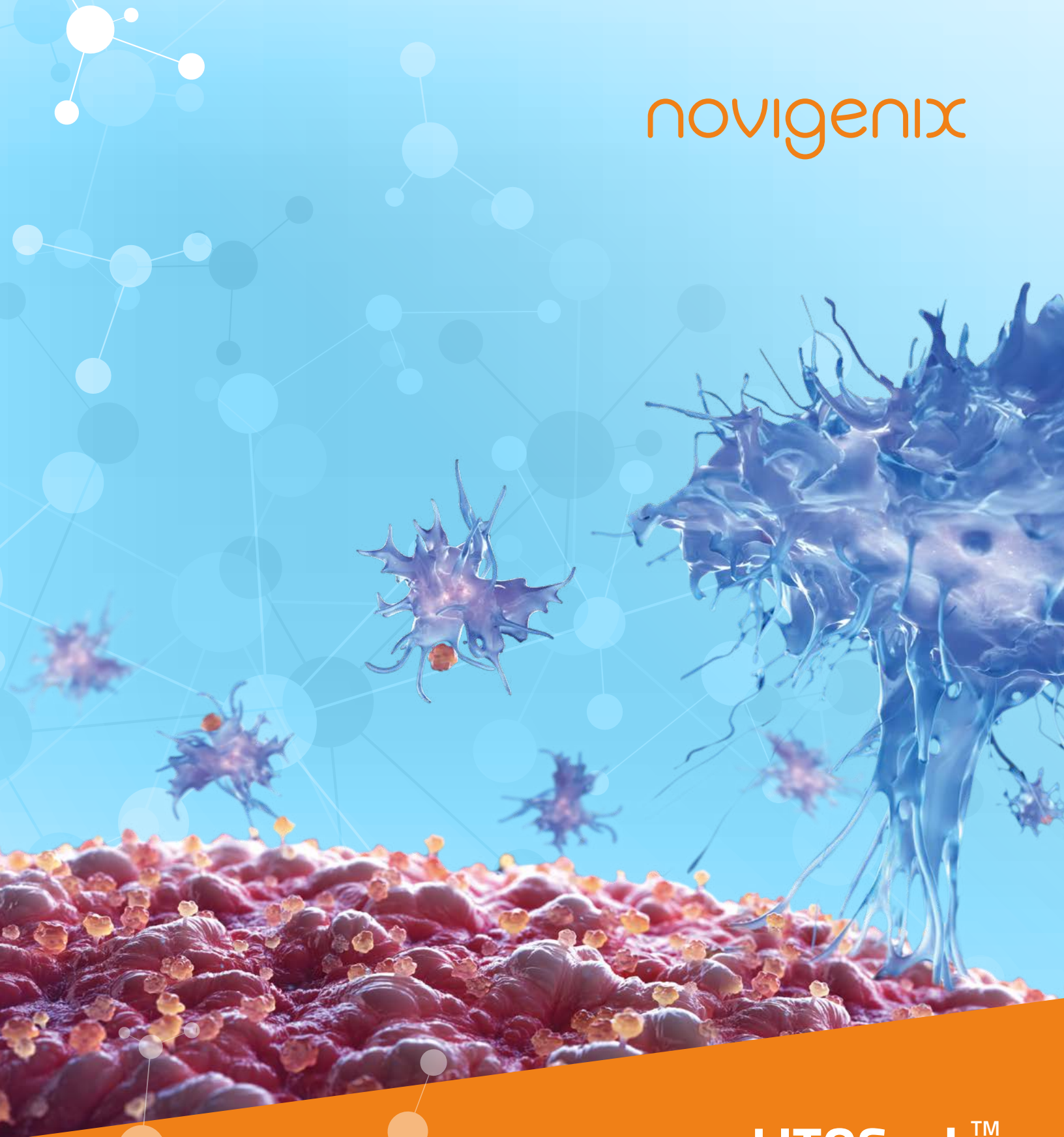
novigenix



LITOSeek™

Immunotherapy Response Prediction

Precise & Predictive Patient Profiling

Introduction

Traditional tumor biopsy techniques, while informative, face limitations due to tumor heterogeneity and accessibility challenges at various metastatic sites throughout a patient's treatment journey. Advances in next-generation sequencing technology (NGS) have enabled the development of non-invasive methods for blood-based biomarker detection, commonly referred to as a liquid biopsy. Novigenix's pioneering liquid biopsy technology platform LITOSeek™ (Liquid Immuno-TranscriptOmics), leverages whole-blood RNA-sequencing to capture patient-specific transcriptomic profiles. By integrating next-generation sequencing and AI technologies, LITOSeek™ excels in discovering robust blood-based RNA biomarkers and creating precise, specialized predictive models. This application note highlights the utility and benefits of LITOSeek™ in clinical trials including prediction of treatment response to immunotherapy with durable therapeutic benefit.

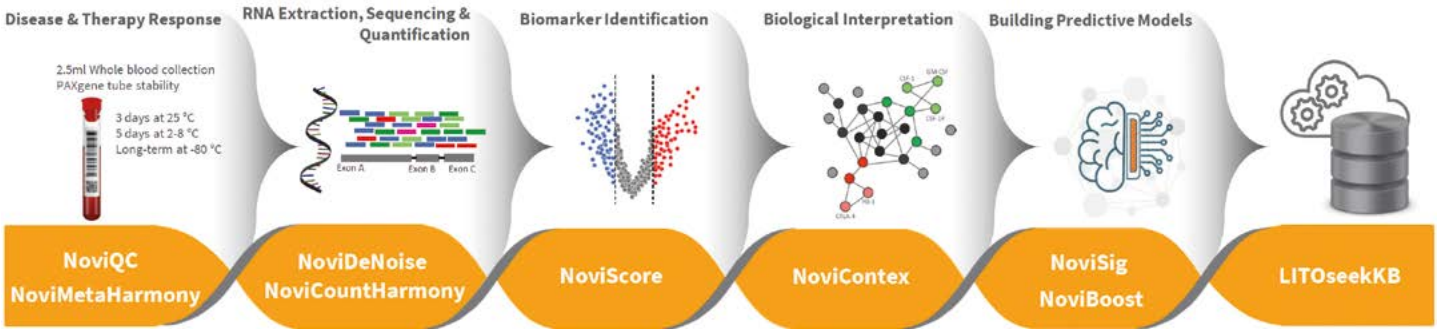
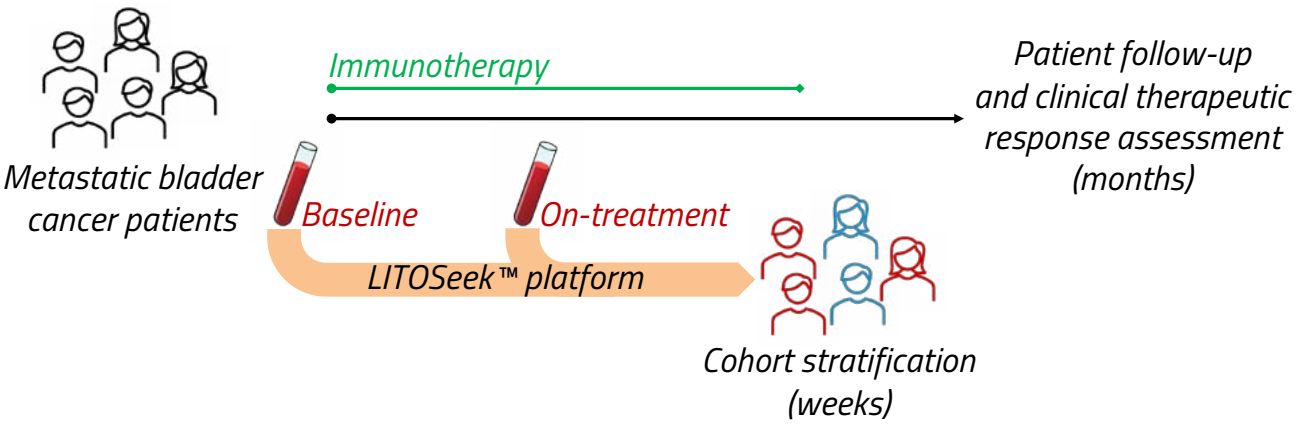


Figure 1: Schematic overview of the LITOSeek™ platform, illustrating workflow from blood sample collection to the construction of precise predictive models.

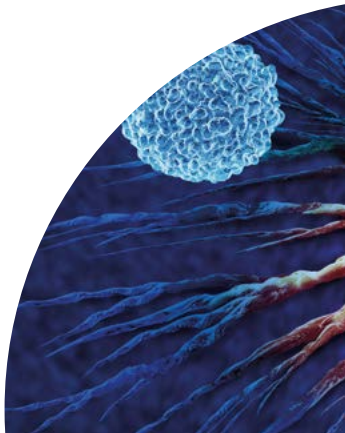
Prediction of durable therapeutic benefit

Bladder cancer patients are frequently treated with anti-PD-1/PD-L1 immunotherapy as a second line treatment option. However, only a small percentage (15-24%) experience a durable benefit. LITOSeek™ was employed to analyze whole blood samples from 89 metastatic bladder cancer patients, both before and during immunotherapy. The patients were divided into three independent cohorts for discovery, confirmation, and validation, with the former aiding in biomarker identification and model training, and the latter for independent validation of predictive models.

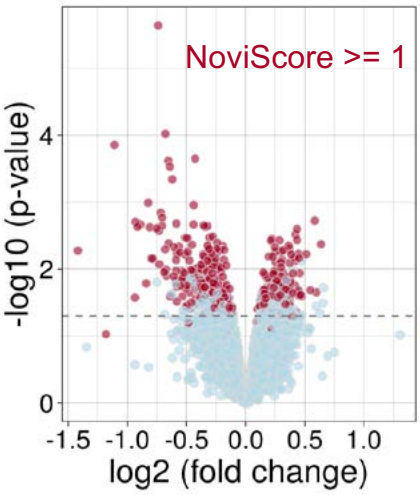
Blood based longitudinal immunotherapy response prediction



A total of 89 metastatic bladder cancer patients underwent immunotherapy over four cycles, and clinical responses were evaluated six months after therapy initiation. Whole-blood PAXgene® Blood RNA Tubes were collected before treatment and on-treatment (either after the first or second cycle), and RNAseq data was generated for analysis to identify gene expression signatures predictive of durable therapeutic benefits to immunotherapy and characterization of immune modulation in patients with metastatic bladder cancer.

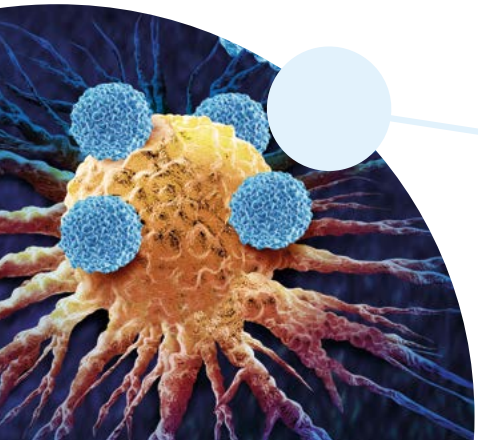


The LITOSeek™ NoviScore has been optimized to accurately pinpoint the most significant Differentially Expressed Genes (DEGs) as shown in this representative volcano plot of NoviScore for discovery of key biomarkers indicative of immune changes associated with effective response to therapy.



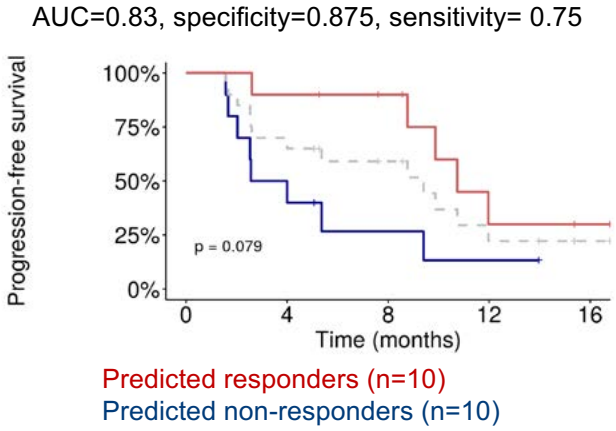
NoviContext uses multiple knowledge-based bioinformatic approaches, such as protein-interaction network analysis and biological pathway analysis to characterize central pathways related to early response to immunotherapy. Contextualization in this cohort has identified key pathways of antigen processing and presentation, T-cell mediated immunity, and cell cycle in patients with durable therapeutic benefit.

The DEGs identified with LITOSeek™ provide deep insights into the immune system´s dynamic response to immunotherapy. Moreover, the results are consistent with multiple other studies concluding that response to immunotherapy is driven by systemic cell responses, with a major role played by T cells which can be predictive of clinical benefit (Fairfax et al., Nature Medicine 2020; Valpione et al, Nature Cancer 2020; Hiam-Galvez, K.J. et al., Nat Rev Cancer, 2021).

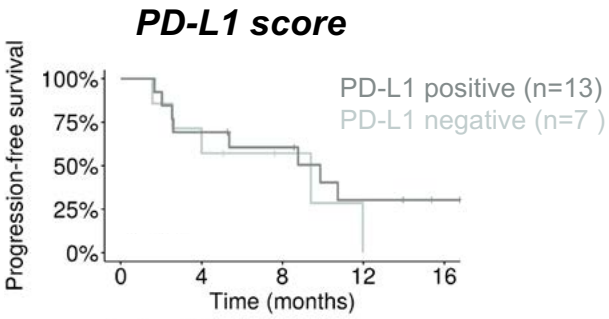


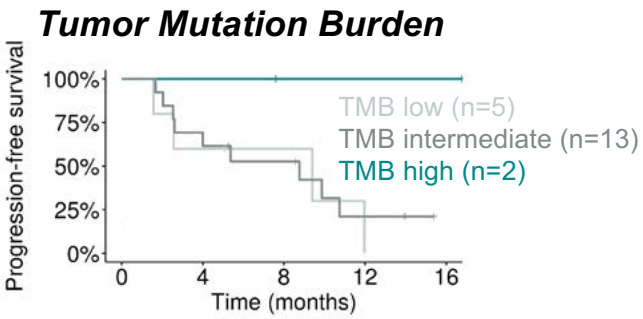
LITOSeek™ AI-enabled modeling precisely predicts response to ICI

LITOSeek™ NoviSig feature reduction machine-learning algorithms identified a set of 10 genes related to relevant group comparisons and central biological pathways for downstream modeling. Predictive models developed based on these 10 early-response biomarkers were trained with NoviBoost algorithms, and further validated on an independent cohort. The Kaplan-Meier curve illustrates the predictive power of LITOSeek™ in stratification of patients into responders and non-responders to immunotherapy:



These results highlight the platform´s capabilities in identifying highly accurate RNA biomarkers of therapeutic response where other traditional biomarkers such as PD-L1 Score and Tumor Mutation Burden fail to have predictive power:





Conclusions

The LITOSeek™ platform has demonstrated a broad range of applicability in precision oncology, offering Precise & Predictive Patient Profiling such as prediction of therapeutic response to immunotherapy, thereby positioning it as a transformative tool in the landscape of novel therapy development. Other platform capabilities available for clinical development of novel therapies include:

- **Immuno pharmaco-dynamics (ImmunoPD) response markers**
- **Predictive biomarkers of response and resistance to therapy**
- **Mechanisms of action and mechanisms of resistance to therapy**
- **Discovery of safety biomarkers**
- **Digital cytometry and cellular deconvolution overcoming logistical hurdles of flow cytometry and CyTOF**

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