

Comprehensive Plasma Epigenomic Profiling in mCRPC Elucidates Lineage States Associated with ¹⁷⁷Lu-PSMA-617 Response and Resistance

Poster #8727

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BACKGROUND

Variable response to ¹⁷⁷Lu-PSMA-617 in PSMA-positive mCRPC highlights the need to characterize sensitivity and resistance. Comprehensive plasma epigenomic profiling infers regulatory activity and gene expression from 1 mL of plasma. Building on prior associations between plasma PSMA and treatment response, consistent with PSMA PET SUVmean, we characterize molecular programs, therapeutic cell-surface targets, and biological changes associated with progression.

METHODS

Baseline plasma from 57 patients with mCRPC initiating ¹⁷⁷Lu-PSMA-617 underwent H3K4me3, H3K27ac, and DNA methylation profiling using Precede Bio Insight™ (1 mL plasma), generating transcriptional activity, therapeutic target expression (PSMA/FOLH1, STEAP1, TROP2), and tumor fraction estimates. GSVA using Hallmark¹, Reactome², and mCRPC subtype gene sets^{3,5}, followed by consensus PAM clustering, identified molecular programs. Baseline features were assessed against time to next treatment (primary endpoint); paired progression samples from 17 patients enabled longitudinal analysis.

Figure 1. Gene Regulation – Chemical Modifications to DNA and Histones Precisely Control and Encode Gene Expression

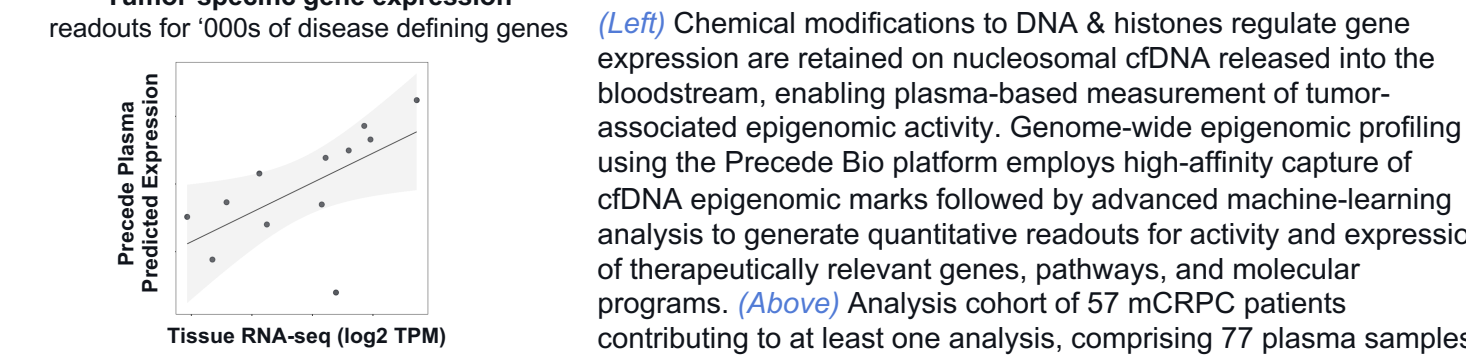
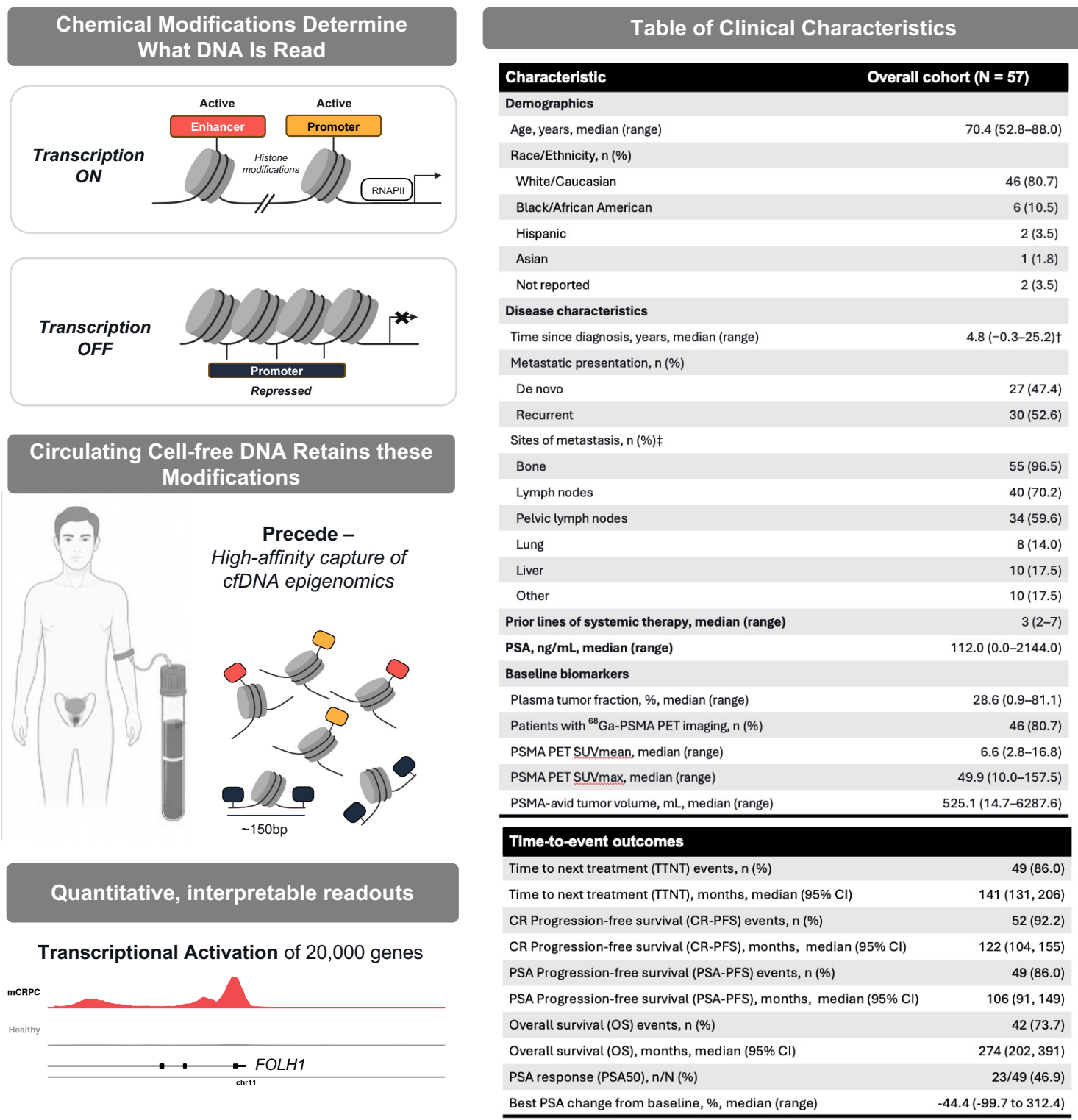


Figure 2. Comprehensive Epigenomic Profiling from 1 ml of Plasma Captures Prostate-cancer-associated Gene and Pathway Activity

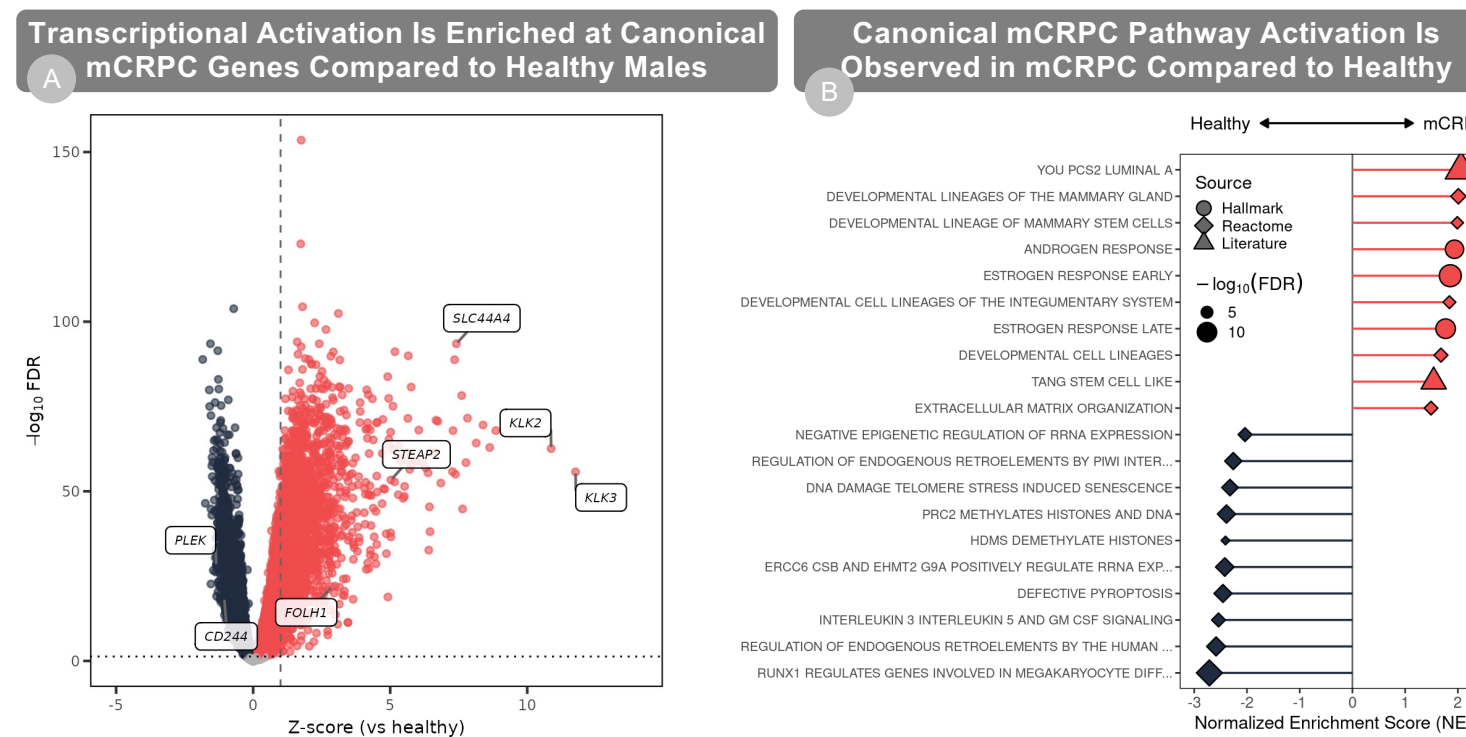


Figure 3. Plasma-derived PSMA Readout Correlates with PET PSMA Scores and Recapitulates Association with Clinical Response

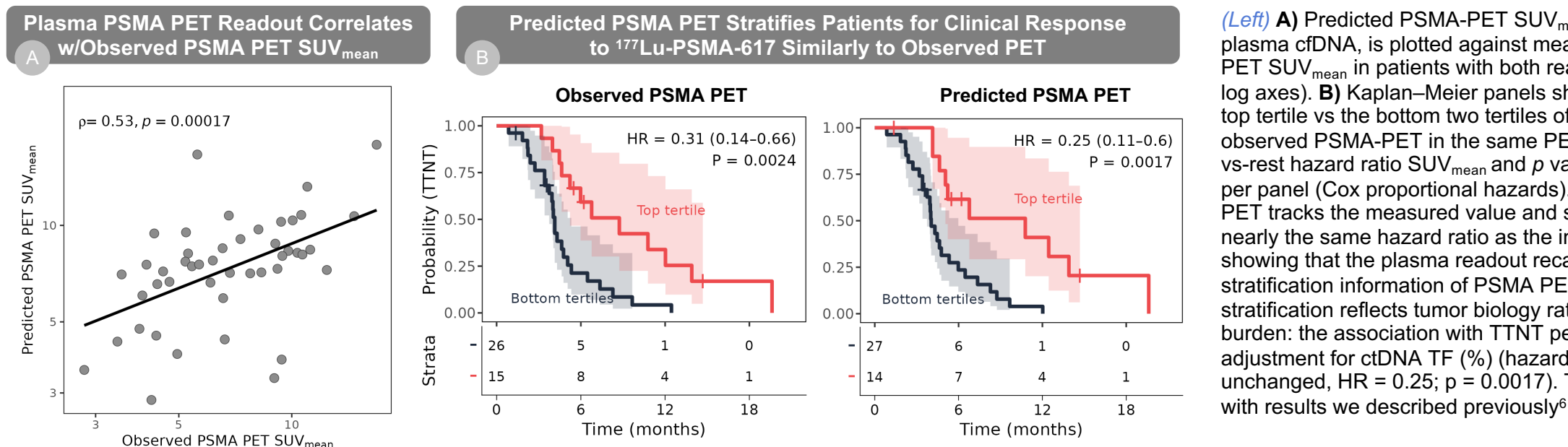


Figure 4. Tumor-specific Gene Expression Readouts from Plasma Show Target Expression Heterogeneity Across Baseline mCRPC Samples

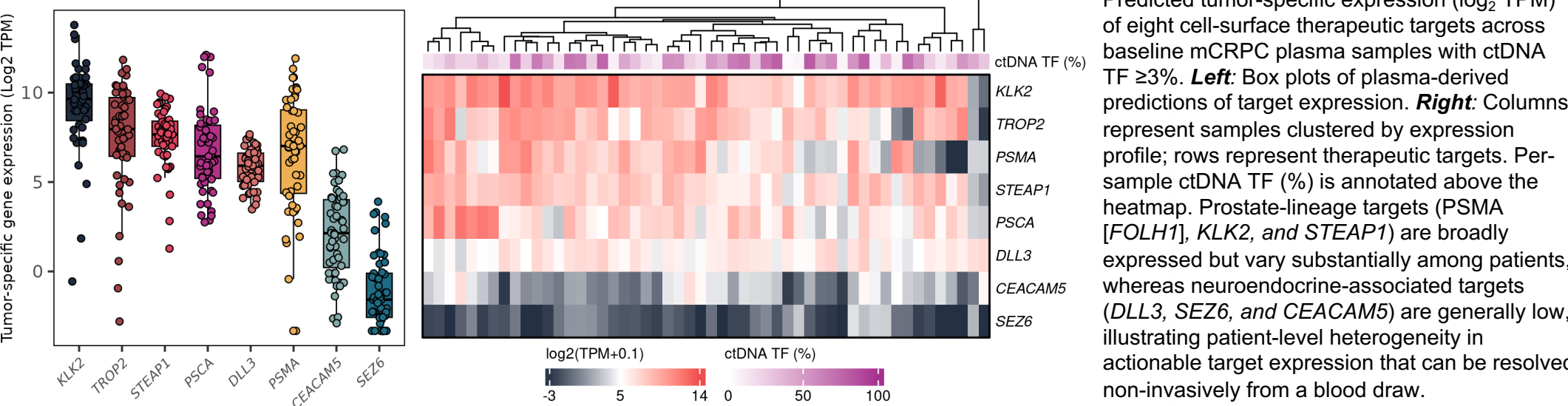


Figure 5. Unsupervised Clustering of Patients' Pathway Activities Resolves Known mCRPC Biological Subtypes and Associations with Clinical Outcomes to ¹⁷⁷Lu-PSMA-617

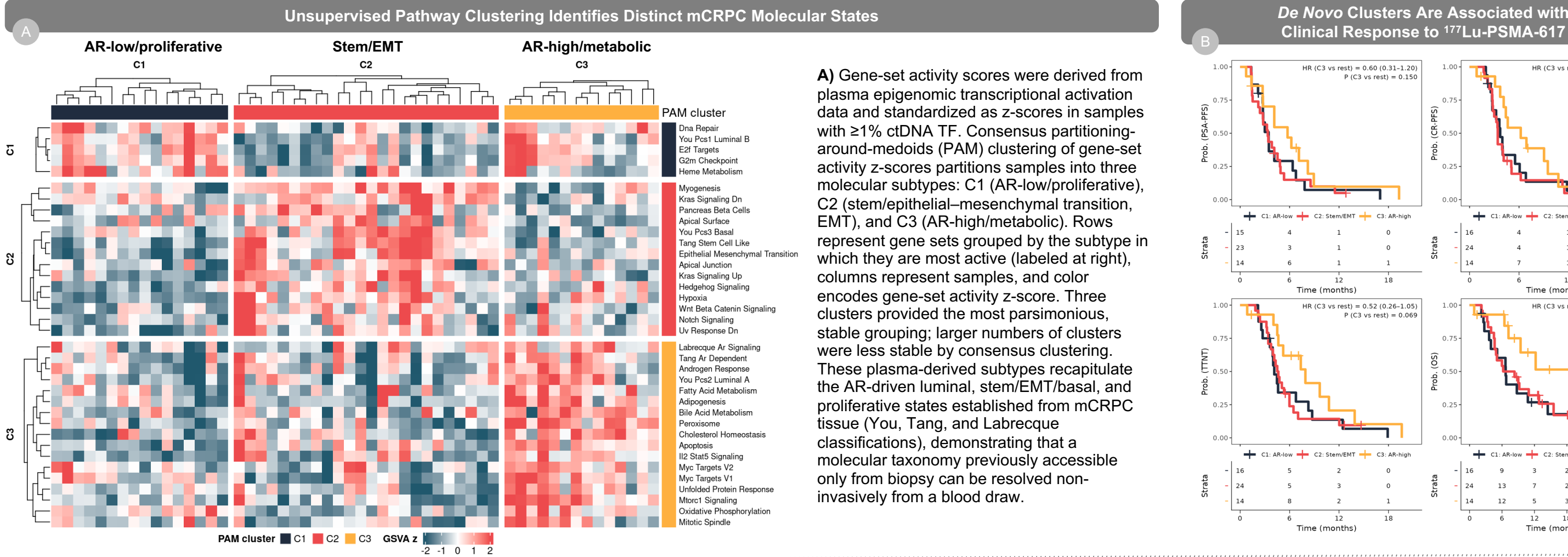


Figure 6. Longitudinal Plasma Profiling Identifies Target and Pathway Changes at Progression

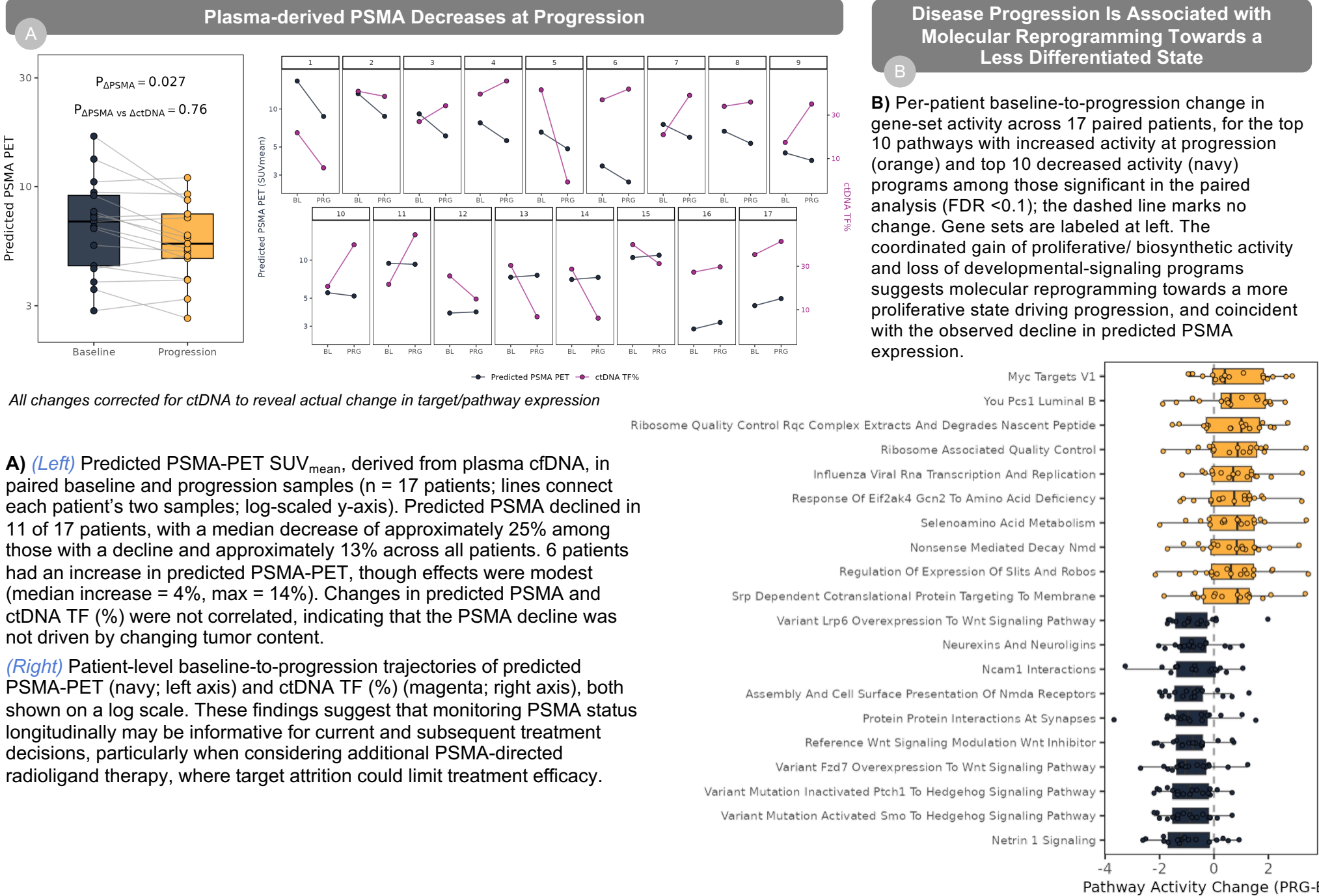
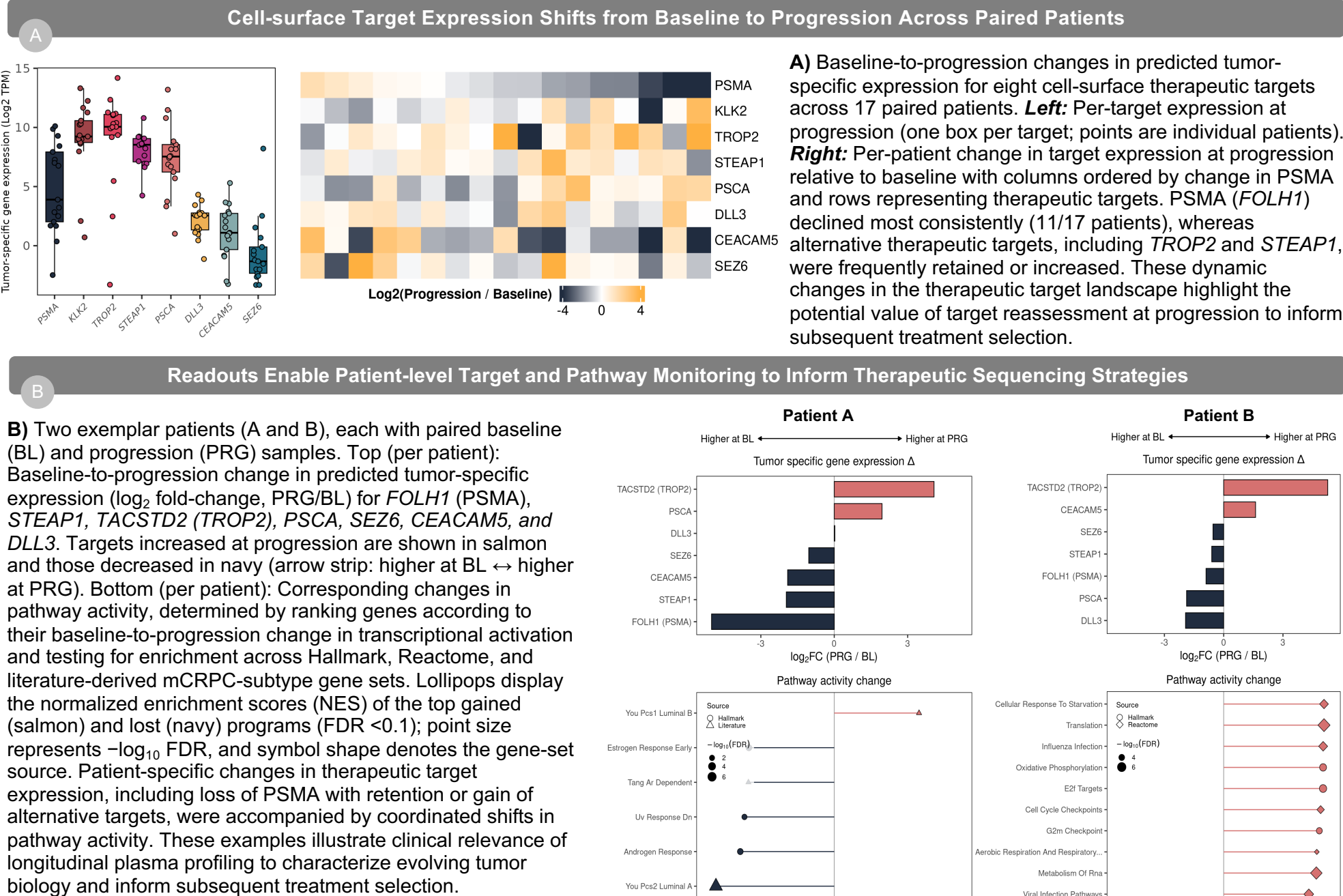


Figure 7. Monitoring Cell-Surface Therapeutic Targets at Progression to Guide Therapeutic Sequencing



CONCLUSIONS

Plasma cfDNA epigenomic profiling identified mCRPC molecular programs associated with outcomes following ¹⁷⁷Lu-PSMA-617. Progression was accompanied by reduced PSMA expression, loss of differentiation-associated programs, and altered therapeutic target expression, supporting further evaluation of this approach to inform patient selection and subsequent treatment strategies.