Urine comprehensive genomic profiling predicts recurrence in patients with non-muscle invasive bladder cancer treated with intravesical therapy

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Background

Intravesical therapy (IVT) is the standard of care for high-grade non-muscle invasive bladder cancer (NMIBC). Despite treatment, patients often recur. Currently, there is no reliable test to assist with risk stratification of patients after treatment. Here, we evaluate a CLIA-validated urinary comprehensive genomic profiling (uCGP) test (UroAmp Assay, Convergent Genomics) for recurrence prediction in a prospective cohort with long-term follow-up.

Methods

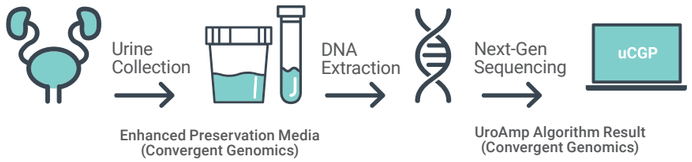

Figure 1. Sample-to-answer: uCGP and usage of mutations and copy number variants to predict risk of urothelial carcinoma (UC) recurrence. Urine specimens were collected in enhance preservation media (Convergent Genomics). Urine DNA was sequenced and profiled across 60 genes using the CLIA-validated UroAmp test (Convergent Genomics). Recurrence predictions were performed using a previously validated algorithm and subjects were grouped into high, intermediate, and low risk of recurrence.

Study Design

- This is a prospectively designed single-site study.
- 26 NMIBC patients deemed to be IVT candidates, and with and no prior history of IVT, were consented and prospectively enrolled from 1/2019 - 3/2020.
- 88% of subjects received BCG while 12% received Gemcitabine induction.
- Urine samples were collected at the beginning of IVT induction and at various time points throughout, including prior to the last cycle or at a follow-up cystoscopy.
- Subjects were longitudinally monitored per standard of care. At the end of 2 years of surveillance, chart review was performed, and patients were evaluated for recurrence status.
- Blinded classification (high, intermediate, & low recurrence risk) was performed. Hazard Ratio, Sensitivity, Specificity, and AUC for the ROC curve were calculated. Kaplan-Meier curves and log-rank tests were analyzed.

Risk Group	Pre-IVT → Post-IVT Algorithm Result	Underlying Risk Factors Identified by Urinary Comprehensive Genomic Profiling	Outcomes Hypothesis
Low	Negative → Negative	Successful complete surgical resection.	Longest recurrence free survival.
Intermediate	Positive → Negative	Molecular disease burden persistent after surgery, significant reduction in genomic disease burden with IVT.	Immune response extends recurrence free survival, elevated risk for tumor evolution and immune escape recurrence.
High	Positive → Positive	Molecular disease burden persistent after surgery, insufficient reduction in genomic disease burden with IVT.	Shortest recurrence free survival.

Table 1. Risk definitions using urine comprehensive genomic profiling and disease classification with UroAmp (Convergent Genomics).

Results

- 26 samples were prospectively collected after visually complete TURBT and prior to IVT instillation. (BCG=88%, Gemcitabine=12%).
- At a mean follow-up of 22 months, 5 (19.2%) patients had a biopsy confirmed recurrence with an additional 2 (7.7%) having positive urine cytology without biopsy-confirmation.
- Assessing both types of recurrence, high and intermediate risk prediction had a sensitivity of 100% and specificity of 63.2%. No low recurrence risk subjects experienced recurrence (NPV 100%). An AUC of 0.85 was achieved.
- High recurrence risk prediction was associated with a 6.5x elevated risk of future recurrence when compared to the other two risk categories, HR=6.5 CI(1.2, 33.8), p=0.026.
- Kaplan-Meier curves confirmed distinct recurrence-free survival between the prediction categories (log-rank p=0.013).
- Among recurrent patients, the high and intermediate risk groups predicted recurrence a median of 293 days ahead of clinical standard of care diagnosis. TP53 mutations were strongly correlated with post-treatment recurrence OR= 28, CI (1.99, 394.42), p=0.038.

Recurrence Risk Group	% of cohort	Average Pre-treatment Mutation Burden (% cells)	Average Post-treatment Mutation Burden (% cells)	Risk Group Interpretation
High	35%	36.3%	36.7%	High mutation burden post-TUR which does not respond to IVT.
Intermediate	19%	21.1%	0.58%	High mutation burden post-TUR which does respond to IVT.
Low	46%	0.70%	0.68%	Low mutation burden post-TUR.

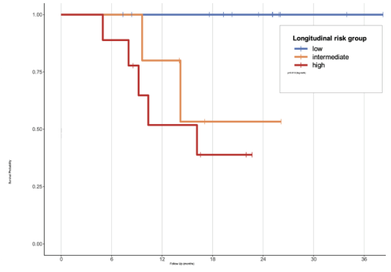

Figure 2. Mutational burden in recurrence risk groups and recurrence free survival by uCGP-predicted risk. Kaplan-Meier curves confirmed distinct recurrence free survival between the prediction categories (log-rank p=0.013).

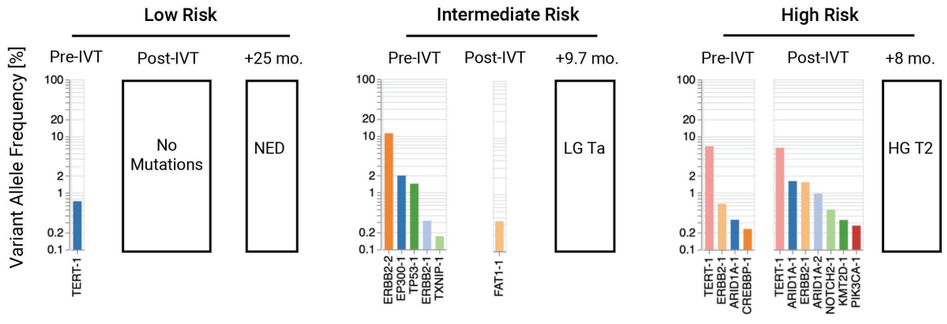

Figure 3. Persistent mutation burden in patients receiving IVT. Mutational burden following TURBT but prior to IVT indicates residual disease in the bladder following surgery. uCGP provides quantitative measures of mutations during IVT and identifies subjects with unresponsive disease that could potentially benefit from more aggressive treatment strategies.

Conclusions:

- uCGP with UroAmp facilitates residual disease detection and quantification during intravesical therapy in high-risk non-muscle invasive bladder cancer.
- uCGP risk prediction identifies patients at increased risk of recurrence following IVT.
- uCGP provides actionable insights that may inform surgical planning, patient-tailored dosing of IVT, risk stratification, and surveillance intensity.

Future Directions for Research:

- Expanded studies will further validate these early promising results.
- Interventional studies are needed to understand how to best utilize this early recurrence lead-time to reduce recurrence and benefit patient care.

IRB
This retrospective study was conducted with approval from Institutional Review Board LU211552.
Subject informed consent was obtained prior to participation.

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Conflicts of Interest Disclosures: VC, PL, BCM, KGP, and TGL are employees with equity in Convergent Genomics.