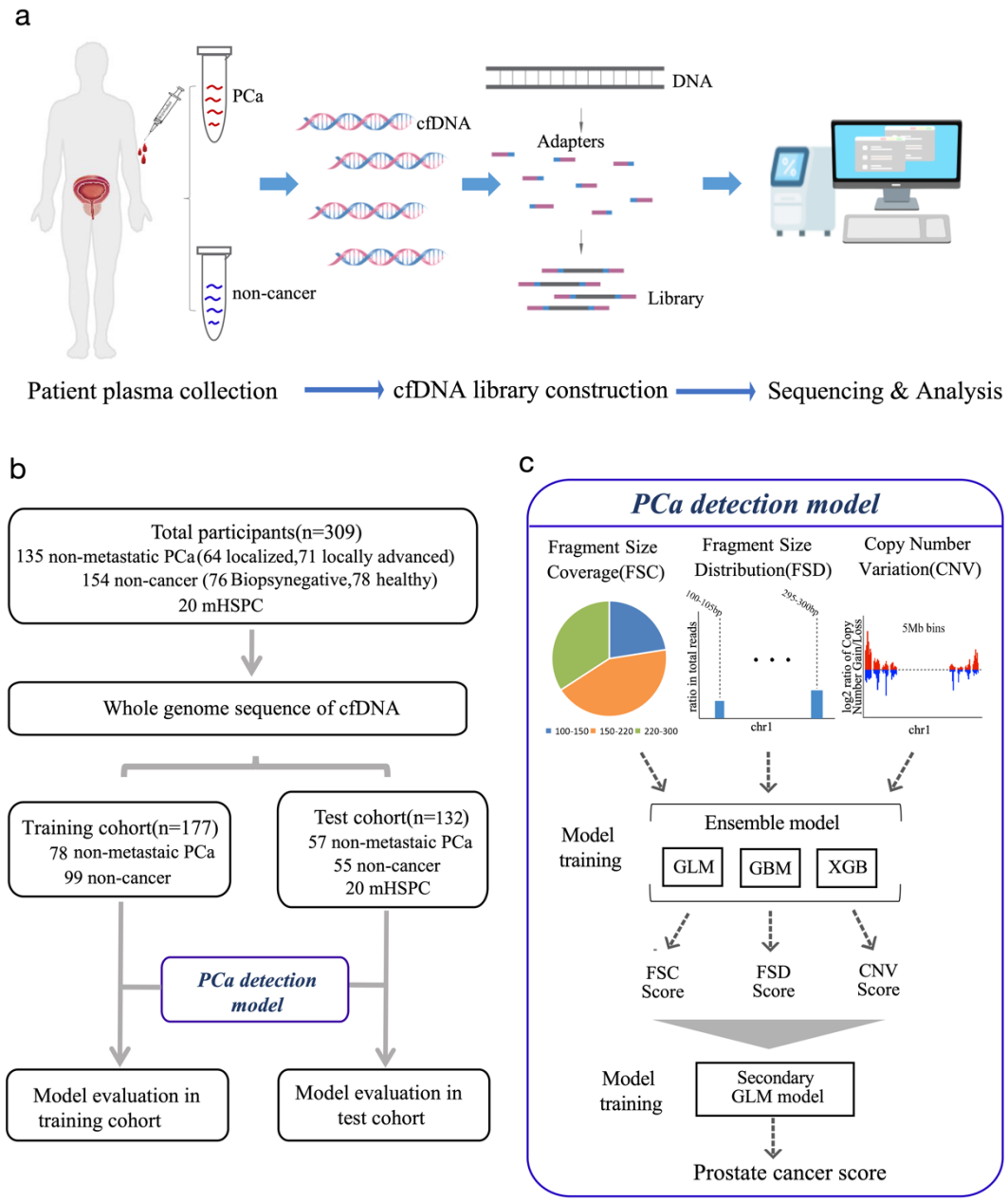
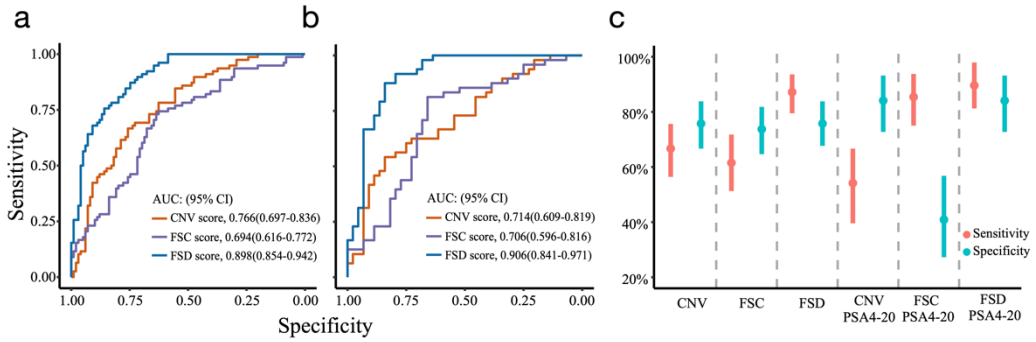
Supplementary Figures

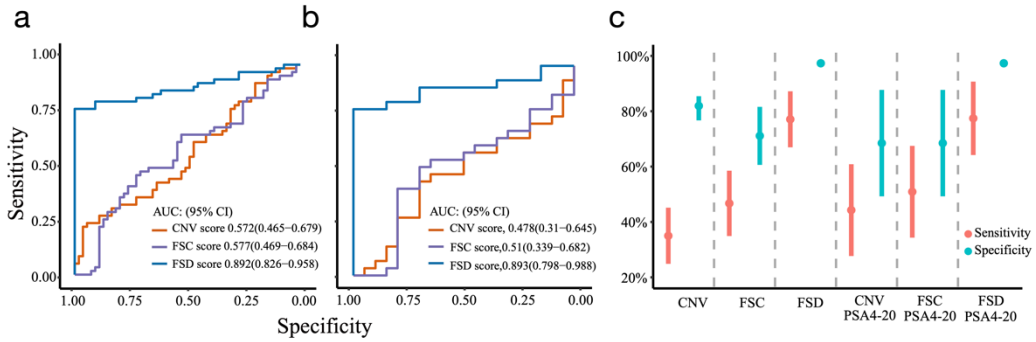


Supplementary Figure 1 | Study Overview. This figure provides an illustrative representation of the study's workflow and participant cohorts. (a) Blood samples were collected from both prostate cancer (PCa) patients and non-cancer controls. Subsequently, cell-free DNA (cfDNA) was extracted from plasma and underwent sequencing library preparation. Whole-genome sequencing (WGS) was performed on the libraries, followed by mapping to a human reference genome. CfDNA fragmentation analysis was then conducted for cancer detection. (b) The study comprised a total of 309 participants, including 135 non-metastatic PCa patients, 20 metastatic hormone-sensitive prostate cancer (mHSPC) patients and 154 non-cancer participants. The training cohort (n=177) was divided into 78 PCa participants (33 localized, 45 locally advanced) and 99 non-cancer participants

(49 BiopsyNegative, 50 healthy), used to train the stacked ensemble model. The independent test cohort (n=132) comprised 57 PCa patients (31 localized, 26 locally advanced), 20 mHSPC patients and 55 non-cancer participants (27 BiopsyNegative, 28 healthy), which was employed to evaluate model performance. (c) Illustration of PCa detection model. PCa detection model first took three distinct types of fragmentomic features as input to predict PCa, including Fragment Size Coverage (FSC), Fragment Size Distribution (FSD), and Copy Number Variation (CNV). For each feature type, we use an ensemble model of Generalized Linear Model (GLM), Gradient Boosting Model (GBM) and XGBoost. Then PCa detection model trained a secondary model using output of three ensembled model by a GLM model, and took the output of the GLM model as prostate cancer score.

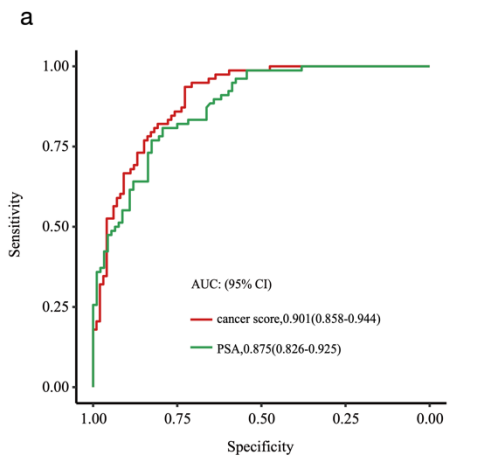


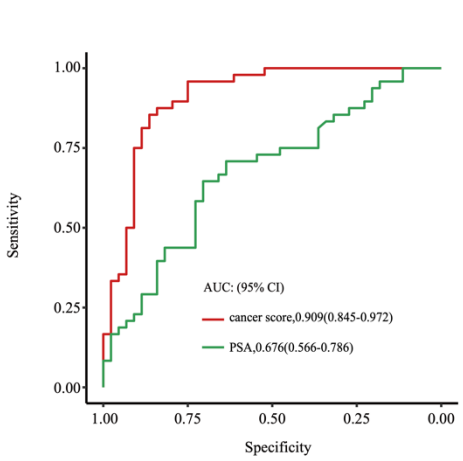
Supplementary Figure 2 | Identification and evaluation of the FSC, FSD, CNV features modeling in the training cohort. (a) Receiver Operating Characteristic (ROC) curve illustrates the predictive model performance based on different features (FSC, FSD, CNV) in distinguishing between PCa and non-cancer individuals across the entire training cohort. (b) ROC curves pertain to subsets of the training cohort with PSA levels above 4 and below 20. (c) Dot plot showcases the sensitivity and specificity of FSC, FSD, and CNV feature models in detecting PCa, both for the complete training cohort WGS data and the subset with PSA levels above 4 and below 20, accompanied by 95% confidence intervals.

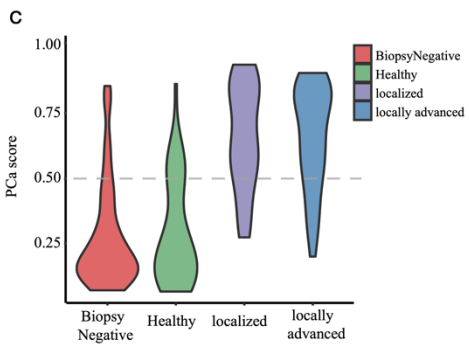


Supplementary Figure 3 | Evaluation of the FSC, FSD, CNV features modeling in the test cohort.

(a) ROC curve portrays the performance of predictive models using various features (FSC, FSD, CNV) to differentiate PCa from non-cancer individuals across the entire test cohort. (b) Corresponding ROC curves are specific to subgroups of the test cohort with PSA levels above 4 and below 20. (c) Dot plot showcases sensitivity and specificity of FSC, FSD, and CNV feature models in detecting PCa, both for the complete test cohort WGS data and the subset with PSA levels above 4 and below 20, accompanied by 95% confidence intervals.







d

		Actual			
		Training cohort		Training cohort(PSA 4-20)	
		PCa	non-cancer	PCa	non-cancer
Predict	PCa	61	16	41	7
	non-cancer	17	83	7	34
Sensitivity		78.20%		85.42%	
Specificity		83.83%		84.10%	
PPV		79.22%		85.42%	
NPV		83%		84.10%	

Supplementary Figure 4 | Performance of the PCa detection model in the training cohort. (a) ROC curve illustrates the performance of the PCa detection model utilizing cancer score feature and the PSA feature model across the entire training cohort, and (b) subsets of the training cohort with PSA levels above 4 and below 20. (c) Violin plot visually represents cancer scores within the whole training cohort categorized by BiopsyNegative, Healthy, localized, and locally advanced participants. The PCa classification threshold is set at 0.5. (d) Table of the PCa detection model performance for the whole training cohort and the subsets of training cohort with PSA > 4 and PSA < 20.