Company Announcement
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MEDICAL COMMUNICATION:

ENHANCED CXBLADDER TESTS DELIVER IMPROVED DIAGNOSTIC PERFORMANCE

DUNEDIN, New Zealand – Pacific Edge (NZX, ASX PEB) today announces the acceptance for publication "Urinary Analysis of FGFR3 and TERT Gene Mutations Enhances Performance of Cxbladder Tests and Improves Patient Risk Stratification" which demonstrates new clinical evidence that shows significant improvements in the performance of its genomic diagnostic Cxbladder tests.

These performance improvements were achieved by the addition of DNA single nucleotide polymorphism (SNP) biomarkers to Cxbladder Triage (CxbT) and Cxbladder Detect (CxbD), Pacific Edge's products for hematuria evaluation. Specifically, the addition of five genotypic biomarkers (*MDK, CDK1, IGFBP5*, *HOXA13*, and *CXCR2*), and digital-droplet PCR to identify SNPs in the *TERT* and *FGFR3* genes - urinary biomarkers known to be associated with urothelial carcinoma (UC).

This published study covered 804 patients across the US and Singapore and demonstrates:

- clinical validity evidence for Cxbladder Triage (CxbT) and Cxbladder Detect (CxbD) in two different patient populations (micro and gross hematuria);
- evidence for the analytical validation of the newly developed CxbT+ and CxbD+ tests that include the DNA SNP biomarkers and considerably enhance the performance; and
- that CxbD+ is the best performing test among those in the study and the primary focus in the publication

The performance characteristics of CxbD+ creates the opportunity for increased utility of Cxbladder in both micro hematuria (risk stratification) and gross hematuria (adjunct to standard of care) to improve the ability of clinicians to identify subclinical or barely visible urothelial cancers and guidance on which patients require prompt assessment because of their risk of invasive UC. The enhanced performance of CxbD+ will also allow clinicians to:

- De-intensify the workup for those patients at low risk of harboring the disease and testing CxbD+ negative
- Intensify the workup for patients at elevated risk of urothelial carcinoma and testing CxbD+ positive

The CxbD+ Evidence Roadmap:

For Pacific Edge, the Lotan et al publication is the successful completion of one step in the evidence roadmap for CxbD+. Our roadmap is focused on providing high-quality clinical evidence

of the validity and utility of the test to build the case for inclusion of Cxbladder in the AUA and NCCN guidelines for hematuria evaluation. The data presented in this publication also demonstrates that the performance of all Cxbladder tests is consistent across Southeast Asian and US populations.

The evidence framework for D+ defined by publication in peer reviewed journals:

- Analytical validity (AV) - Demonstrates that the test is repeatable
- Clinical validity (CV) - Validates that the test performs as expected using an independent cohort of patients
- Clinical utility (CU) - With availability of the test in clinical care, demonstrates the clinical utility of the test through change in patient management

Clinical Evidence	Cxbladder Triage+ and Cxbladder Detect+
AV	Lotan et al. (complete)
CV	• DRIVE (last patient in expected mid-2023) • AUSSIE (last patient in expected late 2024) • microDRIVE (first patient in expected Q3 2023and last patient in expected in Q1 2024)
CU	• STRATA (last patient in expected late 2023 with 12-month follow up by late 2024) will offer initial CU evidence as secondary objective • Additional CU studies are planned for CxbD+

Methods in Brief: two multicenter, prospective studies were undertaken in: (1) US patients with gross hematuria aged ≥18 years, and (2) Singaporean patients with gross hematuria or microhematuria aged >21 years. All patients provided a midstream urine sample and underwent standard of care procedures including cystoscopy. Samples were retrospectively analyzed using enhanced Cxbladder-Triage (CxbT+; risk stratifies patients), Cxbladder-Detect (CxbD+; risk stratifies patients and detects positive UC patients) and the combination CxbT+×CxbD+.

In total, samples from 804 patients (gross hematuria: n=484, microhematuria: n=320) were analyzed. CxbD+ had a sensitivity of 97% (95% CI 89–100%), specificity of 90% (95% CI 88–92%), and negative predictive value of 99.7% (95% CI 99–100%) for detection of UC. Overall, 83% of patients needed no further work-up. Of 133 patients with a positive CxbD+, 59 had a confirmed tumor, of which 19 were low-grade non-invasive papillary carcinoma [Ta] or papillary urothelial neoplasm of low malignant potential. In total, 40 tumors were high-grade Ta, T1–T4, Tis, including concomitant carcinoma in situ. Of the 74 with normal cystoscopy 41 were positive by

SNP analysis. CxbD+ had significantly better sensitivity and specificity than the first-generation Cxbladder test ($p<0.001$).

Cxbladder Detect+ Confirmation with Cystoscopy:

	CxbD+ Test Result		
Cystoscopy Result	Negative	Positive	**Total**
Negative	669	74	743
Positive	2	59	61
Total	671	133	**804**
Tumor grade			
Low impact tumor (LIT)	2	19	21
High-impact tumor (HIT)	0	40	40

Cxbladder identifies 59 out of 61 tumors identified by cystoscopy (Sensitivity of 97%). Cxbladder identifies an additional 74 positive results, which may be tumors missed by cystoscopy, subclinical tumors or Cxbladder false positives. Future clinical studies are planned to validate the superiority of Cxbladder by determining the true proportions of each.*

**A subclinical tumor is early-stage disease that is not detectable by cystoscopy.*

Test Comparisons:

	Sensitivity	Specificity	NPV	PPV	ROR
Cxbladder+ Tests					
CxbT+	95%	78%	99.5%	26%	73%
CxbD+	97%	90%	99.7%	44%	83%
Existing Cxbladder Tests[1]					
CxbT	89%	63%	99%	16%	59%
CxbD	74%	82%	97%	25%	78%

- *Sensitivity is the frequency with which a test correctly identifies patients with a disease.*
- *Specificity is the frequency with which a test correctly identifies patients without a disease.*
- *Negative Predictive Value (NPV) is the percentage of negative tests being true negatives (by standard of care).*
- *Positive Predictive Value (PPV) is the percentage of positive tests being true positives (by standard of care).*
- *Rule-out Rate (ROR) is the percentage of tests that return a negative result.*

These performance enhancements are significant and have the following implications for patient management:

1. A CxbD+ negative patient has a low probability of UC because CxbD+ combines the characteristics of high Sensitivity (97%), NPV (99.7%) and Specificity (90%) with a ROR of 83%.

2. A CxbD+ positive patient conversely has a higher probability of urothelial cancer for the same reasons (improved Sensitivity, Specificity and NPV alongside a ROR of 83%). A positive test therefore can be used to justify an intensification of urologic evaluation and assist the adjudication of diagnostic dilemmas such as equivocal cystoscopy or urine cytology.

In conclusion, these data show that the addition and analysis of DNA biomarkers of SNPs in the *FGFR3* and *TERT* genes to our current RNA biomarkers, enhances the performance of Cxbladder diagnostic tests, providing accurate risk stratification of patients with microhematuria or gross hematuria. Improved risk stratification reduces unnecessary evaluation for UC when at low risk of disease and indicates more intensive evaluation is required because of the risk of invasive UC.

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

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