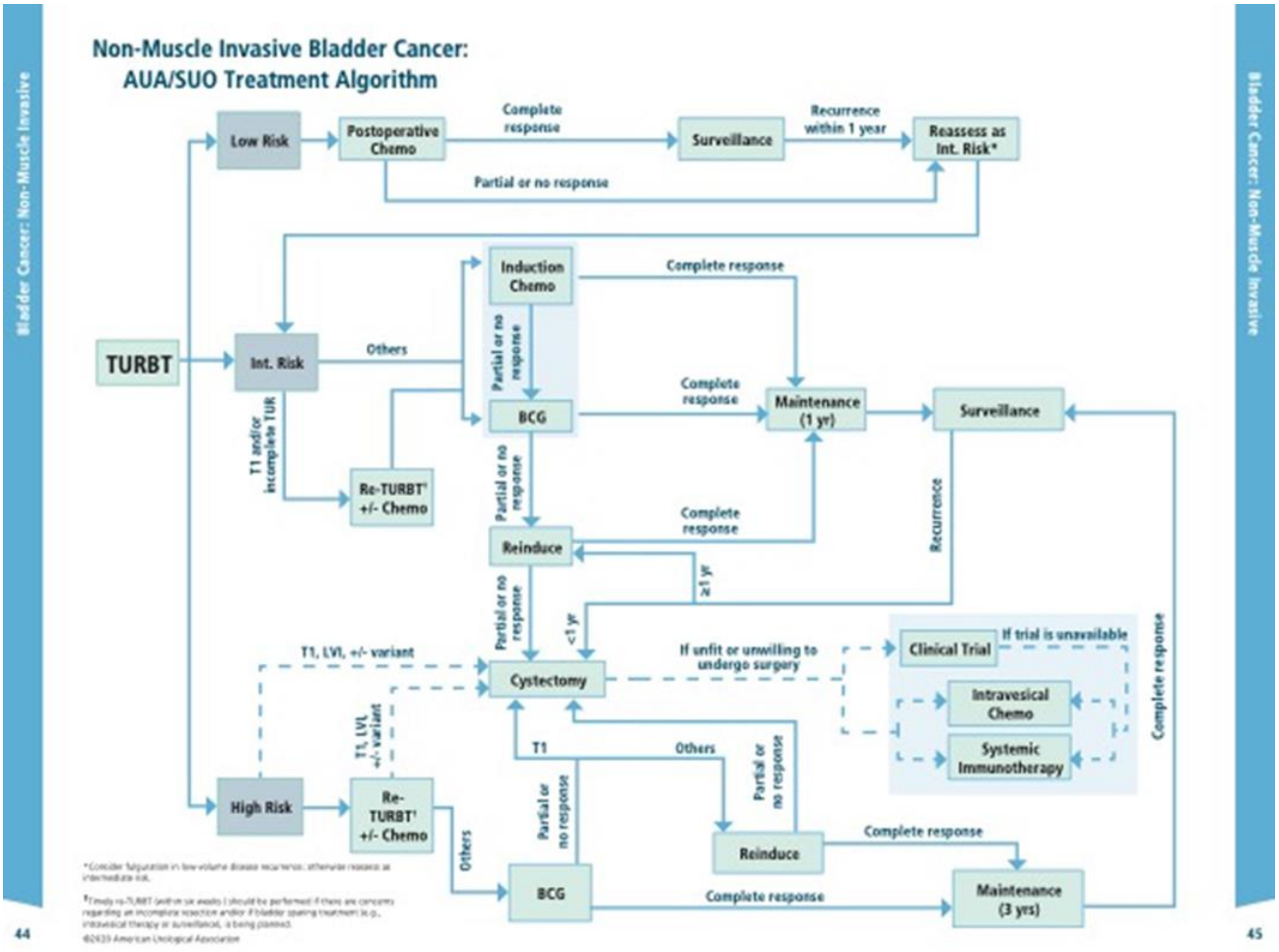
The clinical utility of Monitor is to identify the patients that are at a low enough risk of recurrence so that they can safely alternate cystoscopy with Cxbladder Monitor test within the timeframes of standard of care.

The value to the Medicare population of alternating Monitor with cystoscopy during standard surveillance protocols is to reduce the burden of invasive procedures on the patient and health care system and improve patient compliance with the surveillance protocols. If low risk patients can safely defer the surveillance visit and alternate with the test, the higher risk patients will have priority at the urology office and early detection of any recurrence will be standard of care.

The chart below is AUA guideline for NMIBC.

Table 2. *AUA risk stratification for non-muscle invasive bladder cancer*

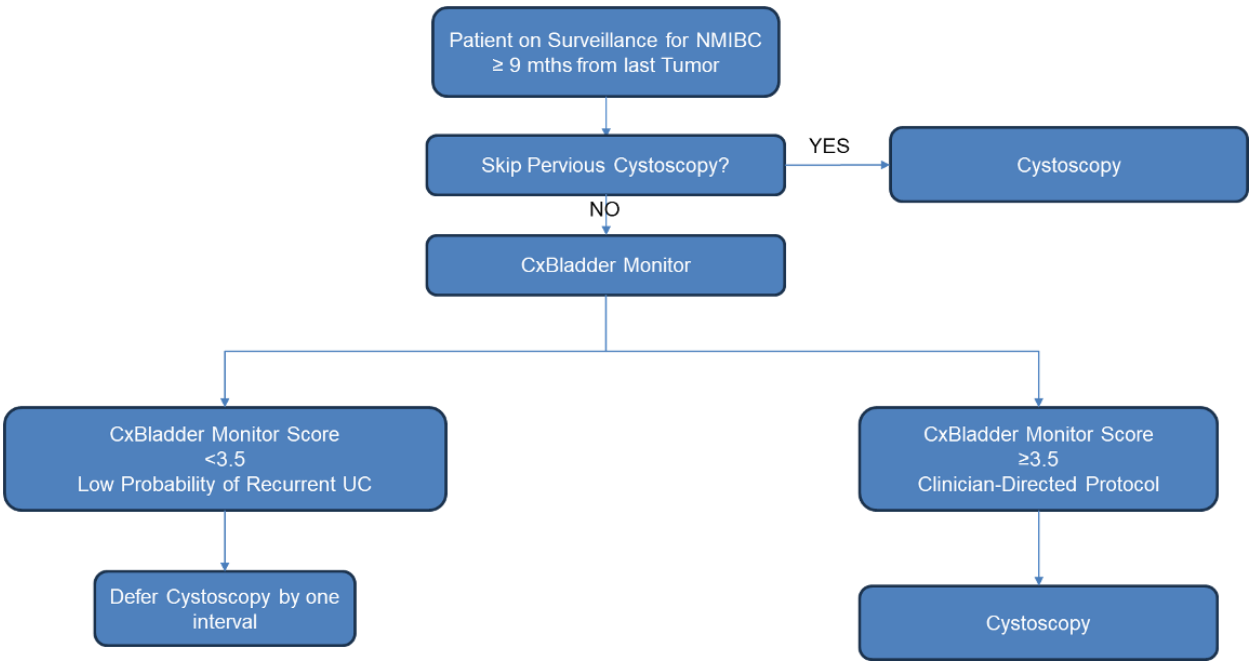
Low Risk	Intermediate Risk	High Risk
Low grade solitary Ta ≤ 3 cm Papillary urothelial neoplasm of low malignant potential	Recurrence within 1 year, low grade Ta Solitary low grade Ta >3 cm Low grade Ta, multifocal High grade Ta, ≤3 cm Low grade T1	High grade T1 Any recurrent, high grade Ta High grade Ta, >3 cm (or multifocal) Any CIS Any BCG failure in high grade case Any variant histology Any LVI Any high grade prostatic urethral involvement



Proposed eligibility criteria for Cxbladder Monitor test:

- Patients with previously diagnosed urothelial cancer (primary or recurrent, any risk classification) have at least 9 months of recurrence free follow up. Those patients may alternate the Cxbladder Monitor test with regular cystoscopy and can prolong the duration between cystoscopies based on a negative Monitor test.

- Low risk patients who have no recurrence for 3 years. Those patients can be setup to receive a Cxbladder Monitor test every 6-12 months in place of regular cystoscopy. Positive Monitor test should be referred for cystoscopy.
- Intermediate and High-risk patients who have no recurrence for 5 years. Those patients can be setup to receive a Cxbladder Monitor test every 6 months in place of regular cystoscopy. Positive Monitor test should be referred for cystoscopy.



Conclusion

Cxbladder Monitor should be a covered benefit for Medicare patients under the LCD because.

- It has demonstrated analytical validity, clinical validity, and clinical utility in published studies (see Appendix for specific studies)
- The current standard of care drives significant overuse of diagnostic procedures, specifically invasive and unpleasant cystoscopy. For lower risk patients the overuse of invasive procedures has a disproportionate impact on elderly patients given the higher rates of complications in patients with multiple co-morbidities. These benefits are exaggerated in the surveillance population due to the repetitive nature of surveillance. The more patients can avoid unnecessary procedures, the better quality of life for those patients.

- The clinical value of expanded use of tests with high negative predictive value also benefits patients as it reduces the financial burden on the health care system by removing patients from unnecessary procedures with no impact on patient outcomes(8).

Support for Request #2

Request 2a -The focus of this LCD is on genetic tests that are performed after a biopsy-proven (histologic or cytologic) diagnosis of cancer or substantiated suspicion of cancer based on histology or urine cytology. As Cxbladder Triage and Cxbladder Detect are indicated for patients with hematuria prior to a diagnosis of cancer. Hematuria appears not to meet the requirements for suspicion of cancer set forth in the draft LCD, yet hematuria is a key factor in determining if a full diagnostic workup for urothelial cancer is warranted according to the urology community standard of care. If in the final LCD hematuria is not recognized as a substantiated suspicion of bladder cancer, **then Cxbladder Triage and Cxbladder Detect tests as well as any other tests performed for the evaluation of hematuria where a diagnosis of bladder cancer has not yet been substantiated based upon histologic or cytology findings should not fall under such LCD.** Neither a coverage determination nor a non-coverage determination is appropriate under this LCD for Cxbladder Triage and Detect because it is not the intended purpose of these tests to be ordered in patients for whom the diagnosis of bladder cancer has already been made. It is also worth noting that the NCCN (National Comprehensive Cancer Network) guidelines, which are used as one of the criteria for coverage in this LCD, do not address hematuria evaluation at all—these guidelines focus on the evaluation and management of patients with bladder cancer. As such, inclusion of tests for the evaluation of hematuria in this proposed LCD is not appropriate given that three knowledge bases referenced in the LCD would not include RNA based test indicated for hematuria evaluation.

Request 2b – If Novitas and First Coast concur that Cxbladder Triage and Detect should not be included in the LCD, **we respectfully request that Medicare coverage continue as it has been since July 2020**. This coverage should include a specific reference in LCA 58917 or other appropriate articles providing clarity to clinicians and Medicare Advantage payers on the positive coverage of Triage and Detect. It would cause significant confusion in the marketplace if Triage and Detect were removed from the current LCD and not referenced in another Novitas document. Any such confusion would be detrimental to Medicare beneficiaries given that these tests have been consistently covered for multiple years.

Request 2c - If Novitas and First Coast determine that Cxbladder Triage and Detect's use falls outside of the current LCD, it will be important to develop an LCD for urinary biomarkers for the evaluation and management of patients with hematuria as that is a critical part of the bladder cancer diagnostic process. **It is our recommendation that a new LCD should be developed with the support of convening a Contractor Advisory Council to ensure that input from clinician experts treating Medicare beneficiaries is part of the LCD development**.

Request 3 - Cxbladder Resolve, Cxbladder Enhanced Triage, and Cxbladder Enhanced Detect are not currently clinically available in the U.S. These tests have not been fully validated at this point. Therefore, we believe it is premature and inappropriate to include a detailed evidentiary review of these tests resulting in preemptive non-coverage in the draft LCD and that **these tests should be excluded from the LCD**.

The Novitas/FCSO review included evaluation of Cxbladder Resolve and the "enhanced" Cxbladder tests that include single nucleotide polymorphisms. These are tests under development and have not been validated for clinical use at this time. None of these are commercially available in the US. Indeed, large prospective multicenter clinical trials are currently underway (Appendix) to provide evidence of clinical validity and clinical utility of those tests and their clinical applications. When these tests have been fully validated and are being offered for clinical use, then it may be appropriate for Novitas/FSCO to evaluate the evidence and determine if these tests meet the requirements to be medically reasonable and necessary.

We thus believe the criticism of these tests as having insufficient evidence is premature and should not influence the assessment for coverage of the commercially available tests, specifically, Triage, Detect, and Monitor.

Request Summary

We respectfully request that Novitas re-evaluate the important clinical role that Cxbladder Triage, Detect, and Monitor have in the hematuria evaluation and recurrence monitoring pathways for bladder cancer. We believe that our requests are supported by the clinical evidence and the needs of clinicians and patients. Our requests are consistent with the LCD and supported by the primary clinical organizations and societies within the urology community.

COMMENTS ON EVIDENTIARY REVIEW OF CXBLADDER PUBLISHED LITERATURE:

Detailed comments responding to the evidentiary review in the draft LCD are presented below for Cxbladder Triage, Detect, and Monitor. These comments form a significant portion of the rationale for inclusion of the Cxbladder tests as covered test in the LCD as the review of the published literature included several incorrect assumptions and misunderstandings. Taken as a whole, the comments below show that the published data on the Cxbladder products surpasses the level of evidence required for Medicare coverage as medically reasonable and necessary.

1) THE HOLYOAKE STUDY IS A BIOMARKER DEVELOPMENT STUDY, NOT A VALIDATION STUDY

Novitas/FSCO considered the Holyoake study to be the initial development study for Cxbladder Triage and Detect and conclude that the study does not show that the tests distinguish among various types of cancers. This assessment is then used as the basis for determining that none of the Cxbladder tests meet the reasonable and necessary coverage criteria because they were built on a faulty foundation. However, the evidentiary review does not reflect the fact that the Holyoake study was designed to identify potentially relevant biomarkers to help inform development of the Cxbladder assays – it was not designed as an initial study supporting the validity of the assays themselves.

In their review, Novitas has claimed that our initial development study(9) was flawed in its design:

> "This means that a well-designed test will be able to not only discriminate between cancer and normal tissue, but also between different types of malignancy."(10) (p.32)

In another portion of the review Novitas states:

> "One very notable gap included a lack of details or definition for non-urothelial cancers, of which many would feed into the urinary system, including prostate cancers, renal cancers, and metastatic or locally invasive cancers from other organs(10)."
>
> *** * ***
>
> "This first paper from 2012 also does not sufficiently address Cxbladder' s ability to distinguish between urothelial carcinoma and other malignancies, which is of particular relevance when a majority of the patient population were male (78%) with a median patient age of 64 years and thus, with higher risk of prostate carcinoma."(10) (p.33)

The Holyoake (2008)(9) paper is fundamentally misinterpreted to be a "development study" for clinical assays. This study was a "biomarker discovery" study aimed to identify which biomarkers play a role in various cancers that could subsequently inform the development of the Cxbladder assays which then would be assessed in future studies to determine the analytical validity, clinical validity, and clinical utility of the specific assays developed. Concluding that the Cxbladder assays do not meet criteria for reasonable and necessary based on a biomarker discovery study is not appropriate because such a study does not evaluate any specific test nor is it intended to provide evidence of the analytical validity, clinical validity, or clinical utility of any test developed comprising any biomarkers discovered in such a study.

Furthermore, these excerpts above from the review show an unfamiliarity with the established clinical pathway for the management of patients presenting with hematuria that supports the clinical utility and intended use of our tests. The Cxbladder Triage and Detect tests were developed to determine if a urine-based test can distinguish between presence or absence of urothelial cancer with the stated goal of reducing the burden of unnecessary invasive procedures (cystoscopy, CT-Urogram, ureteroscopy) for ***patients presenting with hematuria***.

The purpose of the development study was ***not*** to develop a test to distinguish between urothelial carcinoma and other types of cancer. We also point out that prostate cancer does not typically

present with hematuria and neither prostate nor renal cancers are diagnosed by cystoscopy. Both of these cancers have their own presentation symptoms and signs and have pre-defined diagnostic pathways that best represent how they are diagnosed. The Cxbladder tests were developed specifically to address the clinical management of patients presenting with hematuria in the absence of other known benign or malignant disease where there is suspicion of bladder cancer and more invasive evaluation for bladder cancer (i.e., cystoscopy) is being considered. The Cxbladder tests were not designed to address other clinical questions, such as patients presenting with an elevated PSA (Prostate Specific Antigen) being evaluated for prostate cancer or patients presenting with a renal mass being evaluated for renal cell carcinoma. We have heard from the urology community that use our tests are helpful in the clinical evaluation of patients with hematuria and monitoring for recurrence as these tests address the likelihood that the patient has bladder cancer, which is the key question in the evaluation of these patients. We have been told by several urology stakeholders that they plan to comment on the draft LCD reinforcing these points.

Our tests were developed for the purpose of reducing the investigative burden on patients with substantiated suspicion of disease by standard of care, i.e., those patients presenting with hematuria, and for these purposes, Cxbladder tests perform exactly as intended. The tests should remain covered accordingly.

2) THE DRAFT LCD DOES NOT REFLECT THE ESTABLISHED CLINICAL PATHWAYS IN WHICH THE CXBLADDER TESTS ARE USED

Novitas appears to have misunderstood the clinical value and benefits of our tests in their review of literature. In our response above, we have included both written and graphic descriptions of the clinical scenarios in which the Cxbladder products are used to benefit patients. The written descriptions are copied below for your reference. Pacific Edge would strongly support assembling a Clinical Advisory Committee (CAC) comprising experts in the management of patients presenting with hematuria to inform the development of any coverage policy addressing the use of urinary biomarkers in the management of hematuria. Pacific Edge is willing and ready to collaborate with the Novitas/FCSO medical team at any time to provide appropriate additional information on the utility and benefit of the Cxbladder Triage and Detect tests in the Medicare population.

We provide here the intended clinical pathways for the Cxbladder Triage and Detect tests together with the data supporting their Analytical Validation (AV), Clinical Validation (CV), and Clinical Utility (CU).

a- **Cxbladder Triage Test:** Intended to risk stratify and identify lower risk microhematuria patients to reduce the burden of unnecessary investigations. It is intended for use by primary care physicians or advanced practice clinicians (e.g., NPs or PAs) to prioritize

patients and manage unnecessary referrals for more invasive evaluation at the urology office.

b- **Cxbladder Detect Test:** Intended for use in urology practices with any microhematuria patient to risk stratify those patients into low, intermediate, and high risk of bladder cancer. It is intended to reduce the burden of investigations for the low and intermediate risk patients after shared decision making with the patient and prioritize those with high risk for full investigation. The test can also be used to adjudicate diagnostic dilemmas when cytology is equivocal, or cystoscopy is un-informative in both microscopic and gross hematuria patients.

c- **The Cxbladder Monitor Test:** Intended for use in patients with prior diagnosis of NMIBC that are on a surveillance protocol for follow up for recurrence of disease. The test is intended for use starting at 9 months post diagnosis of either primary or recurrent disease with no recurrence in between. The test should be used in an alternating fashion with cystoscopy to reduce the burden on these patients. Patients with a negative test (NPV 97%) can defer the cystoscopy to the next scheduled surveillance visit, those with a positive test, should be referred for cystoscopy.

The Appendix summarizes the studies used to provide the validation and utility of these tests in these specific patients.

3) Patient demographics

The Novitas/FCSO review included a concern that there is a male bias in the studies supporting the use of the Cxbladder Triage and Detect tests. We disagree with this critique of the evidence base. Bladder cancer has a much higher incidence in men than women with diagnoses in the USA 3-4x more frequently in men than women (https://www.cancer.org/cancer/types/bladder-cancer.html). If the studies had an equal balance of men and women, then the studies would not be representative of the target population.

4) Discrimination between Urothelial Cancer and Other Cancer Types

As discussed above, the LCD does not reflect the intended use and clinical value of Cxbladder Triage and Detect. These tests are not designed to distinguish between multiple cancers or serve as multi-cancer early detection (MCED) tests trying to answer whether the patient has a cancer anywhere. These are risk stratification tests that specifically attempt to reduce the use of unnecessary, invasive, and potentially harmful investigations (cystoscopy, CT Urogram, ureteroscopy) in populations with substantiated suspicion of urothelial cancer(11). In the case of Cxbladder Triage this includes patients presenting with hematuria that have a high chance of normal evaluation, but for whom American Urological Association (AUA) guidelines advocate more invasive investigations. Prostate cancer is not diagnosed through cystoscopy or CT Urogram

and rarely presents with hematuria unless very advanced. The fundamental question answered by Cxbladder tests is "can a negative test identify a patient with a low enough risk of the presence of urothelial cancer that can avoid further unnecessary evaluation" and for that question the test has performance characteristics that provide high clinical value. In addition, patients presenting with other types of urogenital cancers have a unique set of symptoms and signs that are specific to those cancers. Urological societies have separate diagnostic pathways in their respective guidelines for evaluation of those patients. In the case of prostate cancer, initial workup depends on an elevated level of PSA and not hematuria. If the PSA level is elevated, patients can undergo multiple imaging studies (U/S, MRI) prior to a decision for biopsy which would be the only true diagnostic step for prostate cancer(12). In the case of renal cell carcinoma, patients will usually present with dull aching pain in their loin with or without a palpable mass. These patients are referred to CT scan to identify the lesion and are managed completely differently than UC in the upper tract(13).

5) Criticism for lack of studies done independently of Pacific Edge

We do not believe that company sponsorship of clinical trials is a valid criticism of our studies as that practice is common in the industry. The Novitas review mentions that part of the problem is lack of confidence in Pacific Edge data since many of the studies reviewed were either funded or performed by Pacific Edge Limited. Most new drugs, biologicals, devices, and diagnostics have the development studies funded by the sponsor because there is no other entity who is likely to conduct the necessary studies to determine the safety/effectiveness (drug/biological/device) or AV/CV/CU (diagnostic). If these studies have appropriate trial designs for the intended uses and the data is analyzed consistent with prospectively established analysis plans, then these studies can be considered appropriate for coverage review. It is imperative for our company and others to maintain the highest quality of evidence by supporting such studies to ensure that patients and physicians have access to high quality data. We would also maintain that although many of the studies were funded by Pacific Edge, there were many well respected thought leaders in the field that participated in the design and execution of these studies to prove the value of these tests for their patients, including Medicare patients. All published data was subject to peer review and external editor questions that is designed to confirm the validity of the data. Finally, Novitas does not mention in its review that several of our recent, most powerful real-world evidence for the clinical utility of Cxbladder tests were done with no company support. Specifically, for Cxbladder Triage in Davidson et al (2019 and 2021)(14, 15) and for Cxbladder Monitor in Li et al (2023)(8) were all conducted completed independently of Pacific Edge with no financial support and no provision of testing resources by the company.

6) Short follow up

Another criticism of the data supporting the use of Cxbladder tests was the short follow up time. The suite of Cxbladder tests address a relative short-term clinical question—when patients present with hematuria, can the tests identify patients with such low risk of bladder cancer that more invasive testing can be avoided at that time. The Cxbladder tests are not intended for

treatment predictive or prognostic uses. Foundationally, this means that they are designed to inform an **immediate decision** regarding whether invasive procedures, e.g., cystoscopy, CT Urogram, ureteroscopy that are mandated by the guidelines can be safely omitted or not for a defined patient population. As they are neither predictive nor prognostic tests, they are not designed to assess the risk of developing cancers in the future. **Therefore, the follow-up included in each study is appropriate for the intended clinical use.**

In the case of Triage and Detect tests, the intended clinical use is for patients presenting with primary or recurrent microhematuria. In the clinical application of these tests, the risk stratification can either determine that the patient has a "Low Probability of UC" (Cxbladder Triage report; see Appendix) or "Normal gene expression score" (Cxbladder Detect report; see Appendix). In each case such a report enables the physician and patient to safely *defer* a full evaluation for Urothelial cancer if they choose to do so. A "not negative" Cxbladder Triage result of "Standard clinical workup" is an indication to follow standard of care. A Cxbladder Detect result of "high gene expression score" is a higher likelihood of disease with a recommendation to follow AUA guidelines evaluation steps and initiate a full workup. In AUA guidelines, the recommendation of low-risk patients with hematuria would be to bring them back at ***6-9 months*** for a repeat urine analysis to assess if the hematuria persists. This means that the follow up provided in our studies is appropriate for those patients.

7) Criticism of low positive predictive value

In the draft LCD, Novitas/FCSO raise concerns about the PPV (Positive Predictive Value) for the Cxbladder Triage and Detect tests. This concern reflects a misunderstanding of the intended use of our tests as a rule out bladder cancer tests. The draft LCD states,

> "These values 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." (10) [(p.35)]

As explained previously in the document, these tests were optimized for high sensitivity and high NPV intended to help identify low risk patients that can be safely ruled out from a diagnosis of bladder cancer in order to reduce the burden of unnecessary procedures on patients. The clinical value of our tests in the hematuria evaluation population (Triage and Detect) is to identify those patients that have the low likelihood of urothelial cancer and thus can defer further unnecessary workup. If any of our tests are ***positive***, the patient is to continue with the normal guidelines recommended investigations for their hematuria. In the absence of such high NPV tests, all patients presenting with hematuria would be subject to a full invasive workup even though the prevalence of UC is low. Thus, if the value of the test is fully understood, no additional burden of testing or morbidity from a positive test will be encountered.

Furthermore, all our marketing materials along with our scientific medical exchanges explain clearly to physicians that point and provide recommended explanations for patients on the value of the negative to reduce the anxiety that may be caused by a non-negative result. In addition,

the evidentiary review included in the draft LCD did not include the fact that the guideline directed standard of care has many more patients receiving a full workup, with many of those patients being disease free, which translates to a much higher rate of anxiety and concern on the part of the patients, as well as an increased financial burden on the system and patients alike(16).

8) Lack of data on patients with Inflammatory processes

The LCD review also notes that our studies excluded patients with inflammatory processes (exclusion of active UTI, UT manipulations, etc.). We find this to be a lack of understanding of how our test is developed and how it is being utilized by over 4,000 physicians in the marketplace. Our Cxbladder Triage and Detect tests are indicated for patients that present with hematuria where inflammatory or infectious causes have been ruled out and the clinical concern is focused on the diagnosis of bladder cancer and the extensive evaluation required.

Cases with high inflammation can negatively impact the test results and may cause an unwarranted false positive or false negative and therefore we exclude patients with conditions that can be associated with inflammation (see below). We attempted to reduce the impact of high inflammation samples by adding the 5th gene (CXCR2) which is an inflammatory gene to reduce that risk(2). Although the inclusion of the 5th gene did reduce the impact of inflammation considerably(2), along with many other minor changes we had made to the process, it did not eliminate it completely. Therefore, in accordance with our commitment to the highest standards and to maintain the best outcomes for our patients, we do not accept any commercial samples from patients with any of these issues. In fact, here are our exclusions for our commercial samples:

Exclusions for COLLECTION PROCESS: (see appendix)

- Visible blood
- Dip sticks cannot be left in urine cup before transferring to Cxbladder tube.

WAIT 6 WEEKS FROM:

- BCG (Bacillus Calmette Guérin) therapy
- Mitomycin therapy
- Radiation therapy
- Any bladder manipulation

WAIT 2 WEEKS FROM:

- Catheterization
- Cystoscopy
- Bladder infection or UTI (should finish antibiotics and wait 2 weeks)
- Trace leukocytes

Thus, we are consistent in our inclusion and exclusion criteria for both our studies and our commercial usage. We excluded those patients from our studies and from our commercial acceptance criteria to provide the highest level of service for the other patients that would benefit from our tests.

SUMMARY OF COMMENTS ON EVIDENTIARY REVIEW

The comments above represent a response to the criticisms Novitas found in their evidentiary review of the Cxbladder data. We believe that Novitas misinterpreted important aspects of our published literature which led to incorrect conclusions about the strength of our data in the clinical care of patients at risk or with confirmed bladder cancer. We respectfully suggest that the criticisms should be re-examined in light of our comments and should not invalidate the clinical data that has been developed for Cxbladder tests.

Appendix - Summary of clinical evidence

		Study	Pop. Type	Sensitivity (Sn)	NPV	Specificity (Sp)	PPV	Comment
Triage	**AV**	Kavalieris et al., 2015	MH + GH*	95%	98%	45%	--	Sn, Sp, NPV values when test-negative rate is 40%
	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**)	(**3**)	--	--	--	Cxbladder (**3**) correctly adjudicated all UC confirmed patients (*n*=26) with atypical urine cytology results (*n*=153, **4**); test-negative rate of 35%.
		Raman et al., 2021	MH + GH* (**5**)	92.6%	99.6%	--	--	Test-negative rate of 52%.
		Lotan et al., 2023	MH + GH*	89%	99%	63%	16%	Pooled data from US and Singapore cohorts (*n*=804), test-negative rate of 59%.
	CU	Davidson et al., 2020	MH + GH*	89.4% (**6**)	98.9% (**6**)	59% (**6**)	--	39% of patients testing negative for CxbT & imaging did not get cystoscopy & were managed at primary care (**7**), test-negative rate of 53%.
		STRATA (unpublished) (**8**)	MH + GH*	--	--	--	--	*Study in progress*

Detect	**AV**	O'Sullivan et al., 2012	GH*	81.8%	97%	85.1%	--	0.12 test score cut-off - CxbD detected 97% of HG tumors & 100% of >T1 tumors
				77%	96%	94%	--	0.23 test score cut-off – PPV 68%; unpublished data after paper O'Sullivan paper publication
	CV	Lotan et al., 2023	MH + GH*	74%	97%	82%	25%	Pooled data from US and Singapore cohorts (*n*=804), test-negative rate of 78%.
		DRIVE (unpublished) (**1**)	MH + GH*	--	--	--	--	*Study in progress*

		Study	Pop. Type	Sensitivity (Sn)	NPV	Specificity (Sp)	PPV	Comment
Monitor	**AV**	Kavalieris et al., 2017	(**1**)	88% (**2**)	97% (**2**)	--	--	(**3**), test-negative rate of 34%.
	CV	Konety et al., 2019	(**4**)	100% (**5**)	--	--	--	Cxbladder (**5**) correctly adjudicated all UC confirmed (*n*=26) with atypical urine cytology results (*n*=153, **6**), test-negative rate of 35%.
	CU	Koya et al., 2020	(**7**)	--	--	--	--	Integration of CxbM into surveillance schedule could reduce annual cystoscopies by 39% (**8, 9, 10,11**)
		Li et al, 2023	(**12**)	100%	100%	78%	33%	A prospective multi-institutional study of CxbM to reduce surveillance frequency during the coronavirus pandemic, test-negative rate of 73%.
		Sfakianos et al (unpublished)	(**13**)	--	--	--	--	A retrospective audit of clinical use of CxbM with patients undergoing surveillance cystoscopy

	References
Triage	Davidson et al., (2019). Inclusion of a molecular marker of bladder cancer in a clinical pathway for investigation of haematuria may reduce the need for cystoscopy. NZ Med J, 132(1497), 55-64.
	Davidson et al., (2020). Assessment of a clinical pathway for investigation of haematuria that reduces the need for cystoscopy. NZ Med J, 133(1527), 71-82.
	Kavalieris et al., (2015). 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 urology, 15(1), 1-12.
	Konety et al., (2019). Evaluation of Cxbladder and adjudication of atypical cytology and equivocal cystoscopy. European urology, 76(2), 238-243.
	Raman et al., (2021). The diagnostic performance of Cxbladder Resolve, alone and in combination with other Cxbladder tests, in the identification and priority evaluation of patients at risk for urothelial carcinoma. The Journal of Urology, 206(6), 1380-1389.
	Lotan et al., (2023). Urinary Analysis of FGFR3 and TERT Gene Mutations Enhances Performance of Cxbladder Tests and Improves Patient Risk Stratification. The Journal of Urology, 209(4), 762-772.

Detect	Lotan et al., (2023). Urinary Analysis of FGFR3 and TERT Gene Mutations Enhances Performance of Cxbladder Tests and Improves Patient Risk Stratification. The Journal of Urology, 209(4), 762-772.
	O'Sullivan et al., (2012). A multigene urine test for the detection and stratification of bladder cancer in patients presenting with hematuria. The Journal of Urology, 188(3), 741-747.

	References
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.
	Konety et al., (2019). Evaluation of Cxbladder and adjudication of atypical cytology and equivocal cystoscopy. European urology, 76(2), 238-243.
	Koya et al., (2020). An evaluation of the real world use and clinical utility of the Cxbladder Monitor assay in the follow-up of patients previously treated for bladder cancer. *BMC urology*, *20*(1), 1-9.
	Li et al., (2023). Cxbladder Monitor testing to reduce cystoscopy frequency in patients with bladder cancer. *Urologic Oncology: Seminars and Original Investigations, 41(7), 326.e1-326.e8.*
	Lotan et al., (2017). Clinical comparison of noninvasive urine tests for ruling out recurrent urothelial carcinoma. *Urologic Oncology: Seminars and Original Investigations*, 35 (8), 531-539.
	Sfakianos et al, unpublished

Appendix: – Cxbladder Test reports

Cxbladder™ DETECT

PACIFIC EDGE DIAGNOSTICS USA LTD

Patient Name:
Patient Date of Birth:
Patient Sex:
Medical Record #:

Sample ID:
Alternate ID:
Specimen Source:
Specimen Collection Date:
Specimen Receipt Date:
Specimen Report Date:
Report Status:
ICD-10 Code:
Ordering Clinician:

Test Result: Cxbladder Detect score

NORMAL Gene Expression Score	ELEVATED Gene Expression Score	HIGH Gene Expression Score

0.00 0.12 0.23 1.00

Negative UC Detection — Positive UC Detection

Comments:

Results Interpretation:

The Cxbladder Detect test was developed and validated on 476 patients recruited under an international multicenter clinical study of patients presenting with macro-hematuria. The patients were allocated to a group of 317 for development and 159 for validation. 100% of T1, T2, and T3 tumors were placed in the 'HIGH Gene Expression Score' region and 67% of the Ta tumors in the 'ELEVATED or HIGH Gene Expression Score' regions. A Cxbladder Detect score of greater than or equal to 0.12 has a sensitivity of 82% and a specificity of 82%. Cxbladder Detect is a development from the clinical study published in J. Urology (2012) 188:741-747.

NORMAL Gene Expression Score < 0.12	A score of < 0.12 has an NPV of 97%. High probability of NO urothelial carcinoma.
ELEVATED Gene Expression Score 0.12 ≤ score < 0.23	A score of 0.12 ≤ score < 0.23 has an NPV of 94%. Low probability of urothelial carcinoma, however a change in the pattern of gene expression of the biomarkers from what is normal suggests further clinical evaluation.
HIGH Gene Expression Score ≥ 0.23	A score of ≥ 0.23 has a specificity of 94% and a PPV of 68%. High probability of urothelial carcinoma.

Assay Description:

Cxbladder Detect is a quantitative test that uses reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) to measure five mRNA biomarkers (CDK1, MDK, IGFBP5, HOXA13 and CXCR2) in a small sample of a patient's urine. An algorithm is applied to the measured quantities of these biomarkers to calculate a composite Cxbladder Detect score ranging from 0.00 to 1.00. Cxbladder Detect test results are intended to aid in the detection of urothelial carcinoma (UC) when used in conjunction with standard clinical assessment.

Reviewed By: Thomas P. Nifong, MD (electronically signed)
Laboratory Director, Pacific Edge Diagnostics USA Ltd

Disclaimer: This is a high complexity clinical test developed by and its performance characteristics determined by Pacific Edge Ltd. This test is for clinical purposes and is intended to aid the clinician in determining the likelihood of the presence of urothelial carcinoma (UC). It should not be regarded as investigational or for research only. This test has not been approved by the US Food and Drug Administration (FDA) and such approval is not required. The laboratory is regulated under Clinical Laboratory Improvement Amendments of 1988 (CLIA).

Pacific Edge Diagnostics USA Ltd, Hershey Center for Applied Research, 1214 Research Boulevard, Suite 2000, Hummelstown, PA 17036
Tel: 1-855-CXBLADR (1-855-292-5237) Fax: (717) 220-7006 Email: us.info@cxbladder.com Web: www.cxbladder.com
CLIA #: 39D2053269 PA Permit #: 032894 MD Permit #: 1976 CA License #: COS 800426 FL License #: 800026956 RI License#: LCO00827 CAP 8714655

Cxbladder™ TRIAGE

PACIFIC EDGE DIAGNOSTICS USA LTD

Patient Name:
Patient Date of Birth:
Patient Hematuria History:
Patient Hematuria Status:
Patient Smoking History:
Patient Sex:
Medical Record #:
Sample ID:
Alternate ID:
Specimen Source:
Specimen Collection Date:
Specimen Receipt Date:
Specimen Report Date:
Report Status:
ICD-10 Code:
Ordering Clinician:

Test Result: Cxbladder Triage score

Comments:

Results Interpretation:

Cxbladder Triage Score <4.0	This test has a Negative Predictive Value (NPV) of 98.5%, and a Sensitivity of 95.1%. Low probability of urothelial carcinoma (UC).
Cxbladder Triage Score ≥4.0	Continue with the clinician-directed standard clinical workup to establish if urothelial carcinoma (UC) is present.

The Cxbladder Triage test was developed and internally validated on 587 patients from three clinical cohorts of patients presenting with macrohematuria, and evaluated on a cohort of 40 patients presenting with microhematuria. The proportion of patients without urothelial carcinoma (UC) was 87.7%. With the test negative rate of 40%, the observed Negative Predictive Value (NPV) was 98.5% and the Sensitivity was 95.1% for the segregation of patients with a low probability of having UC. All false negatives were low-grade Ta tumors (WHO98 classification).

Cxbladder Triage has been developed and validated for the segregation of patients who have a low probability of having UC and is intended to be used in conjunction with standard clinical workup for patients presenting with hematuria who may not require further evaluation for UC. Interpretation of other conditions and/or malignancies in patients have not been validated.

Assay Description:

Cxbladder Triage is a qualitative assay for urothelial carcinoma (UC) that combines the quantitative measure of gene expression from five mRNA biomarkers (CDK1, MDK, IGFBP5, HOXA13, and CXCR2) as measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR) from a small sample of the patient's urine and four patient characteristics: patient age, sex, smoking history and hematuria history. An algorithm is applied to these nine parameters to calculate a Cxbladder Triage Score ranging from 0 to 10 and using a cut-off of 4.0 identifies those patients with a low probability of having UC. Cxbladder Triage is a development from the clinical study published in BMC Urology (2015) 15:23.

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Laboratory Director, Pacific Edge Diagnostics USA Ltd

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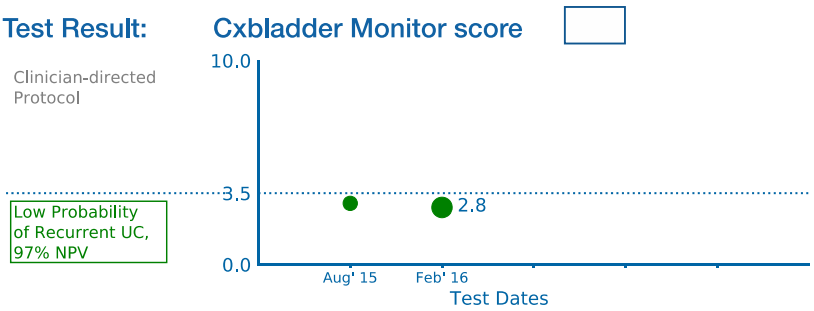
Cxbladder™ MONITOR

PACIFIC EDGE DIAGNOSTICS USA LTD

Patient Name:
Patient Date of Birth:
Patient Sex:
Medical Record #
Date of Last UC Diagnosis:
Last UC Diagnosis:

Specimen Source:
Sample ID:
Alternate ID:
Specimen Collection Date:
Specimen Receipt Date:
Specimen Report Date:
Report Status:
ICD-10 Code:
Ordering Clinician:

Test Result:



Comments:

Results Interpretation:

Cxbladder Monitor Score ≥ 3.5	A clinician-directed protocol to determine the presence of recurrent UC, is warranted.
Cxbladder Monitor Score < 3.5	This test has a Negative Predictive Value (NPV) of 97%, and a sensitivity of 93%. Low probability of recurrent UC.

The Cxbladder Monitor test was developed as a 'rule out' test for recurrence of urothelial carcinoma (UC). A total of 763 patients were recruited (1,036 samples) in a multicenter clinical study of patients undergoing routine clinical surveillance for recurrent UC. A classifier was created that uses two variables (time since last UC diagnosis, and whether the last event was primary or recurrent UC) combined with the concentrations of five mRNA biomarkers (CDK1, MDK, IGFBP5, HOXA13 and CXCR2) to identify those patients who have a low probability of recurrent UC. The classifier was validated using statistically robust iterative methods. A Cxbladder Monitor score less than 3.5 has a Negative Predictive Value (NPV) of 97% and a sensitivity of 93%, with a test negative rate of 34%. Cxbladder Monitor is a development from the clinical study published in J. Urology (2017) 197:1419-1426.

Assay Description:

Cxbladder Monitor is a quantitative assay for recurrent UC that combines the gene expression from five mRNA biomarkers (CDK1, MDK, IGFBP5, HOXA13 and CXCR2) as measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR) from a small sample of urine and two clinical factors associated with the patients prior history of UC. An algorithm is applied to these parameters to calculate a Cxbladder Monitor score ranging from 0 to 10, and using a cut-off of 3.5 identifies those patients who have a low probability of recurrent UC.

Reviewed By: Thomas P. Nifong, MD (electronically signed)
Laboratory Director, Pacific Edge Diagnostics USA Ltd

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Cxbladder MONITOR

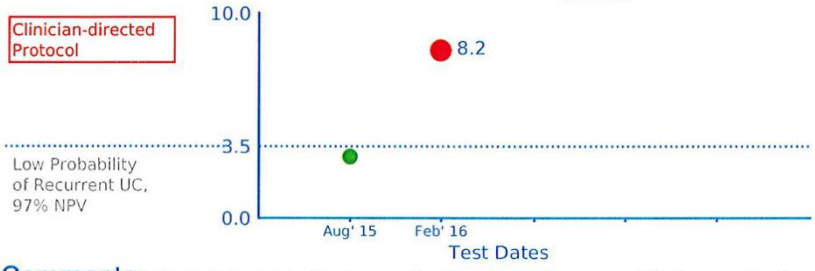
PACIFIC EDGE DIAGNOSTICS USA LTD

Patient Name:	Bridget von Hammersmark
Patient Date of Birth:	06/13/1964
Patient Sex:	Female
Medical Record #	232323
Date of Last UC Diagnosis:	May 2015
Last UC Diagnosis:	Recurrence
Specimen Source:	Urine
Sample ID:	PE000AHJ
Alternate ID:	722839
Specimen Collection Date:	02/01/2016
Specimen Receipt Date:	02/03/2016
Specimen Report Date:	02/04/2016
Report Status:	**Final**
ICD-10 Code:	R31.9
Ordering Clinician:	Dr Hugo Stiglitz

Dr Hugo Stiglitz
Louisiane Medical Clinic
1214 Research Blvd.
Suite 2000
Hummelstown, PA, 17036

Test Result: Cxbladder Monitor score 8.2

95% CI (7.80 - 8.80)



Comments: Example comment that spans the line. Example comment that spans the line. Example comment that spans the line.

Results Interpretation:

Cxbladder Monitor Score ≥ 3.5	A clinician-directed protocol to determine the presence of recurrent UC, is warranted.
Cxbladder Monitor Score < 3.5	This test has a Negative Predictive Value (NPV) of 97%, and a sensitivity of 93%. Low probability of recurrent UC.

The Cxbladder Monitor test was developed as a 'rule out' test for recurrence of urothelial carcinoma (UC). A total of 763 patients were recruited (1,036 samples) in a multicenter clinical study of patients undergoing routine clinical surveillance for recurrent UC. A classifier was created that uses two variables (time since last UC diagnosis, and whether the last event was primary or recurrent UC) combined with the concentrations of five mRNA biomarkers (CDK1, MDK, IGFBP5, HOXA13 and CXCR2) to identify those patients who have a low probability of recurrent UC. The classifier was validated using statistically robust iterative methods. A Cxbladder Monitor score less than 3.5 has a Negative Predictive Value (NPV) of 97% and a sensitivity of 93%, with a test negative rate of 34%. Cxbladder Monitor is a development from the clinical study published in J. Urology (2017) 197:1419-1426.

Assay Description:

Cxbladder Monitor is a quantitative assay for recurrent UC that combines the gene expression from five mRNA biomarkers (CDK1, MDK, IGFBP5, HOXA13 and CXCR2) as measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR) from a small sample of urine and two clinical factors associated with the patients prior history of UC. An algorithm is applied to these parameters to calculate a Cxbladder Monitor score ranging from 0 to 10, and using a cut-off of 3.5 identifies those patients who have a low probability of recurrent UC.

Reviewed By: Thomas P. Nifong, MD (electronically signed)
Laboratory Director, Pacific Edge Diagnostics USA Ltd

Disclaimer: This is a high complexity clinical test developed by and its performance characteristics determined by Pacific Edge Ltd. This test is for clinical purposes and is intended to aid the clinician to rule out the presence of recurrent urothelial carcinoma (UC). It should not be regarded as investigational or for research only. This test has not been approved by the US Food and Drug Administration (FDA) and such approval is not required. The laboratory is regulated under Clinical Laboratory Improvement Amendments of 1988 (CLIA).

Pacific Edge Diagnostics USA Ltd, Hershey Center for Applied Research, 1214 Research Boulevard, Suite 2000, Hummelstown, PA 17036
Tel: 1-855-CXBLADR (1-855-292-5237) Fax: (717) 220-7006 Email: us.info@cxbladder.com Web: www.cxbladder.com
CLIA #: 39D2053269 PA Permit #: 032894 MD Permit #: 1976 CA License #: COS 800426 FL License #: 800026956 RI License#: LCO00827 CAP 8714655

Cxbladder™

Sample Collection Manual

Sample Collection

CRITICAL ELEMENTS FOR SAMPLE COLLECTION

- Check expiration date on USS box, do not use if expired
- The test requires a **FRESH** mid-stream urine sample, preferably the second void of the day.
- The sample must be taken prior to cystoscopy, bladder wash, catheterization, or any treatment and transferred to the Cxbladder tube within **ONE HOUR**.
- Please collect **only midstream** voided samples. Bladder wash/barbotage specimens are not acceptable as they may result in false positives.
- The sample should be collected in a **1st use collection cup.** Do not collect sample through any re-usable device such as a flow meter or re-usable cup.
- Prior to transferring any sample from a specimen cup to the tube, please **INVERT or AGITATE** the specimen to remove cells off of the bottom of the sample cup.
- Samples with **excessive blood or unusual discoloration** could be rejected.
- Cxbladder tube **must be filled** to the fill line on the tube or the sample will be rejected. Requires > 4.5 mls of urine
- Write **patient's full name and date of birth** on the sample collection tube
- **Do not add any preservative or chemical** to the urine

PATIENT CONSIDERATIONS

- **Inflammatory Conditions May Cause a No Result Cxbladder Report**
- Patients undergoing any manipulation, or invasive urothelial cancer detection should have a voided urine specimen collected first OR wait **6 weeks** from the date of the procedure prior to using Cxbladder.
- Patients undergoing any intrathecal therapy that causes an immune response (i.e. BCG/ chemotherapy) should wait **6 weeks** post last therapy prior to using Cxbladder.
- **UTI/Bladder Infection** – Patients with an active bladder infection of ***any kind*** could cause a no result Cxbladder report due to high inflammation or extremely high bacteria counts. Please wait **2 weeks** after the infection has cleared before using the Cxbladder test.

Urine Sample Collection

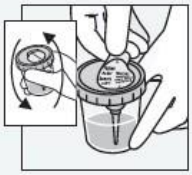
1

Check expiration date on tube, do not use if expired. Label the Cxbladder tube with patient's name, date of birth and the date of sample collection. **Must list this information in addition to barcode on the tube.**

2

Collect mid-stream urine into the Cxbladder urine collection cup until at least 1/3 full. When completed, screw the lid back on the cup securely. **Must be transferred to Cxbladder urine tube within 1 hour of sample collection.**

3



Prior to transferring the urine into the Cxbladder tube, **invert the Cxbladder urine collection cup several times** and then peel back the white protective sticker on the cup to expose the rubber covered needle.

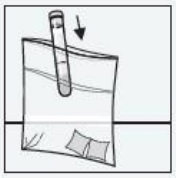
4

Place the Cxbladder urine collection cup on a flat, hard surface (like a desk). Push the Cxbladder tube onto the rubber-covered needle and hold in position until the flow stops **at fill line on tube.** Remove tube and **invert several times.** Do not open the tube as it contains a corrosive buffer.

5

Remove the lid from the Cxbladder urine collection cup and dispose of it in sharps collector. Dispose of urine and collection cup according to your facility's policy.

6



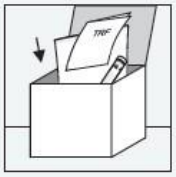
Place the Cxbladder tube into the plastic specimen bag containing absorbent pads and seal.

7

Paperwork

- Complete **all** areas of the TRF form as instructed in the TRF specifics section on the back of this card.
- Have **ordering clinician sign** Statement of Medical Necessity

8



Place specimen bag and **all** paperwork inside the Cxbladder box, place in FedEx shipping bag, and complete waybill.

DO NOT WRITE ANYTHING ON OUTSIDE OF BOX.

9

Ship sample within 2 days so that it arrives at laboratory within 7 days of collection. PEDUSA FEDEX NUMBER:154316620 / For FedEx Pickup call: 800-463-3339. When scheduling a pickup, press "0" until you reach a live representative.

02-MKT-023-US-REV-C

Cxbladder®

TEST REQUISITION FORM

Pacific Edge Diagnostics USA Ltd
1214 Research Boulevard, Suite 2000
Hummelstown, PA 17036 USA
Phone: 1-855-CXBLADR (1-855-292-5237)
Fax: 1-717-220-7006

BARCODE

Processing Code _____

I. SPECIMEN INFORMATION

Test ordered: ☑ Cxbladder Detect ☐ Cxbladder Monitor ☐ Cxbladder Triage

In Office Collection Date (MM/DD/YY) MM/DD/YY In-Home Target Sample Date(MM/DD/YY) _____

Automatic Replacement ☐ Send In-Home Collection System if first sample is Rejected or Qualifying No Result

ICD-10 Code: ☑ R31.0 Gross Hematuria ☐ R31.1 Benign Essential Microscopic Hematuria ☐ R32.21 Asymptomatic Microscopic Hematuria
☐ R31.29 Other Microscopic Hematuria ☐ C67.9 Malignant Neoplasm of Bladder ☐ Z85.51 Hx of Bladder Cancer
☐ Other _____

II. PATIENT INFORMATION

Last Name LAST NAME First Name FIRST NAME MI _____

DOB (MM/DD/YY) MM/DD/YY Sex ☑ Male ☐ Female Medical Record # _____

Address _____ City _____ State _____ Zip _____

Phone _____ ☑ Attached copy of patient's information

III. IMPORTANT PATIENT HISTORY (Required information to generate a Cxbladder Monitor Result)

☐ Yes ☐ No Does the patient have a prior history of Urothelial Carcinoma (UC)?

If No, then request Cxbladder Detect or Cxbladder Triage

What was the date of the patients most recent confirmed tumor? (MM/DD/YY) _____

What was the most recent tumor ? (Check one) ☐ Initial tumor (primary disease) ☐ Recurrent tumor (recurrent disease)

IV. IMPORTANT PATIENT HISTORY (Required information to generate a Cxbladder Triage Result)

Hematuria History (answer both questions)

☐ Yes ☐ No Does the patient have microscopic hematuria?

☐ Yes ☐ No Has the patient had gross hematuria (visible blood in the urine) more than once per day anytime within the last 12 months?

Smoking History

☐ Yes ☐ No Has the patient smoked more than 100 cigarettes in his/her lifetime?

V. BILLING INFORMATION

☐ OPTION 1: Bill Insurance
☑ Copy of the patient's insurance information is attached

Primary Insurance Name _____

Phone _____

Fax _____

Member ID # _____

Group No # _____

Authorization # _____

Secondary Insurance: Does patient have a secondary insurance?

☐ NO ☐ YES, attach a copy of patient's insurance card (front and back)

☐ OPTION 2: Self Pay

Patient agrees to pay for the test and will be billed directly by Pacific Edge Diagnostics USA LTD at the address indicated above.

VI. ORDERING CLINICIAN INFORMATION

Last Name LAST NAME

First Name FIRST NAME

Practice PRACTICE NAME

NPI # NPI NUMBER

Phone PHONE-NUMBER

Address PRACTICE ADDRESS

City CITY State STATE Zip ZIP

Fax FAX-NUMBER

Email _____

The Cxbladder Test Report will be sent by mail and fax unless one of the following is checked:

☐ Mail Only ☑ Fax Only ☐ Secure Email Only

VII. AUTHORIZATION

I confirm the Cxbladder test is medically necessary for the diagnosis or detection of a disease, illness, impairment, symptom, syndrome or disorder, and the results will be used in the medical management and treatment decisions for the patient. I have obtained the patient's consent for Pacific Edge Diagnostics USA Ltd to release the Cxbladder test results to the patient's third party payer when necessary as part of the reimbursement process and the patient's consent for authorization of payment of medical benefits to Pacific Edge. I confirm that the person listed in the ORDERING CLINICIAN INFORMATION (section VI) is authorized by law to order the test(s) requested herein.

☑ **I authorize my printed name above to serve as a digital signature**

Clinician Signature PRINT CLINICAN'S NAME Date (MM/DD/YY) MM/DD/YY

SN 1-4-0009

INSTRUCTIONS FOR COMPLETING THIS FORM AND SHIPPING SPECIMEN ARE INCLUDED ON THE BACK 07-QMS-059-REV-A

Clear Form

Statement of Medical Necessity

Physician Name:	First and Last Name		
Patient Name:	First and Last Name	**Date of Birth:**	MM/DD/YY

Test Name (check one)

- (●) **Cxbladder® Detect (CPT 0012M)** *A urine-based test incorporating the levels of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2) into an algorithm to calculate a risk score for urothelial carcinoma.*
- ( ) **Cxbladder® Monitor (CPT 0013M)** *A urine-based test incorporating the levels of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2) into an algorithm, along with risk factors of time since diagnosis and previous recurrence, to calculate a risk score for recurrent urothelial carcinoma.*
- ( ) **Cxbladder® Triage (CPT 0363U)** *A urine-based test incorporating the levels of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2) into an algorithm, along with risk factors of smoking history and macrohematuria frequency, to calculate a risk score for urothelial carcinoma.*

I ordered Cxbladder® to aid in the evaluation of this patient for urothelial carcinoma because during my examination I have determined that the patient has an increased risk of having cancer due to:

- (●) The presence of Gross Hematuria
- ( ) The presence of Microscopic Hematuria
- ( ) An abnormal or atypical urine cytology result
- ( ) An inconclusive cystoscopic evaluation
- ( ) A history of Urothelial Carcinoma undergoing Surveillance
- ( ) An inconclusive result from testing performed with other diagnostic tests (FISH, etc)
- ( ) Other:_____

I intend to use the results of Cxbladder® along with other outcomes from my urologic evaluation:

- (●) To determine if cystoscopy and/or medical imaging are indicated to further evaluate this patient for urothelial carcinoma
- ( ) To determine if cystoscopy can be avoided in this patient with a history of cystoscopic complications
- ( ) To determine if the interval between surveillance cystoscopies can be increased or a cystoscopy can be skipped during patient's surveillance.
- ( ) To determine whether invasive procedures such as biopsies are necessary to further evaluate the patient for urothelial carcinoma
- ( ) Other:_____

Informed Consent and Statement of Medical Necessity - I confirm that the patient listed above has been informed that Cxbladder® is being requested as part of their evaluation. I consider Cxbladder® to be reasonable and medically necessary for the evaluation of this patient, and intend to use the results in the medical management or treatment decisions. I confirm that I am both the ordering and treating provider.

Provider Signature: First and Last Name Date: MM/DD/YY

Form MUST be returned to Pacific Edge Diagnostics USA, Ltd. via fax: 1-717-220-7006 and included in the patient's medical record.

References:

1. Kavalieris L, O'Sullivan P, Frampton C, Guilford P, Darling D, Jacobson E, 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):1419-26. Epub 20161214. doi: 10.1016/j.juro.2016.12.010. PubMed PMID: 27986532.
2. O'Sullivan P, Sharples K, Dalphin M, Davidson P, Gilling P, Cambridge L, et al. A multigene urine test for the detection and stratification of bladder cancer in patients presenting with hematuria. J Urol. 2012;188(3):741-7. Epub 20120719. doi: 10.1016/j.juro.2012.05.003. PubMed PMID: 22818138.
3. Lotan Y, O'Sullivan P, Raman JD, Shariat SF, Kavalieris L, Frampton C, et al. Clinical comparison of noninvasive urine tests for ruling out recurrent urothelial carcinoma. Urol Oncol. 2017;35(8):531.e15-.e22. Epub 20170331. doi: 10.1016/j.urolonc.2017.03.008. PubMed PMID: 28366272.
4. Kavalieris L, O'Sullivan PJ, Suttie JM, Pownall BK, Gilling PJ, Chemasle C, 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. Epub 20150327. doi: 10.1186/s12894-015-0018-5. PubMed PMID: 25888331; PubMed Central PMCID: PMC4391477.
5. Lotan Y, Raman JD, Konety B, Daneshmand S, Schroeck F, Shariat SF, et al. Urinary Analysis of *FGFR3* and *TERT* Gene Mutations Enhances Performance of Cxbladder Tests and Improves Patient Risk Stratification. J Urol. 2023;209(4):762-72. Epub 20221230. doi: 10.1097/JU.0000000000003126. PubMed PMID: 36583640.
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7. Teoh JY, Kamat AM, Black PC, Grivas P, Shariat SF, Babjuk M. Recurrence mechanisms of non-muscle-invasive bladder cancer - a clinical perspective. Nat Rev Urol. 2022;19(5):280-94. Epub 20220331. doi: 10.1038/s41585-022-00578-1. PubMed PMID: 35361927.
8. Li KD, Chu CE, Patel M, Meng MV, Morgan TM, Porten SP. Cxbladder Monitor testing to reduce cystoscopy frequency in patients with bladder cancer. Urol Oncol. 2023;41(7):326.e1-.e8. Epub 20230302. doi: 10.1016/j.urolonc.2023.01.009. PubMed PMID: 36868882.
9. Holyoake A, O'Sullivan P, Pollock R, Best T, Watanabe J, Kajita Y, 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(3):742-9. doi: 10.1158/1078-0432.ccr-07-1672. PubMed PMID: 18245534.
10. Proposed LCD - Genetic Testing for Oncology (DL39365). https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=39667&ver=92023.
11. Rai BP, Luis Dominguez Escrig J, Vale L, Kuusk T, Capoun O, Soukup V, et al. Systematic Review of the Incidence of and Risk Factors for Urothelial Cancers and Renal Cell Carcinoma Among Patients with Haematuria. Eur Urol. 2022;82(2):182-92. Epub 20220405. doi: 10.1016/j.eururo.2022.03.027. PubMed PMID: 35393159.

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13. Neeraj Agarwal SA, Hilary Bagshaw, Michael, Baine KB, Marian, Birkeland NB, Maria Carlo, Toni Choueiri, Brian Costello, Ithaar, Derweesh AD, Tanya Fischer, Yasser, Ged SG, John Gore, Kristina Gregory, Andrew Gunn, Naomi Haas, Evelyn, Handel EH, Anne Holbrook, Michael Johnson, Eric Jonasch, Payal Kapur,, et al. NCCN Guidelines Version 1.2024 Kidney Cancer. 2023.
14. Davidson PJ, McGeoch G, Shand B. Inclusion of a molecular marker of bladder cancer in a clinical pathway for investigation of haematuria may reduce the need for cystoscopy. N Z Med J. 2019;132(1497):55-64. Epub 20190621. PubMed PMID: 31220066.
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Peter Meintjes
Pacific Edge Diagnostics USA
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Hummelstown, PA 17036
peter.meintjes@pelnz.com
September 5, 2023

Dr Patrick Mann
Novitas Solutions
2020 Technology Pkwy Suite 100
Mechanicsburg, PA 17050
Sent via email

RE: Summary of Comments on DL39365

Dear Dr Mann and Novitas Team,

Thank you for the opportunity to provide comments on DL39365. This letter supports, augments and summarizes the feedback to Novitas concerning DL39365 "Genetic Testing for Oncology".

Pacific Edge is significantly (and adversely) impacted by the changes Novitas proposes to introduce, both in the general sense of relying on certain third party databases to make coverage decisions – of which only NCCN is applicable to MAAA tests like Cxbladder – and in the specific sense regarding the conclusions Novitas reached after conducting an evidentiary review resulting in a non-coverage determination for all of the Cxbladder products.

Since July 2020 Pacific Edge has relied on the unambiguous documented conclusion from Novitas on A58529 "the CxBladder test is now covered utilizing the reasonable and necessary guidelines". Novitas made this decision following a review of the available evidence for the assay and documented this decision in a public comment/response article that remains available on the CMS website, and via e-mail correspondence to Pacific Edge officials in response to questions. For more than two years this sufficed for appropriately guiding coverage and Novitas supported Pacific Edge for positive coverage determinations for Medicare Advantage appeals on this basis. When A58529 was retired, Novitas advised Pacific Edge by email that:

> "*The Review and Comment documents should not be used to determine coverage. The Medicare Advantage plan should be using LCDs and/or LCA for coverage determinations.* ***Since 0012M and 0013M is listed in A58917; Billing and Coding: Molecular Pathology and Genetic Testing, that is the article that should be referenced in determining coverage.***"

A58917 continues to appropriately guide coverage of Cxbladder tests, such that for more than three years, Medicare patients have benefitted from the improvements that Cxbladder offers to the standard of care in urology. In particular, Medicare patients that present to the physician with blood in the urine were offered non-invasive Cxbladder testing to determine whether or not cystoscopy and imaging (that have associated comorbidities) are necessary as part of further evaluation. However, if finalized, the non-coverage determination in DL39365 would eliminate Cxbladder and all non-invasive alternatives to cystoscopy for physicians to order for their Medicare patients with hematuria – a dramatic removal of benefits that may result in more patients receiving unnecessary invasive procedures such as cystoscopies and imaging that have known patient morbidities, thus causing unnecessary harm to Medicare patients.

Simultaneously over the last three years Pacific Edge has continued to generate evidence that supports the adoption of Cxbladder, and continues to a) confirm the performance characteristics of existing tests while b) continuing to develop new tests, thus further

highlighting our commitment to clinical evidence generation and the urology community we serve. This new evidence further supports the performance of the assays, and none of it supports a decision to remove longstanding coverage. We are not aware of any new evidence or adverse reporting event that Novitas can rely on to reverse the established, evidence-based position it established in July 2020.

While Pacific Edge is concerned with the proposed LCD's reliance on 3rd party databases, which have been largely communicated by industry associations, e.g. ACLA and The Coalition for 21st Century Medicine, we are most concerned by the content of the evidentiary review undertaken for our Cxbladder products. Some of the Novitas criticisms indeed have merit – before standardizing our commercial approach, there were occasions where Pacific Edge was ambiguous about which product was the target of the study and some patient cohorts were used to establish the AV and CV on multiple related products. However, this has been clarified through more recent publications (see Appendix in our Medical Rebuttal) and with respect to each product, the necessary requirements for analytical validation and clinical validation have been either peer-reviewed or were submitted to other clinical certification bodies including CLIA and New York State, and the appropriate patient population and use of our tests is articulated in our Test Request Form, while the correct interpretation of results is clearly outlined on our Test Results. These points are all noted in detail in our medical rebuttal.

In the Novitas review there are substantial misunderstandings regarding the appropriate use of our tests, the appropriate patient population in which to use them and the applicable standard of care. The misunderstandings appear to have driven Novitas to the conclusion that our tests do not add value and have been described as 'not medically reasonable and necessary'. In response, our Medical Affairs Team prepared a detailed rebuttal in which we explain in detail why Novitas should reconsider its position, as the reframing of our peer-reviewed publications in the context of the standard of care provide a consistent message that Cxbladder is analytically valid, clinically valid and clinically useful for urologists.

The physicians that use our tests in clinical practice have echoed these sentiments; indeed, more than 20 plan to provide feedback in support of the Cxbladder tests, because they also believe the evidence supporting the tests is sufficient to support continued patient access. All of the largest associations in urology – AUA, LUGPA and AACU – have submitted comments separately regarding this LCD to you, and more than a dozen key opinion leaders have independently co-authored an opinion piece, expected to be published in an appropriate journal at the conclusion of this process.

Regarding the appropriateness of relying solely on NCCN to make Medicare coverage decisions for molecular algorithmic tests, Pacific Edge notes two points. The first is that pre-emptive non-coverage for tests not supported with at least a 2a rating in the NCCN guidelines (or higher) appears to be a re-definition of 'medically reasonable and necessary'. NCCN guidelines aim to develop a consensus of the standard of care – a definition that far supersedes that of 'medically reasonable and necessary'. The current reliance on NCCN substitutes a higher standard, i.e. 'consensus standard of care' for the requirements of the Social Securities Act defined as 'medically reasonable and necessary'. The second point is that this leaves tests with 2b recommendations non-covered, even if such assays have 50-85% support from the guidelines committee. We urge Novitas to reconsider whether NCCN 2b recommendations should at a minimum not be automatically non-covered, allowing Medicare beneficiaries continued access to the tests. This point is significant, as Cxbladder Monitor peer-reviewed evidence was used in the determination of an NCCN 2b recommendation for urinary biomarkers and consequently carries an NCCN 2b recommendation by name.

As a diagnostic testing provider, Pacific Edge is both patient-centric and value-based in its approach to addressing unmet clinical needs. As the average age of patients presenting with

hematuria is ~73 years old (American Urological Association), hematuria patients are majority Medicare patients, and a primary consideration in everything that we do. Consequently, a small number of patients have connected with us as we prepared our written comments and have also sent those comments to you. Pacific Edge also understands that BCAN – a patient advocacy organization well known for keeping out of medical policy discussion – has also submitted comments. They too recognize the impact of the test on Medicare beneficiaries. While separate from clinical evidence considerations, value-based considerations are important for the healthcare system as a whole. The Medicare allowable for Cxbladder tests is $760/test and a recently developed budget impact model (abstract accepted at the WSAUA conference on 10/1-5, 2023) highlights a saving of >$500 per patient for a Cxbladder Detect clinical pathway when compared to the standard of care pathway. The combination of clinical utility and economic utility provides an excellent example of value-based care regarding how new technologies can benefit patients, physicians and payers alike.

Pacific Edge remains committed to contextualizing the clinical value of Cxbladder for Novitas, CMS or any other payor, and providing the peer-reviewed evidence to support our claims. I am personally available to discuss at any time, have members of my team engage with the Medical Affairs Team at Novitas or assist with assembling independent urology experts from among our customer base.

Respectfully,

Peter Meintjes, PhD
Chief Executive Officer
Pacific Edge
+1 (203) 947 2772
Peter.meintjes@pelnz.com