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Review

Applying Pathway and Gene Set Bioinformatics to Prostate Cancer Research: A Scoping Review and Novel Research Framework Aligning Datasets, Research Objectives, and Bioinformatic Techniques

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Simple Summary

The use of bioinformatics has evolved rapidly alongside the development of high-throughput data and large cancer datasets. This study provides a scoping review of the contribution of bioinformatics to our understanding of tumor biology and the discovery of biomarkers and novel targeted therapies for prostate cancer. The findings highlight a potential translation gap, with results to date often not having clinical impact. To facilitate closure this gap, a mapping framework is presented aligning datasets, research objectives, and specific bioinformatic techniques guided by dataset molecular depth, expected biological effect size, and the specific research question being addressed. Such a framework may also promote collaboration between computational scientists and clinicians to ensure deliberate prioritization of translational endpoints and may support findings that have clinical impact for better patient outcomes.

Abstract

Background: Bioinformatics has become an essential hypothesis-generating tool in cancer research, expanding in parallel with the rapid growth of high-throughput genomic and clinical data. Prostate cancer research encompasses a heterogeneous ecosystem of datasets spanning large epidemiological cohorts, controlled clinical and prevention trials, specialized intervention studies, and molecular profiling repositories, each with distinct data characteristics and research objectives. Effective translation of these resources into clinical insights requires principled alignment among dataset characteristics, research objectives, and bioinformatic methodology. This study defines six core bioinformatic techniques (Over-Representation Analysis (ORA), Gene Set Enrichment Analysis/Functional Class Scoring (GSEA/FCS), Pathway Topology Analysis (PTA), Network Topology Analysis (NTA), Individual-level Multi-Omics Pathway Analysis (IMOPA), and Pathway Activity Inference (PAI)) and, through a comprehensive scoping review using PRISMA methodology, describes how these techniques have been used in prostate cancer research from January 2009 to October 2026, **Results:** The PRISMA-compliant scoping review summarizes 105 studies in prostate cancer research with results relating to tumor biology (n = 78), biomarker discovery (n = 66), and novel therapeutics (n = 44), with some studies contributing to more than one category. The emerging pattern suggests a persistent translational gap, with much of the published bioinformatics literature generating biological knowledge that may not readily connect to clinical practice in a meaningful way. We then list 16 key prostate cancer

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datasets within the categories of epidemiological cohorts, clinical and prevention trials, specialized intervention cohorts, and molecular profiling datasets and construct a novel framework aligning specific datasets, research objectives, and the appropriate bioinformatic techniques. **Conclusions:** The scoping review identifies an emerging translational gap. The constructed framework provides clinicians and researchers with a principled guide for selecting analytical strategies in prostate cancer bioinformatics research and aims to close the persistent gap between biological discovery and clinical impact. As well as promoting understanding and collaboration at the interface of basic science and clinical practice, the framework is intended to support clinical translation and may help to improve individual and population cancer outcomes; its utility has yet to be tested prospectively.

Keywords: prostate cancer; bioinformatics; scoping review; biomarker discovery; novel therapeutics; dataset characteristics; clinical translation

1. Background

Modern molecular biology owes much to the development of DNA sequencing methods in the late 1970s, followed by the introduction of polymerase chain reaction techniques in 1983. These techniques led to the discovery of precise nucleotide sequences and the amplification of selected DNA fragments, respectively, generating a prodigious amount of data, particularly via the Human Genome Project (HGP; completed in 2003), which referenced the first fully sequenced human genome [1]. The need to regulate data sharing safely led to the centralization of large biological databases such as the DNA Data Bank of Japan, the European Bioinformatics Institute, and the National Center for Biotechnology Information, which have continued to evolve and offer open access and open sharing, coordinated through the International Nucleotide Sequence Database Collaboration (INSDC) [1].

Cancer is a genetic disease, and the above databases offer great potential to cancer biologists. Consequently, the discipline of bioinformatics has emerged using computational science and mathematical modeling to extract meaningful insights from genomic, transcriptomic, proteomic, and imaging datasets [2]. Specific cancer datasets then became available, such as The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO), as well as online biomarker identification tools (Webgestalt, CBioportal, KM Plotter, RNA-Seq Ontology User Environment [ROGUE], shinyGEO, and University of California Santa Cruz Xena [1,3–7]) and biological pathway tools (GeneMANIA and Database for Annotation, Visualization, and Integrated Discovery (DAVID) [8,9]).

Prostate cancer is the second most commonly diagnosed cancer in men worldwide, with 1,466,680 new cases and 396,792 deaths recorded globally in 2022, and is the most commonly diagnosed male cancer in over 112 countries [10]. It is the fifth leading cause of cancer-related mortality in men globally [10], and its substantial global burden and marked molecular heterogeneity make it a priority focus for advanced bioinformatic research. The molecular and clinical heterogeneity of prostate cancer (PCa) encompasses active surveillance of low-risk indolent localized disease, prolonged post-treatment surveillance of intermediate- and higher-risk disease, and aggressive castration-resistant metastatic states, overall requiring a multifaceted research strategy drawing on diverse data resources and analytical methodologies [11]. Over the past two decades, the PCa research community has generated a rich ecosystem of datasets including population-level cohorts, controlled clinical trials, specialized intervention and active surveillance studies, and high-dimensional molecular profiling repositories. Each dataset type captures distinct biological and clinical information, lending itself to specific research objectives and bioinformatic strategies [12].

Six core bioinformatic techniques have become central to cancer research; Over-Representation Analysis (ORA), Gene Set Enrichment Analysis (GSEA) (which includes Functional Class Scoring [FCS]), network topology-based analysis, pathway topology-based analysis, Individual-level Multi-Omics Pathway Analysis, and Pathway Activity Inference. While each technique has been used in a range of contexts, broader guidance of which methods are most appropriate for specific datasets and research objectives remains limited. Moreover, the results of many studies are speculative and without clinical context, limiting successful clinical translation [13].

This study aims to address this research gap with two main objectives. Firstly, six core bioinformatic techniques are defined and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scoping review is undertaken to illustrate how they have been used in PCa research from 1 January 2009 to 20 October 2026. Secondly, 16 PCa datasets are identified, and a framework is constructed aligning these datasets with specific research objectives (tumor biology, biomarkers, and novel therapies) and recommended bioinformatic techniques providing detailed scientific justification of these recommendations. We then discuss how the framework may serve as a practical decision guide for research initiatives using bioinformatics, potentially bridging the gap between bioinformatic analysis and clinical utility to improve individual patient and population-level cancer outcomes. This scoping review is the first to systematically compare six bioinformatic pathway-analysis technique families applied to prostate cancer research and introduces an original framework aligning 16 datasets with specific research objectives and analytical techniques, representing a novel contribution to the field.

Bioinformatics Techniques

Using bioinformatics to integrate clinical data and omics results affords the opportunity for researchers to unravel the complex molecular biology underlying oncogenesis, acquire a deeper understanding of cancer biology, identify biomarkers, and improve cancer diagnosis and management. Central to the evolution of bioinformatics is the pathway concept in systems biology that has its origins in the first metabolic pathway maps developed in the 1950s, ref. [13] inferring that specific sets of genes function to produce specific biological effects. Data files were broadly separated into two categories—gene datasets or pathway topology datasets—the latter of which may be non-directed (defining connections among components to form a network) or directed (further defining the nature of these connections as activating or inhibitory). Pathway analysis, which can be mechanistic, allowed the discipline to move beyond mere descriptive data lists (e.g., differentially expressed genes) to identifying clustered groups of altered genes or proteins that are specific to certain diseases, thus bridging traditional genomics with functional biology. This methodology included gene ontology (GO) categories for annotating gene functions and relating them to biological processes and molecular functions. Thus, without pathway analysis, bioinformatics would have remained largely descriptive, instead of the important predictive discipline necessary for personalized oncology, therapeutics discovery, and multi-omics integration [14].

Over-representation Analysis. ORA is a hypergeometric or Fisher's exact test method that analyzes whether a predetermined gene set (e.g., a Gene Ontology or Kyoto Encyclopedia of Genes and Genomes [KEGG] pathway) is statistically over-represented in a gene list of interest relative to a background reference. A typical workflow requires the generation of a differentially expressed gene (DEG) list using a statistical threshold, the choice of a specific gene set to test, and then an assessment of whether there are any overlaps with the DEG list greater than might be expected using Fisher's exact or chi-squared tests. This is adjusted for the false discovery rate (FDR) and interpreted to generate novel hypotheses given the biological context [13,15].

Gene Set Enrichment Analysis (and Functional Class Scoring). Unlike ORA, which only considers genes passing a binary significance threshold, GSEA analyzes the entire ranked list of genes to highlight gene sets that show subtle but consistent changes across a disease state. By generating an enrichment score reflecting the degree of over-representation of a gene set, GSEA can detect pathway level shifts without requiring an arbitrary significance cut off. FCS is the broader methodological category of which GSEA is the predominant implementation; any approach that ranks all genes by a continuous metric and evaluates pre-defined gene sets against that ranking is an FCS method. A per-sample extension, ssGSEA, projects individual sample profiles onto gene sets to generate patient-level enrichment scores rather than group-level comparisons [16]; GSVA, which derives a normalized pathway activity matrix across a cohort, is discussed under "Pathway Activity Inference" below as its primary output is a derived activity measure [15].

Pathway Topology Analysis. ORA or GSEA examine DEG lists, including the genes part of a pathway. Pathway Topology Analysis examines how DEG lists interact in a pathway network structure where genes or proteins act as "nodes," and regulatory interactions between nodes form the "edges" [14]. The workflow requires the acquisition of expression data, which are then mapped to pathway databases. The algorithm then calculates an impact score for each gene based on its expression and regulatory influence in the network. Gene impact scores are combined with pathway-level enrichment to furnish a pathway impact score, which can be interpreted within a biological context [13,14]. The advantages of Pathway Topology Analysis are deeper insights into a gene's functional interactions, the nature of pathway dysregulations by gene subsets, and the ability to integrate multi-omics databases including transcriptional regulation and signaling cascades [17].

Network Topology Analysis. This analysis uses graph theory to build and analyze interactive molecular networks. This can identify key pathways, subsets of communities within an overall network, and influential nodes associated with a disease state or biological condition [13]. Network Topology Analysis also incorporates regulatory actions (inhibition vs. activation) and directionality between nodes, as well as identifying network structures in terms of motifs and subcommunities [18]. Network Topology Analysis has the advantage of combining multiple data types to map the flow of signaling and highlight driver networks, utilizing mathematical methods such as pathway network integration, network propagation/diffusion, and active subnetwork/module detection to identify aberrant subnetwork signaling and crucial pathway crosstalk [19].

Individual-level Multi-Omics Pathway Analysis. This analysis assesses multidimensional layers of data (e.g., genomics, epigenomics, transcriptomics, proteomics, and metabolomics) to allow for deeper discovery of pathway- and network-level interactions [20]. There are a number of data integration strategies: early integration (e.g., concatenation-based omics that combine disparate datasets for modeling); intermediate integration (transforming multiple data types into latent representations to detect overlapping patterns and reduce noise such as Similarity Network Fusion [SNF] and iCluster); late integration (ensemble omics that analyze each data layer separately then fuse predictive results); and late factor/graph-based approaches (to highlight common latent factors or network subcommunities/modules that explain trends in data types such as multi-omics factor analysis) [21–23]. IMOPA is distinguished from FCS-based methods (e.g., GSEA) in that it integrates simultaneously measured data from two or more distinct omics layers; where enrichment scores appear within an IMOPA workflow, they serve as one derived input layer rather than the primary analytical method. Typical workflows include targeting network and pathway activity scores (e.g., signaling flux, GSEA type scores, and pathway hubs), causal relationships and regulatory interactions (how genomic changes relate to transcriptomic/proteomic changes), molecular subtyping (subcommunities defined by interactive

signals), and assessing biomarkers and molecular targeted therapies for consistency across omics datasets [20].

Pathway Activity Inference: This type of analysis is deeper than single gene readouts and therefore provides insight into overall signaling pathway activity that may have been highlighted in a multi-omics analysis. The results are more effective for mechanism and therapy discovery. Unlike IMOPA, which integrates raw measured data from multiple distinct omics layers, PAI methods infer a regulatory or activity-level quantity—such as transcription factor activity or pathway flux—from a single data type using curated regulatory models. Workflows that allow Pathway Activity Inference include the following:

- Gene Set Variation Analysis (GSVA), a modification of GSEA, which allows for single-sample pathway activity estimation and calculation of overall sample enrichment scores to provide insights into pathway activity without requiring phenotypic data [24];
- Virtual Inference of Protein-activity by Enriched Regulon analysis (VIPER), which assesses regulatory protein activity from target gene expression in each sample [25];
- Pathway Recognition Algorithm using Data Integration and Graphical Models (PARADIGM), which is a predictive framework that uses different omics datasets to infer network states and pathway activity [26];
- Protein and phosphoprotein-informed activity, which leverages phospho-signaling data and phospho-proteomics to assess pathway fluxes (which may be less available for cancer datasets) [27].

In summary, when planning Pathway Activity Inference, steps may include FCS-based enrichment (e.g., GSEA) as a preliminary pathway assessment, GSVA for sample-level pathway activity, VIPER for protein/regulon activity, and PARADIGM for Pathway Activity Inference from multi-omics, with final integrated subtyping and assessment in a specific PCa context. Protein and phosphoprotein information may be incorporated into overall Pathway Activity Inference analysis or as a specialized analysis [27,28].

2. Scoping Review of Bioinformatics

2.1. Methods

2.1.1. Study Design and Reporting Framework

This scoping review of specific pathway and gene-set-based bioinformatics techniques in PCa focused on research from 1 January 2009 to 20 October 2026 involving six core technique families: ORA, GSEA/FCS, Pathway Topology Analysis, Network Pathway Analysis, Individual-level Multi-Omics Pathway Analysis, and Pathway Activity Inference. This scoping review was designed and reported in accordance with the PRISMA scoping guidelines. A predefined protocol guided the literature search strategy, the process of screening articles, eligibility criteria, and data extraction to ensure transparency and reproducibility.

2.1.2. Pre-Search Scoping and Search String Development

Before the formal database searches were performed, a pre-search scoping exercise was conducted to refine terminology and validate the relevance of each of the six core technique families in PCa research. This involved reviewing key methodological papers, review articles, and domain-specific resources to identify synonyms, abbreviations, and common implementations for each technique (e.g., "ORA" or "hypergeometric test" and "GSEA" or "Fast Gene Set Enrichment Analysis"). Terms were grouped into concept blocks for each technique and then combined with PCa-related keywords using logical operators (AND/OR) and database-specific syntax. Synonyms, variants, and abbreviations were included to enhance search sensitivity. The final Boolean search strings were tailored for individual techniques and adapted for each database.

2.1.3. Literature Search Strategy

Extensive literature searches were performed across PubMed and Web of Science Core Collection individually for each of the six technique families. Searches were limited to published English-language peer-reviewed articles. For each technique, structured Boolean queries were used, combining PCa terms (e.g., "prostate cancer," "prostatic neoplasm," and "prostate carcinoma") with technique-specific keywords (e.g., for ORA: "over-representation analysis" OR "ORA" OR "hypergeometric enrichment"; for GSEA: "gene set enrichment analysis" OR "GSEA"). No restrictions were applied in PubMed to document type, while restrictions were applied in Web of Science searches, which focused on articles and reviews in the Core Collection. Reference lists of included studies were screened for additional eligible articles. The full technique-specific Boolean search strings are given in Appendix A.

Search results per pathway analysis system (after initial retrieval and deduplication across databases) were as follows:

- ORA: 160 unique records;
- GSEA/FCS: 1577 unique records;
- Pathway Topology Analysis: 172 unique records;
- Network Pathway Analysis: 343 unique records;
- Individual-level Multi-Omics Pathway Analysis: 936 unique records;
- Pathway Activity Inference: 1132 unique records.

2.1.4. Eligibility Criteria

Studies were selected according to predefined inclusion/exclusion criteria and adapted to emphasize the application of the six pathway analysis systems in PCa contexts (Table 1). During the broader literature search, the following issues became clear: Firstly, studies and techniques in bioinformatics often presented confused and overlapping terminology, which was presumed to stem from the evolution of these techniques and rapid expansion of their use, as well as the lack of consensus from any overriding body. For example, "topology" and "pathway" are often used interchangeably with reference to network analysis. Secondly, GSEA is the predominant implementation of the broader FCS family; FCS encompasses any method ranking all genes and testing for enrichment at the extremes of the ranked list, and GSEA is by far the most widely adopted FCS implementation in PCa research. Because both approaches share the same analytical philosophy and produce equivalent outputs, GSEA and FCS studies were consolidated and tabulated together. Thirdly, techniques are often combined in a single study, which is highlighted in the tabulated manuscript reviews. The authors acknowledge, partly due to the lack of consensus in terminology, that some studies may have been omitted.

Table 1. Eligibility criteria *.

Domain	Inclusion Criteria	Exclusion Criteria
Disease Focus	Explicit focus on human PCa (e.g., adenocarcinoma, CRPC, metastatic PCa, and NEPC), with technique application in title, abstract, or methods.	Non-PCa studies or pan-cancer analyses without prostate-specific results.
Human Relevance	Human-derived samples (e.g., tumor tissue, biofluids, and cell lines) analyzed using the specified pathway analysis systems.	Animal-only or non-human models without human data.

Table 1. *Cont.*

Domain	Inclusion Criteria	Exclusion Criteria
Data Type	Omics data (genomics, transcriptomics, etc.) processed using one or more of the six pathway analysis systems.	Non-omics data; studies without computational analysis.
Computational Requirement	Substantial use of at least one of the six pathway analysis systems as central to analysis (e.g., pathway enrichment and network inference).	Minimal or no use of the targeted techniques; pure experimental studies.
Study Design	Primary research applying the technique(s) to generate quantitative outputs.	Protocols or non-empirical papers.
Publication Type	Peer-reviewed full-text articles with accessible methods and results.	Abstracts, letters, or inaccessible full texts.
Language	Published in English.	Non-English publications.

* Predefined inclusion and exclusion criteria for study screening and selection after initial literature search Abbreviations: PCa, prostate cancer; CRPC, castration-resistant prostate cancer; NEPC, neuroendocrine prostate cancer.

2.1.5. Study Screening and Selection

Retrieved records for each technique were imported into reference management software and deduplicated within and across databases. Titles and abstracts were independently screened by two reviewers for eligibility criteria; any discrepancies were resolved by consensus, with articles meeting criteria advancing to full-text review. Full texts were then independently reviewed; discrepancies were resolved through consensus. Final included studies per technique were as follows:

- ORA: 20;
- GSEA/FCS: 42;
- Pathway Topology Analysis: 5;
- Network Topology Analysis: 19;
- Individual-level Multi-Omics Pathway Analysis: 8;
- Pathway Activity Inference (including GSVA, VIPER, and PARADIGM): 14.

Studies could qualify for multiple techniques if applicable. The selection process is summarized in PRISMA flow diagrams in Appendix B.

2.1.6. Data Extraction and Curation

For each included study, data were extracted using a standardized template. Key variables included the following:

- Publication metadata (authors, year, and journal);
- Study aims and biological focus (e.g., biomarker discovery and disease progression);
- Primary analysis system used and how they were applied (e.g., software packages, parameters, and integration with data types);
- Key findings and results from the application of the primary analysis systems (e.g., enriched pathways and inferred activities);
- Overall study summary, including translational implications.

Unclear information was noted as "not reported" without inference. Extracted data were cross-verified for accuracy.

2.1.7. Data Synthesis and Analysis

Due to methodological diversity, a narrative synthesis was employed. Studies were grouped by technique family, with cross-comparisons on applications, data modalities, and outcomes in PCa. Quantitative trends (e.g., technique prevalence and common software) were summarized where feasible, highlighting contributions to precision medicine such as biomarker identification and therapy response prediction.

2.1.8. Protocol and Registration

A review protocol was registered on the Open Science Framework and is available at https://osf.io/7fmtb (accessed on 1 November 2026). The registration documents the review objectives, eligibility criteria, search strategy, study selection procedures, and data extraction methods. As the review had already been completed at the time of registration, this should be considered a post hoc registration undertaken to improve transparency and reproducibility.

2.1.9. Use of Generative Artificial Intelligence Tools

To enhance the efficiency of the literature search and the interpretation of technical bioinformatics concepts, an artificial intelligence (AI) tool (SciSpace Version 1.5.10) was utilized as a research assistant. Specifically, SciSpace AI was employed for the following:

- To generate/refine search strings by identifying synonyms, abbreviations, and Boolean syntax for the six pathway analysis systems across different databases;
- To technically conceptualize various algorithms in the context of PCa research.

2.1.10. Human Oversight and Accountability

All AI-generated search strings were manually reviewed, validated for accuracy against database-specific syntax, and finalized by the study author (ZD). Similarly, the screening of abstracts and full texts, the application of eligibility criteria, and the final synthesis of data were performed exclusively by the authors to ensure critical analysis and academic integrity. Moreover, the authors reviewed, edited, and take full responsibility for all content in this publication.

3. Results

For each pathway analysis system and following the application of the eligibility criteria, the number of key studies reviewed were ORA = 20 (Table 2); GSEA/FCS = 43 (Table 3); Pathway Topology Analysis = 5 (Table 4); Network Topology Analysis = 19 (Table 5); Individual-level Multi-Omics Pathway Analysis = 8 (Table 6); and Pathway Activity Inference = 14 (Table 7). Subsequently, the key findings of each study for each pathway analysis system were labeled according to the main aim (e.g., Tumor Biology, Biomarkers, or Novel Therapies). For some studies, there was a lack of clarity regarding specific bioinformatic techniques used when multiple databases were employed. For this reason, databases should only be interpreted in the context of the reviewed study rather than part of an exhaustive catalog.

Overall, this scoping review highlighted 78 studies on oncogenesis and tumor biology, 66 on biomarkers, and 42 on cancer treatment (some studies contributed results to more than one category, so these totals exceed the 105 included studies). With respect to bioinformatic techniques, ORA was used in 17 Tumor Biology, 7 Biomarker, and 7 Treatment studies; GSEA and FCS in 30 Tumor Biology, 29 Biomarker, and 14 Treatment studies; Pathway Topology Analysis in 1 Tumor Biology, 3 Biomarker, and 1 Treatment study; Network Topology Analysis in 16 Tumor Biology, 13 Biomarker, and 11 Treatment studies; Individual-level

Multi-Omics Pathway Analysis in 5 Tumor Biology, 5 Biomarker, and 3 Treatment studies; and Pathway Activity Inference in 9 Tumor Biology, 9 Biomarker, and 6 Treatment studies.

Table 2. Over-Representation Analysis (ORA) as primary analysis system in PCa research.

Study	Summary	Research Focus
Shin et al. (2022) [29]	Assessed molecular pathways and potential therapeutic targets in ETV4 fusion-positive PCa. ORA via ConsensusPathDB on genes most strongly correlated with ETV4 fusion status; significant enrichment of 6 cancer-specific pathways: androgen receptor signaling, metabolism, the irinotecan pathway, the tamoxifen pathway, MAPK/NF-κB signaling, and interferon signaling.	Tumor Biology, Novel Therapeutics
Kim et al. (2022) [30]	Assessed signaling pathways dysregulated by the SLC45A3:ERG fusion and identified candidate drug repurposing targets in ERG fusion-positive PCa. ORA via ConsensusPathDB on ERG fusion-correlated genes revealed strong enrichment of JAK-STAT, Notch, PDGF, TGF-β, VEGFα, FAK/PI3K-Akt, and Wnt signaling pathways, supporting a rationale for pathway-targeted therapies in this molecular subtype.	Tumor Biology, Novel Therapeutics
Xiang et al. (2023) [31]	Identified signature genes and molecular mechanisms underlying PCa metastasis through ORA of differentially expressed genes against GO and KEGG pathway databases. ORA revealed 64 enriched GO and KEGG categories for primary PCa DEGs and 22 enriched categories for metastatic DEGs, delineating distinct pathway landscapes across localized and metastatic disease states.	Tumor Biology, Biomarkers, Novel Therapeutics
Shrestha et al. (2024) [32]	Applied ORA to ATAC-seq-derived open chromatin regions from 70 mCRPC biopsies via rGREAT, benchmarked against MSigDB Hallmark, Reactome, and GO:BP gene sets. ZNF263 target genes were significantly enriched for MYC signaling pathways in the AR−NE−mCRPC subtype, with ZNF263 and RREB1 identified as key transcription factors regulating chromatin accessibility.	Tumor Biology, Biomarkers
Oliveira-Rizzo et al. (2024) [33]	Applied ORA to differentially expressed genes and proteins from multi-omics profiling (RNA-seq and proteomics) of four prostate cancer cell lines with nc886 gain- and loss-of-function. ORA identified significant enrichment of immune system-related pathways including cytokine and interferon signaling, establishing nc886 as a positive regulator of innate immunity via a PKR-independent mechanism in prostate cancer.	Tumor Biology
Wang et al. (2025) [34]	ORA with pathway analysis following TWAS nomination of TAPBP revealed significant enrichment in immune response pathways, particularly antigen processing and presentation. Findings support TAPBP as a prostate cancer susceptibility gene with a role in immune modulation.	Biomarkers, Novel Therapeutics

Table 2. *Cont.*

Study	Summary	Research Focus
Dolgos et al. (2025) [35]	Assessed whether Matrigel-free prostate cancer organoids faithfully recapitulate the cellular heterogeneity and pathway activity of parental tumors for use in drug screening. ORA via enrichGO and clusterProfiler on differentially expressed genes identified universal alterations in metabolic and stress-response pathways across organoid lines, supporting Matrigel-free organoids as representative models for mechanistic and pharmacological studies.	Tumor Biology
Morgan et al. (2025) [36]	Assessed how lncRNA expression patterns differ between African American and European American patients with localized PCa. ORA used to functionally annotate mRNA components of race-specific lncRNA co-expression networks; significant enrichment of immune/inflammatory response, cell migration, and T-cell activation pathways.	Tumor Biology
Li et al. (2025) [37]	Applied ORA to genes at ATAC-seq promoter-region peaks against MSigDB Hallmark gene sets (FDR $\leq$ 0.01) to identify modulators of AR function in advanced prostate cancer. ORA identified PTGES3 as a direct AR modulator; high PTGES3 expression correlated with poorer metastasis-free survival and resistance to AR-directed therapies.	Tumor Biology, Biomarkers, Novel Therapeutics
Irham et al. (2025) [38]	Assessed whether an integrative genomic/bioinformatic pipeline can effectively prioritize existing drugs for repurposing in PCa. ORA across KEGG, GO, PPI networks, and knockout phenotype databases matched dysregulated pathways to existing drugs, identifying 26 novel therapeutic opportunities within cell-cycle and DNA repair pathways.	Novel Therapeutics
Lange et al. (2025) [39]	Applied ORA via STRING to urinary extracellular vesicle (U-EV) proteome cargoes from prostate cancer patients (Gleason scores 6–9) versus healthy controls, using GO, KEGG, Reactome, and disease–gene association databases. Pathway enrichment in GS 8–9 U-EVs was associated with cell–cell communication, immune and stress responses, apoptosis, peptidase activity, platelet aggregation, mitosis, proteasome, mRNA stability, oxytocin signaling, cardiomyopathy, and neurodegenerative disease pathways, supporting U-EV proteomes as non-invasive biomarkers for prostate cancer.	Tumor Biology, Biomarkers
Kalogera et al. (2025) [40]	Investigated ADAR1 expression and function using transcriptomic profiling across prostate cancer cell lines and a clinical cohort of 230 patients with localized PCa. ORA via Cytoscape (v3.10.4)/STRING on 42 genes oppositely regulated by ADAR1 silencing and p150 overexpression identified enrichment of carcinogenesis-related pathways, supporting ADAR1 as a key modulator of A-to-I RNA editing and a novel therapeutic target in PCa.	Tumor Biology, Novel Therapeutics

Table 2. *Cont.*

Study	Summary	Research Focus
Xiao et al. (2025) [41]	Applied GO and KEGG ORA via the DAVID database to 183 intersecting Epimedium Herba–prostate cancer target genes to characterize the herb's multi-target pharmacological mechanisms. ORA identified enrichment of PI3K-AKT, IL-17, TNF, apoptosis, p53, HIF-1, MAPK, and NF-κB signaling pathways, with in vitro experiments confirming quercetin as a key active component through inhibition of ACT-1 cell proliferation and induction of apoptosis.	Tumor Biology
Fan et al. (2025) [42]	Applied GO and KEGG ORA to 17 differentially expressed proteins from urinary large extracellular vesicles (lEV-DEPs) isolated from prostate cancer and prostatitis patients to identify enriched pathways and biological mechanisms. Pathway enrichment implicated lEV-DEPs in the transition from inflammation to cancer via specific post-translational modifications, and a four-protein lEV-DEP panel combined with PSA achieved a discrimination accuracy of 0.875 for distinguishing PCa from prostatitis.	Tumor Biology
Rafiee et al. (2025) [43]	Applied ORA and PPI network analysis to 236 differentially expressed genes (DEGs) from an integrated transcriptomic meta-analysis of three GEO datasets (GSE6919, GSE21034, and GSE3325) comparing primary and metastatic prostate cancer. ORA identified significant enrichment of cell-cycle regulation and metastasis pathways with CDK1 as the central hub gene, subsequently guiding a Light Gradient Boosting Machine virtual screen that identified 67 FDA-approved compounds targeting CDK1, with Tucatinib as the lead repurposing candidate.	Tumor Biology
Wang et al. (2026 [44]	Applied KEGG ORA to super-enhancer-related differentially expressed genes to identify biological mechanisms underpinning biochemical recurrence (BCR) in prostate cancer. A five-gene super-enhancer-related risk score demonstrated moderate BCR discrimination in an independent validation cohort (GSE70769), with exploratory immune-related pathway enrichment characterizing the associated tumor immune microenvironment.	Tumor Biology, Biomarkers
Sabatella et al. (2025) [45]	Applied ORA via GOseq (gene length-aware, GO:BP) and complementary GSEA (fGSEA/MSigDB Hallmarks) to DEGs from bulk RNA sequencing of PC3-PIP cells at 24 h and 72 h following equitoxic [177Lu]Lu-PSMA-I&T and [225Ac]Ac-PSMA-I&T treatment. [225Ac]Ac-PSMA-I&T elicited an early transcriptomic profile of impaired DNA damage response and apoptosis at 24 h, while both treatments showed progressive downregulation of cell migration and adhesion pathways over time.	Tumor Biology

Table 2. *Cont.*

Study	Summary	Research Focus
Kurt et al. (2026) [46]	Applied GO, KEGG, and Reactome ORA to TCGA-derived differentially expressed genes to characterize functional pathway dysregulation in prostate adenocarcinoma. ORA revealed coordinated dysregulation of cell-cycle and interferon-mediated immune signaling pathways, with STAT1 and PLK1 identified as highly connected hub genes in the PPI network.	Tumor Biology
Liu et al. (2026) [47]	Applied Gene Ontology (GO) and KEGG ORA to 60 differentially expressed mitochondrial-related genes (DeMRGs) from TCGA-PRAD, GSE46602, and GSE55945 to investigate their functions and related pathways in prostate cancer. ORA identified enrichment of oxidative phosphorylation, mitochondrial transport, and small-molecule catabolic processes, with PPI network analysis nominating MRPL12, PDK4, ACACB, and GATM as hub genes closely linked to mitochondrial metabolism and immune cell infiltration.	Tumor Biology, Biomarkers

Table 3. Gene Set Enrichment Analysis (GSEA)/Functional Class Scoring (FCS) as primary analysis systems in PCa research.

Study	Summary	Research Focus
Ross et al. (2011) [48]	Assessed gene expression pathways differentiating high-grade (Gleason 8) from low-grade (Gleason 6) localized PCa. GSEA assessed coordinated behaviur of predefined gene sets for enhanced statistical power over single-gene analyses, identifying enrichment in developmental processes, signal transduction pathways (EGFR, TNF-α, Notch, and AR), and embryonic stem cell-related pathways in high-grade tumors.	Tumor Biology, Novel Therapeutics
Miyamoto et al. (2015) [49]	Identified single-cell mechanisms underlying resistance to anti-androgen treatment in metastatic PCa. GSEA detected enriched signaling pathways in diverse CTC populations where single-gene assessments lack statistical power, revealing that noncanonical Wnt signaling was markedly enriched in CTCs from enzalutamide-resistant patients compared to untreated individuals.	Biomarkers
Ebot et al. (2017) [50]	Identified molecular links between obesity and lethal PCa via gene expression alterations in the TME. GSEA identified coordinated pathway-level signals linking obesity with distinct molecular programs, uncovering 15 upregulated and 2 downregulated gene sets in cancer tissue of men with overweight/obesity.	Tumor Biology

Table 3. *Cont.*

Study	Summary	Research Focus
Song et al. (2019) [51]	Identified hub genes with consistent dysregulation across independent PCa datasets. GSEA validated pathway engagement of all four hub genes, confirming significant enrichment in cancer cell proliferation, homologous recombination, and mismatch DNA repair pathways.	Biomarkers
Zhang et al. (2020) [52]	Classified PCa into subtypes based on metabolic pathway activity and constructed a metabolism-related gene prognostic signature. FCS (ssGSEA) characterized the molecular functions of risk gene models, revealing enrichment of high-risk genes in cell-cycle, homologous recombination, DNA replication, spliceosome, and RNA replication pathways.	Biomarkers
Song et al. (2020) [53]	Classified PCa into immunogenomic subtypes using HIF-1 signaling pathway activity and assessed immunotherapy response prediction. FCS (GSEA and GSVA) measured pathway enrichment across HIF-1 subtypes, demonstrating that HIF-1 High tumors were enriched in T-cell differentiation, B-cell receptor, and TNF signaling, with upregulation of HLA genes and immune checkpoints (PD-1 and PD-L1) and greater immune infiltration.	Biomarkers, Novel Therapeutics
Carreño et al. (2021) [54]	Assessed whether fructose serves as an alternative fuel source for PCa and whether fructose transporters are therapeutic targets. GSEA applied to transcriptomic profiles from fructose-exposed cells to validate pathway-level impacts of metabolic shifts; Significant enrichment in gene sets related to proliferation, supporting fructose's role in enhancing PCa aggressiveness.	Biomarkers, Novel Therapeutics
Bolis et al. (2021) [55]	Generated a comprehensive PCa transcriptome atlas by integrating multiple multi-stage transcriptomic cohorts to define a pseudotime trajectory of disease progression from primary PCa through CRPC and neuroendocrine PCa. GSEA using MSigDB gene sets (Camera pre-ranked algorithm) identified progressive upregulation of PRC2, G2-M checkpoint, and M2 macrophage polarization gene sets along the trajectory with concomitant androgen-responsive gene set downregulation, and single-cell GSEA in patient-derived xenograft models confirmed EZH2 inhibition reverts progression-associated transcriptional changes.	Tumor Biology, Novel Therapeutics
Pernar et al. (2021) [56]	Investigated molecular mechanisms linking vigorous physical activity to reduced risk of aggressive prostate cancer using transcriptomic profiling of tumor-adjacent normal tissue. GSEA identified 25 differentially enriched gene sets from KEGG and Hallmark databases between high- and low-activity groups, with gene sets related to PCa progression and immunity downregulated in adjacent normal tissue of physically active individuals.	Tumor Biology, Novel Therapeutics

Table 3. *Cont.*

Study	Summary	Research Focus
Aggarwal et al. (2021) [57]	Assessed whether mCRPC can be classified into luminal and basal subtypes with distinct prognoses and treatment responses. FCS (GSEA) employed with Hallmark gene sets to evaluate pathway activity variations between luminal and basal subtypes, demonstrating that luminal tumors were most enriched in AR signaling-associated genes.	Biomarkers
Zhang et al. (2021) [58]	Developed a metabolism-score based on metabolic pathway activity to predict prognosis in PCa patients. FCS (ssGSEA) quantified enrichment of 41 KEGG metabolic pathways per sample, creating a pathway-centric matrix capturing metabolic heterogeneity; high-scoring metabolic group enriched in β-alanine metabolism, fatty acid metabolism, butanoate metabolism, and propanoate metabolism.	Biomarkers
Feng et al. (2022) [59]	Developed an immune-related gene prognostic index (IGPI) to predict PCa advancement and characterize the TME. GSEA confirmed distinct pathway profiles distinguishing high- and low-risk TME states.	Biomarkers, Novel Therapeutics
Song et al. (2022) [60]	Mapped cellular heterogeneity of epithelial cells in localized PCa and identified distinct recurring tumor-associated cell states through single-cell transcriptomics. ssGSEA assessed gene set enrichment in individual cells, revealing that tumor-associated club cells exhibit enriched androgen signaling states, implicating this population in PCa oncogenesis and highlighting tumor complexity masked by bulk transcriptomic analyses.	Tumor Biology
Han et al. (2023) [61]	Assessed whether TICS can predict BCR and response to ADT and immunotherapy in PCa. FCS (GSEA and ssGSEA) generated immune cell and pathway scores defining TICS subgroups and evaluating mitogenic activities, revealing that low TICS scores were linked to genomic instability (high tumor mutation burden and aneuploidy), DNA replication pathway activation, and an immune desert state.	Biomarkers
Jiang et al. (2024) [62]	Identified genes and pathways contributing to bone metastasis in PCa. GSEA used to confirm biological significance of ML-derived hub genes by identifying enriched KEGG pathways; Enriched pathways (excluding CFH) included mitochondrial metabolic reprogramming, indicating a key role in bone metastatic progression.	Biomarkers, Novel Therapeutics
Kanayama et al. (2024) [63]	Characterized the clinical relevance and oncogenic function of the African-ancestry HOXB13 X285K germline variant in aggressive PCa, integrating germline testing data from 21,393 men with functional analyses in engineered LNCaP95 cell clones. GSEA of RNA-sequencing data from androgen-stimulated X285K versus wild-type HOXB13 clones identified E2F and MYC targets as the top enriched gene sets, revealing a gain-of-function mechanism that raised cyclin B1 and c-Myc expression without altering androgen receptor target gene regulation.	Tumor Biology, Novel Therapeutics

Table 3. *Cont.*

Study	Summary	Research Focus
Su, Hu and Dai (2025) [64]	Assessed whether metabolic pathway activity can predict prognosis in PCa. GSEA used to explore main functions identified by enriched GO categories in combination with KEGG pathway analysis; enriched GO categories for the five-gene signature included DNA repair and sulfur-related metabolic processes.	Biomarkers
Sharifi et al. (2025) [65]	Characterized adverse prognostic gene expression pathways in mCRPC across a cohort of 1012 patients, integrating bulk and single-cell RNA sequencing data. GSEA identified loss of AR signaling, high proliferation, and a glycolytic phenotype as adverse prognostic pathways; scRNA-seq of mCRPC biopsies and circulating tumor cells confirmed their association with poor outcomes and incomplete pathway suppression on AR inhibitor treatment.	Tumor Biology, Biomarkers
Xu et al. (2025) [66]	Characterized immune cell infiltration differences between PCa and healthy prostate tissue and identified a causal relationship between specific immune phenotypes and PCa. GSEA-based functional enrichment combined with CIBERSORT immune deconvolution demonstrated significant differences in immune cell infiltration between tumor and normal tissue, identifying immune phenotypes causally associated with PCa pathogenesis.	Tumor Biology
Alfahed (2025) [67]	Investigated the therapeutic, clinicopathological, and biological relevance of CREB3L4 expression in primary prostate cancer, analyzing TCGA and GEO datasets to determine mechanisms underlying its transcriptional deregulation. GSEA identified enrichment of gene sets predicting biological responses to approved inhibitors in PCa subsets with low CREB3L4 expression, whilst methylation loci and miRNA expression independently predicted CREB3L4 levels, implicating epigenetic regulation as the primary deregulation mechanism.	Tumor Biology
Tang et al. (2025) [68]	Assessed the expression and pathway activity of solute carrier (SLC) family genes to characterize their roles in PCa tumorigenesis and identify prognostic biomarkers. ssGSEA applied to TCGA-PRAD transcriptomic data defined SLC-associated pathway activity profiles; an SLC-based prognostic risk score stratified patients by survival outcome, linking altered solute transport to PCa immune microenvironment remodeling.	Tumor Biology, Biomarkers
Jin et al. (2025) [69]	Investigated the prognostic significance of Dermatopontin (DPT) expression and its immunomodulatory role in the tumor microenvironment of prostate adenocarcinoma. GSEA and KEGG pathway enrichment of differentially expressed genes linked to ImmuneScore and StromalScore demonstrated that DPT expression correlates with overall survival and regulates the immune microenvironment in PRAD, supporting its candidacy as a novel prognostic biomarker.	Tumor Biology, Biomarkers

Table 3. *Cont.*

Study	Summary	Research Focus
Qin et al. (2025) [70]	Developed a stress granule-associated prognostic risk model for PCa by screening GEO and TCGA transcriptomic data, identifying six prognostic genes (SPAG5, FN1, CCK, EGF, SELE, and PTGS2). GSEA using KEGG gene sets demonstrated cell-cycle pathway enrichment in high-risk patients and metabolic/structural pathway enrichment in low-risk patients, with experimental SPAG5 knockdown confirming its role in promoting PCa proliferation, migration, and invasion.	Tumor Biology, Biomarkers
Adler et al. (2025) [71]	Characterized insulin pathway gene expression in localized PCa using the multi-institutional ORIEN database, applying NMF clustering to stratify 433 patients into two distinct insulin pathway expression groups. GSEA using MSigDB Hallmark, C2, and C5 gene sets identified WNT secretion and lipid metabolism pathway enrichment in the insulin-dysregulated cluster and DNA damage repair and testosterone pathway enrichment in the other, with the dysregulated cluster exhibiting higher rates of metastasis despite survival differences resolving after confounder adjustment.	Tumor Biology
Fu et al. (2025) [72]	Elucidated the interaction between metabolic reprogramming and immune microenvironment in PCa using multi-omics analysis, identifying ENO1 and CKB as clinically meaningful metabolic biomarkers. GSEA-based functional pathway enrichment combined with CIBERSORT immune deconvolution and chromatin accessibility analyses identified ENO1 as an indicator of metastatic potential and CKB as a predictor of overall prognosis, bridging tumor metabolism–immune crosstalk with clinical outcomes.	Tumor Biology, Biomarkers
Kong et al. (2025) [73]	Characterized the oncogenic roles of m7G methyltransferases METTL1 and WDR4 in PCa and developed an epigenetic prognostic model based on their expression. GSEA and KEGG pathway enrichment analyses revealed that METTL1 and WDR4 influence ribosome-related pathways and tumor immune microenvironment composition; a prognostic model founded on both genes exhibited superior predictive precision for PCa patient outcomes.	Tumor Biology, Biomarkers
Zhang et al. (2025) [74]	Assessed the prognostic significance of estrogen-related genes (ERGs) in PCa and explored the underlying biological mechanisms using LASSO and multivariate Cox regression on TCGA and GEO transcriptomic data. GSEA alongside GO and KEGG analyses identified cell adhesion molecule pathway activity and epigenetic regulation as key mechanisms, with six ERGs (POU4F1, BMP2, PGF, GAS1, GNAZ, and FGF11) constituting a prognostic model distinguishing low-risk patients with improved outcomes.	Tumor Biology, Biomarkers

Table 3. *Cont.*

Study	Summary	Research Focus
Fan et al. (2025) [75]	Developed a metabolic reprogramming-related gene (MRG) prognostic model in PRAD to stratify patients by survival and immune landscape. GSEA applied to TCGA and GEO datasets characterized MRG-associated pathway activity; high-risk patients exhibited poorer outcomes, reduced immune infiltration, and altered drug sensitivity, providing a stratification framework for precision immunotherapy and drug discovery.	Tumor Biology, Biomarkers, Novel Therapeutics
Tan et al. (2026) [76] (using English translation)	Systematically evaluated the impact of ADT on the PCa immune microenvironment across systemic immunity, PDX model transcriptomics, and single-cell omics levels in 12 patients and 4 tissue samples. ssGSEA immune deconvolution of PDX transcriptomic data identified trending changes in CD8+ T-cell, Treg, TAM, and MDSC infiltration after castration, with scRNA-seq confirming reduced intratumoral effector CD8+ T cells and Treg enrichment after ADT and Hallmark pathway analysis revealing suppression of interferon signaling.	Tumor Biology
Zhang et al. (2025) [77]	Identified dysregulated gene expression pathways associated with PCa prognosis and therapeutic targets using GSEA in a primary clinical cohort. GSEA applied to GEO transcriptomic data characterized pathway-level alterations in PCa, identifying Hallmark gene set enrichment patterns that correlate with patient survival and represent potential targets for intervention.	Tumor Biology, Biomarkers, Novel Therapeutics
Wo et al. (2025) [78]	Identified palmitoylation-related signature genes as potential diagnostic and therapeutic targets in PCa, achieving robust classification accuracy. GSEA identified palmitoylation-associated pathway dysregulation; integration of GEO datasets identified six differentially expressed palmitoylation genes whose diagnostic model achieved an AUC of 0.929, with molecular docking identifying diethylstilbestrol as a candidate therapeutic agent targeting LAMB3 and APOE.	Tumor Biology, Biomarkers, Novel Therapeutics
Gan et al. (2025) [79]	Developed and validated a six-gene hypoxia and immune escape-related diagnostic signature (RBMS3, ALDH2, SLC7A11, FGFR2, GDF15, and NCAM1) for PCa using integrated transcriptomic data from TCGA-PRAD, GTEx, and GEO datasets with a multi-step machine learning framework. GSEA (clusterProfiler, c2.all.v2023.2.Hs.symbols MSigDB) identified significant enrichment of translation-related pathways and smooth muscle contraction distinguishing PCa from controls, whilst GSVA with Hallmark gene sets and ssGSEA immune infiltration analyses characterized pathway activity differences and immune landscape alterations associated with the six-gene RiskScore.	Tumor Biology, Biomarkers

Table 3. *Cont.*

Study	Summary	Research Focus
Niu et al. (2025) [80]	Constructed a competitive endogenous RNA (ceRNA) regulatory network and characterized its relationship with immune biomarkers and prognosis in PCa. ssGSEA immune scoring of 481 PCa samples combined with PPI network analysis identified H2AFJ, THBS1, and HPGD as prognostically significant network hubs with implications for immune-based therapy response in PCa.	Tumor Biology, Biomarkers
Qiu et al. (2025) [81]	Characterized the transcriptomic landscape of cancer-associated fibroblasts (CAFs) in CRPC using scRNA-seq of 71,560 cells, identifying a CRPC-specific CAF subpopulation marked by elevated expression of POSTN, COL1A1, COL1A2, FN1, and COL3A1 and associated with unfavorable recurrence-free survival. GSEA using MSigDB gene sets identified extracellular matrix remodeling pathway activation and androgen response suppression in CRPC-CAFs, whilst ssGSEA demonstrated that high CRPC-CAF abundance correlated with elevated infiltration of Tregs, M2 macrophages, and MDSCs, resistance to immunotherapy, and BGN as an independent prognostic factor for recurrence-free survival.	Tumor Biology, Biomarkers, Novel Therapeutics
Sugiki et al. (2025) [82]	Identified TXN as a novel regulator of stemness and a prognostic gene in prostate cancer stem cells (CSCs) using GSEA-based pathway analysis. GSEA estimated CSC activity and identified TXN as a commonly upregulated gene in CSC-enriched datasets; MYC signaling emerged as a key intracellular pathway through which TXN regulates stemness, suggesting TXN as a candidate therapeutic target in PCa.	Tumor Biology, Biomarkers, Novel Therapeutics
Masur et al. (2025) [83]	Characterized the transcriptional landscape of androgen-indifferent prostate cancer (AIPC), identifying downregulated androgen response and oxidative phosphorylation pathways alongside upregulated EMT and immune signaling. GSEA of AIPC datasets revealed that androgen response and oxidative phosphorylation were the most significantly downregulated gene sets, while epithelial–mesenchymal transition and immune signaling were upregulated, demonstrating predefined AIPC enrichment criteria identify a clinically distinct tumor subtype.	Tumor Biology
Song et al. (2025) [84]	Applied multi-omics Mendelian randomization to assess the genetic causal relationship between ferroptosis gene/protein expression and PCa, identifying cathepsin B (CTSB) as a key causal risk factor mediated through regulation of PD-L1+ monocytes and CD45+ T cells. GSEA demonstrated that high CTSB expression was significantly enriched in pro-cancer pathways including epithelial–mesenchymal transition, angiogenesis, inflammatory response, and apoptosis (NES $>$ 2, FDR $<$ 0.001), whilst scRNA-seq revealed CTSB expression predominantly in normal basal epithelial and myeloid cells with downregulation in tumor tissue, supporting combined CTSB-targeted and immunotherapy strategies.	Tumor Biology

Table 3. *Cont.*

Study	Summary	Research Focus
Cai et al. (2026) [85]	Identified glycolysis as a driver of PCa progression and therapy resistance, establishing a glycolysis risk score (GLY score) with CLN6 as a central therapeutic target. ssGSEA applied to the SU2C mCRPC cohort demonstrated elevated glycolytic activity correlates with poor progression-free and overall survival; enzalutamide-resistant cell lines exhibited heightened glycolysis, and CLN6 knockdown reduced glycolytic activity and proliferation.	Tumor Biology, Biomarkers, Novel Therapeutics
Nie et al. (2026) [86]	Defined a metabolic dysfunction signature (MODS) in PCa integrally linked to patient prognosis, genomic instability, therapeutic resistance, and an immunosuppressive tumor microenvironment. GSEA pathway enrichment and ssGSEA transcriptomic deconvolution (CIBERSORT) of TCGA and GEO cohorts characterized MODS-associated TME remodeling; HPRT1 emerged as a key MODS gene functionally associated with adverse clinical outcomes and distinct therapeutic response profiles.	Tumor Biology, Biomarkers
Dai et al. (2026) [87]	Developed a machine-learning-based prognostic model (fat_stemness_SCR) for biochemical recurrence prediction in PCa, integrating fatty acid metabolism and cancer stem cell features. GSEA-based pathway enrichment informed stemness and fatty acid metabolism signature selection; the fat_stemness_SCR model was encapsulated into an R package (v1.0) and online tool (PCaMLmodel v1.0) for clinical deployment in recurrence risk stratification.	Tumor Biology, Biomarkers
Song et al. (2026) [88]	Identified the endothelial CXCL10–CXCR3 axis as a key driver of bone-metastatic PCa progression and docetaxel resistance using multi-omics integration. GSEA integrated with bulk and single-cell RNA-seq, WGCNA, and immune deconvolution identified the CXCL10–CXCR3 axis as a central mediator of metastatic progression; CXCL10/CXCR3 knockdown reversed endothelial-mediated PCa cell survival and docetaxel resistance in vitro and in vivo.	Tumor Biology
Zhang and Qiu (2026) [89]	Delineated immune infiltration patterns in prostate adenocarcinoma and developed a robust immune-related prognostic signature for biochemical recurrence-free survival. ssGSEA, CIBERSORT, ESTIMATE, xCell, TIMER, EPIC, and MCPcounter deconvolution frameworks characterized the immune microenvironment of TCGA-PRAD; univariate Cox and LASSO-Cox regression identified prognostic immune genes whose risk score, combined with PSA and Gleason grade in a nomogram, improved individualized recurrence-risk prediction.	Biomarkers

Table 4. Pathway Topology Analysis as primary analysis system in PCa research.

Study	Summary	Research Focus
Da Silveira et al. (2022) [90]	Determined the roles of miRNA and lncRNA regulatory networks in suppressing DNA repair and cell-cycle progression in senescent prostate cells. SPIA mapped differentially expressed genes onto KEGG pathway networks and assessed perturbation transmission based on gene interaction directionality, identifying PI3K/AKT activation and MAPK signaling inhibition as the principal perturbations within the prostate cancer pathway in senescent cells.	Biomarkers
Hellstern et al. (2021) [91]	Developed the netgsa R package to enhance the speed and interactivity of topology-based pathway enrichment analysis for large-scale genomic datasets. NetGSA incorporated gene correlation structure via weighted adjacency matrices derived from KEGG and Reactome topologies, using block-diagonal clustering to reduce computational load while preserving topology, achieving improved speed and usability without loss of statistical power.	Biomarkers
Lin et al. (2025) [92]	Identified key ferroptosis regulators in PCa using knowledge-guided multi-level network modeling. A PCa-specific protein–protein interaction network was seeded with ferroptosis-related genes and subjected to random walk with restart to extract a core ferroptosis subnetwork, followed by multi-level topological prioritization using hub-bottleneck filtering, edge co-expression analysis, and community detection, identifying PRKCA as a novel hub-bottleneck tumor suppressor whose reduced expression in PCa promotes ferroptosis evasion through GPX4 downregulation.	Biomarkers, Novel Therapeutics
Bhattacharjee et al. (2026) [93]	Analyzed the Boolean network topology of PCa to identify optimal drug combination strategies, incorporating Berberine alongside standard therapeutic agents. Boolean network Pathway Topology Analysis computed Size Difference scores (Hamming distance analogue) to quantify therapeutic efficacy across drug combinations and fault scenarios, identifying Berberine and standard PCa drugs as synergistic combinations that most effectively restore normal network states.	Tumor Biology

Table 5. Network Topology Analysis as primary analysis system in PCa research.

Study	Summary	Research Focus
Chen et al. (2020) [94]	Identified robust gene biomarkers to aid PCa diagnosis and prognosis using WGCNA combined with PPI network analysis. WGCNA clustered 2688 DEGs into six co-expression modules, with two hub modules most correlated with tumor grade; PPI network construction via STRING and MCODE identified 13 hub genes, of which CCNB1, TTK, CNN1, and ACTG2 were validated as top prognostic candidates involved in cell adhesion and Wnt signaling pathways.	Tumor Biology, Biomarkers
Feng et al. (2021) [95]	Identified four novel prognostic biomarkers for PCa through WGCNA-based co-expression network analysis. WGCNA applied to TCGA RNA-seq data identified a magenta co-expression module strongly correlated with Gleason score and tumor stage; hub gene analysis identified CCNA2, CKAP2L, NCAPG, and NUSAP1 as upregulated in PCa with prognostic value, validated across multiple GEO datasets.	Biomarkers, Novel Therapeutics
Mohammad et al. (2022) [96]	Identified five dysregulated hub genes as biomarkers and therapeutic targets in PCa through WGCNA-based co-expression network analysis. WGCNA applied to TCGA PRAD RNA-seq data (459 cancer vs. 50 normal samples) constructed a turquoise hub module whose PPI network, analyzed using six centrality measures in CytoHubba, identified MAF, STAT6, SOX2, FOXO1, and WNT3A as hub DEGs enriched in cell-cycle and chemokine-mediated signaling pathways, with SOX2 and STAT6 proposed as candidate diagnostic and therapeutic targets.	Tumor Biology, Biomarkers, Novel Therapeutics
Filippi, Aurelian and Mocanu (2024) [97]	Characterized gene networks associated with tissue differentiation across Gleason Grade Groups in PCa using STRING-based PPI network and kNN classification analysis. STRING PPI network analysis of the top 200 Gleason-correlated genes identified two key clusters centered on PLK1/CDC20 (positively correlated) and CAV1/CALM1/PAK3 (negatively correlated); NTA-guided gene selection via Cytoscape combined with kNN analysis identified an eight-gene signature (FOXS1, NSD2, CDC42EP4, AGL, VPS36, TMLHE, ANGPT1, and C22orf23) that accurately classified normal, low-Gleason, and high-Gleason PCa tissues.	Tumor Biology, Novel Therapeutics
Sheibani-Tezerji et al. (2025) [98]	Identified TPX2 as a central hub gene driving aggressive PCa through WGCNA-based co-expression network analysis spanning all major disease stages. WGCNA integrated with explainable machine learning across 1232 PCa samples identified TPX2 as consistently upregulated across all disease transitions, with stage-specific co-expressed drivers including CENPA–MYBL2 in localized PCa, EXO1–NEIL3 in metastatic hormone-sensitive PCa, and TERT as a Hallmark of castration-resistant disease.	Tumor Biology, Biomarkers, Novel Therapeutics

Table 5. *Cont.*

Study	Summary	Research Focus
Lv et al. (2025) [99]	Identified immune-related gene biomarkers for PCa diagnosis through integrated WGCNA, machine learning, and Mendelian randomization analysis. WGCNA applied to GEO datasets identified driver genes within co-expression modules, with machine learning narrowing these to six core diagnostic biomarkers—SLC14A1, ARHGEF38, NEFH, MSMB, KRT23, and KRT15—and Mendelian randomization analysis identifying MSMB as a potential protective factor against PCa.	Biomarkers, Novel Therapeutics
Zhai et al. (2025) [100]	Identified cell-type-specific gene co-expression networks and key prognostic genes in PCa at single-cell resolution using high-dimensional WGCNA. hdWGCNA applied to integrated scRNA-seq and bulk RNA-seq data detected seven gene co-expression modules, four strongly expressed in tumor cell subtypes; subsequent Cox and LASSO regression identified six key genes—CNPY2, CPE, DPP4, IDH1, NIPSNAP3A, and WNK4—forming a prognostic model validated for overall survival stratification.	Biomarkers, Novel Therapeutics
Chen et al. (2026) [101]	Identified three hub genes—EZH2, CDK1, and AURKA—as a prognostic risk signature for biochemical recurrence in PCa through WGCNA-based co-expression and PPI network analysis. WGCNA applied to 554 TCGA-PRAD samples identified a turquoise co-expression module strongly correlated with Gleason score, PSA, and pathological T stage; PPI Network Topology Analysis via CytoHubba identified five hub genes, of which a LASSO Cox and random forest consensus model selected EZH2, CDK1, and AURKA as a three-gene risk score independently predictive of BCR-free survival (HR = 3.21).	Tumor Biology, Biomarkers
Zhang et al. (2026) [102]	Developed an EMT-based three-gene prognostic signature for metastatic recurrence risk stratification in PCa through WGCNA-integrated multi-omics analysis. WGCNA applied to GSE116918 (n = 248) identified key co-expression modules from 1087 EMT-related genes; consensus ML screening (91 algorithm combinations) selected INHBA, FAP, and ITGBL1 as a three-gene risk signature predictive of metastasis-free survival (4-year AUC = 0.93), validated across TCGA-PRAD and two GEO cohorts.	Tumor Biology, Biomarkers
Zhang et al. (2026) [103]	Characterized the proteomic landscape of Chinese familial PCa through integrated WGCNA and STRING-based PPI network analysis to identify module-specific hub proteins distinguishing familial from sporadic disease. WGCNA applied to DIA-based quantitative proteomic data from 99 familial and 30 sporadic PCa tumors identified three DEP-enriched modules (turquoise, black, and blue); PPI Network Topology Analysis via cytoHubba identified ribosomal hub proteins RPS3 and RPL4 (familial turquoise module), cytoskeletal proteins TLN1 and ACTN1 (familial black module), and spliceosome component SNRPD1 (sporadic blue module) as key differential regulators of familial PCa.	Tumor Biology, Novel Therapeutics

Table 5. *Cont.*

Study	Summary	Research Focus
Rafeletou et al. (2026) [104]	Developed a patient-specific biological network framework to identify ZNF268 as a master regulator of rapid progression in clinically low-risk PCa using topological network analysis. Weighted graph-based feature selection applied to TCGA-PRAD (n = 498) encoded multi-omics data into patient-specific networks; topological NTA quantified ZNF268 promoter hypermethylation as a co-expression Rewiring Score independently associated with progression-free survival (HR = 2.79) and validated for biochemical recurrence in two external cohorts.	Tumor Biology
Nisar et al. (2026) [105]	Identified therapeutic targets and candidate repurposed drugs for prostate adenocarcinoma metastasis through integrated WGCNA and PPI network analysis. WGCNA applied to four GEO datasets (GSE8511, GSE3325, GSE27616, and GSE6919) identified co-expression modules, with PPI network analysis via MCODE and CytoHubba in Cytoscape identifying ACTA2, MYLK, and CNN1 as hub genes; Connectivity Map screening followed by molecular docking and MM-GBSA identified Prunetin, Ofloxacin, and ALW-II-49-7 as candidate drugs with favorable binding efficiency against these targets.	Tumor Biology, Novel Therapeutics
Wang et al. (2025) [106]	Identified COMP as a dual biomarker for PCa diagnosis and biochemical recurrence risk prediction through WGCNA-integrated multi-algorithm machine learning. WGCNA applied to GSE116918 identified 16 BCR-related target genes across 11 co-expression modules; multiple machine learning combinations identified COMP as the dominant BCR regulatory gene, validated as both a diagnostic and recurrence-predictive biomarker by in vitro knockdown experiments and in vivo xenograft modeling.	Tumor Biology, Biomarkers
Pashaei et al. (2025) [107]	Developed DiCE (Differential Centrality-Ensemble), a novel NTA-based approach combining differential expression profiling with network centrality analysis to identify key driver genes in PCa independent of prior disease annotations. DiCE identified candidate genes using an information gain filter, reconstructed condition-specific weighted PPI networks, and ranked genes by network centrality measures; validated on PCa datasets, it identified genes significantly over-represented in key cancer pathways and cancer fitness genes that strongly correlated with disease-free survival.	Tumor Biology, Novel Therapeutics
Xia et al. (2025) [108]	Identified DKK3, SNAI2, WIF1, and FOXA1 as core hub genes in PCa through integrated STRING PPI network construction, MCODE module analysis, and machine learning. STRING PPI network analysis of 339 common DEGs from GEO (GSE69223 and GSE46602) and TCGA-PRAD identified key modules via MCODE and MNC algorithms; LASSO and random forest algorithms refined these to four core genes, with DKK3 and WIF1 confirmed as significantly downregulated tumor suppressors in PCa whose loss correlated with elevated PSA levels, higher Gleason scores, and impaired Wnt/TGF-β pathway regulation.	Tumor Biology, Biomarkers

Table 5. *Cont.*

Study	Summary	Research Focus
Lu et al. (2025) [109]	Identified miR-136-3p as a key cross-source biomarker for PCa and constructed a miRNA–mRNA regulatory network through integrated bioinformatics and experimental analysis. PPI network analysis (STRING/Cytoscape) of 948 target genes of two overlapping downregulated miRNAs (miR-146a-3p and miR-136-3p) from serum (GSE112264; n = 1591) and TCGA (n = 497 cancer, 52 normal) identified four hub genes—NSF, HIST2H2BE, IGF2R, and CADM1—with GO/KEGG enrichment implicating mTOR signaling; experimental validation confirmed miR-136-3p as consistently downregulated in both serum and tissue.	Tumor Biology, Biomarkers
Wang et al. (2026) [110]	Identified ANO5 as a PCa-specific key gene with protective clinical significance through integrated WGCNA, Cox regression, and multiple machine learning analysis. WGCNA identified a turquoise module, from which SVM-RFE, random forest, and Cox regression analyses converged on ANO5 and ACTG2 as key genes; higher ANO5 expression correlated with favorable clinical outcomes, and overexpression of ANO5 in PCa cells confirmed its inhibitory role in tumor cell migration and invasion, with a plsRcox model incorporating ANO4, 5, 7, and 8 further validated as a prognostic signature.	Tumor Biology, Biomarkers, Novel Therapeutics
Taylor et al. (2026) [111]	Evaluated the spatial robustness of four PCa prognostic biomarker panels (Oncotype DX, Prolaris, Decipher, and ProClass) using spatial WGCNA and global Moran's I analysis applied to publicly available Visium spatial transcriptomics data across 37 tissue sections from two patients with high-grade localized PCa. Spatial WGCNA identified co-expression modules closely aligned to histopathological annotations; six Oncotype DX genes (KLK2, AZGP1, TPM2, GSN, FLNC, and COL1A1) and two Decipher genes (ANO7 and MYBPC1) were consistently spatially variable (global Moran's I > 0.1) and predominantly localized to stromal networks, whilst Prolaris cell-cycle genes exhibited weak spatially limited expression, and ProClass genes showed insufficient abundance for robust spatial analysis.	Tumor Biology, Biomarkers
Yu et al. (2026) [112]	Elucidated the anti-PCa mechanism of 20(S)-Rg3 using integrated network pharmacology, WGCNA-based bioinformatics, and molecular dynamics simulation, identifying AURKA and CDK1 as core therapeutic targets. Network pharmacology analysis of four drug-target databases identified 451 candidate Rg3 targets, cross-referenced with 2906 WGCNA module genes, 14,886 PCa-related GeneCards genes, and 4515 DepMap essential genes to yield 22 common targets enriched in cell-cycle regulation; 400 ns molecular dynamics simulations confirmed stable binding to AURKA (−33.47 kcal/mol) and CDK1 (−33.51 kcal/mol), supporting selective inhibition of cell-cycle progression in PCa.	Tumor Biology, Novel Therapeutics

Table 6. Multi-Omics Pathway Analysis as primary analysis systems in PCa research.

Study	Summary	Research Focus
Salji et al. (2022) [113]	Investigated the metabolic and functional role of N-acetylaspartate (NAA) and N-acetylaspartylglutamate (NAAG) accumulation in murine models of castration-resistant prostate cancer. MOPA integrated metabolomic and transcriptomic layers to identify functional connections between metabolite accumulation and downstream CRPC-specific signaling, revealing that NAA accumulation drives acetyl-CoA production for sphingolipid synthesis and aspartate/glutamate for nucleotide production, supporting a proliferative role.	Tumor Biology, Novel Therapeutics
Zheng et al. (2023) [114]	Identified molecular subtypes related to cancer stemness in PCa and evaluated their prognostic and therapeutic significance. MOPA integrated stemness-related omics features into pathway-level networks, defining three stemness subtypes (LS, MS, and HS) with distinct pathway profiles and clinical outcomes; a 9-gene stemness predictor was developed and validated to classify patients into these subtypes.	Biomarkers, Novel Therapeutics
He et al. (2025) [115]	Developed a Comprehensive Machine Learning Histone Modification Score (CMLHMS) for PCa risk stratification through MOPA-based GSVA pathway scoring of 122 histone modification gene sets across TCGA-PRAD, MSKCC, and GSE70770 cohorts. MOPA integrated with 10 machine learning algorithms defined two risk groups: high-CMLHMS patients with elevated proliferative and metabolic pathway activity and a CRPC-prone phenotype sensitive to PI3K/EGFR inhibitors and low-CMLHMS patients with stress-adaptive and immune-regulatory profiles sensitive to Paclitaxel/Gemcitabine.	Biomarkers, Novel Therapeutics
Zhao et al. (2025) [116]	Introduced MODA, a graph convolutional network-based multi-omics data analysis framework that addresses integration challenges posed by heterogeneous omics data complexity and sparsity of prior knowledge networks. MODA integrated multi-omics datasets using high data utilization efficiency and low computational cost, with validation in population samples and in vitro PCa experiments identifying carnitine and palmitoylcarnitine, regulated by BBOX1, as key drivers of PCa progression.	Tumor Biology
Li et al. (2025) [117]	Established three sensory perception-associated molecular subtypes (CS1–CS3) in PCa and linked CS1 chemoresistance to immune microenvironment reprogramming via TNF–CCL20 signaling. MOPA integrated sensory perception-linked mRNAs and lncRNAs from TCGA and scRNA-seq data to define these subtypes; validated biomarkers in patient tissues and serum identified the TNF–CCL20 axis as the central mediator of immunosuppressive signaling and chemoresistance in CS1.	Tumor Biology, Biomarkers

Table 6. *Cont.*

Study	Summary	Research Focus
Krossa et al. (2025) [118]	Applied spatially resolved multi-omics integration to 1588 PCa patients to identify molecular stratifiers of aggressive disease and characterize the activity of individual cancer-driver pathways. MOPA identified an APC (aggressive PCa) gene expression signature predictive of relapse and metastasis and a CEG (chemokine-enriched-gland) signature in non-cancerous prostatic glands characterized by upregulated pro-inflammatory chemokines, club-like cell enrichment, and reduced citrate and zinc levels.	Tumor Biology, Biomarkers
Pedersen et al. (2026) [119]	Applied unsupervised multi-omics factor analysis (MOFA) to integrate DNA methylation, gene expression, and metabolic profiles from 57 patients (280 samples), characterizing the biological landscape of normal, malignant, and adjacent prostate tissue. MOFA identified molecular signatures with significant predictive value for disease recurrence, validated in the TCGA cohort; co-enrichment of SP1 and CTCFL binding regions among the identified factors linked epigenetic regulation to metabolic reprogramming in PCa.	Tumor Biology, Biomarkers

Table 7. Pathway Activity Inference analysis (including Gene Set Variation Analysis (GSVA), Virtual Inference of Protein-activity by Enriched Regulon Analysis (VIPER), and Pathway Representation and Analysis by Direct Reference on Graphical Models (PARADIGM)) as primary analysis systems in PCa research.

Study	Summary	Research Focus
Belair et al. (2015) [120]	Investigated the role of DGCR8-mediated microRNA biogenesis in PCa progression following PTEN loss, using a Pten-knockout mouse model with conditional Dgcr8 deletion and small RNA sequencing. PARADIGM was applied as a supporting bioinformatic tool to 334 TCGA-PRAD samples, integrating copy number variation and mRNA expression data to infer AKT2 integrated pathway levels, revealing a positive correlation between DGCR8 expression and AKT2 pathway activity and implicating DGCR8 as a driver of PCa progression in PTEN-deficient tumors.	Tumor Biology, Novel Therapeutics
Drake et al. (2016) [28]	Investigated dominant signaling pathways amenable to novel targeted therapies, used in isolation or combined with androgen inhibition, in castration-resistant prostate cancer (CRPC). VIPER inferred transcriptional and kinase activity from phosphoproteomic and transcriptomic vectors, identifying consistent patient-specific network activities across metastatic sites, supporting personalized therapeutic targeting in CRPC.	Tumor Biology, Novel Therapeutics
Wang and Yang (2020) [121]	Developed a WGCNA-derived, LASSO Cox 3-gene prognostic model (CDC45, ESPL1, and RAD54L) linked to Gleason Grade Group to predict biochemical recurrence in PCa. GSVA was applied as a supporting tool to score pathway activity between risk groups, identifying enrichment of G2M checkpoint, MYC targets, and E2F target pathways in the high-risk group, consistent with cell-cycle dysregulation as a driver of poor prognosis.	Biomarkers

Table 7. *Cont.*

Study	Summary	Research Focus
Hu et al. (2022) [122]	Developed a consensus clustering-derived, LASSO Cox 8-gene pyroptosis-related gene signature to predict biochemical recurrence in PCa using TCGA and GEO datasets. GSVA was applied as a supporting tool to score KEGG pathway activity between the pre-defined pyroptosis clusters, with cluster 2 showing differential enrichment in focal adhesion and ECM receptor interaction pathways, revealing distinct biological landscapes underpinning the prognostic subtypes.	Biomarkers
Fan et al. (2022) [123]	Developed a consensus clustering-derived, LASSO Cox 13-gene prognostic model based on androgen biosynthesis and catabolism pathways to predict biochemical recurrence in PCa. GSVA was applied as a supporting tool to score pathway activity between risk groups, identifying differential enrichment of the CDK-RB-E2F axis, G2M checkpoint, and KRAS signaling pathways in the high-risk group, with BIRC5 and RHOC identified as potential therapeutic targets.	Biomarkers, Novel Therapeutics
Liu et al. (2022) [124]	Developed a random forest and Cox regression-derived 9-gene cell-cycle-related gene risk score to predict prognosis and characterize the molecular landscape of PCa. GSVA was applied as a supporting tool to characterize cell-cycle pathway enrichment between PRAD and normal tissues, while CIBERSORT independently quantified immune cell infiltration, identifying increased M2 macrophage and Treg abundance in high-risk tumors and implicating cell-cycle dysregulation in immune evasion.	Tumor Biology, Biomarkers
Westbrook et al. (2022) [125]	Investigated the influence of enzalutamide on prostate cancer tumor biology and the mechanisms by which treatment may drive progression to castration-resistant disease. VIPER inferred AR transcriptional activity and compared transcription factor profiles in patients shifting to AR-independent signaling, identifying loss of AR activity and gain of E2F1 as predictors of lineage plasticity in enzalutamide-treated patients, supporting E2F1 as a therapeutic target.	Tumor Biology, Biomarkers, Novel Therapeutics
Wang et al. (2023) [126]	Evaluated SRXN1 as a potential prognostic biomarker for radiotherapy response in prostate cancer, examining its relationship with oxidative stress and DNA damage biology. Pathway Activity Inference analysis via GSVA scored DNA damage response pathways to link tumor states with SRXN1 expression and radiotherapy efficacy, finding PC3 prostate cancer cells to be radiotherapy-sensitive with elevated DNA damage, implicating SRXN1 in oxidative stress-mediated radioresistance.	Biomarkers
Xin et al. (2023) [127]	Investigated how TME heterogeneity, particularly immunosuppression, contributes to lymph-node metastasis in PCa. GSVA identified significant upregulation of MYC and oxidative phosphorylation pathways in luminal 1 cells from metastatic lymph nodes, implicating MYC-driven orchestration of an immunosuppressive TME as a key mechanism of PCa lymph-node dissemination.	Tumor Biology

Table 7. *Cont.*

Study	Summary	Research Focus
Baker et al. (2025) [128]	Investigated the functional role of Rac1 in PCa progression using CRISPR/Cas9 knockout, unbiased RNAi screening, and immunohistochemistry of a tissue microarray. PARADIGM was applied as a supporting bioinformatic tool to infer Rac1 pathway activity across 488 TCGA-PRAD samples, with Pearson correlation identifying VAV2 as the most strongly associated guanine nucleotide exchange factor, implicating the Rac1–VAV2 axis as a novel therapeutic target in PCa.	Biomarkers, Novel Therapeutics
Kumaraswamy et al. (2025) [129]	Characterized the transcriptional basis of enzalutamide extreme non-response (ENR) to identify molecular drivers of primary treatment resistance in metastatic castration-resistant prostate cancer. VIPER inferred master transcription factor and kinase activity in ENR versus long-term responder tumors, identifying E2F4, FOXM1, E2F1, and JUN as the most activated transcription factors and CDK2 as the top activated kinase in ENR patients, functionally validated by CDK2 suppression restoring treatment sensitivity.	Tumor Biology, Biomarkers, Novel Therapeutics
Hakkola et al. (2026) [130]	Investigated how AR inhibition rewires transcription factor regulatory programs to engage a SOX4-driven mechanism of enzalutamide resistance in PCa. GSVA scored SOX4-linked program activity across clinical CRPC bulk RNA-seq cohorts, demonstrating that elevated SOX4 program scores stratified patient survival in enzalutamide-treated patients and implicating the PTEN–PI3K/AKT–SOX4 axis as a driver of AR-independent therapeutic resistance.	Tumor Biology
Zhai et al. (2026) [131]	Investigated how TCF3 loss disrupts tumor-intrinsic interferon competence to simultaneously drive PCa progression and immune evasion. GSVA profiled Hallmark pathway activity across multiple independent clinical cohorts, demonstrating that TCF3 loss consistently downregulated interferon-α/γ response programs whilst upregulating MYC-target and PI3K–AKT–mTOR pathway activity, identifying TCF3 as a transcriptional gatekeeper of immune surveillance in PCa.	Tumor Biology
Hu et al. (2026) [132]	Evaluated whether AR transcriptional activity in human cancers is linked to tumor immune infiltration and response to immunotherapeutic agents across cancer types and sexes. VIPER inferred AR transcriptional activity using a network-based approach across 33 TCGA cancer types, identifying the highest AR activity in prostate adenocarcinoma with an inverse correlation to leukocyte abundance and IFN-γ signaling, supporting AR as a pan-cancer driver of immune evasion.	Tumor Biology, Biomarkers

Framework Proposal: Alignment of Datasets, Research Objectives, and Bioinformatic Techniques (See Appendix C for Dataset Details)

The following sections present a principled mapping of 16 major PCa research datasets to three overarching research objectives (Tumor Biology, Biomarkers, and Novel Therapies) and propose suitable bioinformatic analytical techniques for each dataset group. Figure 1 illustrates the overall mapping framework. Table 8 is a summary of bioinformatic technique selection across PCa dataset groups and research categories. Although not identified by systematic review, these datasets have been chosen to represent the breadth of clinical research, dataset types, and disease states. The datasets are discussed below in categories

relating to epidemiological cohorts, clinical and prevention trials, specialized intervention cohorts, molecular profiling cohorts, and metastatic and advanced disease cohorts.

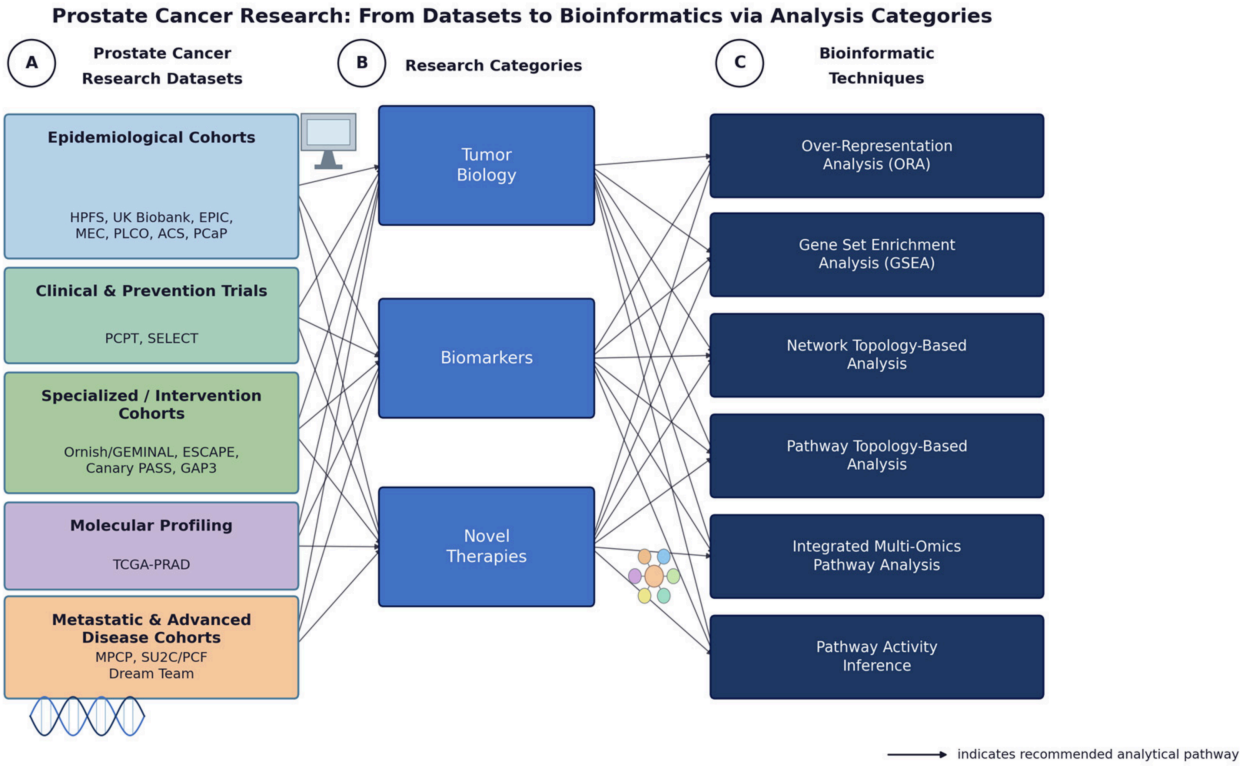


Figure 1. Mapping of 16 major PCa research datasets across three research domains (Tumor Biology, Biomarkers, and Novel Therapies) and six bioinformatic analytical techniques. Arrows flow strictly left to right: dataset group → research category → bioinformatic technique.

Epidemiological Cohorts (including HPFS [133]; UK Biobank [134]; European Prospective Investigation into Cancer and Nutrition (EPIC) [135]; Multiethnic Cohort (MEC) [136]; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [137]; American Cancer Society Cancer Prevention Study-II (ACS CPS-II Nutritional Cohort) [138]; North Carolina–Louisiana Prostate Cancer Project (PCaP) [139]): These seven cohorts capture population-level data linking environmental exposures, lifestyle factors, germline genetics, and ancestry to PCa incidence and progression [140–142]. The UK Biobank links germline variants to electronic health records; HPFS and EPIC contribute prospective lifestyle and dietary data; MEC and PCaP provide multi-ethnic and racial-disparity insights; PLCO and ACS CPS-II Nutritional Cohort offer longitudinal PSA dynamics and pre-diagnostic biomarker linkage, supporting biomarker discovery via GWAS and TWAS [141–143]. These characteristics make them suited to the investigation of tumor biology e.g., linking environmental exposures or racial disparities to PCa oncogenesis as well as being the primary resource for discovering and validating biomarkers.

The recommended bioinformatic techniques include the following:

- Over-Representation Analysis (ORA): Reduces large GWAS-derived gene lists from PLCO and HPFS into interpretable biological themes (e.g., androgen signaling and DNA repair) [143].
- Gene Set Enrichment Analysis (GSEA): Detects coordinated pathway-wide transcriptional shifts across transcriptomic data from HPFS prostate tissue where effect sizes are small and widely distributed [50,56].

- Individual-level Multi-Omics Pathway Analysis (IMOPA): Integrates pQTLs, eQTLs, and expression data from the UK Biobank to identify causal germline risk variants and tumor initiation mechanisms [141,143].

Clinical and Prevention Trials (including Prostate Cancer Prevention Trial (PCPT) [144]; Selenium and Vitamin E Cancer Prevention Trial (SELECT) [145]): The PCPT and SELECT are randomized controlled trials collecting matched pre- and post-intervention biospecimens [144–151]. The PCPT evaluates finasteride (5α-reductase inhibition), demonstrating that finasteride-induced prostate volume reduction introduces a detection bias into biopsy-based cancer diagnosis rates [147]. SELECT examines selenium and vitamin E supplementation, providing insight into micronutrient-based molecular signatures and their influence on cancer signaling pathways [145,148]. Both trials collected biospecimens, generating matched pre- and post-intervention samples that are ideal for identifying predictive biomarkers. They are also specifically designed to evaluate the biological impact of pharmaceutical or nutritional interventions at the tissue level.

The recommended bioinformatic techniques include the following:

- Gene Set Enrichment Analysis (GSEA): Evaluates the whole ranked gene list and can therefore detect modest, coordinated pathway-level transcriptional shifts, such as those that might be expected after finasteride or supplementation, that a threshold-based ORA may miss [15]; head-to-head benchmarks of GSEA and ORA are context-dependent and, in some prostate-cancer datasets, have favored gene-list methods [149]; this recommendation is therefore a methodological rationale rather than demonstrated superiority [150].
- Pathway Topology-Based Analysis (PTA): Identifies where within a signaling cascade each intervention acts, providing positional specificity important for therapeutic discovery [17].
- Pathway Activity Inference (PAI): Translates aggregate transcriptomic changes into patient-level pathway activity scores, facilitating identification of biological responders to each intervention.

Specialized and Intervention Cohorts (including Ornish/GEMINAL (intensive lifestyle intervention with paired tissue biopsies) [151]; ESCAPE (Effect of Sulforaphane on prostate CAncer PrEvention; glucoraphanin-rich broccoli dietary intervention) [152]; Canary Prostate Active Surveillance Study (PASS) [153]; Movember Global Action Plan Prostate Cancer Active Surveillance (GAP3) [154]): Ornish/GEMINAL provides paired prostate needle biopsies taken before and 3 months after an intensive nutrition and lifestyle intervention in 30 men with low-risk PCa, in which transcriptome-wide profiling detected changes in prostate gene expression, predominantly in histologically normal tissue [151]. ESCAPE was a 12-month, randomized, double-blind, three-arm trial in 49 men on active surveillance, in which weekly broccoli soup containing standard, approximately 3-fold or approximately 7-fold glucoraphanin was given, and paired prostate biopsies were profiled by RNA sequencing (primary outcome) and tissue metabolomics (secondary outcome) [152]. PASS and GAP3 follow active surveillance patients longitudinally, enabling study of indolent-to-aggressive progression and characterization of early intervention targets, although the latter has limited genomic characterization [153,155]. These cohorts are uniquely valuable for studying the biology of low-risk and indolent disease and the molecular mechanisms underlying disease progression. By characterizing the molecular triggers of progression in active surveillance cohorts (PASS and GAP3), researchers can identify early intervention targets. In ESCAPE, non-neoplastic prostate tissue in the control arm showed increased the expression of potentially oncogenic pathways (including inflammatory response and epithelial–mesenchymal transition) over 12 months, and this was attenuated in a dose-dependent manner by glucoraphanin-rich broccoli, with no significant gene expression

change in the highest-dose arm [152]. These findings are hypothesis-generating because the trial was small and not powered for clinical progression; the intervention was dietary, so ESCAPE provides no evidence on the effects of exercise [152]. Ornish/GEMINAL, a single-arm pilot study, reported changes in the expression of genes involved in processes relevant to tumorigenesis (protein metabolism and modification, intracellular protein traffic, and protein phosphorylation), providing hypothesis-generating support for studying combined lifestyle- and pharmacological-based therapeutic strategies [151].

The recommended bioinformatic techniques include the following:

- Gene Set Enrichment Analysis (GSEA): Paired longitudinal transcriptomic analysis of Ornish/GEMINAL (paired differential expression followed by pathway-level enrichment testing) can identify pathway changes induced by the intervention within the same individuals, which cross-sectional analyses cannot capture [152]; this is a single-omics analysis.
- Network Topology-Based Analysis (NTA): WGCNA has the potential to identify hub genes and co-expression modules underlying indolent-to-aggressive progression in PASS and GAP3 to identify novel therapeutic targets, but according to our literature search, published application of WGCNA to these cohorts specifically has not yet been performed [95].
- Pathway Activity Inference (PAI): Quantifies patient-level pathway activation across longitudinal timepoints, providing biological measures of dietary and lifestyle intervention response [156].
- Individual-level Multi-Omics Pathway Analysis (IMOPA): Applicable where two or more omics layers are available from the same participants; GEMINAL [153] provides a transcriptomic layer alone, so IMOPA is recommended when additional matched omics layers (e.g., DNA methylation or proteomics) become available [142,151].

Molecular Profiling (The Cancer Genome Atlas Prostate Adenocarcinoma (TCGA-PRAD) [157]): TCGA-PRAD is the most comprehensive publicly available multi-omics PCa resource, encompassing genomics, epigenomics, transcriptomics, proteomics, and clinical annotation from ~500 patients with predominantly localized PCa [157–163]. It defines molecular subtypes (e.g., PMOC), characterizes somatic alterations (ETS fusions, SPOP, TP53, and CDK12 mutations), identifies multi-gene prognostic signatures for biochemical recurrence and metastasis, and supports immunotherapeutic target discovery and AR signaling inhibitor sensitivity prediction [156]. This makes TCGA-PRAD an effective dataset for studying all three research objectives: Tumor Biology, Biomarkers, and Novel Therapies.

The recommended bioinformatic techniques include the following:

- Individual-level Multi-Omics Pathway Analysis (IMOPA)—Primary: Integrates mRNA, miRNA, DNA methylation, somatic mutations, CNAs, and RPPA data via SNF or MOVICS to capture full molecular heterogeneity and predict clinical outcomes [60,101].
- Pathway Topology-Based Analysis (PTA): Accounts for pathway topology and regulatory feedback loops, revealing mechanistic differences between, e.g., upstream PIK3CA activation and intermediate PTEN loss [17].
- Pathway Activity Inference (PAI): Generates individualized AR Signaling Activity scores predicting AR signaling inhibitor response, contributing to precision oncology in PCa [156].
- Network Topology-Based Analysis (NTA): WGCNA identifies co-expression hub genes as prognostic biomarkers with improved accuracy when compared to individual gene signatures [95,99].

Metastatic and Advanced Disease Cohorts, Stage IV mCRPC—SU2C/PCF Dream Team Cohort (444 tumors from 429 patients; WES; RNA-seq in 332 tumors from 323 pa-

tients; [164]); MPCP Count Me In Cohort (N = 706; 333 with molecular data; WES of tumour tissue and cfDNA, ULP-WGS of cfDNA; no transcriptomic data; [165]): The SU2C/PCF Dream Team prospective multi-institutional study provides the most comprehensive genomic characterization of mCRPC to date, identifying AR enhancer amplifications, DNA repair defects (CDK12 and BRCA2), and transcriptomic subtypes of castration resistance, enabling precision oncology research in metastatic prostate cancer [164]. The MPCP Count Me In patient-partnered cohort captures tumor and circulating cell-free DNA from patients across the US and Canada, supporting mutation and copy-number analyses, including the detection of AR amplification by ultra-low-pass whole-genome sequencing of cfDNA, with serial blood sampling under way to enable future longitudinal analysis. No transcriptomic data are available for this cohort [165].

Table 8. Summary of bioinformatic technique selection across PCa dataset groups and research categories. ✓ = recommended; (✓) = applicable in specific contexts. ORA = Over-Representation Analysis; GSEA = Gene Set Enrichment Analysis; NTA = Network Topology-Based Analysis; PTA = Pathway Topology-Based Analysis; IMOPA = Individual-level Multi-Omics Pathway Analysis; PAI = Pathway Activity Inference; highlighted rows denote newly added metastatic and advanced disease cohorts (MPCP = Metastatic Prostate Cancer Project; SU2C/PCF = Stand Up To Cancer/Prostate Cancer Foundation Dream Team). Blank cells indicate that the technique is not recommended for the specified research category in that dataset group, owing to dataset molecular depth, expected effect size, or absence of supporting evidence; historically applied methods may differ from recommended methods (see individual table entries in Tables 2–7 for applied methods). Within "Metastatic and Advanced Disease Cohorts", expression-based techniques (GSEA, NTA, and PAI) and IMOPA apply to the SU2C/PCF cohort, for which matched whole-exome sequencing and RNA-seq data are available (RNA-seq in 332 tumors from 323 patients); the MPCP cohort (WES and cfDNA sequencing only; no transcriptomic data) supports ORA and mutation- or copy-number-based PTA only. In "Specialized Cohorts", (✓) for IMOPA indicates applicability only where two or more omics layers are available from the same participants. Table 8 represents conceptual framework guidance rather than a prescriptive or exhaustive catalogue.

Dataset Group	Research Category	ORA	GSEA	NTA	PTA	IMOPA	PAI
Epidemiological Cohorts	Tumor Biology	✓	✓			(✓)	
	Biomarkers	✓	✓			✓	
Clinical Trials	Biomarkers		✓		(✓)	(✓)	✓
	Novel Therapies		✓		✓		✓
Specialized Cohorts	Tumor Biology		(✓)	✓		(✓)	✓
	Novel Therapies			✓		(✓)	✓
TCGA-PRAD	Tumor Biology		✓	✓	✓	✓	✓
	Biomarkers		✓	✓	(✓)	✓	✓
	Novel Therapies			(✓)	✓	✓	✓
Metastatic and Advanced Disease Cohorts	Tumor Biology	(✓)	✓	✓	(✓)	✓	✓
	Biomarkers		✓	✓	(✓)	✓	✓
	Novel Therapies		✓	(✓)	✓	✓	✓

The recommended bioinformatic techniques include the following:

- Over-Representation Analysis (ORA): Detects significantly enriched pathways in differentially mutated gene sets from WES data, identifying recurrent alterations driving metastatic progression in the MPCP cohort [165].

- Gene Set Enrichment Analysis (GSEA): Identifies enriched oncogenic pathways from mCRPC transcriptomes, including AR-driven programs and neuroendocrine dedifferentiation signatures in the SU2C/PCF Dream Team cohort [164].
- Pathway Activity Inference (PAI): Infers upstream regulatory activity—including AR Signaling Activity—from mCRPC transcriptomes, supporting prediction of ARSI sensitivity and mechanisms of acquired castration resistance [164].
- Pathway Topology-Based Analysis (PTA): Maps somatic mutations and copy-number alterations to pathway network positions, identifying recurrently disrupted nodes and providing mechanistic context for tumor and ctDNA-detected alterations in the MPCP cohort [165].
- Network Topology-Based Analysis (NTA): WGCNA of the SU2C/PCF Dream Team RNA-seq data (332 tumors from 323 patients) could identify co-expression modules and hub genes associated with castration resistance and ARSI response [164]. Whether such modules predict outcomes better than individual-gene signatures has not been directly tested in the PCa studies reviewed and would require head-to-head comparison with external validation. WGCNA requires a sample-by-gene expression matrix and is therefore not recommended for the MPCP cohort, for which only WES and cfDNA sequencing data are available [165].

4. Discussion

The scoping review presented in the first part of the manuscript identified 105 papers spanning the PCa bioinformatics literature across six analytical categories (ORA, GSEA, PTA, NTA, IMOPA, and PAI). Of these, 78 studies focused on oncogenesis and tumor biology, 66 on biomarkers (diagnostic, prognostic, and predictive), and 42 on novel therapeutics. Across all six techniques, 63% of published studies had a focus on biomarker discovery, with approximately 40% each linking analytical findings to clinically actionable therapeutic targets, although for the latter, this was often referred to with speculative statements such as "potential novel therapeutic target". Translational application of these findings to prevention or treatment strategies at this stage remains limited. For example, the bioinformatically derived signatures reported across the 105 reviewed studies represent candidate biomarkers and computationally predicted therapeutic sensitivities; none has achieved formal clinical validation or regulatory approval, and conclusions are accordingly limited to the reviewed evidence. Moreover, in vitro or in vivo functional corroboration of bioinformatically derived findings was not a primary component of the reviewed studies, consistent with their computational scope, and represents a translational gap shared across all six analytical categories. This pattern may lead to a persistent translational gap with much of the published bioinformatics literature generating biological knowledge that may not readily connect to clinical practice in a meaningful way. The proposed mapping framework presented here aims to outline methodological alignments linking datasets and bioinformatics techniques to specific research objectives and to help promote collaboration between computational biologists and clinicians to close this translational gap. Several themes emerge from the analysis and proposed framework construction.

Dataset depth determines technique ceiling. The use of bioinformatic techniques that can be productively applied to a dataset is constrained by its molecular depth. Epidemiological cohorts, while offering statistical power for genetic association studies, typically provide only one or two molecular layers (e.g., germline genotype and/or transcript expression). This restricts effective analyses to ORA, GSEA, and single-omics pathway enrichment. By contrast, TCGA-PRAD's six matched molecular layers make it a dataset capable of supporting the full repertoire of techniques, including allowing IMOPA to deliver its full analytical potential.

Technique sensitivity must match effect magnitude. A consistent theme across dataset groups is the importance of matching analytical sensitivity to the expected biological effect size. In epidemiological cohorts, where risk factor associations are modest and distributed, ORA and GSEA may be appropriate in prioritizing broad pathway-level patterns over individual gene signals, depending on the study design and available molecular data. In clinical trial and intervention cohorts, where therapeutic effects are similarly distributed across pathways rather than concentrated in single genes, GSEA and PAI may be preferred over threshold-based methods. Where effects are subtle and pathway-coordinated, a threshold-based technique such as ORA may be less able to detect them than a ranked-list method such as GSEA, although comparative benchmarks are mixed and depend on the dataset and effect size [149,166]. Dataset-specific evaluation is therefore advisable.

Pathway Activity Inference as the precision medicine bridge. PAI occupies a uniquely important position in this framework: unlike ssGSEA, which also generates per-sample pathway activity scores at the gene-set level, PAI methods such as VIPER infer upstream regulatory activity—including transcription factor and kinase activity—from downstream gene expression patterns. This mechanistically distinct capacity makes PAI the direct analytical bridge between population-level molecular profiling and personalized clinical decision making, whether inferring individual AR Signaling Activity in a TCGA-PRAD patient to predict ARSI response or quantifying regulatory pathway-level change in a GEMINAL participant over a 3-month lifestyle intervention. These mechanistic inferences are hypothesis-generating and require prospective validation; the SU2C/PCF Dream Team cohort [164], which combines RNA-seq data with ARSI treatment outcomes (AR transcriptional output was assessed in 128 patients on first-line ARSI), represents an appropriate dataset for validating ARSI response predictions based on expression-derived AR Signaling Activity scores. The MPCP Count Me In cohort [165] lacks transcriptomic data and could support only DNA-based correlates, such as AR copy number in cfDNA.

Expanding this framework approach but focusing on a more clinical structure may be effectively provided by the driver-based chronic disease paradigm described by Mechanick et al. [167,168]. This model conceptualizes chronic diseases across four progressive stages: Stage 1 (risk, initiated and impelled by genetic, environmental, and behavioral/lifestyle primary drivers), Stage 2 (pre-disease, initiated and impelled by detectible pathophysiological secondary drivers), Stage 3 (disease, characterized by phenotypic changes satisfying diagnostic criteria), and Stage 4 (metastatic disease and/or complications). For future study in oncology, a bioinformatics-stage matrix has the potential to offer a clinically meaningful organizing structure for screening, case finding, diagnostic testing, preventive care, and therapeutic intervention. Specifically, secondary bioinformatic analyses of datasets similar to those presented in this scoping review along the lines of the driver based chronic disease paradigm, using PCa as an index case for cancer as a chronic disease, can lead to structured collaboration between bioinformaticians and clinicians, ensuring that analytical outputs are interpreted within clinically relevant contexts.

Strengths and Limitations

The manuscript provides a comprehensive scoping review of the use of bioinformatics in PCa research and constructs a novel framework that provides a principled guideline aiming to facilitate clinical translation of research findings. The technique recommendations in Figure 1 and Table 8 are expert-derived syntheses of the reviewed literature; they have not been benchmarked against one another or validated in independent datasets, and claims of comparative performance between techniques should be read in that light. The proposed framework is based on current best practices and the published literature

as of 2026. Methodological advances—particularly in single-cell multi-omics and spatial transcriptomics—may create new analytical paradigms that extend or revise these recommendations. Furthermore, the framework addresses pathway-level bioinformatic analyses and does not encompass machine-learning-based or deep learning approaches to biomarker discovery, which increasingly complement traditional pathway methods in large-scale studies [159]. The scoping review from which this combined analysis is derived was conducted with English-language publications only, which may have introduced a language bias and excluded relevant contributions from non-English-language literature. No formal quality assessment instrument (e.g., QUADAS-2 or the Newcastle-Ottawa Scale) was applied to the included studies, which also limits the ability to formally appraise methodological rigor. Moreover, substantial heterogeneity exists across the included studies in terms of dataset choice, analytical platforms, bioinformatic pipelines, and outcome definitions, precluding quantitative synthesis and limiting direct cross-study comparisons. Finally, the rapid pace of development in this field means that newly published methodological tools—including transformer-based genomic models and foundation models for single-cell data—were not captured in the review period.

5. Conclusions

This combined scoping review and dataset mapping framework provides a structured synthesis of the PCa bioinformatics literature alongside a principled guide for selecting appropriate analytical techniques across 16 major research datasets. The scoping review identified a substantial body of work across six analytical categories, with a clear emphasis on biomarker discovery. The mapping framework sets out the methodological alignments proposed to improve the accuracy and interpretability of analytical results from each dataset group, suggesting that technique selection should be guided by dataset molecular depth, expected biological effect size, and the specific research question being addressed. To close the persistent gap between biological discovery and clinical impact, PCa bioinformatics requires sustained collaboration between computational scientists and clinicians, deliberate prioritization of translational endpoints, and adoption of structured analytical frameworks that align dataset selection with patient-stage-specific clinical questions. Employing the same narrative and framework concept, future research that integrates clinically focused models such as the driver-based chronic disease model may provide a clinical organizing framework that maps these datasets and techniques to the progression of PCa from risk factors to advanced disease, supporting a systematic approach to evidence generation and translational research prioritization.

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Abbreviations

ACS CPS-II	American Cancer Society Cancer Prevention Study-II
ADAR1	Adenosine Deaminase RNA-Specific 1
ADT	Androgen Deprivation Therapy
AI	Artificial Intelligence
AIPC	Androgen-Independent Prostate Cancer
AKT	Protein Kinase B
AR	Androgen Receptor
ATAC-seq	Assay for Transposase-Accessible Chromatin with Sequencing
AUC	Area Under the Curve
BCR	Biochemical Recurrence
CAF	Cancer-Associated Fibroblast
CCL20	C-C Motif Chemokine Ligand 20
CDK	Cyclin-Dependent Kinase
ceRNA	Competing Endogenous RNA
CKB	Creatine Kinase B
CMLHMS	Comprehensive Machine Learning Histone Modification Score
CREB3L4	cAMP Responsive Element Binding Protein 3-Like 4
CRPC	Castration-Resistant Prostate Cancer
CSC	Cancer Stem Cell
CTSB	Cathepsin B
CXCL10	C-X-C Motif Chemokine Ligand 10
CXCR3	C-X-C Motif Chemokine Receptor 3
DAVID	Database for Annotation, Visualization, and Integrated Discovery
DEGs	Differentially Expressed Genes
DeMRGs	Differentially Expressed Methylation-Related Genes
DiCE	Differential Centrality-Ensemble
DKK3	Dickkopf WNT Signaling Pathway Inhibitor 3
DPT	Diffusion Pseudotime
E2F1	E2F Transcription Factor 1
E2F4	E2F Transcription Factor 4
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial-to-Mesenchymal Transition
ENO1	Enolase 1
ENR	Extreme Non-Response
EPIC	European Prospective Investigation into Cancer and Nutrition
ERG	ETS-Related Gene
ESCAPE	Effect of Sulforaphane on prostate CAncer PrEvention
ETV4	ETS Variant Transcription Factor 4
FABP5	Fatty Acid Binding Protein 5
FAK	Focal Adhesion Kinase
FASN	Fatty Acid Synthase
FCS	Functional Class Scoring
FDR	False Discovery Rate
FOXM1	Forkhead Box M1
GAP3	Movember Global Action Plan Prostate Cancer Active Surveillance
GEO	Gene Expression Omnibus
GO	Gene Ontology
GPX4	Glutathione Peroxidase 4

GSEA	Gene Set Enrichment Analysis
GSVA	Gene Set Variation Analysis
hdWGCNA	High-Dimensional Weighted Gene Co-expression Network Analysis
HIF-1	Hypoxia-Inducible Factor 1
HPFS	Health Professionals Follow-up Study
IFN	Interferon
IFN-α/γ	Interferon-Alpha/Gamma
IL-17	Interleukin-17
JAK-STAT	Janus Kinase–Signal Transducer and Activator of Transcription
JUN	Jun Proto-Oncogene
KEGG	Kyoto Encyclopedia of Genes and Genomes
kNN	k-Nearest Neighbor
LASSO	Least Absolute Shrinkage and Selection Operator
lncRNA	Long Non-Coding RNA
m7G	N7-Methylguanosine
MAPK	Mitogen-Activated Protein Kinase
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MDSC	Myeloid-Derived Suppressor Cell
MEC	Multiethnic Cohort
METTL1	Methyltransferase-Like 1
MODA	Multi-Omics Data Analysis
MOFA	Multi-Omics Factor Analysis
MOPA	Multi-Omics Pathway Analysis
MRG	Methylation-Related Gene
mRNA	Messenger RNA
MSigDB	Molecular Signatures Database
mTOR	Mammalian Target of Rapamycin
MYC	MYC Proto-Oncogene
NAA	N-Acetylaspartate
NAAG	N-Acetylaspartylglutamate
NES	Normalized Enrichment Score
NetGSA	Network-based Gene Set Analysis
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells
NMF	Non-negative Matrix Factorization
NTA	Network Topology Analysis
ORA	Over-Representation Analysis
PAIA	Pathway Activity Inference Analysis
PARADIGM	Pathway Representation and Analysis by Direct Reference on Graphical Models
PASS	Canary Prostate Active Surveillance Study
PCa	Prostate Cancer
PCaP	North Carolina–Louisiana Prostate Cancer Project
PCPT	Prostate Cancer Prevention Trial
PDGF	Platelet-Derived Growth Factor
PDX	Patient-Derived Xenograft
PI3K	Phosphatidylinositol 3-Kinase
PKR	Protein Kinase R
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PLK1	Polo-Like Kinase 1
PPAR	Peroxisome Proliferator-Activated Receptor
PPI	Protein–Protein Interaction
PRAD	Prostate Adenocarcinoma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRKCA	Protein Kinase C Alpha
PSA	Prostate-Specific Antigen
PSMA	Prostate-Specific Membrane Antigen
PTA	Pathway Topology Analysis
PTEN	Phosphatase and Tensin Homologue
PTGES3	Prostaglandin E Synthase 3
RAC1	Ras-Related C3 Botulinum Toxin Substrate 1
RNA-seq	RNA Sequencing
scRNA-seq	Single-Cell RNA Sequencing
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SLC	Solute Carrier

SLC45A3	Solute Carrier Family 45 Member 3
SNF	Similarity Network Fusion
SOX4	SRY-Box Transcription Factor 4
SPIA	Signaling Pathway Impact Analysis
SRXN1	Sulfiredoxin 1
ssGSEA	Single-Sample Gene Set Enrichment Analysis
STAT1	Signal Transducer and Activator of Transcription 1
SVM-RFE	Support Vector Machine-Recursive Feature Elimination
TAM	Tumor-Associated Macrophage
TCF3	Transcription Factor 3
TCGA	The Cancer Genome Atlas
TCGA-PRAD	The Cancer Genome Atlas Prostate Adenocarcinoma Dataset
TF	Transcription Factor
TGF-β	Transforming Growth Factor Beta
TME	Tumor Microenvironment
TNF	Tumor Necrosis Factor
Treg	Regulatory T Cell
TWAS	Transcriptome-Wide Association Study
TXN	Thioredoxin
U-EV	Urinary Extracellular Vesicle
VAV2	Vav Guanine Nucleotide Exchange Factor 2
VEGFα	Vascular Endothelial Growth Factor Alpha
VIPER	Virtual Inference of Protein-activity by Enriched Regulon Analysis
WDR4	WD Repeat Domain 4
WGCNA	Weighted Gene Co-expression Network Analysis
WIF1	WNT Inhibitory Factor 1
Wnt	Wingless-Type MMTV Integration Site

Appendix A

Technique	Database/Platform	Search String
Over-Representation Analysis (ORA)	Web of Science (TS)	TS = (“prostate cancer” OR “prostatic neoplasm” OR “prostate tumor*”) AND TS = (“over-representation analysis” OR “overrepresentation analysis” OR “hypergeometric test” OR “Fisher’s exact test” OR “WebGestalt” OR “Enrichr” OR “DAVID database” OR “clusterProfiler”) AND TS = (“pathway*” OR “differentially expressed genes” OR “DEG*” OR “gene ontology”) NOT TI = (“acoustic” OR “noise” OR “pollution”)
Over-Representation Analysis (ORA)	PubMed	(“Prostatic Neoplasms”[Mesh] OR “prostate cancer”[Title/Abstract] OR “prostatic cancer”[Title/Abstract]) AND (“over-representation analysis”[Title/Abstract] OR “overrepresentation analysis”[Title/Abstract] OR “ORA”[Title/Abstract] OR “hypergeometric test”[Title/Abstract] OR “Fisher’s exact test”[Title/Abstract] OR “WebGestalt”[Title/Abstract] OR “Enrichr”[Title/Abstract] OR “DAVID”[Title/Abstract] OR “clusterProfiler”[Title/Abstract]) AND (“pathway”[Title/Abstract] OR “gene ontology”[Title/Abstract] OR “GO term”[Title/Abstract]) NOT (“acoustic”[Title] OR “traffic”[Title] OR “pollution”[Title])

Technique	Database/Platform	Search String
Pathway Topology-based Analysis	PubMed	(“prostate neoplasms”[MeSH Terms] OR “prostate cancer”[Title/Abstract]) AND (“pathway topology”[Title/Abstract] OR “topology-based”[Title/Abstract] OR “topology-aware”[Title/Abstract] OR “graph-based pathway”[Title/Abstract] OR “network-based pathway”[Title/Abstract] OR “signaling pathway impact analysis”[Title/Abstract] OR “SPIA”[Title/Abstract] OR “NetGSA”[Title/Abstract] OR “topologyGSA”[Title/Abstract] OR “Clipper algorithm”[Title/Abstract] OR “pathway-express”[Title/Abstract] OR “CePa”[Title/Abstract]) NOT (“over-representation analysis”[Title])
Pathway Topology-based Analysis	Web of Science (TS)	TS = (“prostate cancer” OR “prostate neoplasm*”) AND (TS = (“pathway topology” OR “topology-based” OR “topology-aware”) OR TS = (“pathway impact score” OR “regulatory influence” OR “network structure” OR “node interaction”) OR TS = (“SPIA” OR “NetGSA” OR “topologyGSA” OR “Clipper” OR “DEGraph” OR “TAPPA” OR “PathNet”)) NOT TI = (“Over-representation”)
Gene Set Enrichment Analysis (GSEA)	PubMed	((“Gene Set Enrichment Analysis”[Title/Abstract]) OR (“GSEA”[Title])) AND (“Prostate Cancer”[Title/Abstract] OR “Prostate Neoplasms”[MeSH Terms]) NOT (“G8”[Title/Abstract] OR “Geriatric”[Title/Abstract])
Gene Set Enrichment Analysis (GSEA)	Web of Science/PubMed (mixed)	(TI = (“Gene Set Enrichment Analysis” OR “GSEA”) OR TS = (“Gene Set Enrichment Analysis” NEAR/3 “Prostate”)) AND TS = (“prostate cancer” OR “prostate adenocarcinoma”) NOT TS = (“G8” OR “Geriatric” OR “over-representation analysis”)
Individual-level Multi-Omics Pathway Analysis (IMOPA)	PubMed	(“Prostatic Neoplasms”[Mesh] OR “prostate cancer”[Title/Abstract]) AND (“Multiomics”[Mesh] OR “multi-omics”[Title/Abstract] OR “integrative omics”[Title/Abstract] OR “pan-omics”[Title/Abstract]) AND (“Pathway Analysis”[Mesh] OR “Signal Transduction”[Mesh] OR “Systems Biology”[Mesh] OR “pathway enrichment”[Title/Abstract] OR “network analysis”[Title/Abstract] OR “Similarity Network Fusion”[Title/Abstract] OR “MOFA”[Title/Abstract] OR “iCluster”[Title/Abstract]) AND (integration[Title/Abstract] OR “cross-omics”[Title/Abstract] OR “data fusion”[Title/Abstract] OR “latent factors”[Title/Abstract])
Network-based Pathway Analysis	PubMed	(“Prostatic Neoplasms”[Mesh] OR “prostate cancer”[Title/Abstract] OR “prostate carcinoma”[Title/Abstract]) AND (“protein-protein interaction”[Title/Abstract] OR “PPI network”[Title/Abstract] OR “network-based pathway”[Title/Abstract] OR “pathway network”[Title/Abstract] OR “module detection”[Title/Abstract] OR “community detection”[Title/Abstract] OR “network module”[Title/Abstract] OR “MCODE” OR “cluster analysis” OR “PPI module”) AND (“pathway”[Title/Abstract] OR “enrichment” OR “interaction network”) NOT (“over-representation analysis”[Title] OR “topology”[Title])

Technique	Database/Platform	Search String
Network-based Pathway Analysis	Web of Science (TS)	TS = (“prostate cancer” OR “prostatic neoplasm*” OR “prostate tumor*”) AND (TS = (“protein-protein interaction” OR “PPI network” OR “network-based pathway” OR “pathway network” OR “module detection” OR “community detection” OR “network module” OR “MCODE” OR “WGCNA” OR “module identification”)) AND TS = (“pathway*” OR “gene ontology” OR “enrichment”) NOT TI = (“over-representation” OR “topology-based”)
Functional Class Scoring Methods	PubMed	(“Prostatic Neoplasms”[Mesh] OR “prostate cancer”[Title/Abstract]) AND (“functional class scoring”[Title/Abstract] OR “GSVA”[Title/Abstract] OR “gene set variation analysis”[Title/Abstract] OR “ssGSEA”[Title/Abstract] OR “single-sample GSEA”[Title/Abstract] OR “PLAGE”[Title/Abstract] OR “Z-score”[Title/Abstract] OR “single-sample enrichment”) AND (“pathway”[Title/Abstract] OR “gene set” OR “enrichment score”) NOT (“over-representation analysis”[Title] OR “ORA”[Title])
Functional Class Scoring Methods	Web of Science (TS)	TS = (“prostate cancer” OR “prostate neoplasm*”) AND (TS = (“GSVA” OR “gene set variation analysis” OR “ssGSEA” OR “single-sample GSEA” OR “functional class scoring” OR “PLAGE” OR “Z-score method” OR “single sample enrichment”)) AND TS = (“pathway activity” OR “pathway*” OR “gene set”) NOT TI = (“over-representation”)
Pathway Activity Inference	PubMed	(“Prostatic Neoplasms”[Mesh] OR “prostate cancer”[Title/Abstract]) AND (“pathway activity inference”[Title/Abstract] OR “pathway activity”[Title/Abstract] OR “pathway scoring”[Title/Abstract] OR “PROGENy”[Title/Abstract] OR “DoRothEA”[Title/Abstract] OR “PARADIGM”[Title/Abstract] OR “pathway activation”[Title/Abstract] OR “transcription factor activity”[Title/Abstract] OR “regulon activity”) AND (“inference” OR “estimation” OR “scoring”)
Pathway Activity Inference	Web of Science (TS)	TS = (“prostate cancer” OR “prostatic neoplasm*”) AND (TS = (“pathway activity” OR “pathway inference” OR “pathway scoring” OR “activity estimation” OR “PROGENy” OR “DoRothEA” OR “CARNAVAL” OR “PARADIGM” OR “regulon activity” OR “transcription factor activity”)) AND TS = (“inference” OR “scoring” OR “activation”) NOT TI = (“over-representation”)

Appendix B

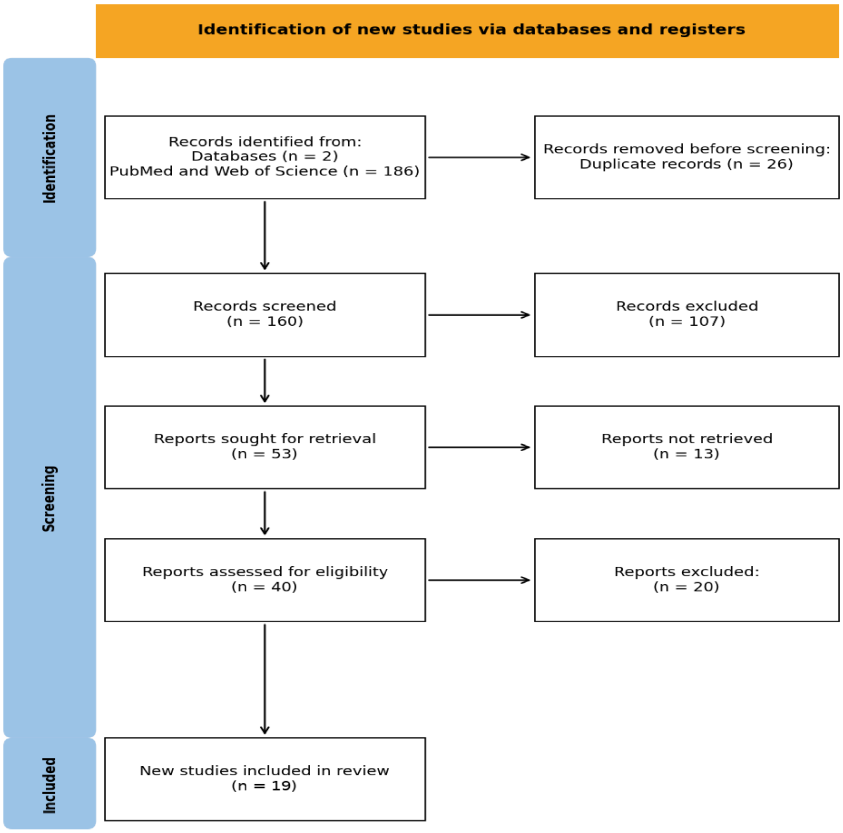


Figure A1. Over-Representation Analysis.

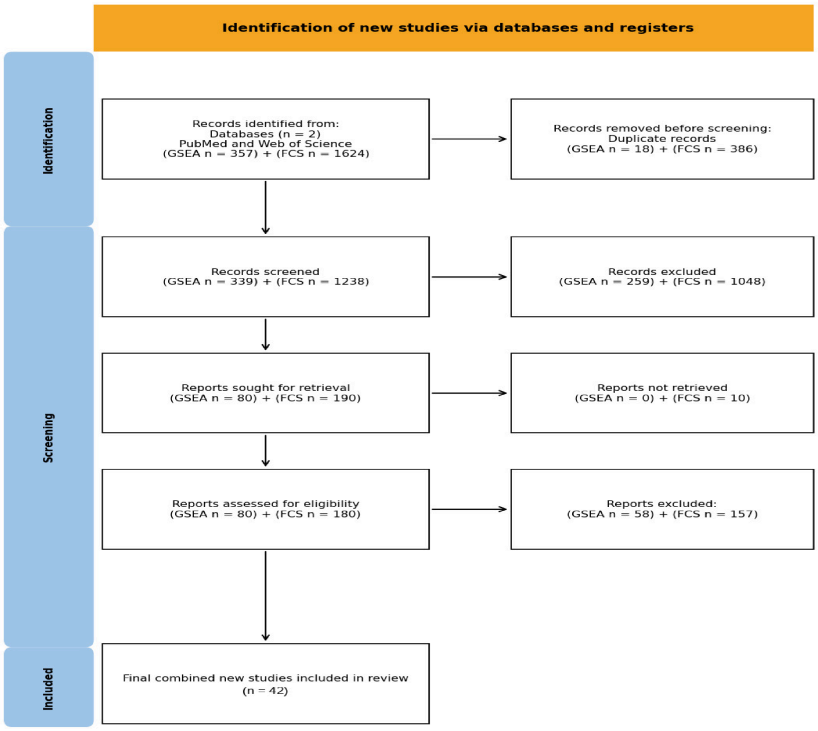


Figure A2. Gene Set Enrichment Analysis and Functional Class Scoring.

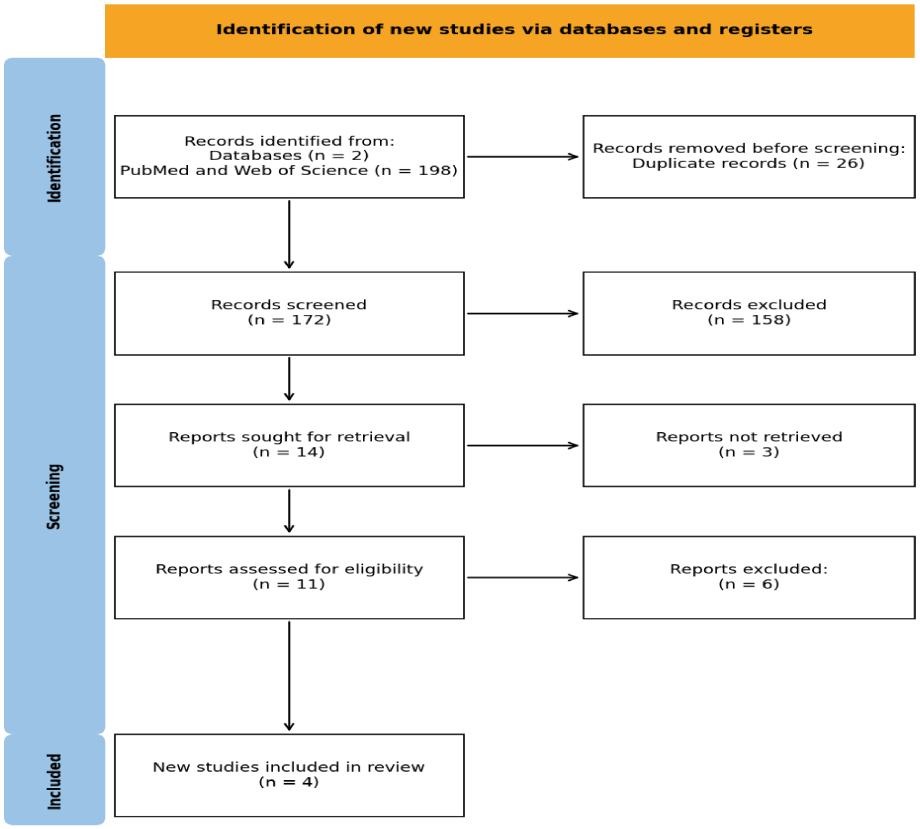


Figure A3. Pathway-based Topology Analysis.

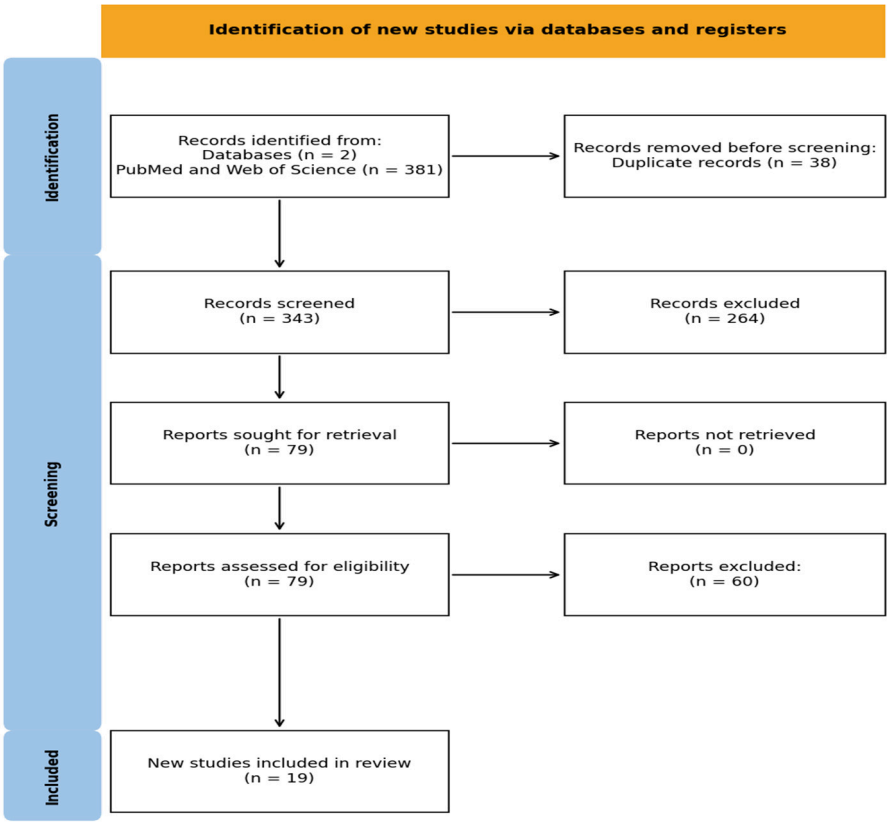


Figure A4. Network-based Topology Analysis.

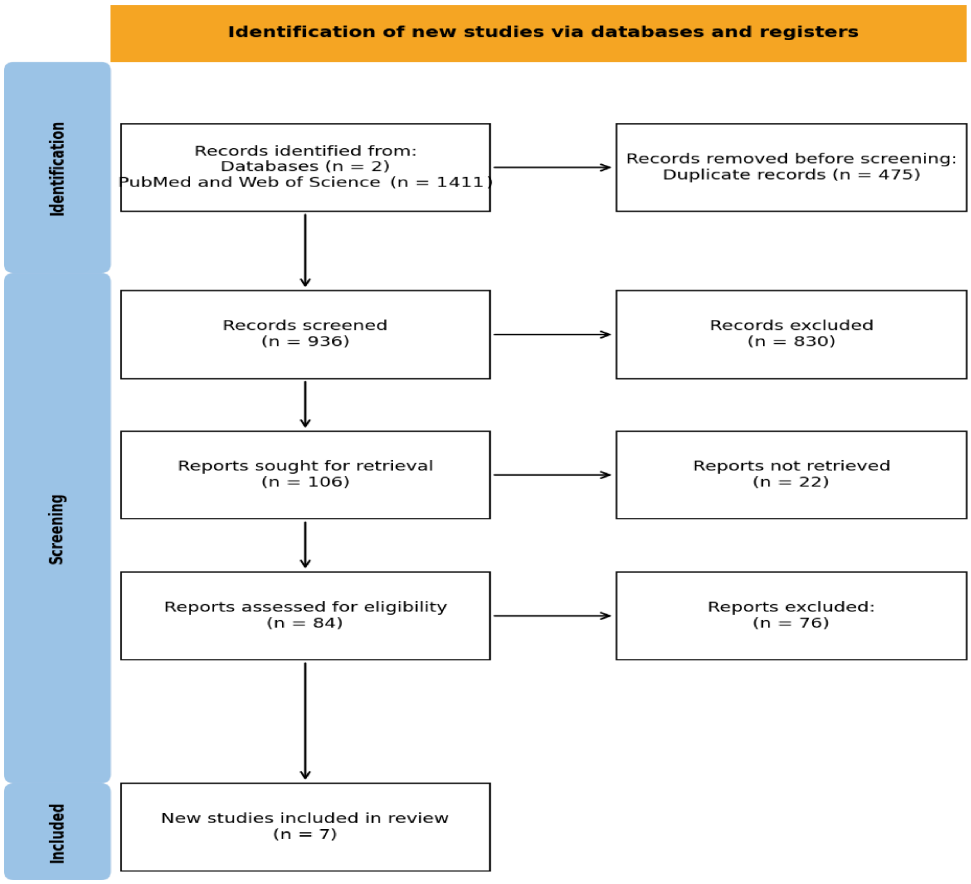


Figure A5. Individual Multi-Omics Pathway Analysis.

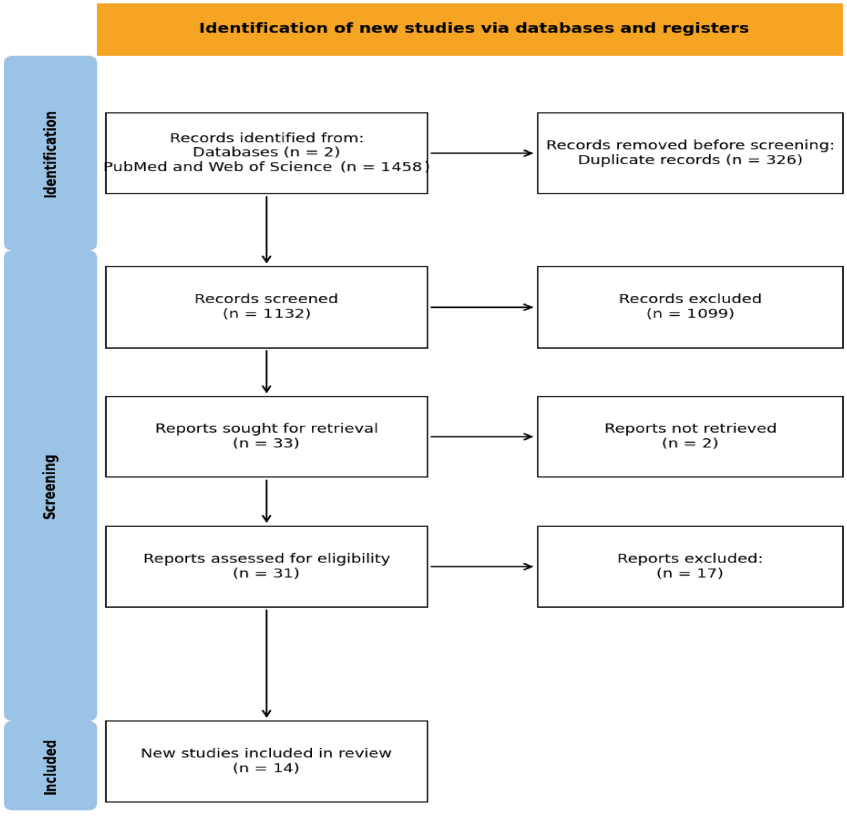


Figure A6. Pathway Activity Inference.

Appendix C

Sixteen prostate cancer datasets: country, design, and key data types (reference numbers are the same as the those in the manuscript).

Dataset	Country/ Region	Design	Key Data Types	N (Approx.)	Key Reference
UK Biobank	UK	Prospective cohort	Genetics, imaging, EHR, proteomics	500,000	[134]
HPFS	USA	Prospective cohort	Diet, lifestyle, biomarkers	51,000	[133]
EPIC	Europe	Multi-national cohort	Diet, biomarkers, genomics	521,000	[135]
MEC	USA/Hawaii	Multi-ethnic cohort	Diet, genetics, ethnicity	215,000	[136]
PLCO	USA	RCT (screening)	PSA, DRE, biomarkers	155,000	[137]
ACS CPS-II	USA	Prospective nutritional cohort	Lifestyle, mortality	1,200,000	[138]
PCaP	USA	Case-control	Ethnicity, clinical, biomarkers	3268	[139]
PCPT	USA	RCT (chemoprevention)	PSA, biopsy, finasteride	18,882	[144]
SELECT	USA/Canada	RCT (chemoprevention)	PSA, selenium/VitE, biopsy	35,533	[145]
Ornish/GEMINAL	USA	Intervention study	Gene expression	30	[151]
ESCAPE	UK	Feasibility RCT	Transcriptomics, dietary intervention (glucoraphanin-rich broccoli)	61 (49 completers)	[152]
Canary PASS	USA	Active surveillance	PSA kinetics, biopsy, genomics	1300	[153]
GAP3	International	AS registry	Clinical, biopsy; limited genomic characterization	15,000	[154]
TCGA-PRAD	USA	Retrospective molecular	WES, RNA-seq, methylation, CNV, RPPA	499	[157]
SU2C/PCF Dream Team	USA	Prospective multi-institutional	WES, RNA-seq, WGS	444	[164]
MPCP Count Me In	USA (multi-regional)	Direct-to-patient cohort	WES (tumor + cfDNA), ULP-WGS	706	[165]

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