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Dissecting the Significance of Acid Phosphatase 1 Gene Alterations in Prostate Cancer

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ABSTRACT

PURPOSE The acid phosphatase 1 (*ACP1*) gene encodes low-molecular-weight protein tyrosine phosphatase, which is overexpressed in prostate cancer (PC) and a potential therapeutic target. We analyzed *ACP1* expression in primary/metastatic PC and its association with molecular profiles and clinical outcomes.

METHODS NextGen sequencing of DNA (592-gene/whole-exome sequencing)/RNA(whole-transcriptome sequencing) was performed for 5,028 specimens. *ACP1*-High/*ACP1*-Low expression was defined as quartile (Q4/1) of RNA transcripts per million (TPM). DNA mutational profiles were analyzed for *ACP1*-quartile-stratified samples. Gene set enrichment analysis was used for Hallmark collection of pathways. PD-L1+(≥2+, ≥5%; SP142) was tested by immunohistochemistry. Tumor microenvironment's (TME) immune cell fractions were estimated by RNA deconvolution/quanTIseq. Overall survival (OS) was assessed from initial diagnosis/treatment initiation to death/last follow-up.

RESULTS We included 3,058 (60.8%) samples from the prostate, 634 (12.6%) from lymph node metastases (LNMs), and 1,307 (26.0%) from distant metastases (DMs). *ACP1* expression was higher in LNM/DM than prostate (49.8/47.9 *v* 44.1 TPM; $P < .0001$). *TP53* mutations were enriched in *ACP1*-Q4 (37.9%[Q4] *v* 27.0%[Q1]; $P < .001$) among prostate samples. Pathways associated with cell cycle regulation and oxidative phosphorylation were enriched in *ACP1*-Q4, whereas epithelial-mesenchymal transition and tumor necrosis factor-alpha signaling via nuclear factor kappa-light-chain-enhancer of activated B-cell pathways were enriched in *ACP1*-Q1. Neuroendocrine and androgen receptor signaling was increased in *ACP1*-Q4. M2 macrophages and natural killer cell fractions were increased, whereas T cells and M1 macrophages were decreased in *ACP1*-Q4. While OS differences between *ACP1*-Q1/Q4 were not statistically significant, there was a trend for worse OS among *ACP1*-Q4 prostate samples (Q4 *v* Q1: hazard ratio [HR], 1.19 [95% CI, 0.99 to 1.42]; $P = .06$) and DM (HR, 1.12 [95% CI, 0.93 to 1.36]; $P = .22$) but not LNM (HR, 0.98 [95% CI, 0.74 to 1.29]; $P = .87$).

CONCLUSION ACP1-High tumors exhibit a distinct molecular profile and cold TME, highlighting *ACP1*'s potential role in PC pathogenesis and novel therapeutic targeting.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Prostate cancer (PC) is the most common cancer among men in the United States.[1] Most patients present with local disease and are cured with definitive local treatment.[2] However, some patients develop disease recurrence or present with de novo metastatic disease.[3] The backbone of systemic therapy for patients with recurrent or advanced disease is androgen deprivation therapy (ADT).[4] While most patients respond to ADT, some develop metastatic castration-resistant PC, which is universally fatal.[5] An increased understanding of disease progression drivers is needed to ultimately improve patient outcomes and enhance therapeutic strategies in advanced settings.

Recently, there has been increased enthusiasm about protein tyrosine phosphatases as potential oncologic therapeutic targets, given their role in cancer progression and metastasis.[6-9] Low-molecular-weight protein tyrosine phosphatase (*LMPTPs*) are 18-kDa enzymes expressed in

CONTEXT

Key Objective

To understand the association of acid phosphatase 1 (*ACP1*) expression with molecular profiles and clinical outcomes in prostate cancer (PC).

Knowledge Generated

In this study involving over 5,000 patients who underwent in-depth molecular profiling, we observed varying patterns of *ACP1* expression across tumor sites, with higher levels in lymph nodes and distant metastases, notably in the liver. In addition, we found that *TP53* alterations, *AR-V7* alterations, and genomic loss of heterozygosity were enriched among *ACP1*-High tumors. We also identified, through gene expression analysis, an upregulated cell cycle signaling and increased neuroendocrine PC and androgen receptor signaling in *ACP1*-High tumors. Moreover, the tumor microenvironment of *ACP1*-High tumors was immunosuppressive.

Relevance

The molecular insights collectively indicate that high *ACP1* expression is associated with worse clinical outcomes. Thus, our work provides a rationale for investigating low-molecular-weight protein tyrosine phosphatase–targeting therapies in advanced PC and aggressive phenotypes.

many tissues.[10] Recent reports demonstrate that *LMPTP* is highly expressed in PC tumors and its expression is associated with increased resistance and inferior survival.[9,11]

Preclinical studies from our group demonstrate that *LMPTP* promotes PC growth, invasiveness, tumorigenesis, and bone metastasis development.[12] Through metabolomics, *LMPTP* was found to promote PC cell glutathione synthesis by dephosphorylating glutathione synthetase. PC cells lacking *LMPTP* showed reduced glutathione, enhanced activation of eukaryotic initiation factor 2–mediated stress response, and enhanced reactive oxygen species (ROS) when exposed to taxane chemotherapy. In addition, Ruela-de-Sousa et al[9] reported that *LMPTP* plays a role in promoting anchorage-independent growth of cancer cells by enhancing the activation of Src family kinases and focal adhesion kinase, leading to increased cell survival and proliferation in the absence of cell-matrix interactions. These mechanisms likely contribute to increased tumor aggressiveness and metastatic potential, providing a rationale for our investigation of *LMPTP* in PC.

LMPTP is encoded by the acid phosphatase 1 (*ACP1*) gene, which is upregulated in several malignancies.[13] Data from the Cancer Genome Atlas Program (*TCGA*) revealed that *ACP1* expression is increased in PC compared with normal prostate tissue and expression appears to be associated with higher Gleason score.[12] Furthermore, studies have demonstrated that *ACP1* expression was higher in lymph node metastases (LNMs) compared with the primary prostate.[12] While these data have been informative in identifying *ACP1* and *LMPTP* significance in PC, these studies have been limited in scope and sample.

Given the potential implications of *ACP1* and *LMPTP* in PC pathogenesis and with *LMPTP* emerging as a potential therapeutic target, we analyzed a large multi-institutional clinic-genomics database to dissect the significance of *ACP1* expression in primary and metastatic prostate adenocarcinomas. We also characterized the DNA mutational profile, gene expression profile, tumor microenvironment (TME), and clinical outcomes in primary and metastatic prostate adenocarcinomas among tumors with high versus low *ACP1* expression.

METHODS

Study Cohort

The study cohort included patients with PC (N = 5,028) with formalin-fixed paraffin-embedded (FFPE) samples submitted to a commercial Clinical Laboratory Improvement Amendments-certified laboratory for molecular profiling (Caris Life Science, Phoenix, AZ). Eligible patients included those with a requisition diagnosis of prostatic adenocarcinoma (PRAD) with the availability of next-generation sequencing (NGS) through Caris Life Sciences. This study was led conformally to the guidelines of the Declaration of Helsinki, Belmont Report, and US Common Rule.

DNA NGS and Genomic Loss of Heterozygosity

Genomic DNA was isolated for NGS using the NextSeq platform (Illumina, Inc, San Diego, CA) for 592 cancer-relevant genes (n = 1,004 samples) or the Illumina NovaSeq 6000 platform (Illumina, Inc, San Diego, CA) for whole-exome sequencing (n = 4,024 samples). Targeted tissue was harvested using manual microdissection techniques to maximize tumor enrichment before molecular testing. Sequencing was performed as previously described.[14] Board-certified molecular geneticists followed the criteria

established by the American College of Medical Genetics and Genomics to characterize genomic variants. Pathogenic and likely pathogenic variants were included, whereas benign, likely benign, and variants of unknown significance were excluded. Tumor mutational burden (TMB)-High was defined as ≥10 mutations per megabase.[15] Genomic loss of heterozygosity (gLOH) was determined as previously described.[16]

RNA Whole-Transcriptome Sequencing and Fusion Detection

Tumors were characterized as having high or low *ACP1* expression on the basis of the percentile of RNA transcripts per million (TPM; ≥75th *v* <25th) to allow for more granularity in data analysis across quartiles. All *LMPTP* transcripts were captured. FFPE specimens underwent pathology review to assess percent tumor content; a minimum of 10% of tumor content in the area for microdissection was required to enable enrichment and extraction of tumor-specific RNA. Illumina NovaSeq 6500 was used to sequence the whole transcriptome from patients to an average of 60M reads, as previously described.

Gene Expression Profiling

Deconvolution of RNA expression was performed using quaTIseq[17] to estimate immune cell fractions comprising the TME. Pathway analysis was performed using gene set enrichment analysis[18] to assess the Hallmark collection of cancer pathways (MSigDB)[19] in *ACP1*-High (Q4) versus *ACP1*-Low (Q1) tumors. Potential sensitivity to immunotherapy (IO) treatment was assessed using a transcriptional signature previously shown to be predictive of response to the *PD-1* checkpoint blockade.[20]

Immunohistochemistry

PD-L1 protein expression was tested by immunohistochemistry (IHC; SP142 antibody). Staining was scored for intensity (0 = no staining; 1+ = weak, 2+ = moderate, 3+ = strong) and percentage (0%-100%). *PD-L1* positivity was determined if ≥5% of cancer cells demonstrated moderate (2+) membranous protein expression.

Survival Analysis

Real-world overall survival (OS) data were sourced from an insurance claims repository, with calculations spanning from the date of initial diagnosis (on the basis of the first cancer-related International Classification of Diseases-10 code used) to either death or last contact or from the time of treatment initiation to either death or last contact. The stage of disease was not available in the database. Cox proportional hazard ratios (HRs) were calculated for each comparison group, and significance was determined by log-rank test $P < .05$.

Statistical Analysis

The JMP V13.2.1 (SAS Institute, New York, MY), R Version 3.6.1 (R-project[21]), and standard Python packages (Pandas, NumPy, and SciPy) were used. Continuous data were analyzed using a Mann-Whitney *U* test, and categorical data were analyzed using chi-square or Fisher's exact test, with *P* values adjusted for multiple hypothesis testing using the Benjamini-Hochberg procedure, where appropriate.

RESULTS

Study Cohort and Patient Characteristics

The study cohort comprised 5,028 patients with a median age at specimen collection of 68 years (range, 35 to 90+). The majority of samples were derived from the prostate (n = 3,058, 60.8%), followed by distant metastasis (DM) sites (n = 1,307, 26%), LNM (n = 634, 12.6%), and 29 samples (0.6%) with an undetermined sequencing site. Appendix Tables A1 and A2 show the distribution of tumor biopsy sites.

ACP1 Expression Varies Across Tumor Biopsy Sites

ACP1 expression varied by specimen site and was increased in LNM and DM compared with prostate tissue (49.8 and 47.9, respectively, *v* 44.1 TPM; $P < .0001$ each; Fig 1A). Further analysis of DM sites revealed significantly higher *ACP1* expression in genitourinary and hepatic metastases compared with the primary prostate (55.4 and 54.1, respectively, *v* 44.1 TPM; $P < .0001$ each) and the lowest median expression observed among GI metastases (37.4 *v* 44.1 TPM in prostate; $P = .68$; Fig 1B). Among 29 patients who had a biopsy profiled from both the prostate and a metastatic site, *ACP1* expression was also higher in the metastatic site compared with the prostate sample (Appendix Table A3).

Analysis of various tumor types represented in the TCGA database suggests robust *ACP1* expression across several normal tissues (as seen in Fig 1C) and numerous tumor types (including pheochromocytoma/paraganglioma, cholangiocarcinoma, liver hepatocellular carcinoma), with higher *ACP1* expression observed in many tumor types (including rectum adenocarcinoma, colon adenocarcinoma, uterine corpus endometrial carcinoma, and PRAD) compared with normal tissue (Fig 1C).

DNA Mutational Profiles Associated With ACP1 Expression

We analyzed the DNA mutational profiles of prostate, LNM, and DM samples stratified by *ACP1* expression quartiles. Among the most frequent recurrent mutations observed in PC (>3% overall prevalence), *TP53* mutations were enriched in *ACP1*-Q4 (37.9% *v* 27.0% in *ACP1*-Q1; $P < .001$) among prostate samples but not LNM or DM (Fig 2). Most other DNA gene alterations were not significantly associated with *ACP1* expression. Prevalence of *AR-V7* alterations increased with *ACP1*

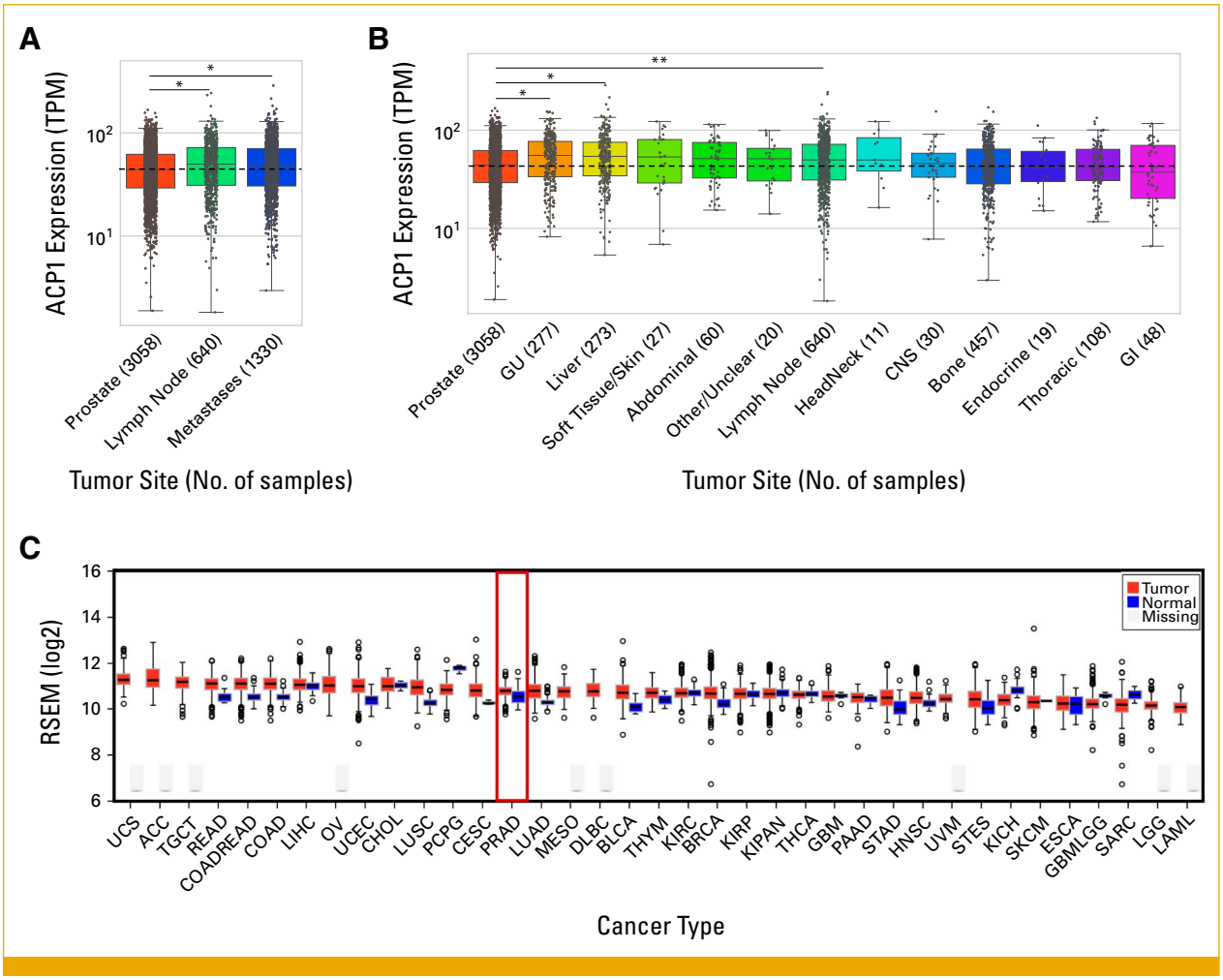

FIG 1. Transcriptional expression of *ACP1* in prostate cancer across tumor biopsy sites. (A) Differential expression of *ACP1* in tumor samples collected from prostate, lymph node, and any distant metastatic site (Metastases); (B) *ACP1* expression across individual metastatic sites. For (A) and (B), sample sizes are noted in parentheses for each tumor site. (C) Differential expression of *ACP1* across various cancer and normal tissues from the TCGA database (FireBrowse). TCGA abbreviations legend can be found in Appendix Table A5. *ACP1*, acid phosphatase 1; GU, genitourinary; RSEM, RNA-Seq by expectation-maximization; TCGA, the Cancer Genome Atlas Program; TPM, transcripts per million. *P < .0001, **P < .001.

expression in prostate samples (9.6% Q4 *v* 2.9% Q1; P < .001), with similar trends observed for LNM (46.8% Q4 *v* 33.8% Q1; P = .75) and DM samples (38.3% Q4 *v* 26.7% Q1; P = .10). *gLOH* was more frequent with increasing *ACP1* expression in DM (51.9% Q4 *v* 34.3% Q1; P < .05).

Gene Expression Profiles Associated With ACP1 Expression

Gene expression was similar across tumor sites, with most transcript levels increased among *ACP1*-High (Q4) compared with *ACP1*-Low (Q1) tumors (Figs 3A-3C). Pathways associated with cell cycle regulation (*E2F* targets, *G2M* checkpoint, myelocytomatosis oncogene [*MYC*] targets, and mitotic spindle) were enriched in *ACP1*-High tumors, along with oxidative phosphorylation and androgen response pathways. However, myogenesis, epithelial-mesenchymal transition, and tumor necrosis factor-alpha signaling via the nuclear factor kappa-light-chain-enhancer of activated B-cell pathways were enriched in *ACP1*-Low tumors (Fig 3D). Transcriptomic signatures of neuroendocrine prostate cancer (*NEPC*) and androgen receptor (*AR*) signaling also increased with *ACP1* expression (Figs 3E and 3F).

TMEs Associated With ACP1 Expression

We then performed RNA deconvolution to estimate immune cell fractions in the TME. The total immune cell fraction increased with *ACP1* expression in prostate samples, with significantly increased fractions of macrophage M2, natural killers cells, and neutrophils, among others (Fig 4A). Among the cell types examined, the strongest positive and negative correlation with *ACP1* expression was observed for macrophage M2 and M1 cell fractions, respectively, suggestive of an immunosuppressive TME, and consistent with the strong negative correlation between *ACP1* expression and a T-cell–

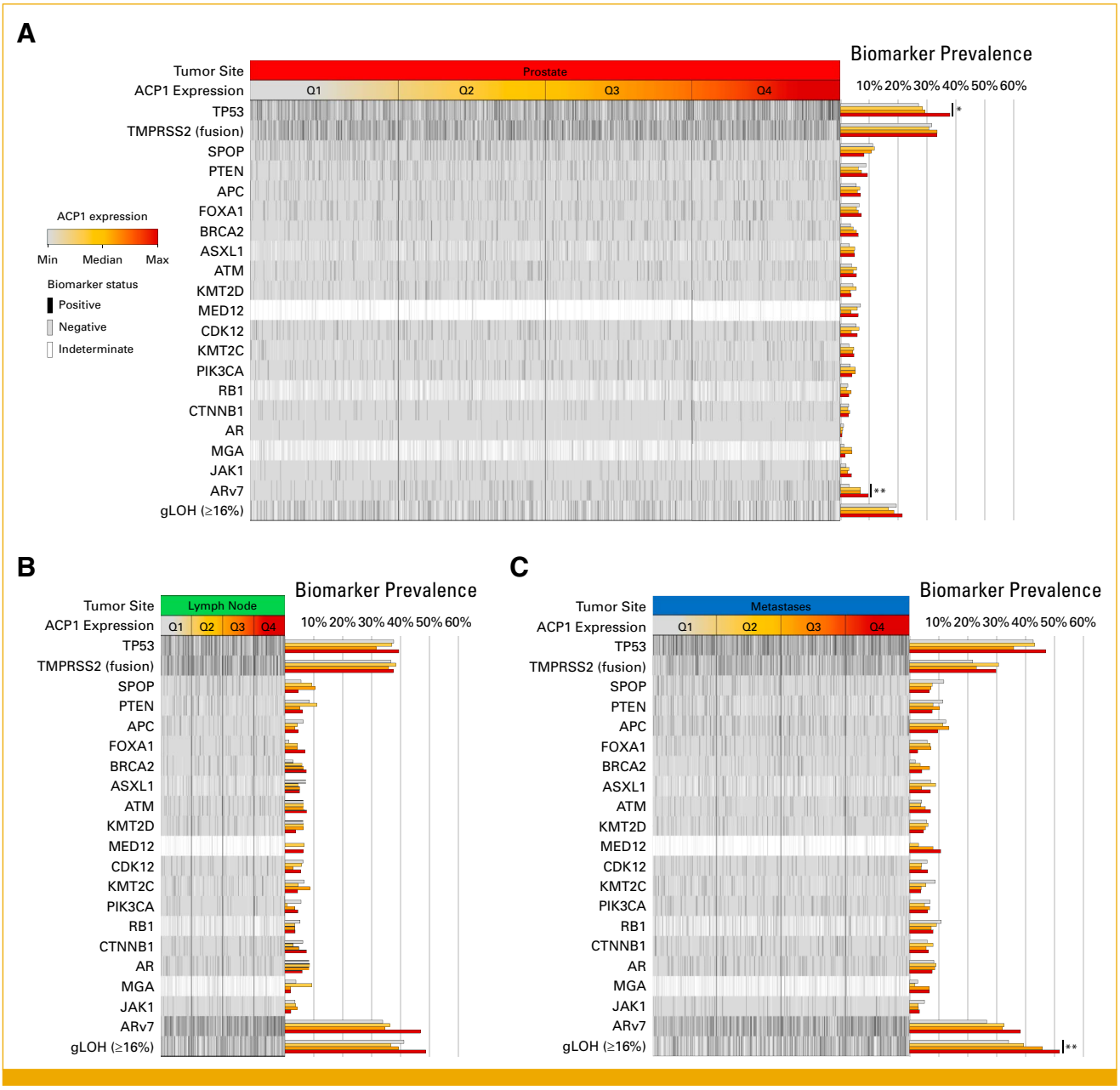

FIG 2. Genomic landscape associated with *ACP1* expression in prostate cancer by tumor site. Oncoprint of recurrent alterations occurring in >3% of the overall study among (A) prostate, (B) lymph node, and (C) metastasis subpopulations stratified by *ACP1* expression. *ACP1*, acid phosphatase 1; *AR*, androgen receptor; gLOH, genomic loss of heterozygosity. *P < .001, **P < .05.

inflamed transcriptional signature that is predictive of response to IO[20] (Fig 4B). Similar associations with *ACP1* expression were observed for LNM and DM. However, across tumor sites, the prevalence of IO-related biomarkers, such as *PD-L1* IHC, TMB, and mismatch repair deficient/microsatellite instability-high, was not significantly different among *ACP1* expression quartiles (Fig 4C).

Clinical Outcomes Associated With ACP1 Expression

To determine the potential prognostic and predictive utility of *ACP1* expression in PC, we evaluated real-world clinical outcomes among patients with available insurance claim data to infer OS from the date of initial diagnosis or the start of treatment (Appendix Table A4). Although not statistically significant, patients with high *ACP1* expression had worse OS from the date of initial diagnosis among those with prostate tissue samples (Q4 *v* Q1: HR, 1.19 [95% CI, 0.99 to 1.42]; P = .06), with a similar trend observed among DM (HR, 1.12 [95% CI, 0.93 to 1.36]; P = .22) but not LNM (HR, 0.98 [95% CI, 0.74 to 1.29]; P = .87; Fig 5A). Across tumor sites, *ACP1* expression was not associated with differences in OS from the start of first taxane chemotherapy (total n = 883; docetaxel or cabazitaxel) or AR pathway inhibitor (total n = 1,149;

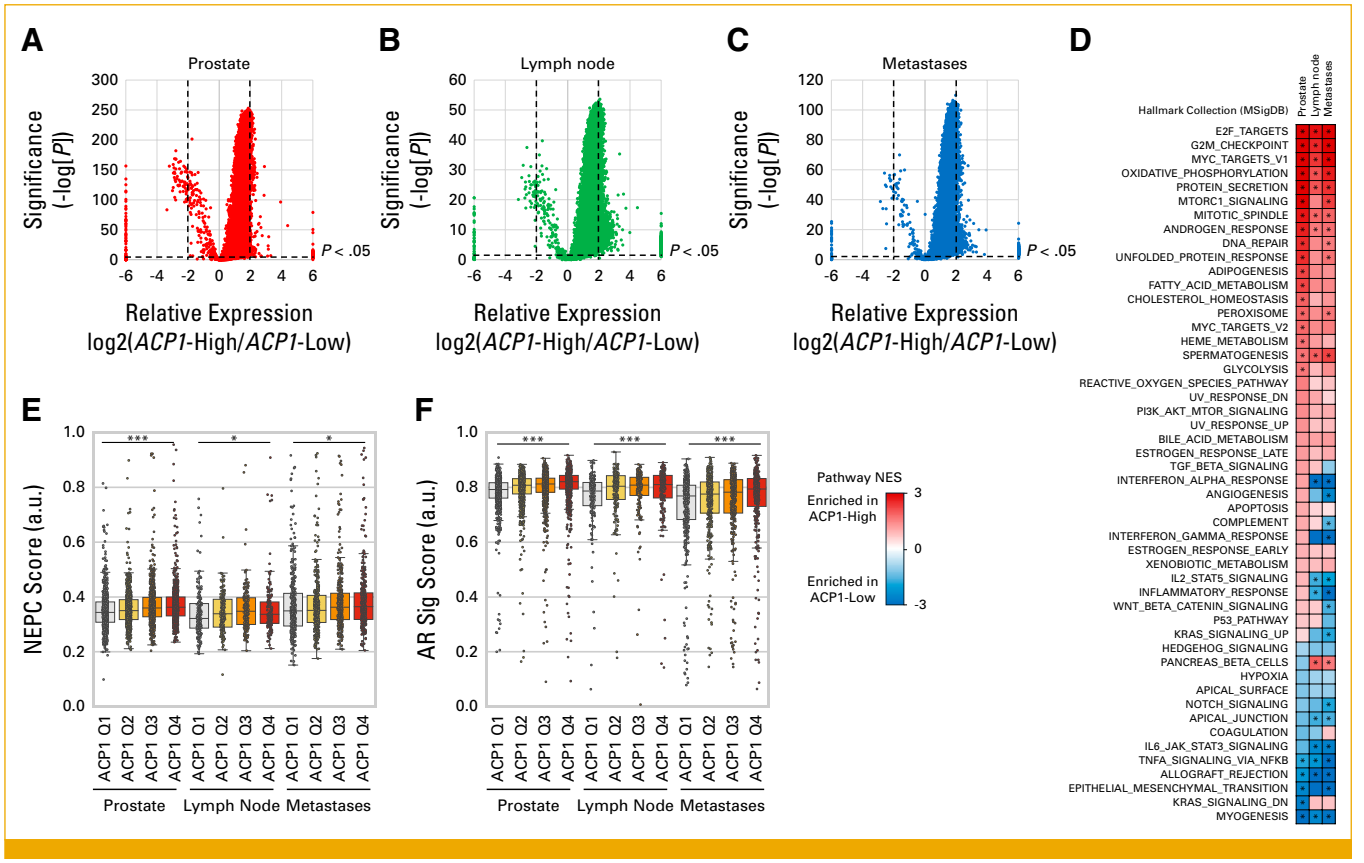

FIG 3. *ACP1* expression is associated with changes in cell cycle and metabolic pathways. (A-C) Volcano plot of differentially expressed genes in *ACP1*-High versus *ACP1*-Low samples across tumor sites. (D) Gene set enrichment analysis of the Hallmark collection of gene sets (MSigDB). (E and F) NEPC and AR signaling transcriptional expression scores across *ACP1* quartile subgroups by tumor site. *ACP1*, acid phosphatase 1; *AR*, androgen receptor; MSigDB, Molecular Signatures Database; NEPC, neuroendocrine prostate cancer; NES, not elsewhere specified; NK, natural killers.

abiraterone or enzalutamide) or IO (pembrolizumab [most common], nivolumab, ipilimumab; total n = 98; Fig 5B).

DISCUSSION

In this study, we comprehensively evaluate *ACP1* expression across PC tumors and its impact on disease outcomes. To our knowledge, this is the largest study to date investigating *ACP1* expression in PC with a data set comprising over 5,000 patients having undergone in-depth molecular profiling.

First, we demonstrate that *ACP1* expression was higher in PC tissue compared with normal prostate tissue, concordant with a previous study.[9] We also found that *ACP1* expression was increased in LNM and DM compared with primary prostate tissue. This suggests that *ACP1* expression is associated with more aggressive disease. Indeed, higher *ACP1* expression was demonstrated to be significantly associated with aggressive behavior, such as an increased biochemical, local recurrence, castration resistance, and cancer-related death.[9,11] The association between a high *ACP1* and PC severity was also concluded in previous studies as a higher *ACP1* reflected higher Gleason scores and the presence of metastasis.[12] Moreover, we found that *ACP1* expression was significantly higher in hepatic metastases. This further highlights the association of *ACP1* with worse outcomes in PC, given that the liver is the most lethal metastatic PC site with an ominous prognosis and a median OS of 10-14 months.[22-25] Liver metastases in PC were found to have aggressive genomic features, including *MYC* amplification, *PTEN* deletion, *PIK3CB* amplification, *RB-1* loss, and *APC* mutations, leading to poor outcomes.[26,27] Other studies also highlighted the re-expression of E-cadherin (epithelial) in the liver because of the interaction of metastatic PC cells and hepatocytes that increases the chemoresistance of cancerous cells and thus the poor prognosis of patients with liver metastasis.[28,29] While the presence of liver metastasis is associated with worse outcomes, it is still understudied, and standard treatments offer few benefits for these patients.[30] Thus, given the association of higher *ACP1* expression with advanced and more aggressive disease, notably in the liver, it is mechanistically logical for future projects to investigate *ACP1* function and implications of therapeutic targeting in this aggressive phenotype.

Second, we demonstrate that *TP53* alterations were enriched in *ACP1*-High prostate tumors. However, we did not observe the same correlation for LNM and DM. This discrepancy is

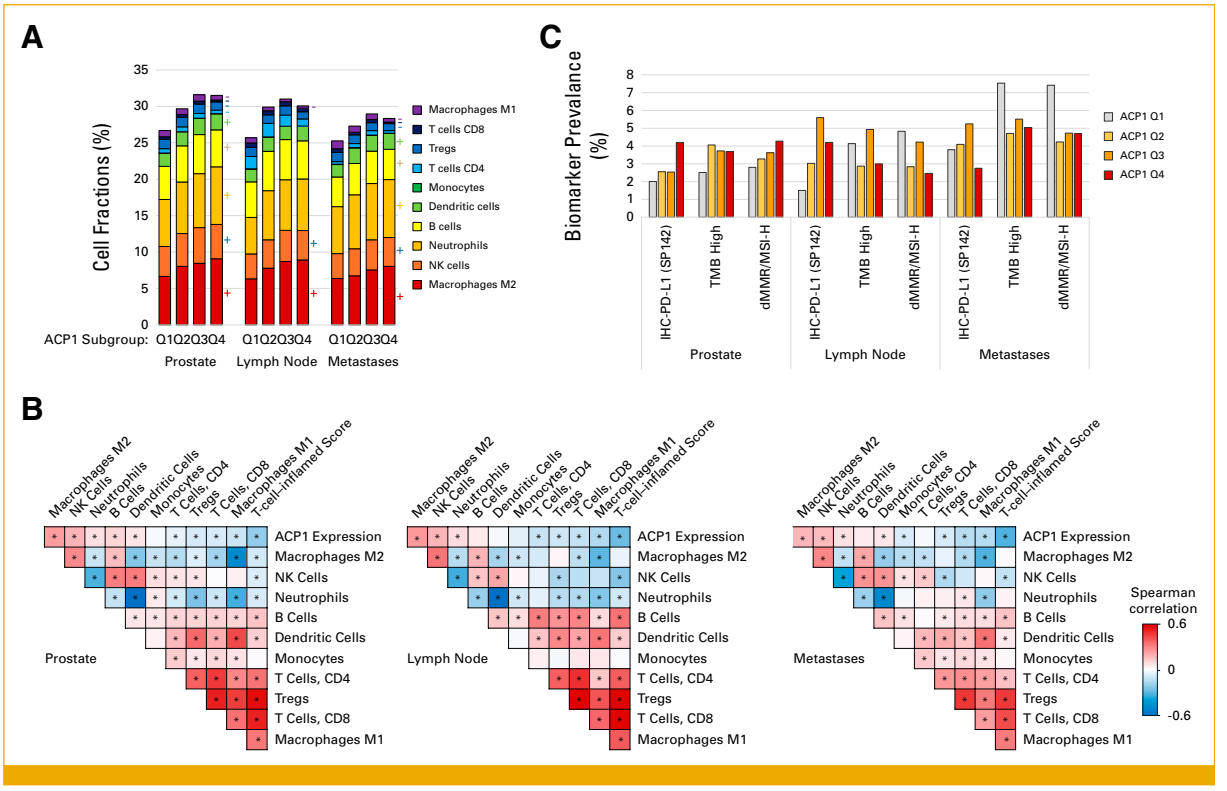

FIG 4. *ACP1* expression is associated with cold tumor microenvironments and infiltration of immunosuppression cell types. (A) Median immune cell fractions for populations estimated by RNA deconvolution (quanTIseq); + and − indicate statistically significant ($P < .05$) increases or decreases, respectively, among *ACP1* Q4 compared with *ACP1* Q1 subpopulations. (B) Matrix of Spearman correlations for *ACP1* expression, immune cell types, and a T-cell–inflamed score predictive of response to IO. (C) Prevalence of common IO-related biomarkers across *ACP1* quartile subgroups by tumor site. *ACP1*, acid phosphatase 1; dMMR/MSI-H, mismatch repair–deficient/microsatellite instability-high; IHC, immunohistochemistry; IO, immunotherapy; TMB, tumor mutational burden. *$P < .05$.

likely due to the differing prevalence of *TP53* alterations across these tissue types. In DM, the *TP53* alteration rate was 40%-50% across *ACP1* expression quartiles and 30%-40% across *ACP1* expression quartiles in LNM. However, in prostate tumors, except for the highest *ACP1* expression quartile, *TP53* prevalence was generally <30%. This suggests that *TP53* alterations may play a more prominent role in metastatic progression, regardless of *ACP1* expression levels, whereas in primary prostate tumors, high *ACP1* expression may be associated with an increased likelihood of *TP53* alterations. Indeed, a comprehensive analysis of *TP53* mutations and their impact on survival of patients with PC concluded a negative prognosis of these mutations.[31] While *TP53* mutations are detected in about 10% of primary PC samples, their frequency may be as high as 50% in advanced or metastatic PC samples.[32,33] In addition, one of the most common mutations detected in liver metastasis of PC is *TP53*,[34] which is the most lethal site of metastasis, as previously discussed. Genomic interrogation also detected increased *AR-V7* prevalence among increasing quartiles of *ACP1* expression. This mutation has been linked to more aggressive disease, castration resistance, and shorter survival.[35,36] *AR-V7* is typically an acquired mutation that has been associated with resistance to enzalutamide and abiraterone.[37-40] In our data set, 10% of primary prostate tumors had *AR-V7* and prevalence increased among increasing quartiles of *ACP1* expression, suggesting inherent ADT resistance in such tumors. Additional studies are warranted to further investigate the relevance of such alterations and strategies to therapeutically target them. Finally, we found that *gLOH* was more frequent with increasing *ACP1* expression in DMs. Previous studies concluded that *gLOH* is often detected in patients with PC having a mutation in homologous recombination repair[41,42] and could be a marker of response to PARP inhibition or platinum chemotherapy.[43-46]

Next, we demonstrated that *ACP1* expression is associated with cell cycle pathway alterations (*E2F* targets, *G2M* checkpoint, *MYC* targets, and mitotic spindle). This is especially intriguing as new molecular target agents have been recently investigated in the setting of advanced PC, such as the use of cyclin-dependent kinase 4 and 6 inhibitors.[47,48] Current strategies to target this pathway have proven to be unsuccessful in PC, and alternative methods or biomarker-based strategies are warranted to yield clinically meaningful results. Thus, the importance of increasing the knowledge of the mutational profile in PC is guiding the development of

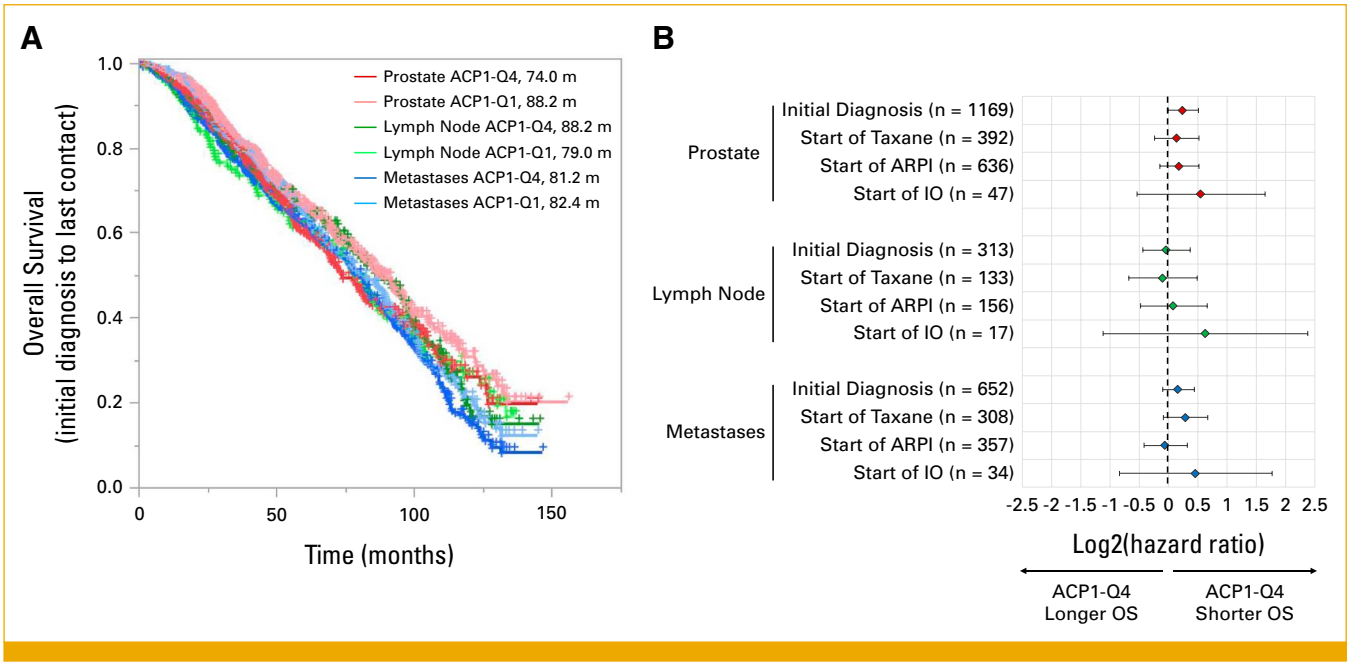

FIG 5. Real-world OS among patients stratified by *ACP1* expression and tumor biopsy site. (A) OS from the date of biopsy for patients with *ACP1*-High (Q4) and *ACP1*-Low (Q1) tumors by biopsy site. (B) Forest plot of overall survival from the date of biopsy (same as (A)), the start of taxane therapy, the start of ARPI, and the start of IO. *ACP1*, acid phosphatase 1; ARPI, androgen receptor pathway inhibitors; IO, immunotherapy; OS, overall survival. *P < .05, **P < .001.

targeted treatments. Furthermore, we see elevated *AR* and *NEPC* signature scores in *APC1*-High tumors, suggesting an admixture of these tumors, which can be seen in later stages.

We also concluded that *ACP1* expression is associated with an immunosuppressive environment, which was consistent with the strong negative correlation between *ACP1* expression and a T-cell–inflamed transcriptional signature predictive of IO response. However, our analysis is crude and lacks single-cell level and spatial assessment within the TME.

Finally, patients with high *ACP1* expression had worse OS, concordant with previous studies.[9,49] The analysis of two large independent data sets showed that high *ACP1* expression correlated with substantially lower survival probability.[12] These findings align with molecular insights we previously discussed, such that higher *ACP1* was associated with an increase in liver metastasis, *TP53* alterations, and *NEPC* signature. These conclusions emphasize the potential prognostic function of *ACP1* and potential predictability for survival.

Overall, our findings provide a rationale for novel therapeutic targeting of *ACP1*-High tumors through *LMPTP* inhibition, a landscape that has been recently evolving rapidly. Initially, *LMPTP* was identified as a promising treatment target for metabolic diseases, particularly type 2 diabetes.[50] Thereafter, several promising small-molecule inhibitors have been identified and are in various stages of preclinical development for metabolic disorders and cancer. The development of *LMPTP* inhibitors has faced several challenges, including achieving high selectivity for *LMPTP* over other phosphatases and optimizing pharmacokinetic properties. However, recent advances in structure-based drug design and high-throughput screening have led to the discovery of more potent and selective compounds, such as compound 13, a purine-based *LMPTP* inhibitor with favorable pharmacokinetic properties, including good oral bioavailability in mice and over 100-fold selectivity for *LMPTP* compared with other phosphatases.[51]

In the context of PC, Stanford et al[12] recently showed promising results for *LMPTP* inhibition as a potential therapeutic strategy as *LMPTP* deletion and pharmacologic inhibition reduced the in vitro invasiveness, anchorage-independent growth, and growth in the bone of the PC cells. Furthermore, targeting *LMPTP* could sensitize PC cells to taxane chemotherapy by impairing the cells' ability to respond to drug-induced *ROS*-dependent insults,[12] opening up new avenues for combination treatments. The researchers used both genetic and pharmacologic approaches to inhibit *LMPTP*,[12] including the application of the small-molecule inhibitor developed in their previous work.[51]

These advancements in *LMPTP* inhibitor development, from initial applications in metabolic disorders to recent findings in cancer research, highlight the versatility and potential of these compounds. The ability to modulate both cellular metabolism and signaling pathways makes *LMPTP* an

attractive target for further development, notably in clinical trials for PC.

There are several limitations to our study. Given the retrospective nature of our work, selection bias might have occurred. We used insurance claims as a surrogate for clinical outcomes, and the population might be skewed to advanced/metastatic disease. Future prospective studies with larger populations and longer follow-up are warranted to establish the usefulness of the *ACP1* gene as a prognostic factor in PC.

In conclusion, to our knowledge, in the largest study investigating the significance of *ACP1* expression in PC, we demonstrate that a higher *ACP1* expression is associated with a distinct molecular profile enriched for *TP53*, *AR-V7*, and *gLOH* alterations and with a cold TME. Patients with *ACP1*-High tumors also had worse clinical outcomes. While we provide a rationale for the novel therapeutic targeting of *ACP1*, future studies are warranted to further explore its potential for the treatment of primary and metastatic prostate tumors.

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AUTHOR CONTRIBUTIONS

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Administrative support: Neeraj Agarwal
Provision of study materials or patients: Neeraj Agarwal, Rohan Garje
Collection and assembly of data: Andrew Elliott, Neeraj Agarwal, Rohan Garje, Rana R. McKay
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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Consulting or Advisory Role: Nerio Therapeutics, Knoubis Bio, Inc
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Travel, Accommodations, Expenses: Pfizer, Exelixis

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APPENDIX

TABLE A1. Distribution of Tumor Biopsy Sites and Corresponding Median Age

Tumor Biopsy Site	Total Samples, No. (%)	Age, Years, Median (range)	*P*
Overall	5,028 (100)	68 (35 to 90+)	—
Prostate	3,058 (60.8)	67 (35 to 90+)	<.0001
Lymph node	634 (12.6)	69 (43 to 90+)	
Metastases	1,307 (26.0)	71 (39 to 90+)	
Unclear	29 (0.6)	72.5 (45 to 90+)	

TABLE A2. Distribution of Tumor Biopsy Sites

Tumor Biopsy Site	Total Samples, No.	Total, %
Prostate	3,058	60.82
Lymph node	640	12.73
Bone	457	9.09
GU	277	5.51
Liver	273	5.43
Thoracic	108	2.15
Abdominal	60	1.19
GI	48	0.96
CNS	30	0.60
Soft tissue/skin	27	0.54
Other/unclear	20	0.40
Endocrine	19	0.38
Head neck	11	0.22

Abbreviation: GU, genitourinary.

TABLE A3. Average Fold Change of *ACP1* Expression in the Metastatic Sample Relative to the Prostate Sample

Metastatic Site	Patients, No.	*ACP1* Fold Change Relative to Prostate
Bone	11	1.48
Lymph node	8	1.31
Liver	7	1.45
Genitourinary	3	2.36

Abbreviation: *ACP1*, acid phosphatase 1.

TABLE A4. Overall Survival of Patients From the Date of Initial Diagnosis or the Start of Treatment According to *ACP1* Expression

Site	Metric	Samples, No.	Hazard Ratio	Lower	Upper	*P*
Prostate	Initial diagnosis	1,169	1.19	0.99	1.42	.06
	Taxane	392	1.10	0.85	1.44	.46
	ARPI	636	1.14	0.90	1.44	.27
	IO	47	1.47	0.69	3.14	.32
Lymph node	Initial diagnosis	313	0.98	0.74	1.29	.87
	Taxane	133	0.93	0.62	1.40	.74
	ARPI	156	1.06	0.72	1.58	.76
	IO	17	1.55	0.46	5.23	.48
Metastases	Initial diagnosis	652	1.12	0.93	1.36	.22
	Taxane	308	1.22	0.94	1.59	.13
	ARPI	357	0.97	0.75	1.25	.79
	IO	34	1.38	0.56	3.41	.48

Abbreviations: *ACP1*, acid phosphatase 1; ARPI, androgen receptor pathway inhibitor; IO, immunotherapy.

TABLE A5. TCGA Abbreviations

TCGA Abbreviation	Cancer Type
ACC	Adrenocortical carcinoma
BLCA	Bladder urothelial carcinoma
BRCA	Breast invasive carcinoma
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL	Cholangiocarcinoma
COAD	Colon adenocarcinoma
COADREAD	Colorectal adenocarcinoma
DLBC	Lymphoid neoplasm diffuse large B-cell lymphoma
ESCA	Esophageal carcinoma
GBM	Glioblastoma multiforme
GBMLGG	Glioma
HNSC	Head and neck squamous cell carcinoma
KICH	Kidney chromophobe
KIRC	Kidney renal clear cell carcinoma
KIPAN	Pan-kidney cohort (KICH + KIRC + KIRP)
KIRP	Kidney renal papillary cell carcinoma
LAML	Acute myeloid leukemia
LGG	Brain lower grade glioma
LIHC	Liver hepatocellular carcinoma
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
MESO	Mesothelioma
OV	Ovarian serous cystadenocarcinoma
PAAD	Pancreatic adenocarcinoma
PCPG	Pheochromocytoma and paraganglioma
PRAD	Prostate adenocarcinoma
READ	Rectum adenocarcinoma
SARC	Sarcoma
SKCM	Skin cutaneous melanoma
STAD	Stomach adenocarcinoma
STES	Stomach and esophageal carcinoma
TGCT	Testicular germ cell tumors
THCA	Thyroid carcinoma
THYM	Thymoma
UCEC	Uterine corpus endometrial carcinoma
UCS	Uterine carcinosarcoma
UVM	Uveal melanoma

Abbreviation: TCGA, the Cancer Genome Atlas Program.