

Robust characterization of response & resistance to 177Lu-PSMA-617 in mCRPC by plasma-based epigenomic profiling

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BACKGROUND

Metastatic castration-resistant prostate cancer (mCRPC) is an advanced stage of prostate cancer with poor outcomes and limited therapeutic options.

The FDA-approved radiopharmaceutical therapy 177Lu-PSMA-617 targets PSMA, offering a novel approach for mCRPC treatment.

However, response to therapy is heterogeneous, and resistance mechanisms remain poorly understood.

Benchmarking molecular signatures to clinical outcomes could provide critical insights into predicting response and resistance to therapy.

We applied a multimodal epigenomic liquid biopsy platform to profile tumor-specific transcriptional activation and resistance pathways in plasma from patients treated with 177Lu-PSMA-617.

METHODS

Baseline plasma samples were collected from patients with mCRPC at the time of PSMA PET imaging and initiation of 177Lu-PSMA-617 therapy.

Epigenomic profiling of genome-wide signals from promoters, enhancers, and DNA methylation was performed on 1mL of plasma (N=81, ctDNA ≥0.5%).

We tested the association of androgen receptor (AR) activity, neuroendocrine-ness (NEPC-ness), and pathway activities with response using Cox proportional hazards models (CoxPH).

Androgen receptor (AR) activity assessed by enhancer signals at AR binding sites, NEPC-ness was assessed via gene-activity of NEPC marker genes, and pathway activities were calculating using gene set variation analysis (GSVA) scores based on gene-proximal epigenomic signals.

Response to 177Lu-PSMA-617 was assessed by clinical-radiographic progression free survival (crPFS), PSA-PFS, time to next treatment (TTNT) and overall survival (OS).

Figure 1. Overview of Precede's epigenomics liquid biopsy platform

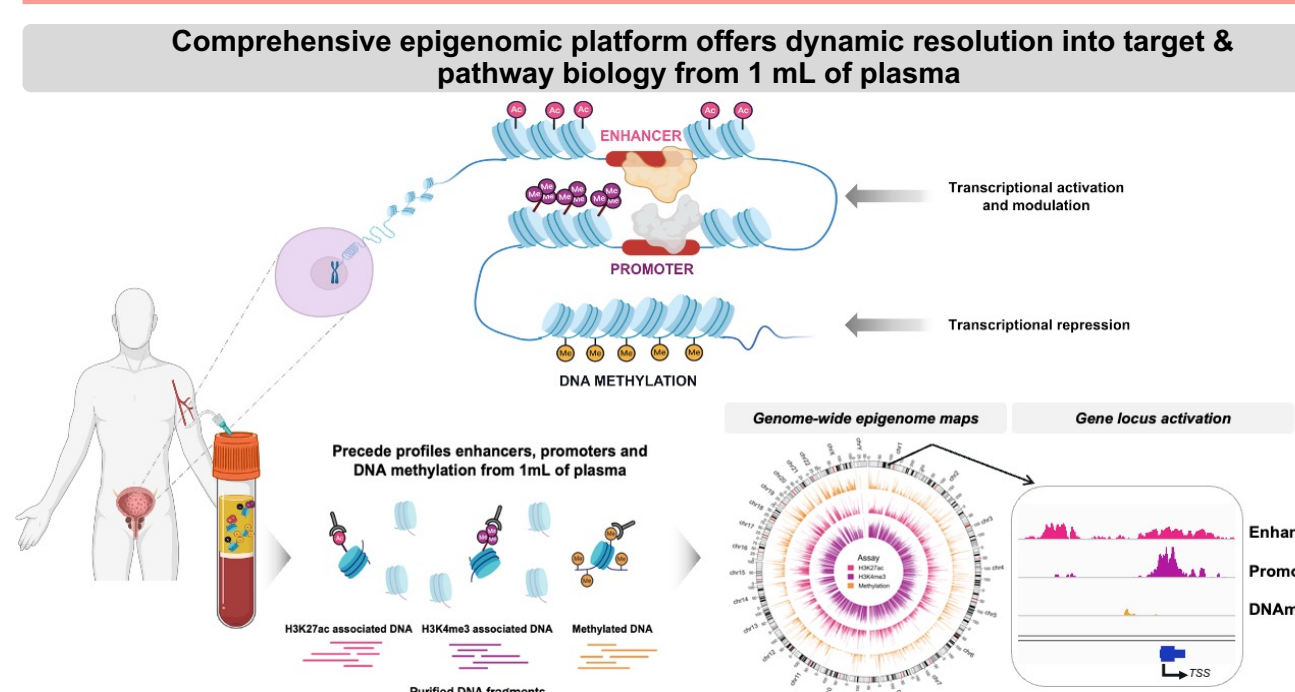
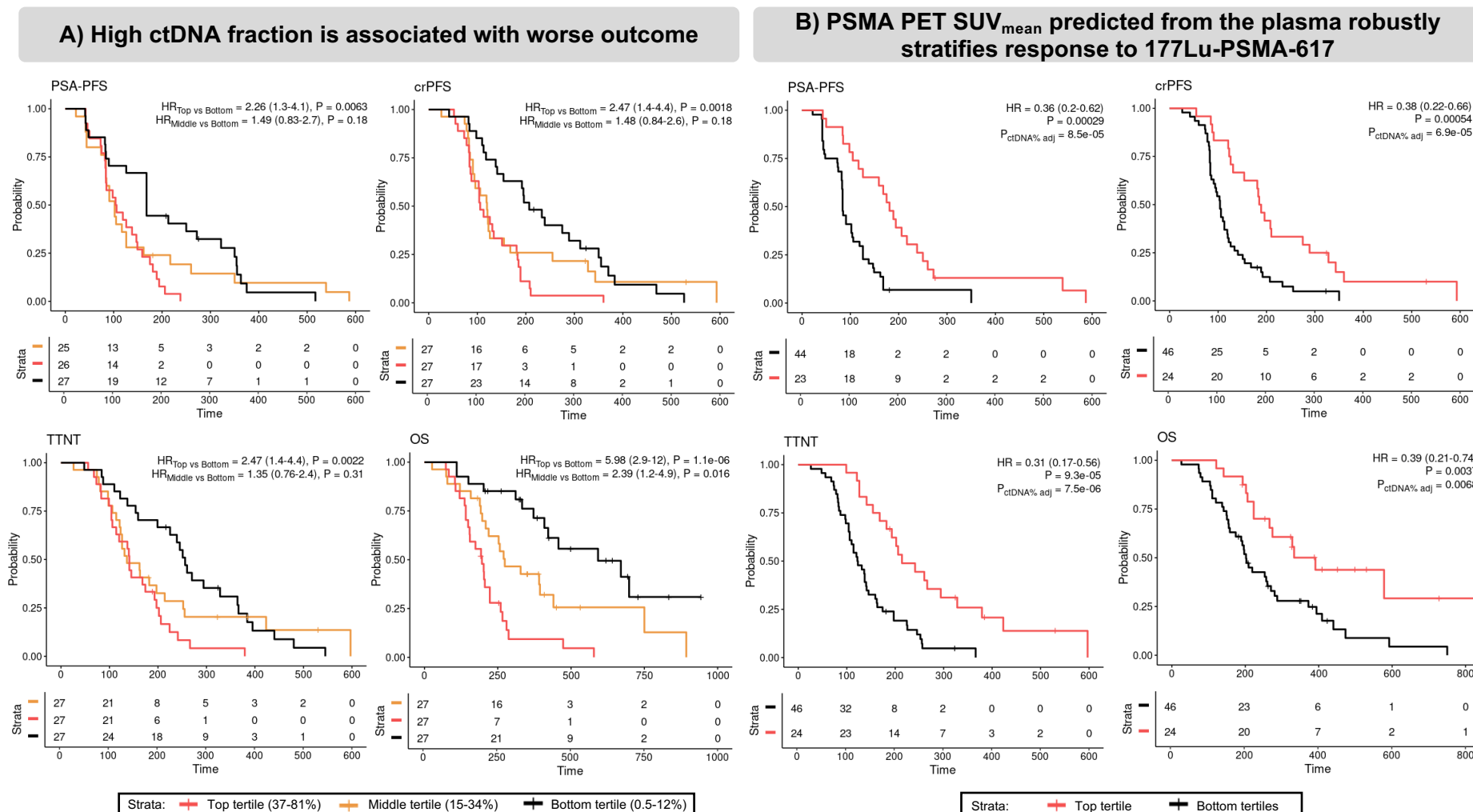


Table 1 – Clinical Cohort Overview		Total N=81
COHORT DESCRIPTION		
Patient characteristics		
Age in years, median(range)		72.2 (52.8-85.7)
Race, number (%)		
White		70 (86.2%)
Black or AA		6 (7.4%)
Hispanic		3 (3.7%)
Disease characteristics		
Stage at Diagnosis, number (%)		
Localized		40 (49.4%)
Metastatic		41 (50.6%)
Lymph Node		54 (66.7%)
Bone		80 (98.8%)
Lung		10 (12.4%)
Liver		14 (17.3%)
Other		11 (13.6%)
# of Prior Line of Systemic Therapies for Metastatic Disease, median (range)		4 (2-7)
PSA at Diagnosis in ng/mL, median (range, N=81)		91.7 (0-2144)
PSMA PET SUV _{mean} , median (range, N=41)		6.9 (2.8-18.3)
Days from PSMA PET scan to plasma collection, median (range, N=41)		66 (20-164)
Clinical Outcomes		
PSA-PFS in days, median (range)		122.5 (22-587)
crPFS in days, median (range)		126 (26-593)
Time to next treatment in days, median (range)		168 (26-597)
Overall Survival in days, median (range)		260 (26-942)

Cell free DNA derived from tumors exists in circulation as chromatin fragments that faithfully maintain tumor-associated epigenetic modifications on the histones and DNA. Antibodies against H3K27ac marking active enhancers, H3K4me3 marking active promoters and DNA methylation are used to enrich for associated DNA fragments from 1mL plasma and sequenced to define genome-wide epigenomic maps that capture the underlying transcriptional state of the tumor cells.

Figure 2. Plasma epigenome-based detection of ctDNA and PSMA transcriptional activation associates with clinical outcomes



(Left) Patient plasma samples were stratified into ctDNA-high (≥ median) and ctDNA-low (< median) groups. We tested for a ctDNA group association across four clinical endpoints: progression-free survival (PFS) via PSA (PSA-PFS, recorded time from start of therapy to first PSA increase that is >25% and >2ng/mL above the nadir and is confirmed by a second value 3 weeks later), clinical/radiographic PFS (crPFS), time to next treatment (TTNT), and overall survival (OS). HR values measure relative risk of ctDNA-high group compared to ctDNA-low group.

(Right) Analysis similar to (A) but we instead stratified patients using predicted PSMA PET SUV_{mean}. Patients in the top tertile of PSMA values were compared to the bottom two tertiles via CoxPH. We also tested whether PSMA value added significant explanatory variance beyond ctDNA group by comparing models with ctDNA group to models with PSMA and ctDNA group via analysis of deviance (P_{ctDNA+adj}). Only plasma samples with ctDNA ≥3% were used for this assessment.

Figure 3. Plasma epigenomic profiles of AR & neuroendocrine programs reveal heterogeneity driving response to 177Lu-PSMA-617 therapy

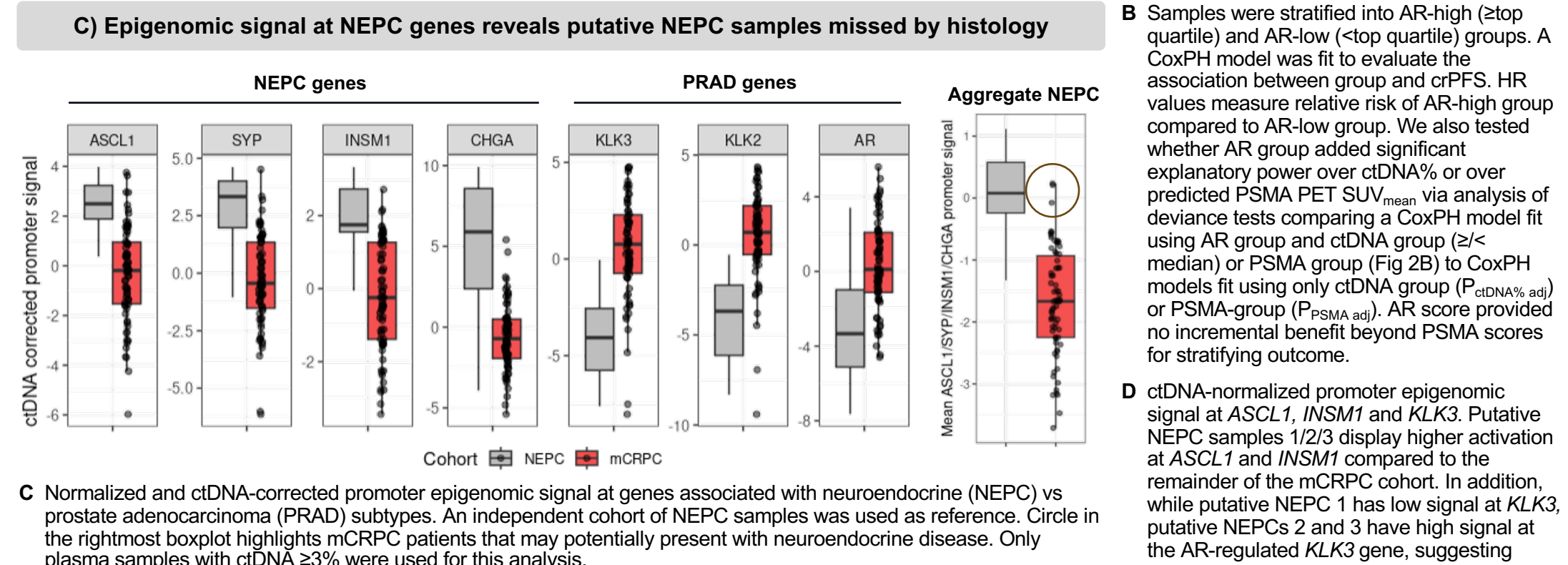
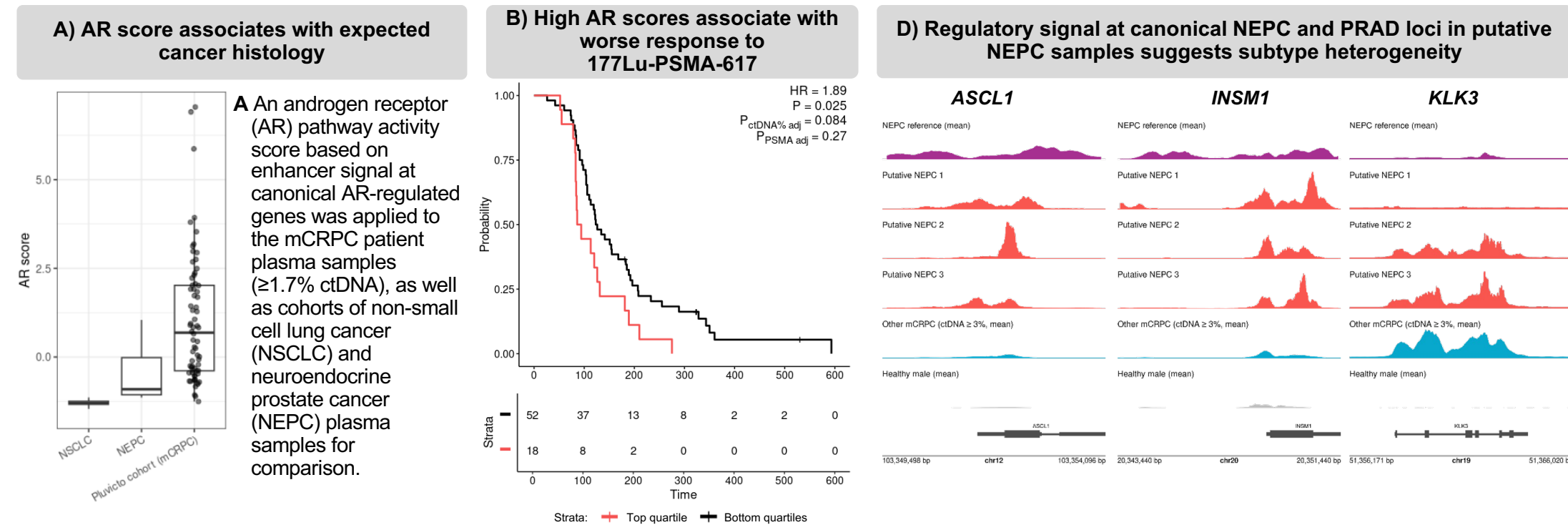
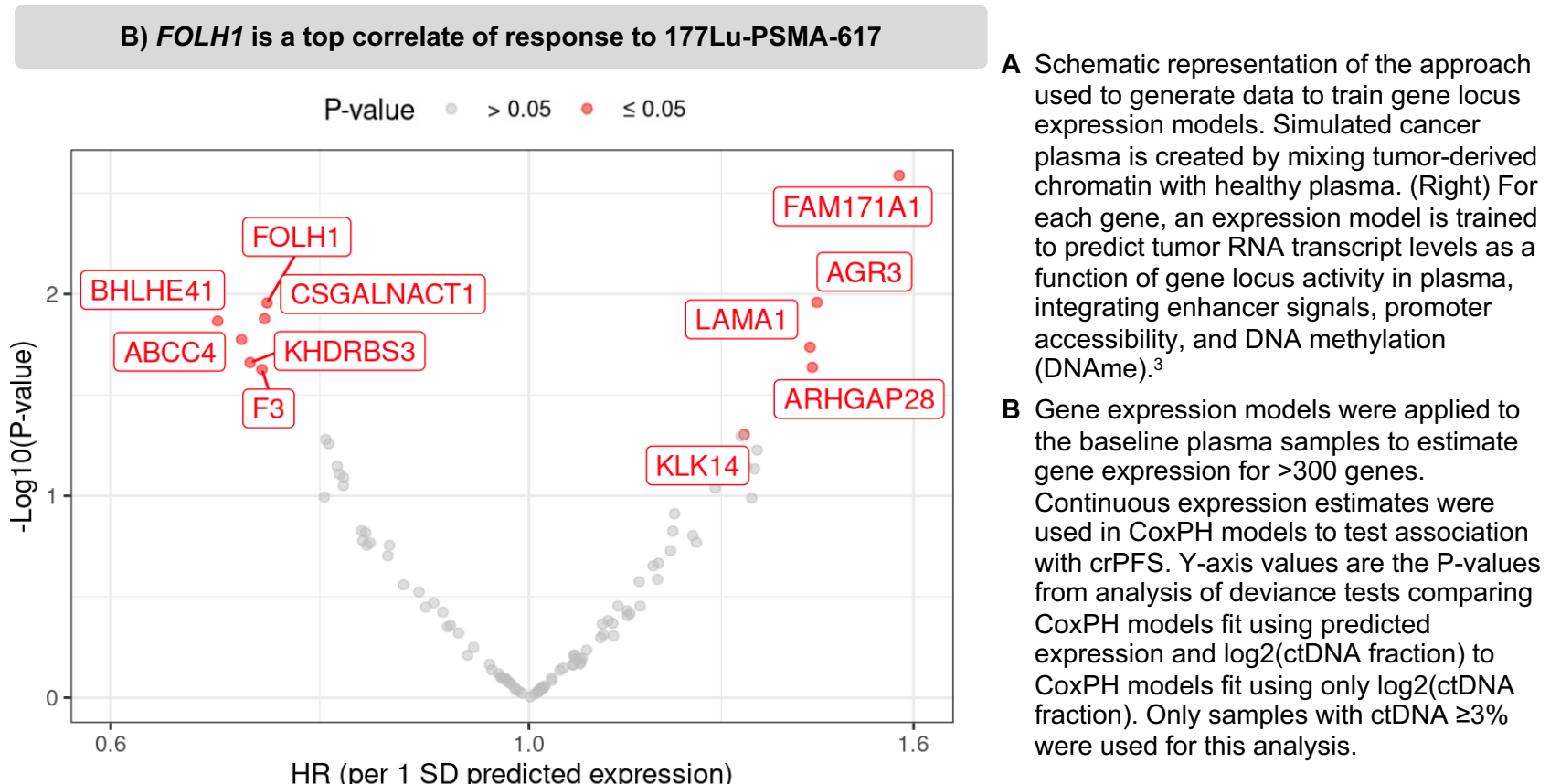
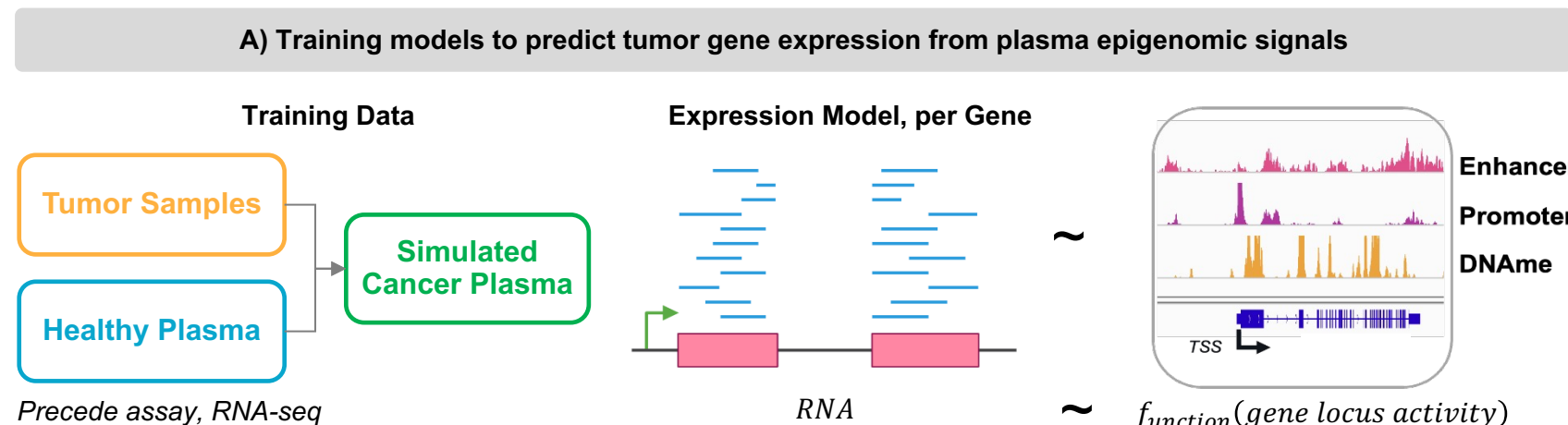
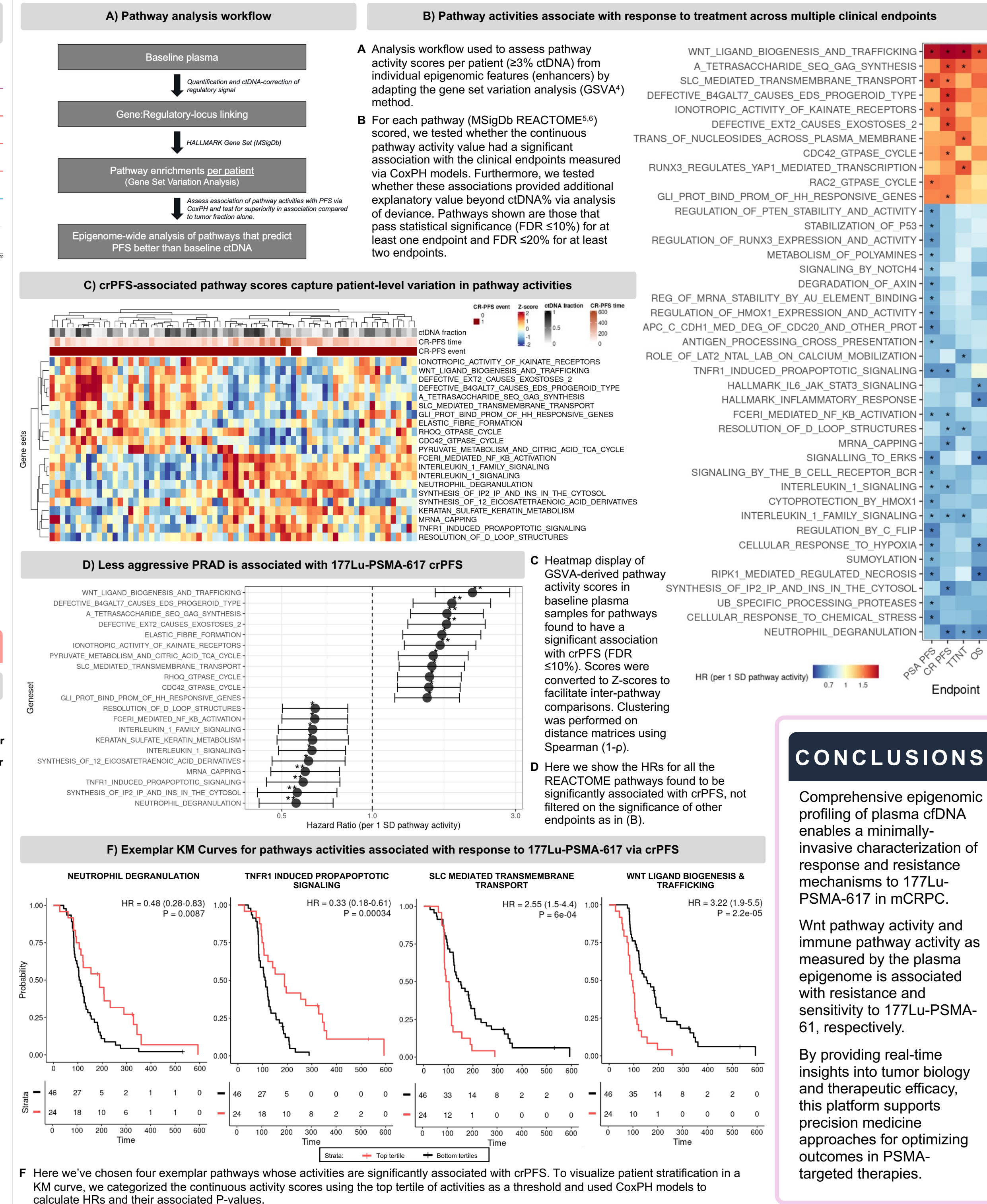


Figure 4. FOLH1 and ECM gene expression are associated with 177Lu-PSMA-617 efficacy



RESULTS

Figure 5. Wnt, metabolic and immune signaling are associated with response to 177Lu-PSMA-617 therapy



CONCLUSIONS

Comprehensive epigenomic profiling of plasma ctDNA enables a minimally-invasive characterization of response and resistance mechanisms to 177Lu-PSMA-617 in mCRPC.

Wnt pathway activity and immune pathway activity as measured by the plasma epigenome is associated with resistance and sensitivity to 177Lu-PSMA-61, respectively.

By providing real-time insights into tumor biology and therapeutic efficacy, this platform supports precision medicine approaches for optimizing outcomes in PSMA-targeted therapies.