

Pan-cancer blood plasma cell-free RNA profiles reveal cancer type and patient-specific changes

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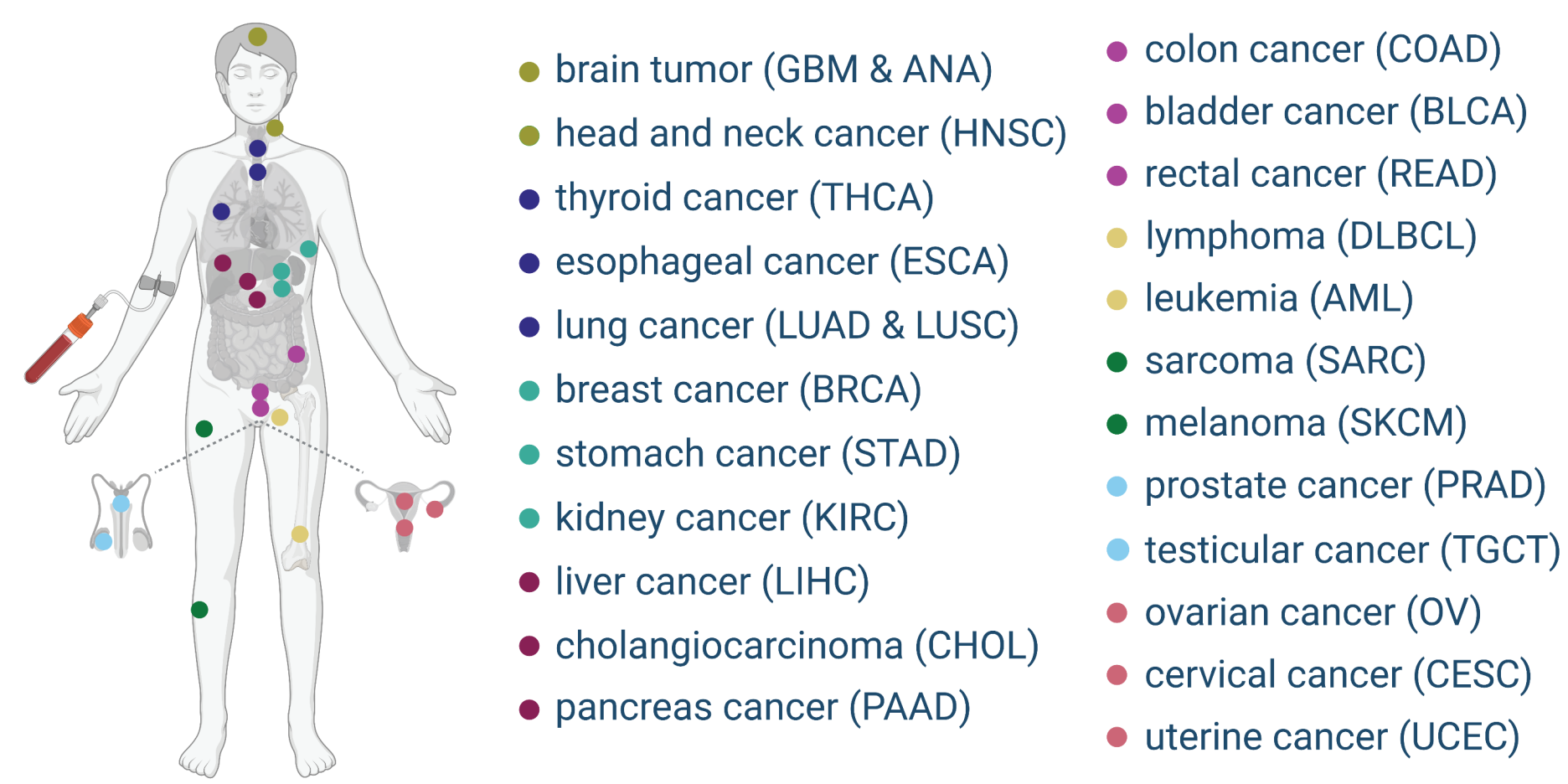
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introduction

Liquid biopsy-based biomarkers, such as circulating nucleic acids in blood plasma, have emerged as promising tools for cancer diagnosis and monitoring. Contrary to tissue biopsies, liquid biopsies are minimally invasive and allow serial collection. Most studies to date focused on circulating tumor DNA (ctDNA). However, cell-free RNAs (cfRNA) may provide an additional cancer biomarker resource given their dynamic nature and tissue specificity. Even though the presence of cfRNA in liquid biopsies is firmly established, the utility for cancer detection and monitoring remains underexplored.

cancer signal in cell-free mRNA profiles



Blood plasma cell-free mRNA (capture sequencing) profiles from late stage to metastatic cancer patients and cancer-free controls in two independent cohorts: a pan-cancer cohort (n=208, 25 cancer types) and a three-cancer cohort (n=58; ovarian (OV), prostate (PRAD) and uterine cancer (UCEC))

Pan-cancer systemic signals

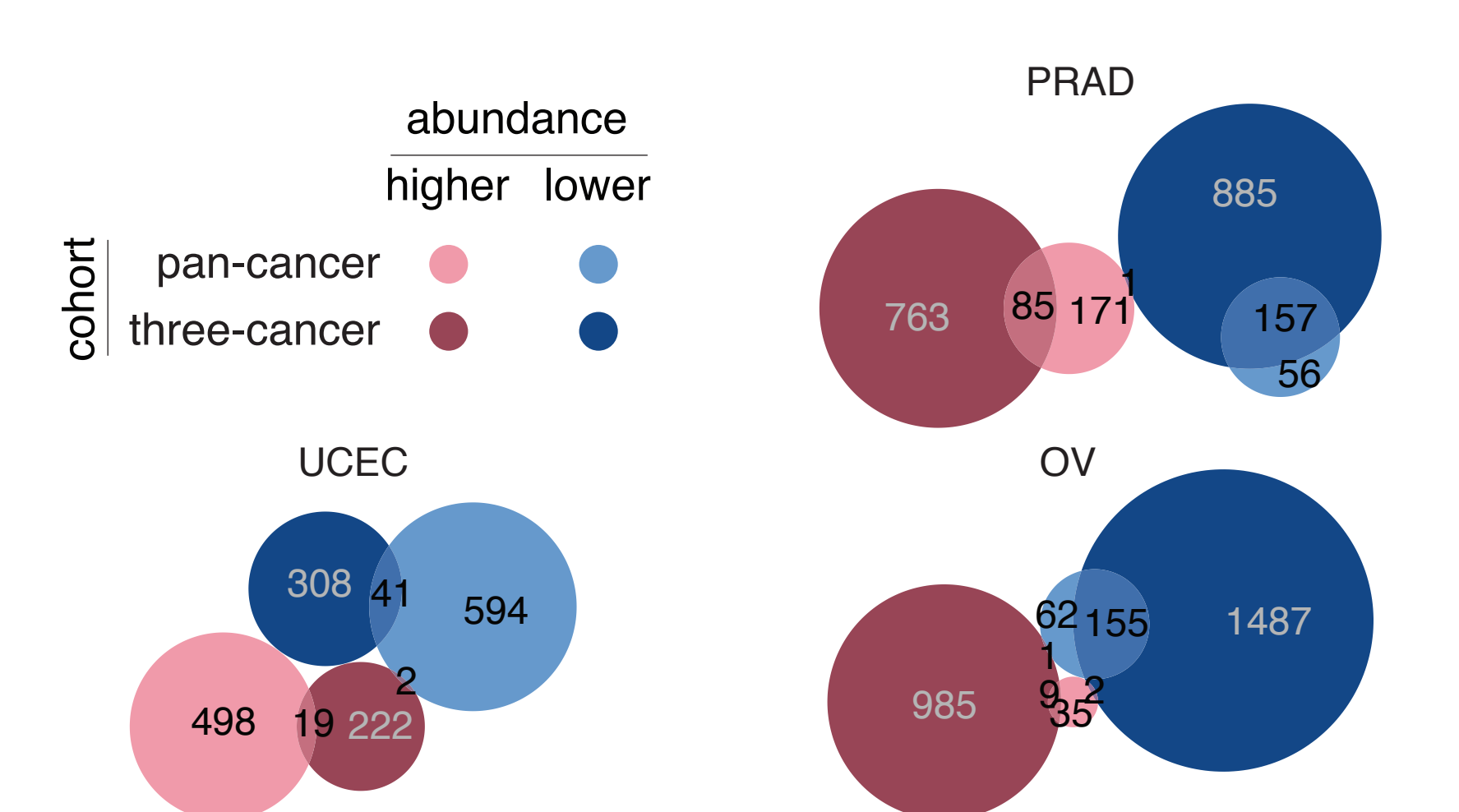
Distinct acute myeloid leukemia profiles

5310 differentially abundant mRNAs
PML::RARA fusion transcripts
 Myeloid progenitor cell contribution
 Lower platelet contribution

Limited type-specific signal in solid tumor profiles

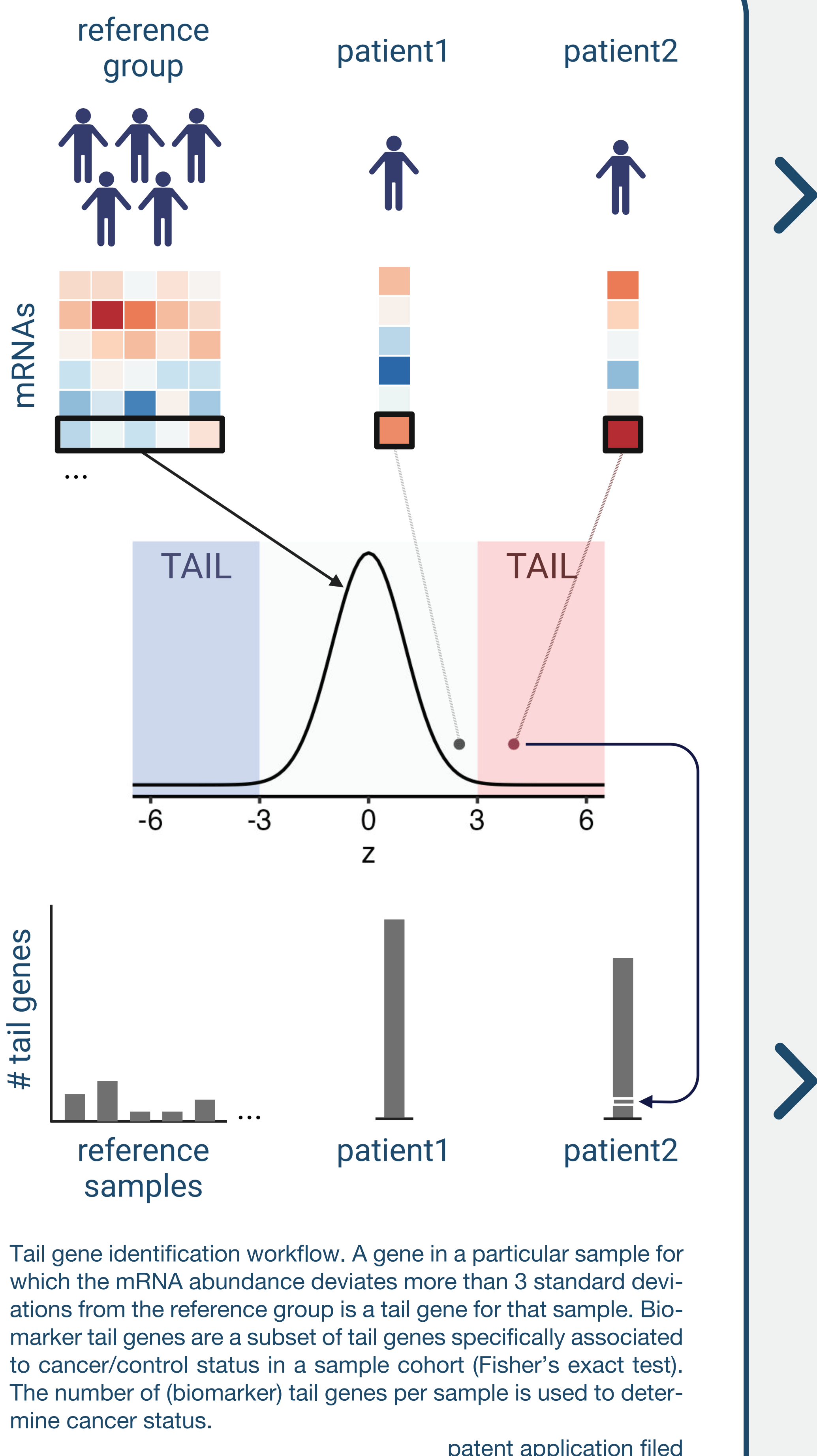
127 to 1154 differentially abundant mRNAs
 Enrichment of liver-related gene sets in liver cancer patients

Heterogeneity among patients and cohorts

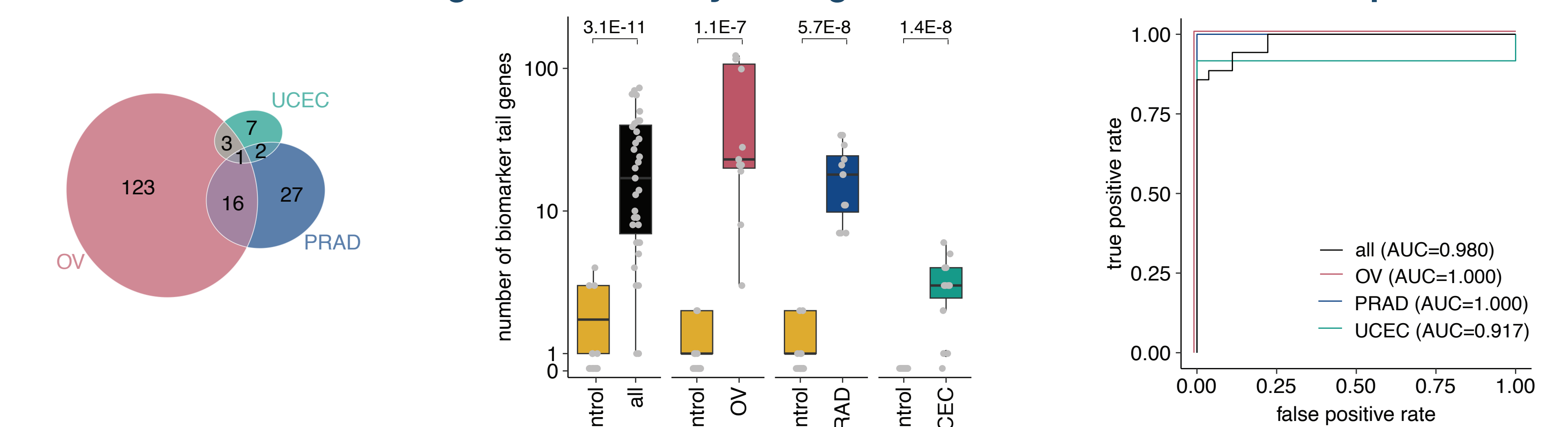


Significant but limited overlap of differentially abundant mRNAs between same cancer type and controls in two cohorts (Jaccard indices < 15%).

exploit heterogeneity for cancer classification

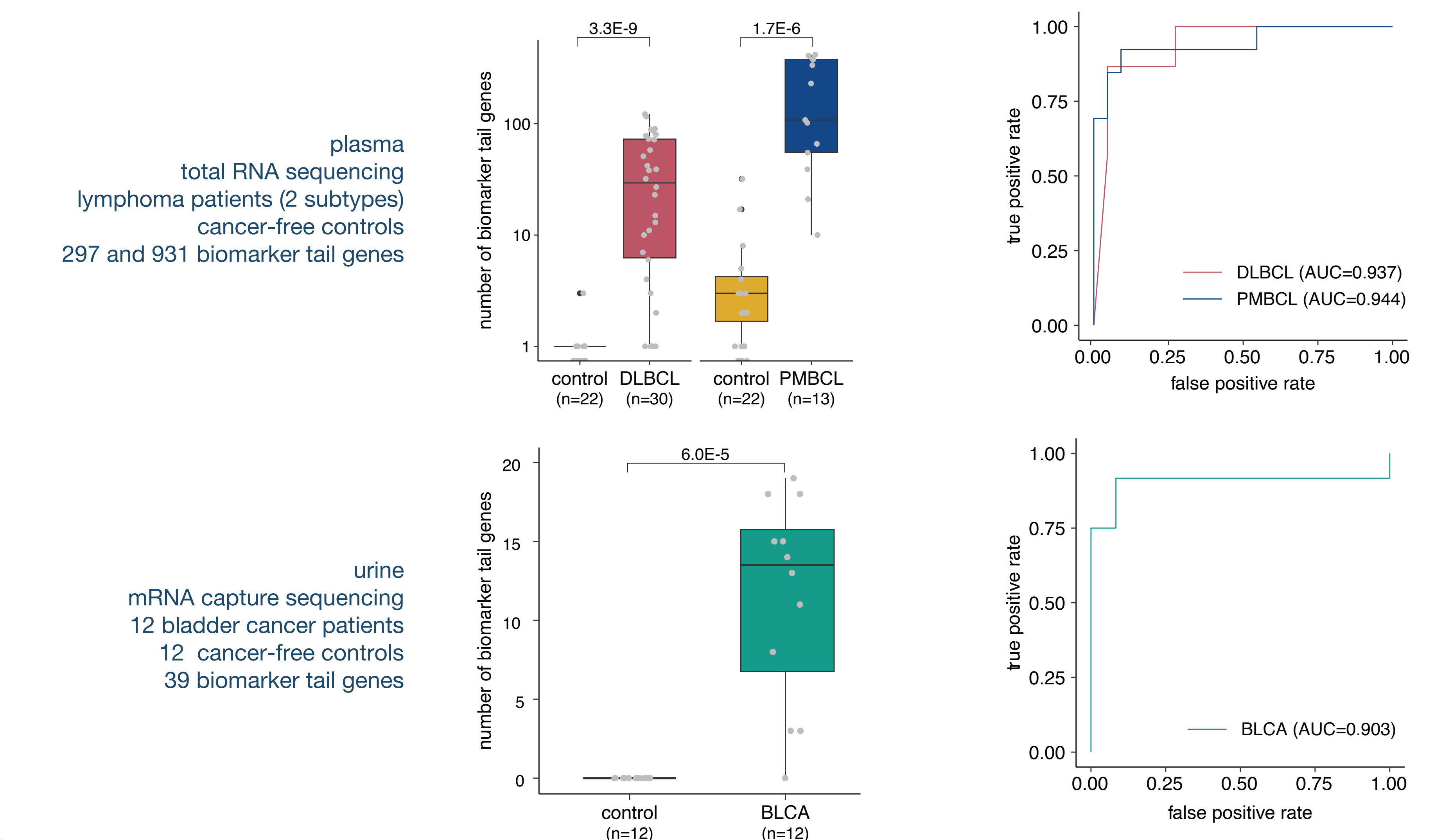


Number of biomarker tail genes accurately distinguishes cancer from control samples



Higher number of biomarker tail genes in cancer patient plasma samples compared to controls. Left: Overlap of type-specific biomarker tail genes. Middle: Boxplot of number of biomarker tail genes per subset in control (n=27) and cancer samples (OV n=11, PRAD n=12, UCEC n=12, all n=35). 108 biomarker tail genes considered for all cancer versus control. Grey dots represent individual sample counts. Two-sided Wilcoxon rank-sum p-values indicated in plot. Right: ROC curve of leave-one-out cross-validated classifier for binary cancer/control classification based on the number of biomarker tail genes belonging to the respective biomarker tail gene set.

Concept validated in independent plasma and urine sample cohorts



Abbreviations

AUC: area under the ROC curve; cfRNA: cell-free RNA; ctDNA: circulating tumor DNA; DLBCL: diffuse large B-cell lymphoma; mRNA: messenger RNA; OV: ovarian cancer; PRAD: prostate cancer; UCEC: uterine cancer; PMBCL: primary mediastinal large B-cell lymphoma; ROC: receiver operating characteristic

Illustrations created with BioRender.com