**Title:** Circulatory Nucleic Acid Based Applications in Metastatic Prostate Cancer

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Metastatic prostate cancer is associated with heterogeneous somatic genetic alterations for which multiple drug therapies have been recently approved. The effectiveness of each drug therapy is variable and the ability to monitor or predict efficacy in individual patients under developed. This has ushered in a new generation of nucleic-acid-based biomarker development.

Our team followed a longitudinal prospective cohort of metastatic prostate cancer patients for a period of 9 years and determined plasma cfDNA/circulating tumor DNA (ctDNA) fractions and clonal evolution before, during, and after androgen deprivation therapy (ADT) in 4 independent patient groups starting from untreated metastatic hormone sensitive prostate cancer (mHSPC) to metastatic castrate resistant prostate cancer (mCRPC). We also performed Next generation sequencing on the ctDNA fraction and germline DNA to characterize somatic alterations and their associations with clinical outcomes in each state of progression.

This presentation will summarize findings from the longitudinal cohort on cfDNA yields which were different in progressive mHSPC and mCRPC states. We will illustrate that ctDNA fractions can be used as predictive of ADT efficacy in mHSPC, and that cfDNA yield or ctDNA tumor fractions taken together with clinical factors like volume of metastatic disease in mHSPC and with serum alkaline phosphatase levels prognosticate survival better than clinical factors alone in these metastatic states. We will discuss how the ctDNA-based AR, APC mutations were increased in mCRPC compared to mHSPC and TP53 mutations, RB1 loss, and AR gene amplifications correlated with poorer survival in mCRPC as well as mutations in multiple DNA repair genes (ATM, BRCA1, BRCA2, CHEK2) which were associated with time to ADT treatment failure and survival in mHSPC.

Finally, we will summarize novel directions we are taking in metastatic prostate cancer circulatory nucleic acid biomarker development in order to make effective routine use of ctDNA, miRNA based profiling using novel technical approaches that can offer a high degree of multiplexing, quantitation, ultrasensitivity, low cost, simplicity, integrated sample processing, and robust instrumentation suitable for point-of-care settings.