Cancer genomics has identified common genetic alterations in metastatic tumors. While genomic profiling of metastatic tumors may identify patients with actionable targets, the response to novel therapies is often limited. There is a need to better understand tumor evolution and better characterization of subclonal tumor types, mechanisms of resistance, and sensitivity of individual circulating tumor cell (CTC) subtypes to novel therapies such as androgen receptor signaling inhibitors (ARSi) and taxanes. A better understanding of tumor heterogeneity at the single cell level could provide insight into disease evolution, inform treatment decisions for individual patients, and guide new drug development.

Methods: A CTC detection method based on a validated single cell isolation platform was used to isolate CTCs from 150 mCRPC patient samples. CTCs were genotypically characterized using digital pathology and phenotypic characterization using microfluidics and RNA sequencing. Genotypic characterization was performed using Digital Pathology and Genomic Imputation, with Cancer Genome Atlas (CGA) data used for genotype imputation.

Results: Phenotypic CTC subtypes were associated with distinct gene signatures. Genotypic characterization revealed enrichment of copy number variation (CNV) and genomic instability. Treatment outcomes were correlated with CTCs representing each subtype by low pass sequencing for genomic instability.

Conclusions: Specific CTC subtypes are enriched in samples with high heterogeneous scores. Detecting specific CTC phenotypic subtypes in patients can aid the development of personalized therapies and guide new drug development. Longitudinal monitoring of phenotypic CTC subtypes in multiple clinical trials is currently underway.