**Background**

- Chromosomal Instability (CIN) is associated with the rapid evolution of drug resistant tumor phenotypes and the development of metastases.
- CIN is a potentially useful biomarker within CTCs. However, NGS of all CTCs in a large cohort of patients is not realistic at multiple levels.
- Our goal was to develop a cost/time effective predictor of CIN in a liquid biopsy and determine its value at predicting therapy response in mCRPC.

**Methods**

- **Epic Sciences CTC Detection**
  - Automated from patient blood samples to identify and classify CTCs.
  - Image analysis to identify CTCs based on morphological, genetic, and proteomic features.
  - Digital image analysis for CTC identification and quantification.

- **Genomics Processing & LST determination**
  - From 26,608 CTCs input, pathology features (X1..n) were extracted and predicts whether or not a CTC has Chromosomal Instability (Y).
  - Hypothesis: A computer vision algorithm can be developed that takes as input CTC digital images all CTCs, extracted digital pathology features, and sequenced to determine the number of LSTs.

- **Phenotypic LST (pLST) Algorithm Development**
  - From 26 mCRPC patients (608 detectable CTCs), the algorithm was developed to predict LSTs.
  - The algorithm determines whether a CTC has Chromosomal Instability (Y).

- **Training Cohort**
  - We selected 26 mCRPC patients (608 detectable CTCs) with resistant disease.
  - Determined a threshold of single CTC positivity for predicted LST (pLST).
  - Explored the clinical association of CIN within CTCs to patient outcomes from baseline to therapy response.

- **Blinded Analytic Validation Cohort**
  - Explored the clinical association of CIN within CTCs to patient outcomes from baseline to therapy response.

- **Comparison of predicted #LSTs to actual #LSTs by patient in the AV cohort**
  - Patient Level pLST Scoring Guide Performance
    - Accuracy: 76.6%
    - Sensitivity: 54.1%
    - Specificity: 87.7%

- **Clinical Level pLST Biomarker**
  - The pLST Biomarker Provides Additive Prognostic Value to Baseline
  - Clinical Variables
    - Therapy Line
    - Patient Demographics (N=419)
      - Median Age: 69 (45, 91)
      - PSA: 29.5 (0, 1627)
      - ALK: 106 (25, 2170)
      - ALB: 4.2 (2.9, 4.9)
      - HGB: 29.5 (6.3, 15.7)
      - LDH: 219 (124, 2115)
      - Therapy - No. (%)
        - ARSi: 240 (57.3%)
        - Taxane: 119 (28.4%)
        - Platinum: 32 (7.6%)
        - 1st Line: 142 (33.9%)
        - 2nd Line: 101 (24.1%)
        - 3rd Line: 176 (42.0%)
        - 3rd+ Line: 176 (42.0%)

- **Discussion**
  - CIN can accurately be measured through the phenotypic profiling of CTCs.
  - Patients who are pLST positive have poor OS to standard of care therapies (except platinum chemotherapy) in mCRPC.
  - Prospective testing of the clinical utility of the pLST biomarker as a predictor of PARPi response (see NCT03712930, BOARD N4: Abstract: TP5328) are underway.