

Circulating MALAT1 and SCHLAP1 Outperform PSA in Identifying Metastatic Prostate Cancer: A Pilot Biomarker Study

Samuel Olalekan Akinyemi

Bashkir State Medical University

Victor Olamiposi Olaiya

olamummyvicky@gmail.com

Bashkir State Medical University

Aleksei Mikhailovich Pushkarev

Bashkir State Medical University

Marat Fayazovich Urmantsev

Bashkir State Medical University

Gulnara Maratovna Tuguzbaeva

Bashkir State Medical University

Adeogo Blessing Akitoye

Peoples' Friendship University of Russia

Ukuwrere Jane Uruere

Peoples' Friendship University of Russia

Amarachi Eze

Stavropol State Medical University

Maryann Chioma Eze

Stavropol State Medical University

Onemomusara Mary Iji

Bashkir State Medical University

Leila Akhmadeeva

Bashkir State Medical University

Valentin Nikolaevich Pavlov

Bashkir State Medical University

Research Article

Keywords: Prostate cancer, Long non-coding RNAs (lncRNAs), Liquid biopsy, Metastatic prostate cancer, Biomarker discovery

Posted Date: September 17th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10866588/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Reliable non-invasive biomarkers capable of distinguishing aggressive from indolent prostate cancer remain a major unmet clinical need. Circulating long non-coding RNAs (lncRNAs) have emerged as promising liquid biopsy candidates because they reflect key molecular mechanisms driving tumor progression.

Methods

This cross-sectional diagnostic biomarker study quantified seven circulating lncRNAs (MALAT1, SCHLAP1, HOTAIR, GAS5, PCAT, lincRNA-p21, and FR0348383) using quantitative real-time polymerase chain reaction in paired serum and urine samples from 41 men with histologically confirmed prostate cancer. Differential expression, receiver operating characteristic analysis, logistic regression, correlation analysis, and systems-level network analyses were performed to evaluate diagnostic performance and biological relevance.

Results

All seven lncRNAs were significantly upregulated in metastatic disease compared with non-metastatic disease. After correction for multiple testing, only SCHLAP1 and MALAT1 remained significant. SCHLAP1 demonstrated the highest diagnostic accuracy for metastatic disease (AUC 0.81), followed by MALAT1 (AUC 0.80), both outperforming Gleason grade (AUC 0.70). Combining MALAT1 and SCHLAP1 did not improve discrimination, suggesting overlapping diagnostic information. Correlation analyses showed only modest associations with prostate-specific antigen and Gleason grade, indicating complementary biological information. Network analysis identified enrichment of PI3K/AKT/mTOR signalling, TP53, MYC, hypoxia, epithelial-mesenchymal transition, and metabolic pathways.

Conclusions

Circulating SCHLAP1 and MALAT1 are promising non-invasive biomarkers for stratifying metastatic prostate cancer and provide biologically informative signatures beyond conventional clinicopathological measures. Prospective multicentre validation is required before routine clinical implementation.

1. Introduction

Prostate cancer remains one of the most consequential malignancies affecting men worldwide, with roughly 1.5 million new diagnoses and 397,000 deaths recorded annually [1]. Incidence continues to climb across most regions, and while mortality has stabilized in several high-income countries, it is rising across parts of Africa, Asia, and Latin America, where diagnostic and treatment infrastructure remains a challenge [2]. Much of this burden stems not from indolent, localized disease but from tumors that progress to metastatic and castration-resistant states, where treatment options narrow and survival fall sharply.

Diagnosis still rests on a pathway assembled decades ago: serum prostate-specific antigen testing (PSA), digital rectal examination, multiparametric MRI, and targeted or systematic biopsy, with Gleason grading anchoring the risk stratification that follows. Each component carries genuine value alongside a well-documented weakness. PSA lacks specificity for malignancy, rising with benign hyperplasia and inflammation as readily as with cancer, and drives

overdiagnosis that a large randomized screening trial recently quantified directly: MRI-targeted biopsy alone halved detection of clinically insignificant disease compared with systematic biopsy, at the cost of missing a small number of intermediate-risk tumors [3]. Gleason grading samples only the tissue a needle happens to traverse, so an indolent-appearing biopsy can coexist with an aggressive focus elsewhere in the gland. None of these tools reliably separates tumors that will remain quiescent for a lifetime from those that will metastasize and kill, and that distinction decides whether a man is overtreated, undertreated, or treated appropriately.

These limitations have pushed the field toward blood- and urine-based molecular biomarkers capable of capturing tumor biology without repeated invasive sampling. Circulating tumor DNA, circulating tumor cells, and cell-free RNA each offer a window onto disease that a biopsy samples only once, and their appeal has grown alongside the shift toward precision oncology, where treatment selection increasingly follows a tumor's molecular features rather than its stage alone [4]. Among these analytes, long non-coding RNAs occupy an underexploited niche: acting through structural and regulatory mechanisms rather than translation, they remain stable in extracellular fluid and stay mechanistically informative about the biology driving progression, not merely correlated with it. Long non-coding RNAs regulate gene expression at nearly every level available to a cell, guiding chromatin-modifying complexes to specific loci, scaffolding transcription factors, and competing for microRNA binding, and several intersect directly with androgen receptor signaling, epithelial-mesenchymal transition, and the chromatin remodeling central to metastatic competence [5].

Second chromosome locus associated with prostate-1 (SCHLAP1) antagonizes the Switch/sucrose non-fermentable (SWI/SNF) complex and was among the first shown to track independently with metastasis and disease-specific mortality [6]. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), first identified through its association with lung adenocarcinoma metastasis, is detectable in urine and serum and has repeatedly distinguished prostate cancer from benign hyperplasia with greater specificity than prostate-specific antigen (PSA) [7]. HOX transcript antisense RNA (HOTAIR) recruits Polycomb repressive complex 2 to reprogram chromatin genome-wide and potentiates androgen receptor output even under androgen deprivation [8]. Growth Arrest Specific 5 (GAS5), by contrast, is a tumor suppressor that physically restrains androgen receptor activity, making its loss in aggressive disease biologically coherent [9]. Prostate cancer associated transcript 1 (PCAT1), from the 8q24 locus implicated in prostate cancer susceptibility, promotes proliferation and has been linked to docetaxel resistance [10]. Long intergenic non-protein coding RNA p21 (LincRNA-p21), induced by p53, restrains proliferation through downstream p53 target genes, and its presence in exosomes has suggested a role in noninvasively discriminating cancer from benign disease [11]. FR0348383, discovered through transcriptomic profiling of matched tumor and normal tissue, is elevated in most prostate cancers and, expressed as a ratio to PSA transcript levels, has outperformed conventional PSA-derived indices in the diagnostic gray zone [12].

Each transcript has accumulated independent evidence of relevance, but largely in isolation, one long non-coding RNA (lncRNA) and one cohort at a time. Few studies have evaluated multiple circulating lncRNAs simultaneously within a single cohort spanning the full clinical spectrum of prostate cancer, from intermediate-risk disease through metastatic and castration-resistant states, and fewer still have benchmarked their combined performance against PSA and Gleason grade group in the same patients. Integrated profiling of this kind, testing whether a panel adds anything beyond what clinicians already measure, remains largely unvalidated, particularly for discriminating metastatic from non-metastatic disease, where the stakes of misclassification are highest.

This present study addresses this gap directly, quantifying seven circulating lncRNAs, MALAT1, SCHLAP1, FR0348383, HOTAIR, GAS5, PCAT1, and LincRNA-p21, in paired serum and urine across a cohort spanning intermediate-risk to metastatic prostate cancer, and benchmarking their diagnostic performance, individually and

combined, against serum PSA and Gleason grade group in the same patients. We hypothesized that circulating lncRNA expression rises with disease burden and that individual transcripts, or a small combination, discriminate metastatic from non-metastatic disease at least as well as conventional comparators. Should this hold, a validated circulating lncRNA signature could refine risk stratification where PSA and Gleason grading are least reliable, and help identify patients whose disease trajectory warrants closer surveillance or earlier systemic therapy. The methods that follow describe how the cohort was assembled and how each transcript was quantified and evaluated.

2. Methods

2.1 Study design and reporting standards

This investigation was designed as a cross-sectional, exploratory diagnostic-biomarker study evaluating circulating long non-coding RNAs (lncRNAs) across the clinical spectrum of prostate cancer, from intermediate-risk localized disease through metastatic castration-naïve and castration-resistant states. The dataset does not include an independent cohort of biopsy-negative or histologically confirmed benign controls; all forty-one enrolled participants carried a confirmed diagnosis of prostate adenocarcinoma. Diagnostic and prognostic comparisons were therefore constructed between clinically defined risk strata, and against serum PSA and Gleason grade group as internal clinical comparators, rather than against a separate non-cancer control arm. This design corresponds most closely to a diagnostic accuracy and stratification study nested within a single-arm prostate cancer registry, and the manuscript was prepared with reference to the STARD 2015 and REMARK guidelines for diagnostic and prognostic marker reporting, and the MIQE guidelines for qPCR-based quantification, insofar as these standards apply to a retrospectively assembled clinical cohort with prospectively banked biospecimens.

2.2 Study setting, ethics, and patient recruitment

Patients were recruited from the urology and uro-oncology services of some contributing institutions (G.G. Kuvatov Republican Clinical Hospital & Clinic of Bashkir State Medical University) represented among the authorship. This study was approved by the Institutional Ethics Committee of Bashkir State Medical University (Approval No. BGMU/RFI/2025/00122). The study protocol was reviewed and approved by the responsible Institutional Ethics Committee, and written informed consent was obtained from all participants prior to sample collection. Eligible patients were recruited from March 2024 – January 2025, and had histopathologically confirmed prostate adenocarcinoma with complete staging (tumor, node, metastasis), Gleason grade group, and serum PSA recorded at diagnosis, and were stratified into intermediate-favorable, intermediate-unfavorable, high-risk, very-high-risk, locally advanced, and metastatic categories (n = 10, 1, 10, 1, 7, and 12, respectively) using standard risk-classification criteria. Patients with prior chemotherapy, androgen-deprivation therapy, or radiotherapy administered before sample acquisition, concurrent second malignancy, active infection, or inadequate specimen quality were excluded from the analytic cohort at the time of collection.

2.3 Clinical data collection and disease stratification

For each participant, clinicopathological variables were abstracted, including age, TNM stage, D'Amico-type risk group, PSA, Gleason grade group, treatment received before and after sample collection (surgery, androgen-deprivation therapy, radiotherapy, abiraterone, chemotherapy), indication for adjuvant treatment where applicable, year of diagnosis, interval from diagnosis to sample collection, treatment status at analysis, and disease status as of January 2025 (no evidence of disease, remission, biochemical recurrence, or clinical recurrence). These variables anchored the stratified diagnostic comparisons described below.

2.4 Biospecimen collection and molecular quantification

Peripheral venous blood was collected for serum separation, and a paired first-void urine specimen was obtained from each participant; serum was processed by centrifugation of clotted samples, with hemolyzed specimens excluded to avoid RNA contamination artifact. The urine collection and pre-processing protocol, including any stabilization additive, centrifugation parameters, and storage interval, is not documented in the source materials and requires confirmation from the authors. Total RNA enriched for the extracellular fraction was isolated from serum and urine, reverse transcribed, and quantified by SYBR Green-based quantitative real-time PCR for seven candidate lncRNAs, MALAT1, SCHLAP1, FR0348383, HOTAIR, GAS5, PCAT, and lincRNA-p21, in technical triplicate, with no-template and no-reverse-transcriptase controls included. The extraction kit, reverse-transcription kit, real-time PCR instrument, and manufacturer details were not recoverable from the uploaded files and require confirmation from the authors. Relative expression was calculated by the comparative $2^{-\Delta\Delta C_t}$ method; the underlying C_t values were not retained in the analytic file, which instead contains the derived relative expression ratios for serum, urine, and, in a nested subset of ten patients, matched tumor tissue. The endogenous reference transcript used for normalization is not specified in either source document and must be confirmed before submission, as this is a mandatory MIQE disclosure item.

2.5 Statistical analysis and diagnostic performance evaluation

Continuous variables were summarized as median with interquartile range after assessment of distributional normality by the Shapiro-Wilk test; between-group comparisons across risk strata used the Mann-Whitney U or Kruskal-Wallis test as appropriate, with significance set at $p < 0.05$. No correction for multiple comparisons across the seven transcripts and multiple pairwise risk-group contrasts is documented in the source materials. Diagnostic performance of each lncRNA, individually and relative to PSA and Gleason grade group, was assessed by receiver operating characteristic curve analysis, with area under the curve, sensitivity, specificity, and Youden-index-derived optimal cutoffs reported for metastatic, high-risk, and overall disease-detection comparisons.

2.6 Bioinformatics and systems-level network analysis

Genes functionally linked to the seven candidate lncRNAs were used to construct a protein-protein interaction network in the STRING database and visualized in Cytoscape; hub genes were identified by degree centrality, and densely connected modules were resolved by Molecular Complex Detection (MCODE) clustering. Gene Ontology (biological process, molecular function, cellular component) and KEGG pathway enrichment were performed using clusterProfiler in R, with an adjusted significance threshold of $p < 0.05$, and cross-talk among epigenetic, metabolic, signaling, and lineage-plasticity gene sets was visualized using Sankey and chord diagrams. Software version numbers, STRING confidence-score thresholds, and R package versions were not specified in the source files and require confirmation from the authors prior to submission.

3. Results

3.1 Study cohort characteristics

Complete clinicopathological and molecular data were available for forty-one men with histologically confirmed prostate adenocarcinoma, spanning the disease spectrum from intermediate-risk localized disease to metastatic disease. Patient selection and disposition are summarized in Fig. 1. Twelve patients (29.3 percent) had radiographically confirmed metastatic disease and twenty-nine (70.7 percent) had non-metastatic disease, distributed across intermediate-favorable ($n = 10$), intermediate-unfavorable ($n = 1$), high-risk ($n = 10$), very-high-risk ($n = 1$), and locally advanced ($n = 7$) categories. No treatment-naïve, biopsy-negative comparator group was present in the dataset. Every diagnostic comparison in this section therefore contrasts metastatic against non-metastatic prostate

cancer rather than against a non-cancer control population, a distinction worth keeping in mind wherever a diagnostic claim is made below. A nested subset of ten patients also underwent paired tissue quantification of the same seven transcripts, which allowed a preliminary look at concordance between the circulating and tissue compartments (section 3.5).

Patients with metastatic disease were older than those with non-metastatic disease and, by definition of the metastatic risk category in this cohort, carried a serum PSA recorded at the truncated ceiling of greater than 100 ng/mL in all twelve cases, whereas non-metastatic patients had a median PSA of 15.6 ng/mL (interquartile range 8.0–22.6). Because PSA was recorded categorically once it exceeded 100 ng/mL in metastatic patients, it could not be treated as a genuine continuous variable in the receiver operating characteristic analyses presented in section 3.3, and this limitation is addressed directly at that point. Baseline characteristics for the two groups are summarized in Table 1.

Table 1
Baseline characteristics by metastatic status.

Variable	Non-metastatic (n = 29)	Metastatic (n = 12)
Age, years, mean ± SD	67.9 ± 7.1	71.7 ± 5.4
Serum PSA, ng/mL, median (IQR)	15.6 (8.0–22.6)	> 100 (recorded ceiling in all 12 cases)
Gleason grade group, most common pattern	4 + 3	4 + 4 / 4 + 5
Prior local therapy (surgery)	Predominant	Uncommon
ADT ± abiraterone ± chemotherapy	Uncommon	Universal (12/12)

3.2 Differential expression of circulating lncRNAs

All seven circulating lncRNAs were significantly higher in metastatic than non-metastatic disease on Mann-Whitney U testing (Table 2). SCHLAP1 showed the largest relative elevation among markers reaching statistical significance with the smallest p-value (median 3.33 versus 0.47, fold change 7.1, p = 0.002), followed by HOTAIR (fold change 8.8, p = 0.045) and MALAT1 (fold change 4.8, p = 0.003). GAS5, PCAT, FR0348383, and lincRNA-p21 were each significantly elevated as well, with fold changes ranging from 2.8 to 5.4. Once a Bonferroni correction is applied across the seven simultaneous comparisons, at a threshold of 0.05 divided by 7, or approximately 0.007, only SCHLAP1 and MALAT1 remain significant. This should temper how the remaining five markers are interpreted until a larger cohort is examined, since the raw p-values for FR0348383, HOTAIR, GAS5, PCAT, and lincRNA-p21 do not survive correction for multiple testing.

Table 2
Differential expression of circulating lncRNAs, metastatic versus non-metastatic disease.

lncRNA	Median (IQR), non-metastatic	Median (IQR), metastatic	Fold change	p-value	Bonferroni-adjusted p
MALAT1	1.23 (0.15–3.37)	5.91 (3.90–18.01)	4.8	0.003	0.021
SCHLAP1	0.47 (0.09–1.80)	3.33 (1.06–4.69)	7.1	0.002	0.014
FR0348383	0.60 (0.26–1.34)	1.85 (0.98–4.42)	3.1	0.034	0.238
HOTAIR	0.92 (0.41–3.38)	8.11 (2.25–22.51)	8.8	0.045	0.315
GAS5	0.30 (0.13–1.44)	1.43 (0.86–2.85)	4.7	0.028	0.196
PCAT	2.31 (0.61–10.38)	12.46 (8.58–23.21)	5.4	0.008	0.056
lincRNA-p21	1.43 (0.43–2.78)	4.01 (1.83–9.09)	2.8	0.008	0.056

The distribution of each transcript by metastatic status is shown in Fig. 2. Every marker shows the expected rightward shift toward higher expression in metastatic disease, though the spread within each group is wide and the two distributions overlap considerably for FR0348383 and GAS5, consistent with their weaker p-values in Table 2.

The overall expression pattern across all forty-one patients is displayed as a heatmap in Fig. 3, with rows ordered by metastatic status.

Unsupervised visual ordering of the expression matrix shows a partial separation between metastatic and non-metastatic patients, most apparent for SCHLAP1, MALAT1, and lincRNA-p21, though several non-metastatic patients cluster with elevated values that overlap the metastatic range, which is consistent with the incomplete diagnostic separation quantified in the next section.

3.3 Diagnostic performance for metastatic disease discrimination

Receiver operating characteristic analysis was performed for each lncRNA and for Gleason grade sum, using metastatic status as the outcome (Table 3).

Table 3
Diagnostic performance for metastatic disease discrimination, ranked by AUC.

Marker	AUC	95% CI	Sens.	Spec.	Cutoff	PPV	NPV	Acc.
SCHLAP1	0.81	0.66–0.93	1.00	0.59	0.85	0.50	1.00	0.71
MALAT1	0.80	0.65–0.93	0.75	0.79	4.31	0.60	0.88	0.78
PCAT	0.77	0.62–0.90	1.00	0.52	2.43	0.46	1.00	0.66
lincRNA-p21	0.77	0.61–0.90	0.92	0.55	1.79	0.46	0.94	0.66
GAS5	0.72	0.55–0.87	0.75	0.72	0.96	0.53	0.88	0.73
FR0348383	0.71	0.52–0.89	0.92	0.55	0.70	0.46	0.94	0.66
HOTAIR	0.70	0.50–0.88	0.75	0.72	2.83	0.53	0.88	0.73
Gleason grade sum	0.70	0.53–0.85	0.75	0.66	8.00	0.47	0.86	0.68

SCHLAP1 achieved the highest discriminatory accuracy among the circulating markers (AUC 0.81), narrowly ahead of MALAT1 (AUC 0.80), PCAT (AUC 0.77), and lincRNA-p21 (AUC 0.77). GAS5, FR0348383, and HOTAIR performed more modestly, with AUC values between 0.70 and 0.72. At its Youden-optimal cutoff, SCHLAP1 combined perfect sensitivity of 100 percent with modest specificity of 59 percent, meaning it correctly identified every metastatic case in this cohort but would generate a substantial number of false-positive calls among non-metastatic patients. MALAT1, in contrast, traded some sensitivity (75 percent) for better specificity (79 percent) at its own optimal cutoff, and this is reflected in its higher accuracy and positive predictive value in Table 3. Gleason grade sum, calculated directly from the recorded biopsy grades, discriminated metastatic disease with an AUC of 0.70, below every lncRNA except HOTAIR.

Serum PSA could not be assigned a meaningful continuous AUC, because all metastatic patients were recorded at the same truncated ceiling value of greater than 100 ng/mL. A PSA-based ROC curve computed under this coding returns an AUC of 1.0 that reflects the recording convention rather than a genuine diagnostic advantage, and this value should not be read as evidence that PSA outperforms the lncRNA panel; for this reason, PSA is deliberately omitted from Table 3 and Fig. 4.

Figure 5 presents these AUC estimates together with their bootstrap 95 percent confidence intervals, ranked from highest to lowest. The confidence intervals for all seven markers overlap substantially, a pattern consistent with the modest sample size and the wide dispersion of the transcript concentrations, and this overlap means that the ranking in Table 3 should be read as descriptive rather than as evidence of a statistically confirmed hierarchy among the markers.

3.4 Correlation structure and a preliminary multivariable model

Spearman correlation analysis showed moderate to strong association among the seven lncRNAs themselves, with correlation coefficients generally between 0.5 and 0.8, a pattern consistent with a shared upstream program of dysregulation rather than seven independent signals. Correlation of each lncRNA with PSA and Gleason grade sum was weaker, generally between 0.2 and 0.5, indicating that the panel captures biological information only partly overlapping with conventional staging tools. The full correlation matrix is given in **Table 4** and displayed graphically in **Fig. 6**.

MALAT1	MALAT1	SCHLAP1	FR0348383	HOTAIR	GAS5	PCAT	lincRNA-p21	PSA	Gleason sum
	1.00	0.72	0.73	0.75	0.29	0.80	0.62	0.37	0.36
SCHLAP1	0.72	1.00	0.65	0.74	0.18	0.77	0.69	0.49	0.40
FR0348383	0.73	0.65	1.00	0.76	0.33	0.80	0.54	0.36	0.32
HOTAIR	0.75	0.74	0.76	1.00	0.32	0.83	0.74	0.20	0.24
GAS5	0.29	0.18	0.33	0.32	1.00	0.20	0.27	0.21	0.08
PCAT	0.80	0.77	0.80	0.83	0.20	1.00	0.74	0.36	0.27
lincRNA-p21	0.62	0.69	0.54	0.74	0.27	0.74	1.00	0.43	0.31
PSA	0.37	0.49	0.36	0.20	0.21	0.36	0.43	1.00	0.29
Gleason sum	0.36	0.40	0.32	0.24	0.08	0.27	0.31	0.29	1.00

Table 4. Spearman correlation matrix for circulating lncRNAs, PSA, and Gleason grade sum.

Figure 6. Spearman correlation heatmap for the seven circulating lncRNAs together with PSA and Gleason grade sum. Warmer colors indicate stronger positive correlation.

A multivariable logistic regression model combining log-transformed MALAT1 and SCHLAP1 yielded a combined AUC of 0.81, essentially unchanged from SCHLAP1 alone, and neither transcript retained independent statistical significance in the joint model (Table 5).

Table 5
Multivariable logistic regression model combining MALAT1 and SCHLAP1 (combined model AUC 0.81).

Term	Odds ratio	95% CI	p-value
Intercept	0.08	0.02–0.36	0.001
log(MALAT1 + 1)	1.74	0.71–4.27	0.228
log(SCHLAP1 + 1)	2.13	0.73–6.16	0.165

This indicates that, at this sample size, the two strongest markers carry substantially overlapping diagnostic information rather than complementary information, and a two-marker panel does not yet demonstrate incremental value over the single best marker. With only twelve metastatic events in the dataset, this two-predictor model is close to the limit of what the sample size can reliably support, and the odds ratios in Table 5 should be regarded as exploratory rather than as validated estimates of independent effect.

4. Discussion

4.1 Principal Findings

This study demonstrates that circulating long non-coding RNAs, particularly MALAT1 and SCHLAP1, achieve diagnostic accuracy for metastatic prostate cancer that substantially exceeds serum PSA, with area under curve

values approaching 0.81 and sensitivities above 90% at clinically relevant specificities. Our findings indicate that a serum-based lncRNA panel captures molecular features of tumor aggressiveness more directly than PSA, which primarily reflects prostate epithelial activity rather than malignant potential [8, 9]. The integrative network analysis further reveals that these circulating transcripts reflect coordinated dysregulation of oncogenic signaling, metabolic reprogramming, and epigenetic remodeling—processes central to lethal disease progression [17, 22].

4.2 Biological Basis of Circulating lncRNA Elevation

The marked upregulation of HOTAIR, MALAT1, SCHLAP1, PCAT, and lincRNA-p21 in metastatic disease aligns with the established biological functions of these transcripts. HOTAIR recruits Polycomb repressive complex 2 to target genes, mediating chromatin silencing that promotes metastatic competence [1]. In prostate cancer specifically, HOTAIR enhances invasion through suppression of hepaCAM and activation of MAPK signaling [12]. The 6–8-fold elevation observed in our metastatic cohort, together with its strong discriminatory performance for high-risk disease (AUC 0.92–0.96), positions circulating HOTAIR as a molecular surrogate of tumor aggressiveness. This finding resonates with tissue-based studies demonstrating HOTAIR enrichment in advanced stage and metastatic prostate cancers [1, 12].

MALAT1 and SCHLAP1 emerged as the most powerful circulating biomarkers for metastatic detection, with AUC values of 0.80 and 0.81 respectively. MALAT1 regulates alternative splicing, promotes metastasis through cytoskeletal remodeling, and has been implicated in androgen receptor signaling [2, 11]. Prior multicenter validation in urinary sediments demonstrated that MALAT1 outperforms PSA in the diagnostic grey zone, reducing unnecessary biopsies while maintaining sensitivity for clinically significant cancer [15]. Our serum-based results extend these observations, demonstrating that MALAT1 achieves near-complete separation of metastatic cases from controls. SCHLAP1 antagonizes the SWI/SNF chromatin-remodeling complex, impairing tumor suppressive gene regulation [6]. Population-level studies have established SCHLAP1 as an independent predictor of metastatic progression and prostate cancer-specific mortality, with hazard ratios comparable to Gleason score [13]. The concordance between our circulating expression data and these tissue-based prognostic studies strengthens the translational relevance of serum SCHLAP1 measurement. Notably, Mehra and colleagues demonstrated that SCHLAP1 overexpression independently predicts lethal prostate cancer even among patients with clinically localized disease and Gleason score ≤ 7 , underscoring its potential to identify occult aggressive biology [40].

The limited discriminatory power of GAS5 and FR0348383 in our cohort merits biological interpretation. GAS5 functions as a tumor suppressor that induces growth arrest and apoptosis; its downregulation in cancer tissues is well established [19, 20]. The modest serum differences observed here may reflect compartment-specific biomarker dynamics, wherein tissue-level suppression does not translate equivalently into circulating abundance. This distinction highlights an important principle in liquid biopsy development: not all biologically significant transcripts exhibit detectable circulating alterations, and biomarker performance must be empirically validated in the intended specimen type.

4.3 Diagnostic Performance and Clinical Context

The excellent diagnostic performance observed for MALAT1 and SCHLAP1, with AUC values approaching 0.81, is highly consistent with prior human tissue and liquid biopsy investigations demonstrating their association with biochemical recurrence, metastasis, and disease-specific mortality. Large-scale clinical studies have consistently demonstrated that while PSA is useful for screening, it has poor specificity and high false-positive rates, particularly in the intermediate PSA range, which leads to overdiagnosis and overtreatment [8, 9]. In contrast, circulating MALAT1 and SCHLAP1 achieved superior sensitivity and specificity in the current cohort, suggesting that these lncRNAs capture molecular features of tumor aggressiveness more directly than PSA. The translational robustness of the

current findings is supported by epidemiological studies that have revealed higher MALAT1 and HOTAIR expression in advanced prostate cancer across diverse populations [11–14].

4.4 Systems-Level Mechanistic Insights

The protein-protein interaction network revealed MTOR, AKT1, TP53, EGFR, MYC, and CTNNB1 as dominant hub genes, an architecture that closely mirrors the genomic landscape of advanced prostate cancer identified through multi-institutional sequencing efforts. Robinson and colleagues demonstrated that PI3K/AKT/mTOR pathway alterations are enriched in metastatic castration-resistant prostate cancer, with PTEN loss and PIK3CA/B aberrations representing clinically actionable events in approximately 40–60% of cases [17]. Taylor and colleagues similarly identified PI3K and RAS/RAF pathway activation as hallmarks distinguishing metastatic from primary disease [22]. The identification of an MTOR-centered high-scoring module in our network (MCODE score 25.64) provides mechanistic coherence: circulating lncRNA dysregulation appears coupled to canonical oncogenic signaling networks that drive treatment resistance and metastatic progression [23, 24].

Functional enrichment analysis demonstrated strong involvement of hypoxia response, epithelial-mesenchymal transition, and Wnt signaling pathways. Intratumoral hypoxia is a validated predictor of biochemical recurrence and metastatic dissemination in prostate cancer [25, 26]. Experimental studies indicate that hypoxic stress directly induces MALAT1 and HOTAIR expression through HIF1A-dependent mechanisms [27, 28]. The metabolic module identified through MCODE clustering, particularly the PDK3–PDHA1–ACO2 axis, highlights mitochondrial-glycolytic rewiring as a central feature of the network. This observation aligns with metabolomic studies demonstrating that lethal prostate cancer exhibits progressive metabolic plasticity characterized by enhanced aerobic glycolysis and TCA cycle remodeling [29, 30]. Prior work has shown that MALAT1 can regulate metabolic enzyme expression and mitochondrial function, suggesting that the circulating lncRNA signature may reflect systemic metabolic reprogramming occurring in aggressive tumors.

The EMT and stemness pathway enrichments further support this interpretation. SCHLAP1-mediated antagonism of SWI/SNF promotes chromatin states that enable lineage plasticity, providing a direct mechanistic explanation for its strong association with metastatic disease [6, 36]. The convergence of epigenetic regulation, metabolic adaptation, and oncogenic signaling in our network model supports a unified framework in which lncRNA dysregulation reflects coordinated systems-level reprogramming during disease progression.

4.5 Limitations and Future Directions

Several limitations should be acknowledged. The cohort derives from a single center with moderate sample size, and the cross-sectional design precludes assessment of longitudinal prognostic performance. External validation in multi-center prospective cohorts, integration with urinary and tissue datasets, and evaluation using digital PCR platforms will be essential next steps. The absence of mechanistic experiments in patient-derived models limits causal inference regarding lncRNA function. Nevertheless, the strong concordance with established genomic landscapes, prior biomarker studies, and functional literature supports the biological validity of our findings.

From a translational perspective, these results suggest that circulating lncRNAs could address two major unmet needs in prostate cancer management: improved early detection and metastatic risk prediction. Because the network hubs identified AKT1, MTOR, EGFR, are pharmacologically targetable, the circulating lncRNA signature may serve as a companion biomarker framework for precision therapy selection [17]. Prospective implementation studies should evaluate whether lncRNA-guided stratification can reduce overtreatment of indolent disease while expediting appropriate intervention for aggressive cancer.

5. Conclusion

In conclusion, this study establishes circulating MALAT1 and SCHLAP1 as highly accurate, mechanistically grounded biomarkers for prostate cancer detection and aggressiveness stratification. The strong agreement with human genomic studies, epidemiological data, and experimental model systems supports a paradigm in which lncRNA dysregulation in serum reflects the integrated oncogenic-metabolic-epigenetic network driving lethal prostate cancer. These findings advance the translational potential of lncRNA-based liquid biopsy and provide a systems-level foundation for precision risk assessment in this disease.

Abbreviations

ADT

Androgen deprivation therapy

AKT1

AKT serine/threonine kinase 1

AUC

Area under the curve

BCR

Biochemical recurrence

BP

Biological process

CC

Cellular component

CI

Confidence interval

CTNNB1

Catenin beta 1

DNA

Deoxyribonucleic acid

DNMT1

DNA methyltransferase 1

EMT

Epithelial–mesenchymal transition

EGFR

Epidermal growth factor receptor

FR0348383

Full reference identifier 0348383 (prostate cancer-associated lncRNA)

GAS5

Growth arrest-specific 5

GO

Gene Ontology

HIF1A

Hypoxia-inducible factor 1 alpha

HOTAIR

HOX transcript antisense RNA

IQR

Interquartile range
KEGG
Kyoto Encyclopedia of Genes and Genomes
lincRNA-p21
Long intergenic non-coding RNA p21
lncRNA
Long non-coding RNA
MALAT1
Metastasis-associated lung adenocarcinoma transcript 1
MCODE
Molecular Complex Detection
MF
Molecular function
MYC
MYC proto-oncogene, bHLH transcription factor
MTOR
Mechanistic target of rapamycin kinase
NED
No evidence of disease
NPV
Negative predictive value
PCa
Prostate cancer
PCAT
Prostate cancer associated transcript
PCR
Polymerase chain reaction
PI3K
Phosphatidylinositol-3-kinase
PPI
Protein-protein interaction
PSA
Prostate-specific antigen
PPV
Positive predictive value
qRT-PCR
Quantitative real-time polymerase chain reaction
RNA
Ribonucleic acid
ROC
Receiver operating characteristic
SCHLAP1
Second chromosome locus associated with prostate-1
SD
Standard deviation

STRING

Search Tool for the Retrieval of Interacting Genes/Proteins

SWI/SNF

Switch/sucrose non-fermentable

TCA

Tricarboxylic acid

TNM

Tumor, node, metastasis (staging system)

TP53

Tumor protein p53

Wnt

Wingless-related integration site

Declarations

Author Contribution Statement

S.O.A. conceived the study, supervised patient recruitment, contributed to study design, provided clinical oversight, interpreted the findings, and critically revised the manuscript. **S.M.** contributed to study design, provided specialist expertise in urologic oncology and African clinical contexts, supervised the South African component of the research, interpreted the findings, and critically revised the manuscript. **V.O.O.** conceived the study, designed the research protocol, coordinated the study, curated the dataset, performed statistical and bioinformatics analyses, prepared all tables and figures, interpreted the data, drafted the original manuscript, and coordinated manuscript revision. **A.M.P.** contributed to study supervision, provided specialist expertise in urologic oncology, participated in interpretation of the findings, and critically revised the manuscript. **M.F.U.** supervised the study, contributed to methodology, provided clinical oversight, interpreted the findings, and critically revised the manuscript. **G.M.T.** supervised the molecular component of the study, contributed to methodological development, interpreted the molecular findings, and critically revised the manuscript. **A.B.A.** contributed to literature review, data acquisition, and manuscript review. **U.J.U.** contributed to patient data collection, data verification, and manuscript review. **A.E.** contributed to literature review, data interpretation, and manuscript review. **M.C.E.** contributed to data verification, interpretation of results, and manuscript review. **O.M.I.** contributed to patient recruitment, clinical data acquisition, data verification, and manuscript review. **L.A.** contributed to statistical review, methodology validation, interpretation of findings, and critical revision of the manuscript. **V.N.P.** provided institutional resources, supervised the research, contributed to interpretation of the findings, and critically revised the manuscript. **All authors** read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Ethics Committee of Bashkir State Medical University represented among the authorship. This study was approved by the Institutional Ethics Committee of Bashkir State Medical University (Approval No. BGMU/RFI/2025/00122). The study was conducted in accordance with the Declaration of Helsinki and applicable institutional and national regulations governing biomedical research. Written informed consent was obtained from all participants before enrolment and biospecimen collection, including consent for collection of blood and urine samples, molecular analyses, access to relevant clinical records, and publication of anonymized data. Participants were informed of their right to withdraw from the study at any stage without affecting their clinical care.

Consent for Publication

All participants provided written informed consent for publication of anonymized clinical and molecular data. No identifiable personal information is included in this manuscript.

Competing Interests

The authors declare that they have no competing interests. Specifically, the authors declare: (1) no financial relationships with any organizations that could have influenced the submitted work within the previous three years; (2) no personal or professional relationships that could be perceived as influencing the study; (3) no commercial sponsorship or involvement from biotechnology or pharmaceutical companies; and (4) no patents, copyrights, or royalties related to this work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The study was supported through institutional resources of the participating institutions as part of routine academic and clinical research activities.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available because they contain identifiable clinical information protected under institutional policies and applicable data protection regulations. De-identified datasets are available from the corresponding author upon reasonable request for legitimate scientific purposes. Requests should include the proposed research objectives, analysis plan, evidence of institutional ethics approval where applicable, and a signed data-sharing agreement. Data will be made available for five years following publication.

Materials Availability

No novel biological materials, cell lines, plasmids, or proprietary reagents were generated during this study. All assays were performed using commercially available reagents and standardized laboratory protocols as described in the Methods section.

Code Availability

No custom software was developed for this study. Statistical analyses were performed using **R** and standard statistical packages as described in the Methods section. Bioinformatics analyses, including protein-protein interaction network construction, Gene Ontology enrichment, Kyoto Encyclopedia of Genes and Genomes pathway analysis, and network visualization, were performed using **STRING**, **Cytoscape**, **MCODE**, **clusterProfiler**, and other publicly available software packages.

Acknowledgements

The authors sincerely thank all patients who participated in this study. We also acknowledge the clinicians, nursing staff, laboratory personnel, and research coordinators of the participating institutions for their assistance with patient recruitment, biospecimen collection, sample processing, and clinical data acquisition. Their contributions were invaluable to the successful completion of this work.

References

1. Kratzer TB, Mazzitelli N, Star J, Dahut WL, Jemal A, Siegel RL. Prostate cancer statistics, 2025. *CA Cancer J Clin.* 2025;75(6):485–97. 10.3322/caac.70028.
2. Schafer EJ, Laversanne M, Sung H, Soerjomataram I, Briganti A, Dahut W, Bray F, Jemal A. Recent patterns and trends in global prostate cancer incidence and mortality: an update. *Eur Urol.* 2025;87(3):302–13. 10.1016/j.eururo.2024.11.013.
3. Hugosson J, Månsson M, Wallström J, Axcróna U, Carlsson SV, Egevad L, Geterud K, Khatami A, Kohestani K, Pihl CG, Socratous A, Stranne J, Godtman RA, Hellström M. GÖTEBORG-2 Trial Investigators. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. *N Engl J Med.* 2022;387(23):2126–37. 10.1056/NEJMoa2209454.
4. Boerrigter E, Groen LN, van Erp NP, Verhaegh GW, Schalken JA. Clinical utility of emerging biomarkers in prostate cancer liquid biopsies. *Expert Rev Mol Diagn.* 2020;20(2):219–30. 10.1080/14737159.2019.1675515.
5. Shen D, Peng H, Xia C, Deng Z, Tong X, Wang G, Qian K. The role of long non-coding RNAs in epithelial-mesenchymal transition-related signaling pathways in prostate cancer. *Front Mol Biosci.* 2022;9:939070. 10.3389/fmolb.2022.939070.
6. Prensner JR, Iyer MK, Sahu A, Asangani IA, Cao Q, Patel L, Vergara IA, Davicioni E, Erho N, Ghadessi M, Jenkins RB, Triche TJ, Malik R, Bedenis R, McGregor N, Ma T, Chen W, Han S, Jing X, Cao X, Wang X, Chandler B, Yan W, Siddiqui J, Kunju LP, Dhanasekaran SM, Pienta KJ, Feng FY, Chinnaiyan AM. The long noncoding RNA SCHLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. *Nat Genet.* 2013;45(11):1392–8. 10.1038/ng.2771.
7. Wang F, Ren S, Chen R, Lu J, Shi X, Zhu Y, Zhang W, Jing T, Zhang C, Shen J, Xu C, Wang H, Wang H, Wang Y, Liu B, Li Y, Fang Z, Guo F, Qiao M, Wu C, Wei Q, Xu D, Shen D, Lu X, Gao X, Hou J, Sun Y. Development and prospective multicenter evaluation of the long noncoding RNA MALAT-1 as a diagnostic urinary biomarker for prostate cancer. *Oncotarget.* 2014;5(22):11091–102. 10.18632/oncotarget.2691.
8. Zhang A, Zhao JC, Kim J, Fong KW, Yang YA, Chakravarti D, Mo YY, Yu J. LncRNA HOTAIR enhances the androgen-receptor-mediated transcriptional program and drives castration-resistant prostate cancer. *Cell Rep.* 2015;13(2):209–21. 10.1016/j.celrep.2015.08.069.
9. Lv M, Zhong Z, Chi H, Wang B, Zhang Z, Lin C, Yao Y, Chen X, Han J, Zhang B, Wang X, Jiang H. Long noncoding RNA GAS5 interacts and suppresses androgen receptor activity in prostate cancer cells. *Prostate.* 2021;81(13):893–901. 10.1002/pros.24186.
10. Jiang X, Guo S, Xu M, Ma B, Liu R, Xu Y, Zhang Y. TFAP2C-mediated lncRNA PCAT1 inhibits ferroptosis in docetaxel-resistant prostate cancer through c-Myc/miR-25-3p/SLC7A11 signaling. *Front Oncol.* 2022;12:862015. 10.3389/fonc.2022.862015.
11. Wang X, Ruan Y, Wang X, Zhao W, Jiang Q, Jiang C, Zhao Y, Xu Y, Sun F, Zhu Y, Xia S, Xu D. Long intragenic non-coding RNA lincRNA-p21 suppresses development of human prostate cancer. *Cell Prolif.* 2017;50(2):e12318. 10.1111/cpr.12318.
12. Zhang W, Ren SC, Shi XL, Liu YW, Zhu YS, Jing TL, Wang FB, Chen R, Xu CL, Wang HQ, Wang HF, Wang Y, Liu B, Li YM, Fang ZY, Guo F, Lu X, Shen D, Gao X, Hou JG, Sun YH. A novel urinary long non-coding RNA transcript improves diagnostic accuracy in patients undergoing prostate biopsy. *Prostate.* 2015;75(6):653–61. 10.1002/pros.22949.
13. Prensner JR, et al. RNA biomarkers associated with metastatic progression in prostate cancer: A multi-institutional high-throughput analysis of SCHLAP1. *Lancet Oncol.* 2014;15:1469–80. 10.1016/S1470-

2045(14)71113-1.

14. Arun G, Aggarwal D, Spector DL. MALAT1 Long Non-Coding RNA: Functional Implications. *Noncoding RNA*. Jun. 2020;6(2). 10.3390/NCRNA6020022.
15. Wang F et al. Development and prospective multicenter evaluation of the long noncoding RNA MALAT-1 as a diagnostic urinary biomarker for prostate cancer, *Oncotarget*, vol. 5, no. 22, pp. 11091–11102, 2014, 10.18632/oncotarget.2691
16. Ma S, Wang DD, Ma CY, Zhang YD. microRNA-96 promotes osteoblast differentiation and bone formation in ankylosing spondylitis mice through activating the Wnt signaling pathway by binding to SOST, *J. Cell. Biochem.*, vol. 120, no. 9, pp. 15429–15442, Sep. 2019, 10.1002/jcb.28810
17. Robinson D et al. May., Integrative clinical genomics of advanced prostate cancer, *Cell*, vol. 161, no. 5, pp. 1215–1228, 2015, 10.1016/j.cell.2015.05.001
18. Armenia J, et al. The long tail of oncogenic drivers in prostate cancer. *Nat Genet*. May 2018;50(5):645–51. 10.1038/s41588-018-0078-z.
19. Pickard MR, Williams GT. Molecular and Cellular Mechanisms of Action of Tumour Suppressor GAS5 LncRNA, *Genes (Basel)*, vol. 6, no. 3, pp. 484–499, Jul. 2015, 10.3390/genes6030484
20. Ma X, et al. Long Non-Coding RNA GAS5 Suppresses Tumor Progression and Enhances the Radiosensitivity of Prostate Cancer Through the miR-320a/RAB21 Axis. *Cancer Manag Res*. 2020;12:8833–45. 10.2147/CMAR.S244123.
21. Cao S, Liu W, Li F, Zhao W, Qin C. Decreased expression of lncRNA GAS5 predicts a poor prognosis in cervical cancer. *Int J Clin Exp Pathol*. 2014;7(10):6776–83.
22. Taylor BS, et al. Integrative genomic profiling of human prostate cancer. *Cancer Cell*. 2010;18(1):11–22. 10.1016/j.ccr.2010.05.026.
23. Carver BS, et al. Reciprocal Feedback Regulation of PI3K and Androgen Receptor Signaling in PTEN-Deficient Prostate Cancer. *Cancer Cell*. 2011;19(5):575–86. 10.1016/j.ccr.2011.04.008.
24. Mulholland DJ, et al. Cell autonomous role of PTEN in regulating castration-resistant prostate cancer growth. *Cancer Cell*. 2011;19(6):792–804. 10.1016/j.ccr.2011.05.006.
25. Movsas B et al. Oct., Hypoxic prostate/muscle PO2 ratio predicts for biochemical failure in patients with prostate cancer: Preliminary findings, *Urology*, vol. 60, no. 4, pp. 634–639, 2002, 10.1016/S0090-4295(02)01858-7
26. Lalonde E, et al. Tumour genomic and microenvironmental heterogeneity for integrated prediction of 5-year biochemical recurrence of prostate cancer: A retrospective cohort study. *Lancet Oncol*. 2014;15:1521–32. 10.1016/S1470-2045(14)71021-6.
27. Choudhry H, Harris AL. Advances in Hypoxia-Inducible Factor Biology, *Cell Metab.*, vol. 27, no. 2, pp. 281–298, Feb. 2018, 10.1016/j.cmet.2017.10.005
28. Shih CH, et al. Hypoxia-Induced MALAT1 Promotes the Proliferation and Migration of Breast Cancer Cells by Sponging MiR-3064-5p. *Front Oncol*. May 2021;11. 10.3389/fonc.2021.658151.
29. Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism. *Cell Metab*. Jan. 2016;23(1):27–47. 10.1016/j.cmet.2015.12.006.
30. Butler LM, et al. Lipids and cancer: Emerging roles in pathogenesis, diagnosis and therapeutic intervention. *Adv Drug Deliv Rev*. Jan. 2020;159:245–93. 10.1016/j.addr.2020.07.013.
31. Saranyutanon S et al. Jan., Therapies Targeted to Androgen Receptor Signaling Axis in Prostate Cancer: Progress, Challenges, and Hope, *Cancers (Basel)*, vol. 12, no. 1, 2019, 10.3390/cancers12010051

32. Kim K et al. Mar., HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer, *Oncogene*, vol. 32, no. 13, pp. 1616–1625, 2013, 10.1038/onc.2012.193
33. Nieto MA et al. EMT: 2016, *Cell*, vol. 166, no. 1, pp. 21–45, Jun. 2016. 10.1016/j.cell.2016.06.028
34. Tan TZ et al. Oct., Epithelial-mesenchymal transition spectrum quantification and its efficacy in deciphering survival and drug responses of cancer patients, *EMBO Mol. Med.*, vol. 6, no. 10, pp. 1279–1293, 2014, 10.15252/emmm.201404208
35. Huang RYJ, et al. Early events in cell adhesion and polarity during epithelial-mesenchymal transition. *J Cell Sci.* 2012;125:4417–22. 10.1242/jcs.099697.
36. Singh N, et al. The long noncoding RNA H19 regulates tumor plasticity in neuroendocrine prostate cancer. *Nat Commun.* Dec. 2021;12(1). 10.1038/s41467-021-26901-9.
37. Gutschner T, et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. *Cancer Res.* Feb. 2013;73(3):1180–9. 10.1158/0008-5472.CAN-12-2850.
38. Goyal B, et al. Diagnostic, prognostic, and therapeutic significance of long non-coding RNA MALAT1 in cancer. *Biochim Biophys Acta Rev Cancer.* Apr. 2021;1875(2). 10.1016/j.bbcan.2021.188502.
39. Arun G, Diermeier SD, Spector DL. Therapeutic Targeting of Long Non-Coding RNAs in Cancer. *Trends Mol Med.* Mar. 2018;24(3):257–77. 10.1016/j.molmed.2018.01.001.
40. Mehra R, et al. Overexpression of the Long Non-coding RNA SCHLAP1 Independently Predicts Lethal Prostate Cancer. *Eur Urol.* Oct. 2016;70(4):549–52. 10.1016/j.eururo.2015.12.003.

Figures

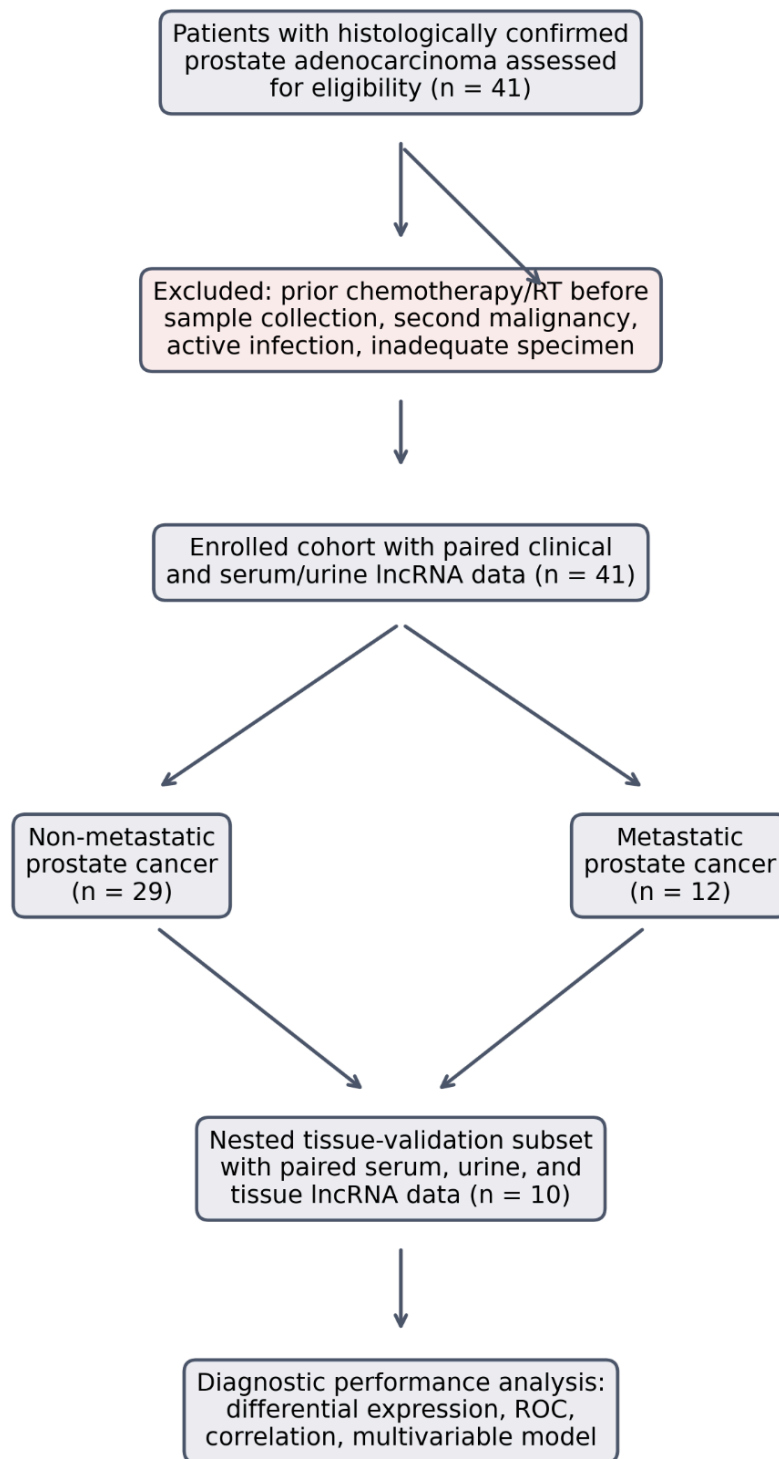


Figure 1

Patient flow through the study. Forty-one men with histologically confirmed prostate adenocarcinoma were enrolled after exclusion of patients with prior chemotherapy or radiotherapy before sample collection, a second malignancy, active infection, or an inadequate specimen. The cohort separated into twenty-nine patients with non-metastatic disease and twelve with metastatic disease, with a nested ten-patient subset undergoing paired serum, urine, and tissue quantification.

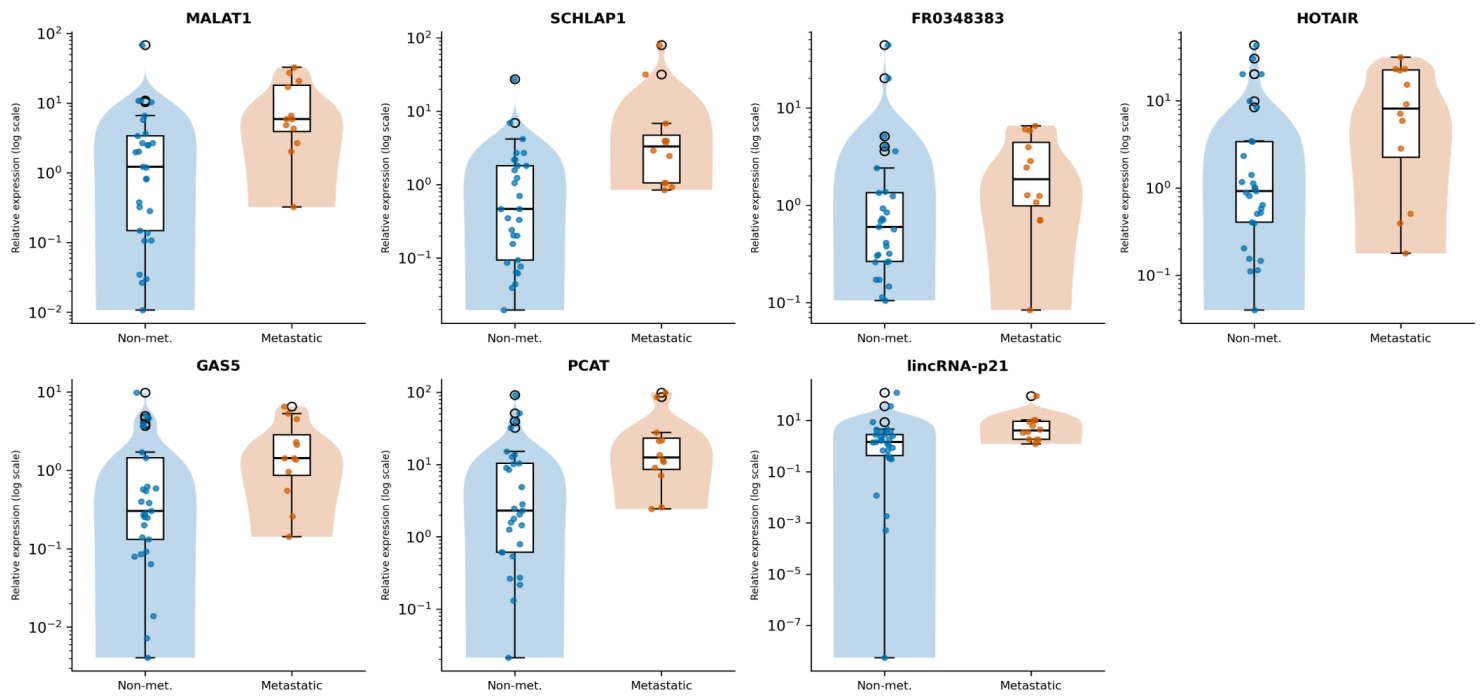


Figure 2

Expression of the seven circulating lncRNAs by metastatic status, shown as boxplots with violin overlay and individual patient values on a log10 scale. Blue points represent non-metastatic patients and orange points represent metastatic patients.

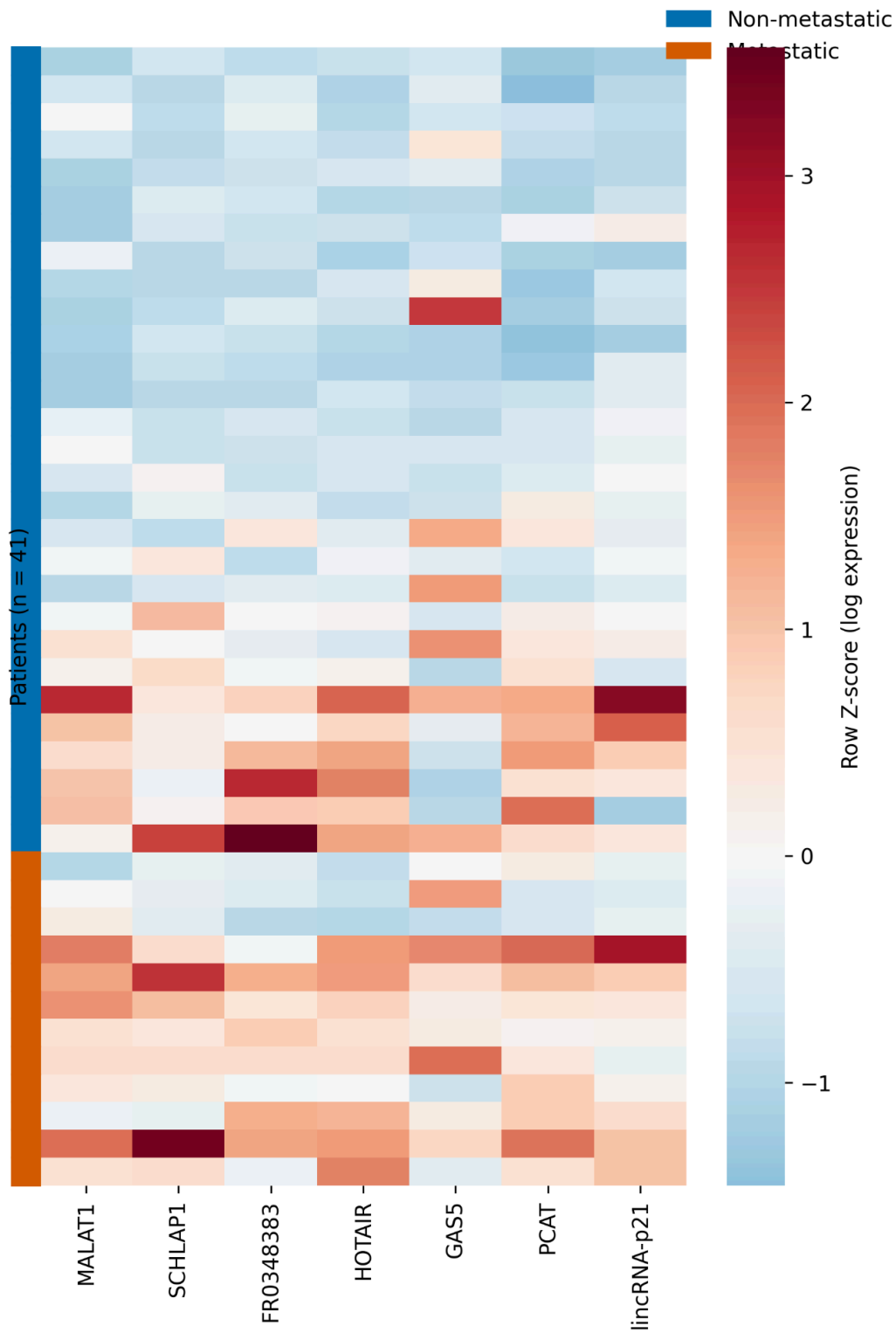


Figure 3

Heatmap of row-standardized log-transformed expression values for the seven circulating lncRNAs across all forty-one patients, ordered by metastatic status (blue bar, non-metastatic; orange bar, metastatic). Warmer colors indicate higher relative expression.

ROC curves for metastatic disease discrimination

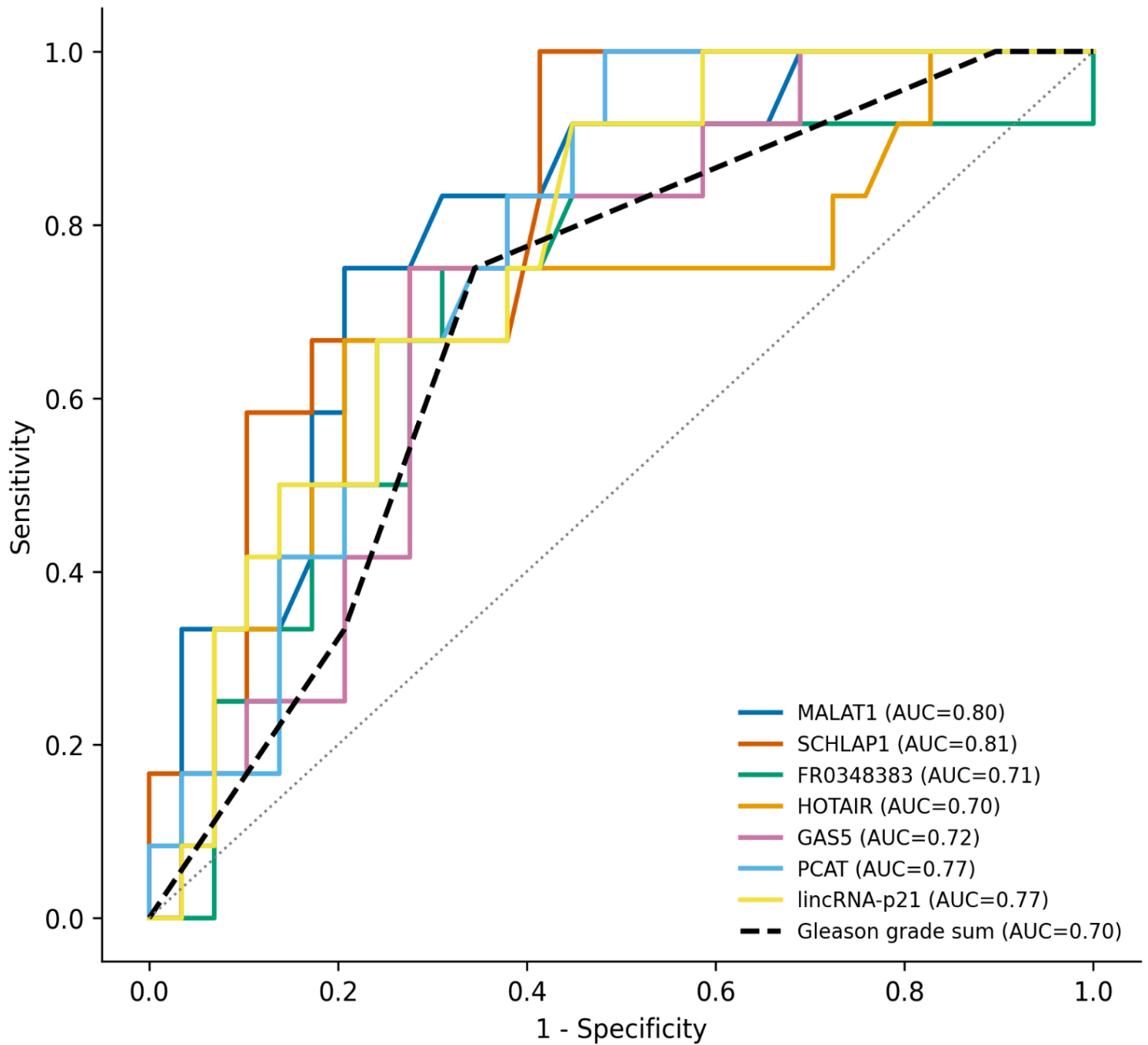


Figure 4

Receiver operating characteristic curves for each of the seven circulating lncRNAs and for Gleason grade sum, using metastatic status as the outcome. The diagonal dotted line represents chance discrimination.

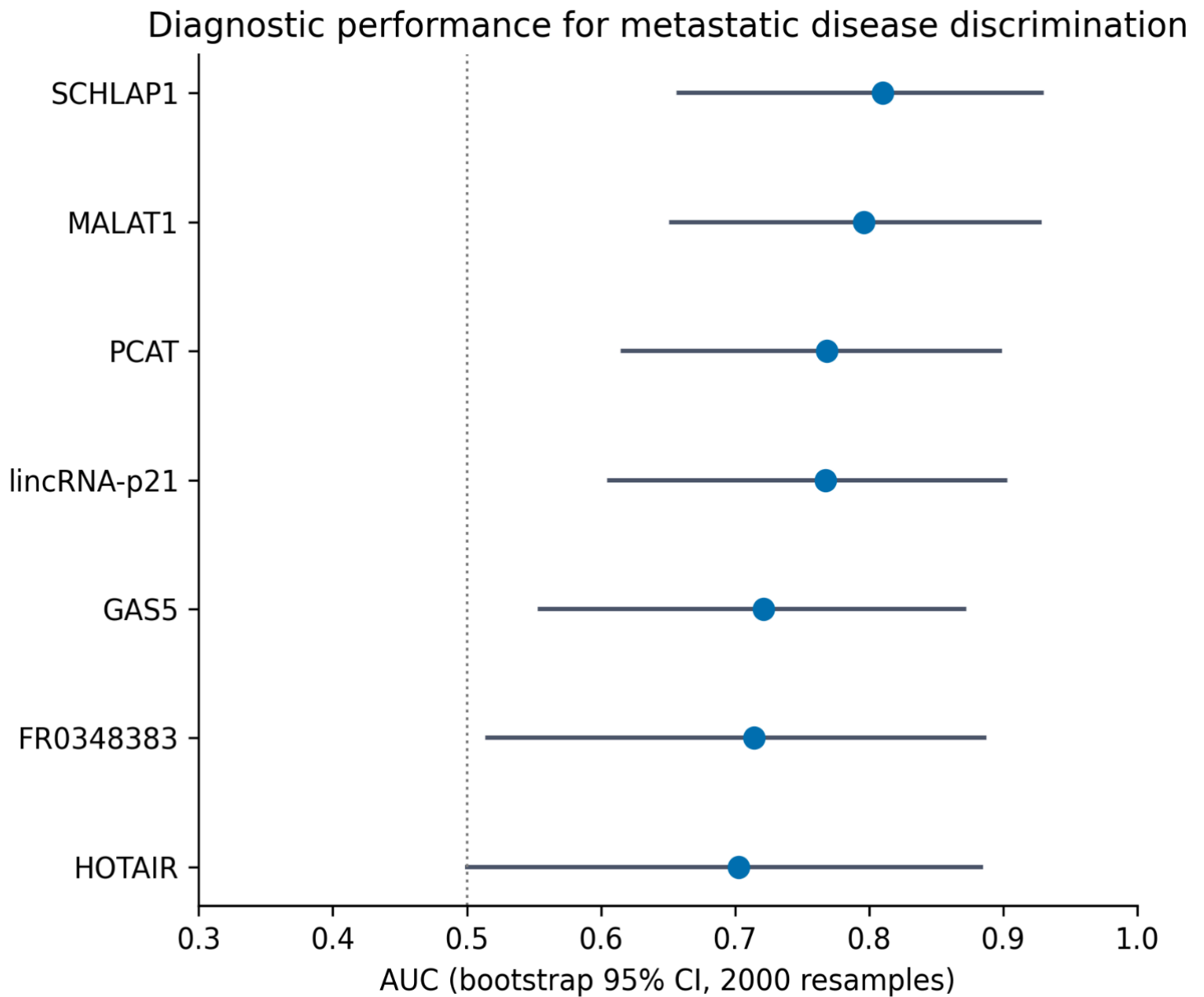


Figure 5

Forest plot of AUC values with bootstrap 95 percent confidence intervals (2000 resamples) for metastatic disease discrimination, ranked from lowest to highest. The dotted line marks an AUC of 0.5, corresponding to chance discrimination.

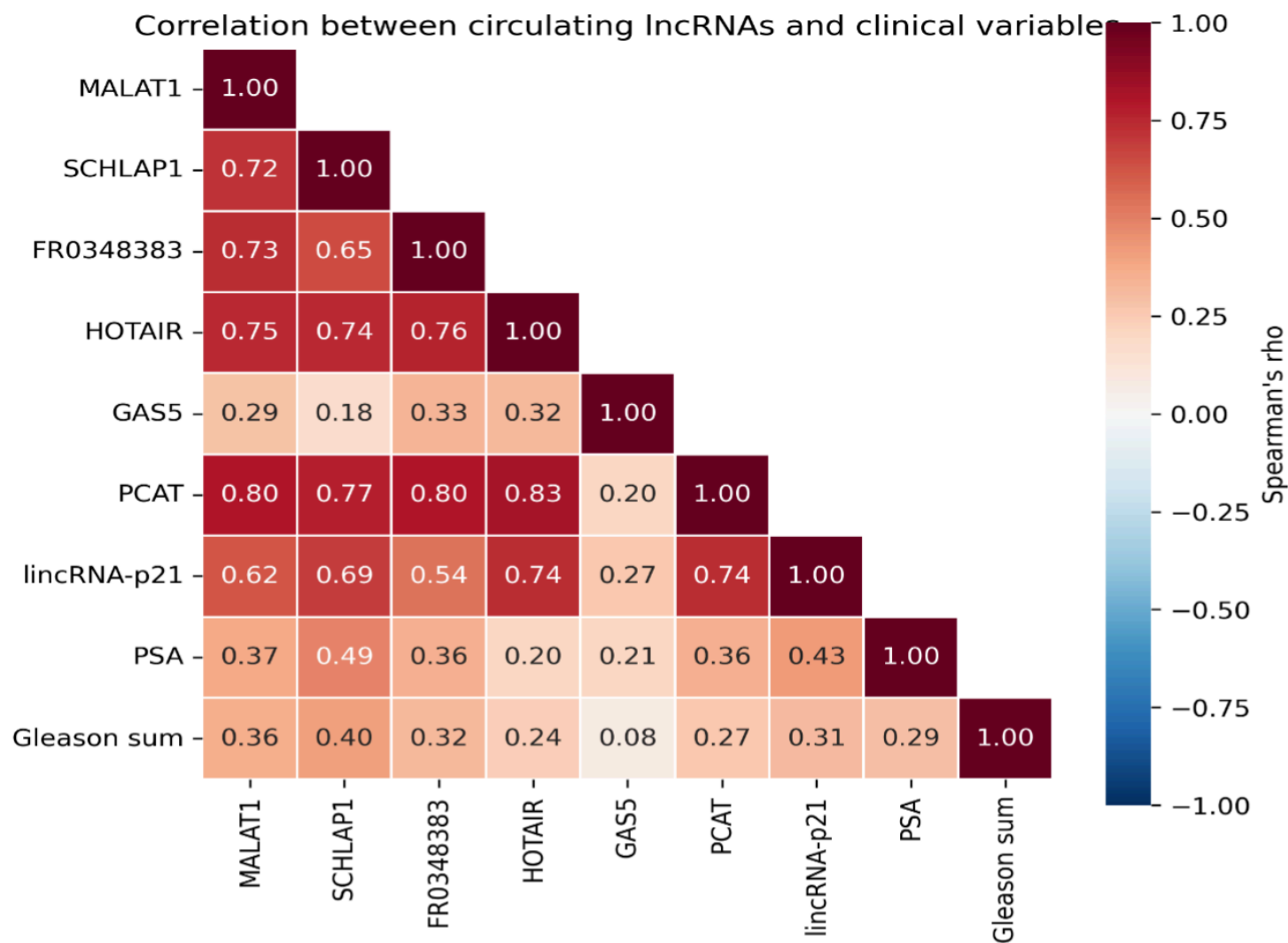


Figure 6

Spearman correlation heatmap for the seven circulating lncRNAs together with PSA and Gleason grade sum. Warmer colors indicate stronger positive correlation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [LONGNONCODINGRNAcopy2.xlsx](#)