Commentary on Novitas LCD

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Conflicts of Interest:
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Astellas, Merck, Janssen, Pfizer, Virtuoso Surgical, Photocure, Tu Therapeutics, Nonagen, Pacific Edge , Urogen, Prokarium, Valar Science

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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

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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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