Journal of High School Science

Evaluating gaps and future directions in prostate cancer treatment across clinical stages

Pantangi A

Submitted: August 18, 2025, Revised: version 1, October 7, 2025, version 2, October 8, 2025, version 3, October 15, 2025, version 4, December 1, 2025, version 5, December 23, 2025
Accepted: January 7, 2026

Abstract
Prostate cancer remains a major global health challenge, with outcomes closely tied to precise clinical staging and individualized, response-adapted management. Standard options across stages include radical prostatectomy and contemporary radiotherapy for localized disease, and systemic approaches for advanced disease such as androgen-deprivation therapy, chemotherapy, immunotherapy, and targeted agents. Important limitations persist in static risk models that emphasize Gleason grading and bulk Prostate-Specific Antigen (PSA). Emerging molecular tools —particularly PSA glycosylation readouts and composite PSA "glycan indices"—provide orthogonal, probabilistic information that can improve discrimination of malignant from benign conditions and offer insight into tumor biology, although these measures show broad inter-patient overlap and do not provide stage-defining cutoffs. A recent analytical study reported a glycan-based PSA score that; in an early 30-patient discovery cohort; demonstrated high specificity for distinguishing prostate cancer from Benign Prostatic Hyperplasia (BPH) under controlled experimental conditions; however, this requires validation in larger, independent populations. Other reports associate shifts toward α2,3-linked sialylation, increased core fucosylation, greater N-glycan branching, and truncated O-glycans on PSA with adverse pathological features. When interpreted alongside PSA kinetics, Grade Group, and imaging findings, glycan-aware measures may support improved risk stratification, treatment selection, and longitudinal surveillance. This review synthesizes treatments across clinical stages, integrates glycan-based biomarkers at stage-appropriate decision points within conceptual decision frameworks, and outlines research priorities spanning assay harmonization, prospective validation, artificial-intelligence-enabled decision tools, and patient-reported outcomes. A literature-derived composite glycosylation index was explicitly calculated across clinical stages using literature reported feature ranges, normalization, interpolation where necessary, and fixed heuristic weights.

Keywords
Prostate cancer, Clinical staging, Gleason score, Prostate-Specific Antigen (PSA), Glycosylation, Glycan index, Biomarkers, Androgen Deprivation Therapy (ADT), Radiation therapy, Radical prostatectomy

Amulya Pantangi, Argyle High School, 191 S Highway 377 Argyle, TX 76226, USA, amulya.pantangi@gmail.com

https://doi.org/10.64336/001c.155782

1. Introduction

In the United States, 236,659 new cases of prostate cancer were reported in 2021 (1). This persistent cancer can be deadly if not treated correctly (2). Additionally, the quality of life can be severely reduced without significant care. While receiving proper care is important, it is also essential to understand the causes of cancer. Cancer can develop due to genetic mutations that disrupt normal cell function (3). These mutations often occur during cell division and replication. As mutations accumulate, cells lose their normal regulatory controls, causing them to grow and divide uncontrollably (3). Cancer cells bypass cell cycle regulation and evade apoptosis, allowing them to continue replicating without restraint (3).

Another key characteristic of cancer cells is metastasis. Metastasis occurs when cancer cells invade surrounding tissues, break through basement membranes, and enter the bloodstream or lymphatic system (4). Additionally, cancer cells reprogram their energy metabolism (5). This metabolic shift involves switching from oxidative phosphorylation to glycolysis, even in the presence of oxygen (5). This change supports rapid cell growth and proliferation (5).

Additionally, cancer cells can evade the immune system by producing proteins that inhibit immune cell activity, preventing the immune system from recognizing them as foreign (6). As tumors grow, inflammation may develop, which can further promote cancer cell growth and progression in inflamed tissues (6). As cancer cells continue to progress, they accumulate more mutations and bypass cell cycle checkpoints, leading to increased genetic instability. This instability contributes to the development of drug resistance, allowing the cancer to progress even further (7).

1.1 Cancer stages

Understanding the stage of prostate cancer and the most effective treatment for each stage is vital. Although prostate cancer may not appear lethal in its early stages, it can become highly dangerous if not diagnosed and treated promptly. There are important differences between the stages of prostate cancer. Determining the specific stage requires an understanding of the prostate-specific antigen (PSA) test, Grade Group, and Gleason score, all of which are obtained from biopsy tissue samples (8).

The Gleason score is a system used to grade cancer cells found in a biopsy sample. It ranges from 2 to 10 but is usually reported as two separate scores in order to account for prostate cancer heterogeneity, for example, ‘3+3’ or ‘4+5’ (8). The first and the second numbers represent the most dominant or widespread pattern, followed by the next most common pattern of cancer cells found in the tissue sample. A low Gleason score indicates that the cancer cells closely resemble normal cells and are more likely to grow slowly and be less aggressive (8). The Gleason score provides the basis for the Grade Group classification. Grade Group 1 is based on a Gleason score of 6 or less, Grade Groups 2 and 3 on a score of 7, Grade Group 4 on a score of 8, and Grade Group 5 on a score of 9 or 10 (8).

Another widely used diagnostic test is the Prostate-Specific Antigen (PSA) test, which measures the level of PSA—an enzyme produced by the prostate—in the blood.

Elevated PSA levels may indicate the presence of prostate cancer (9). A Roman numeral (I–IV) indicates prostate cancer stage; higher stages reflect greater extent of disease (10).

Stage I prostate cancer is confined to the prostate, classified as Grade Group 1, with a PSA level <10. The cancer is not detectable by Digital Rectal Exam (DRE) or imaging and is often found incidentally during surgery for other prostate conditions (11).

Stage II prostate cancer remains confined to the prostate and is divided into three subgroups. **Stage IIA**: Grade Group 1, PSA levels between 10 and 20, with cancer that may or may not be detectable by DRE or imaging and may involve a small portion or more of the prostate. **Stage IIB**: Grade Group 2, PSA levels < 20, with the tumor still confined to the prostate and possibly detectable. **Stage IIC**: Grade Groups 3 or 4, PSA levels < 20, with cancer still limited to the prostate (11).

Stage III prostate cancer includes three subgroups. **Stage IIIA**: Cancer confined to the prostate, Grade Groups 1–4, with PSA levels of 20 or higher. **Stage IIIB**: Cancer has spread beyond the prostate to nearby tissues (such as the seminal vesicles) but not to lymph nodes, with any PSA level and Grade Groups 1–4. **Stage IIIC**: Cancer may be confined to or locally extended beyond the prostate, classified as Grade Group 5, with any PSA level and no lymph node involvement (11).

Stage IV prostate cancer is divided into two subgroups. **Stage IVA**: Cancer has spread to nearby lymph nodes but not to distant sites, with any PSA level and Grade Group. **Stage IVB**: Cancer has spread to distant parts of the body, such as bones or distant lymph nodes, regardless of PSA level or Grade Group (11).

1.2 Rationale for moving beyond bulk PSA concentration

Bulk PSA concentration lacks disease specificity because Benign Prostatic Hyperplasia (BPH), prostatitis, and recent procedures can elevate levels. Since PSA is a glycoprotein, tumor-associated changes in glycosyltransferase activity alter its N- and O-glycan structures in ways not captured by total PSA. Across multiple independent investigations, prostate cancer has been associated with a higher proportion of α2,3-linked relative to α2,6-linked sialic acids, increased core fucosylation, greater N-glycan branching, and a higher frequency of truncated O-glycans compared with BPH or healthy controls (12–15). These biochemical differences reflect underlying tumor biology and can be summarized in composite readouts such as a PSA glycan index, which demonstrated a strong differentiation between prostate cancer and BPH in small discovery-phase cohorts (16); however, its performance in larger and more heterogeneous populations remains unknown.

PSA glycosylation can be measured using lectin affinity capture followed by LC–MS/MS of intact glycopeptides or released glycans, or by capillary electrophoresis with laser-induced fluorescence. Conceptual trends in malignant-associated glycosylation are illustrated in Figure 1. The figure summarizes qualitative associations reported across studies rather than providing stage-specific cutoffs.

Composite measures such as the glycan index aggregate malignant-associated glycoforms—

including α2,3-sialylated N-glycans, core-fucosylated structures, and selected truncated O-glycans—and normalize them to the total PSA glycan signal (12,17). Although the direction of effect is consistent across reports, considerable interpatient variability leads to broad overlaps across clinical groups. Because of this, glycan measures should be viewed as probability-shifting indicators of tumor biology rather than deterministic markers of anatomical T, N, or M extent. Mechanistic work in glycobiology (18) supports the biological plausibility of these associations by linking changes in sialylation, fucosylation, branching, and O-glycan elongation to altered adhesion, signaling, and immune interactions.

When interpreted alongside MRI findings, PSA kinetics, and established reflex tests, glycan indices have the potential to refine pre-biopsy risk classification, support active surveillance monitoring, and guide decision-making at biochemical recurrence. Definitive clinical utility, however, requires multicenter validation using standardized analytical platforms and prespecified endpoints. The stage-wise literature ranges, representative midpoints, normalization procedure, feature weights, and the resulting composite glycosylation index values referenced conceptually in this section are provided in Supplementary Table S1(1-4) (section 18). These limitations motivate the development of a glycosylation-informed composite index capable of capturing disease progression beyond bulk PSA concentration.

1.3 Construction of a glycosylation-based composite progression index

To quantitatively integrate multiple PSA glycosylation features associated with prostate cancer progression, a composite glycosylation progression index was constructed using literature-derived data (see Section 10). Stage- and substage-specific ranges for α2,3/α2,6 sialylation, core fucosylation, N-glycan branching, truncated O-glycan abundance, and glycan heterogeneity were extracted from published glycomics studies of PSA and PSA-associated glycoproteins. These sources include mass spectrometry–based analyses and lectin profiling studies that report systematic differences between benign tissue, localized disease, and advanced prostate cancer.

For each glycosylation feature and clinical stage or substage, reported numerical ranges were recorded and a representative midpoint was calculated. In cases where direct quantitative separation between adjacent substages (e.g., IIIA–IIIC or IVA–IVB) was not available, values were estimated by linear interpolation within biologically plausible stage-bounded ranges while preserving monotonic trends reported across studies. Estimated values are explicitly indicated in Supplementary Table S1(1-4) (section 18).

1.3.1 *Data extraction and digitization procedure (Supplementary Table S1)*

Quantitative glycosylation feature ranges were extracted from published mass spectrometry– and lectin-based studies of PSA and prostate cancer–associated glycoproteins. Where numerical values were not explicitly tabulated, values were digitized from published figures. For clinical stages not directly reported, values were estimated using linear interpolation between adjacent stage anchors within biologically plausible bounds. For each stage and feature, a literature-supported range and representative midpoint were defined and used for normalization and composite index

calculation. All extracted values, interpolation steps, and source references are reported in Supplementary Table S1 (section 18).

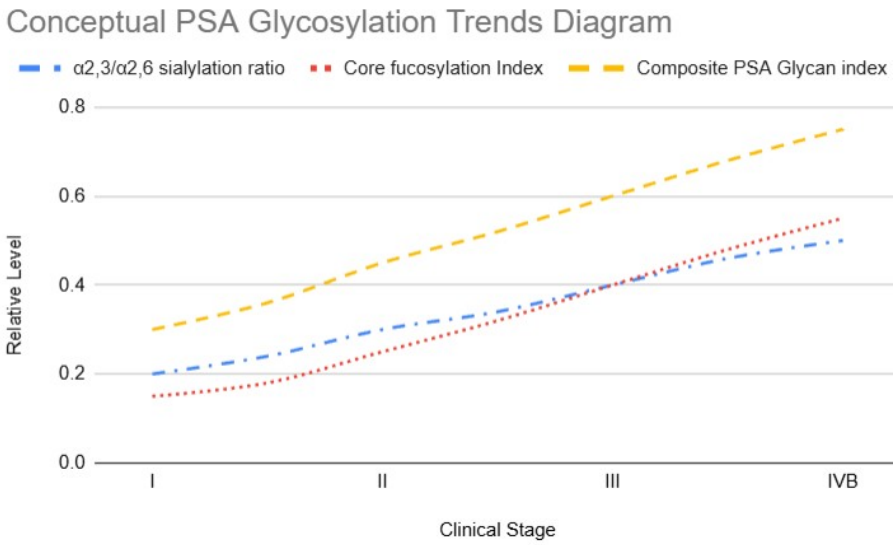

Figure 1. Stage-wise PSA glycosylation biomarker trends. This figure is a conceptual schematic based on qualitative trends reported in the literature (refs 12–17). It does *not* represent empirical, stage-stratified patient data.

Figure 1 is a schematic illustration of qualitative directional changes in α2,3/α2,6 sialylation ratio, core-fucosylated versus non-fucosylated PSA, and a composite PSA glycan index across clinical stages (I–IVB). The curves are conceptual only and are not drawn from a unified, stage-stratified empirical dataset. Instead, they summarize trend-level biological associations reported across multiple glycomics investigations (12–17), in which malignant and high-risk disease tends to show enrichment of α2,3-linked sialic acids, increased core fucosylation, and higher malignant glycoform burden. Since the underlying studies use heterogeneous populations and analytical platforms, the figure does not imply precise stage-specific cutoffs or non-overlapping distributions; it is intended solely to depict qualitative trends in PSA glycosylation with increasing aggressiveness. Stage IVB is included to reflect metastatic disease biology and is not intended to imply linear continuity with localized stages.

2. Effective therapeutic interventions in the early stages of prostate cancer

The differences between the stages of prostate cancer are significant, and the effectiveness of treatments can vary depending on the stage. In both Stage I and Stage II, the cancer is considered localized or early-stage, as it is confined to the prostate gland and has not spread to other parts of the body. The most common treatments for early prostate cancer include radiation, surgery, and hormone therapy. Other options may include cryosurgery, which uses freezing temperatures to kill cancer cells, as well as cryotherapy, high-intensity focused ultrasound therapy, and proton beam radiation therapy.

There are various types of radiation therapy that can be used, but the main types include External Beam Radiation Therapy (EBRT), Brachytherapy, and Radiopharmaceuticals (19). EBRT involves radiation beams directed at the prostate gland from a machine located outside the body (20). This method can be used to attempt to cure early-stage cancers, treat cancers that have extended beyond the prostate, or alleviate symptoms such as bone pain when the cancer has spread to specific bone areas (20). Most types of external radiation therapy is typically administered five days a week in a patient setting over several weeks (20). However, many centers now offer hypo fractionated radiation, where slightly higher doses of radiation are delivered over fewer sessions (21). This approach shortens the overall treatment time and appears to be equally effective. Each treatment is like receiving an X-ray, though the radiation dose is much stronger. The treatment itself is painless and usually lasts only a few minutes, but the setup time—positioning the individual for the procedure—takes longer (21).

Modern EBRT techniques allow for more precise targeting of the tumor, which enables doctors to deliver higher doses of radiation to the tumor, minimizing the exposure to surrounding healthy tissues (22). The most common form of external radiation therapy for prostate cancer is Intensity-Modulated Radiation Therapy (IMRT), an advanced form of 3D Conformal Radiation Therapy (22). This technique makes use of a computer-controlled machine that can move around the patient while radiation is dispensed by the machine in beams, shaped and directed at the prostate from several different angles (22). The beams are of variable intensity to minimize unnecessary irritation of surrounding healthy tissue as much as possible (22). This allows doctors to expose the cancer to a higher dose of radiation.

Randomized evidence also supports radiotherapy dose intensification strategies. The ASCENDE-RT trial (23) demonstrated that adding a low-dose-rate brachytherapy boost to external-beam radiotherapy significantly improved biochemical progression-free survival in intermediate- and high-risk localized prostate cancer. However, this benefit was accompanied by higher rates of genitourinary toxicity, underscoring the need for careful patient selection when considering brachytherapy augmentation.

IMRT is often combined with image-guided radiation therapy (IGRT). IGRT uses imaging tests immediately before each treatment to create detailed pictures of the prostate, ensuring that radiation is delivered precisely to the target area, since the prostate's position can vary slightly each day (24). A related approach, called Stereotactic ABlative Radiotherapy (SABR) or Stereotactic Body RadioTherapy (SBRT), uses advanced image-guided techniques to deliver very high doses of radiation to a small area, such as the prostate, over just a few treatment sessions (25). SBRT may also be used to treat cancer that has spread to a limited number of sites within the bones (26).

Another effective treatment for early-stage prostate cancer is surgery, with the primary procedure being a radical prostatectomy (27). In this surgery, a urologist removes the entire prostate gland along with surrounding tissues, including the seminal vesicles (27). In some

cases, nearby lymph nodes are also removed depending on disease risk.

There are two main approaches to performing a radical prostatectomy. In an open prostatectomy, the surgeon removes the prostate and surrounding tissues through a single long incision (28). In a laparoscopic prostatectomy, several small incisions are made, and long, thin instruments are used to remove the prostate and nearby tissues (28). Laparoscopic procedures may be performed using conventional instruments or with robotic assistance, in which the surgeon controls robotic arms from a console (28).

In some cases, pelvic lymph node dissection may also be performed at the time of radical prostatectomy to assess lymph node involvement (28).

However, the rates of two significant quality-of-life side effects that most concern men—related to erectile dysfunction and urinary incontinence—appear to be similar for robotic and open prostatectomy (29). The frequency of positive surgical margins did not differ significantly between the two techniques (29). Both techniques demonstrate comparable functional and oncologic outcomes when performed by experienced surgeons (29).

Another treatment option for prostate cancer is cryotherapy. This therapy has been used as a primary treatment option for patients with localized or locally advanced prostate cancer (30). During cryotherapy, transrectal ultrasound (TRUS) guidance is used to accurately place cryoprobes within the prostate, where cycles of freezing and thawing are applied to destroy prostate tissue (30). Warmer gases are then used to thaw the treated area (30). This method has been associated with effective cancer control and modest treatment-related morbidity (30).

Long-term follow-up demonstrated favorable biochemical disease-free survival rates across risk groups, low rates of positive biopsy, and no serious complications reported in most patients (30). Although rare, serious complications such as the development of an abnormal connection between the bladder and rectum (fistula) have been reported following cryotherapy and may require surgical repair (30).

Yet another effective treatment option is hormone therapy, also known as Androgen Deprivation Therapy (ADT). This approach aims to reduce levels of male androgens or block their effects on prostate cancer cells. Prostate cancer can be managed using specific hormone therapies (31). Androgens play a key role in the growth and development of prostate cancer cells, with the primary androgens in the body being testosterone and DiHydroTestosterone (DHT) (32). Although the testes produce most androgens, the adrenal glands and prostate cancer cells can also generate them. Lowering androgen levels or preventing their interaction with prostate cancer cells can often cause tumors to shrink or slow their growth temporarily. However, hormone therapy alone does not cure prostate cancer, and many tumors eventually become resistant to this treatment over time.

A range of treatments is available to reduce androgen levels, one of which is orchiectomy. Although orchiectomy is a surgical procedure, its primary effect is comparable to that of

hormone therapy. During this procedure, the testes—which produce most circulating testosterone (the main androgen)—are removed, leading to a rapid and profound reduction in testosterone levels (33). As a result, prostate cancer growth often slows or temporarily regresses. These approaches are among the primary treatments for prostate cancer in stages I and II, where the tumor remains localized and treatment outcomes are generally more favorable. However, management differs for non-localized or advanced-stage cancers. In later stages, treatment options may include immunotherapy, chemotherapy, hormone therapy, and targeted drug therapy.

2.1 Glycan-aware decision refinement in localized disease

Beyond standard clinical treatments, emerging biomarkers such as PSA glycosylation provide additional biological insight. In men with elevated PSA and equivocal risk following MRI and standard reflex tests (percent-free PSA, PHI, 4Kscore), a malignancy-weighted PSA glycan index provides orthogonal specificity (12, 15–17). Associations of α2,3-biased sialylation and core fucosylation of PSA with biopsy-proven cancer indicate that thresholded glycan indices (e.g., α2,3/α2,6 and core-fucosylated/non-fucosylated ratios) can reduce unnecessary biopsies in BPH while increasing the proportion of clinically significant tumors among biopsy-detected cases (13, 15, 16). During active surveillance for Grade Group 1–2 disease, serial glycan indices combined with PSA doubling time may reveal biologic progression prior to changes in total PSA, justifying earlier confirmatory biopsy or shortened surveillance intervals (12–17). These hypotheses require prospective, stage stratified validation with predefined endpoints.

3. Effective therapeutic intervention in the later stages of prostate cancer

An effective treatment option for advanced stages of prostate cancer is immunotherapy, which harnesses the patient's immune system to recognize and attack cancer cells (34). One FDA-approved immunotherapeutic approach is Sipuleucel-T (Provenge®), a therapeutic cancer vaccine indicated for metastatic castration-resistant prostate cancer (35). This treatment involves leukapheresis, during which the patient's antigen-presenting immune cells are collected and processed ex vivo. In the laboratory, these cells are exposed to a prostate cancer–associated antigen, prostate acid phosphatase, to stimulate an immune response (35). The activated cells are then reinfused into the patient, promoting a targeted immune response against prostate cancer cells. Although Sipuleucel-T does not significantly reduce PSA levels or directly inhibit tumor growth, it has been shown to improve overall survival in patients with advanced prostate cancer (35).

Additionally, chemotherapy is commonly used in advanced prostate cancer, particularly in metastatic castration-resistant prostate cancer (mCRPC) (36). Several chemotherapeutic agents may be used, including docetaxel and cabazitaxel (36). Docetaxel is often the first taxane-based chemotherapy and is frequently given with a corticosteroid such as prednisone (36). If disease progresses after docetaxel or the drug is not tolerated, cabazitaxel may be used as a subsequent option, also in combination with prednisone (36). In men with mCRPC previously treated with docetaxel and

one androgen-signaling–targeted inhibitor, cabazitaxel significantly improved overall survival and imaging-based progression-free survival compared with abiraterone or enzalutamide (36).

Chemotherapy for prostate cancer is most often delivered through intravenous (IV) administration, typically in outpatient or hospital-based settings. While some agents, such as estramustine, can be taken orally, most chemotherapy drugs are given directly into a vein to ensure controlled dosing and systemic exposure (37). Treatment is organized into defined cycles, in which medication is administered over a set period followed by a planned break to allow the body to recover from treatment-related toxicities (37). These cycles commonly last about three weeks, although the exact duration and schedule depend on the specific drug and regimen selected (37). Some medications are given on a single day at the start of each cycle, whereas others may be administered weekly or over multiple consecutive days. After the rest period concludes, the next cycle begins if treatment is continued (37).

Chemotherapeutic agents primarily target rapidly dividing cells, a characteristic that makes them effective against cancer cells. However, other normal tissues in the body—including the bone marrow, oral mucosa, gastrointestinal lining, and hair follicles—also exhibit high rates of cell division. As a result, these tissues may be adversely affected by chemotherapy, leading to a range of treatment-related side effects.

Other effective treatment options for prostate cancer include radiation therapy and hormone therapy (38). Some therapies commonly employed in stages I–II may also be utilized in more advanced stages, though their effectiveness in early-stage disease is largely due to their ability to rapidly reduce tumor burden. Patients who prefer treatments with prompt therapeutic effects often opt for radiation or hormone-based approaches (38). In stage IVA disease, a combination of external beam radiation and hormone therapy has demonstrated clinical efficacy (24,31,38). Alternatively, hormone therapy alone may be employed as a treatment strategy in advanced prostate cancer (31). In selected patients, hormone therapy may be intensified with next-generation androgen pathway inhibitors to improve disease control (31).

Surgery may be considered when prostate cancer spreads to regional lymph nodes, allowing for their removal alongside the primary tumor. However, in stage IVB disease, cancer has typically metastasized to distant organs, such as the bones, at the time of diagnosis. While most stage IVB cases are not curable, treatment can help control disease progression and improve quality of life (39). Common approaches include various forms of hormone therapy, which may involve newer agents such as abiraterone, apalutamide, or enzalutamide. Hormone therapy may also be combined with external beam radiation directed at the primary prostate tumor (39). In certain cases, surgical interventions such as transurethral resection of the prostate (TURP) are performed to relieve urinary obstruction or other symptomatic complications (40).

Active surveillance and observation are additional management strategies, particularly for patients with limited symptoms or

significant comorbidities. Active surveillance involves regular monitoring of disease progression, with intervention initiated if clinical or laboratory findings indicate tumor growth. Typical protocols include PSA testing every six months, digital rectal examinations approximately once per year, and periodic prostate biopsies or imaging every one to three years, with the frequency adjusted based on individual patient circumstances (41). Watchful waiting is a related approach in which patients undergo less intensive monitoring, and subsequent diagnostic or therapeutic interventions are guided primarily by the development of symptoms, making it suitable for older patients or those with serious comorbid conditions (41).

Participation in clinical trials represents another treatment option. These studies evaluate novel medications, therapeutic strategies, and interventions in human participants, providing access to potentially innovative treatments while contributing to the advancement of prostate cancer care.

Yet another treatment approach is targeted drug therapy. Like chemotherapy and hormone therapy, targeted therapies can be effective against cancers that have metastasized to distant sites (42). These agents circulate systemically, reaching cancer cells throughout the body. One class of targeted drugs, poly (ADP-ribose) polymerase (PARP) inhibitors, interferes with tumor cells harboring defective DNA repair genes, such as BRCA1 or BRCA2, preventing the cells from repairing DNA damage and leading to cell death (42). PARP inhibitors are effective only in cancers with mutations in these DNA repair genes; therefore, patients are typically screened through blood or tumor testing before initiating treatment to confirm the presence of relevant genetic alterations (42).

PARP inhibitors are administered orally, usually once or twice daily in tablet or capsule form (43). They are often prescribed in combination with hormone therapy, such as an LHRH agonist, or following surgical castration (orchiectomy) (43). Common adverse effects include nausea, vomiting, diarrhea, fatigue, loss of appetite, anemia, constipation, skin rash, liver enzyme abnormalities, hyperglycemia, cough, and other symptoms (43). While these therapies can control or eliminate detectable cancer, recurrence is possible, and subsequent treatments may involve additional targeted therapies or immunotherapy (43).

No single treatment approach for prostate cancer can be considered universally superior. Each therapy presents specific advantages and limitations that may be influenced by the stage or aggressiveness of the disease, as well as the patient's overall health, age, and personal preferences. A comprehensive evaluation of treatment options requires comparison across multiple dimensions, including therapeutic efficacy, invasiveness, potential adverse effects, and long-term outcomes for the patient.

3.2 PSA glycosylation as an indicator of aggressiveness

Multiple studies across prostate cancer and other solid tumors link glycan remodeling to invasion, altered stromal interactions, and metastatic behavior. In prostate cancer, a higher proportion of α2,3-linked relative to α2,6-linked sialic acids, an increased fraction of core-fucosylated PSA, greater N-glycan branching, and more frequent truncated O-

glycans have each been associated with higher Gleason patterns and adverse pathology (12–16). These features can be summarized through interpretable glycan ratios, including α2,3 to α2,6 sialylation, core-fucosylated to non-fucosylated PSA, branched to non-branched N-glycans, and truncated to extended O-glycans (Table 1).

Biologically, increased N-glycan branching through MGAT5 can reduce cell adhesion and modify signaling pathways that support invasion. Higher α2,3 sialylation can alter immune interactions and promote motility, while core fucosylation mediated by FUT8 influences receptor activation and contributes to invasive growth. Loss of C1GALT1 or COSMC leads to accumulation of truncated O-glycans, which has been repeatedly linked to more aggressive tumor phenotypes (13,14).

Table 1. Stage-specific prostate cancer interventions and corresponding glycan-based diagnostic indicators

Stage	**Clinical Focus / Standard Intervention**	**Key Biomarkers or Glycan Ratios**	**Analytical Chemistry / Assay**
I – Low-Risk Localized (GG1; PSA < 10; confined)	Active surveillance; radical prostatectomy; EBRT/IMRT; brachytherapy (selected cases)	Baseline PSA glycan index; lower α2,3/α2,6 sialylation ratio; lower core-fucosylation	ELISA with LC–MS/MS; lectin microarray; HILIC-UPLC
II – Intermediate (Favorable/Unfavorable)	Radical prostatectomy ± pelvic lymph-node dissection; EBRT/IMRT ± brachy boost; short-term ADT	Trend toward PSA glycan index; trend toward α2,3/α2,6 ratio; trend toward core-fucosylated / non-fucosylated PSA	LC–MS/MS glycoform analysis; MALDI-TOF; lectin capture
III – Locally Advanced	EBRT/IMRT/SABR + ADT; radical prostatectomy (selected) ± adjuvant/salvage RT	Relative increase in core-fucosylation; higher tendency toward N-glycan branching (MGAT5); trend toward truncated O-glycans	LC–MS/MS of glycopeptides; CE-LIF; quantitative ratio panels
IVA – Regional Nodes	EBRT to prostate/pelvis + long-term ADT; consider systemic intensification	Trend toward α2,3/α2,6; higher tendency toward core-fucosylation; track PSA glycan index over time	Serial LC–MS profiling; PSMA-PET-correlated glycan indices
IVB – Metastatic (mHSPC → mCRPC)	ADT + Docetaxel or novel AR-pathway inhibitors; PARP inhibitors (BRCA1/2, HRR); immunotherapy (Sipuleucel-T); radiopharmaceuticals; bone-targeted agents	Highly heterogeneous glycan profile; trend toward α2,3/α2,6; trend toward core-fucosylation; trend toward truncated O-glycans; dynamic PSA glycan index tracking	Longitudinal LC–MS/MS panels; composite glycan score algorithms

These mechanistic associations provide a rationale for evaluating glycan ratios as probabilistic indicators of tumor behavior. Early findings suggest that higher α2,3 to α2,6 ratios and increased core fucosylation are more common in poorly differentiated cancers and may correlate with early metastatic spread, while more fully elongated glycans appear in indolent disease. Prospective studies using standardized assays are needed to determine

whether these ratios can predict adverse pathology, biochemical recurrence, or metastasis-free survival when combined with established variables such as PSA kinetics, MRI findings, and genomic classifiers. Because glycan remodeling reflects cellular phenotype rather than anatomical extent, these ratios cannot substitute for T, N, or M staging and must be evaluated as probability-shifting markers rather than deterministic classifiers.

4. Optimal treatment strategies for early stage prostate cancer (Stages I and II)

The goals of therapy in early-stage prostate cancer include eradicating or ablating malignant cells while preserving as much function of the prostate as possible. Surgery, radiation therapy, and newer technologies are the standard treatments for localized prostate cancer; these newer technologies include radical prostatectomy, EBRT or IMRT, and cryotherapy.

Surgery, particularly a radical prostatectomy, is the most definitive treatment whereby the entire prostate and surrounding tissues are removed; the chances of recurrence are hence significantly reduced (41). It does, however, carry significant risks of urinary incontinence and erectile dysfunction that considerably affect a patient's quality of life (41). In addition, while both open surgery and laparoscopic-robot-assisted prostatectomy seem to be as effective – in that there is no significant difference in the long-term results between the two methods - robotic surgery usually has a faster recovery time (29). Ultimately, while a radical prostatectomy is indeed highly successful for those patients in the early stages of cancer, side effects- more importantly, quality-of-life ones outweigh its consideration and choice for some individuals.

Furthermore, radiation therapy has gained increasing acceptance, particularly with the advent of advanced techniques such as IMRT and SBRT, which minimize damage to surrounding healthy tissues while maintaining precise radiation delivery (22, 25, 44). This modality is especially attractive to patients because it avoids the invasiveness associated with surgical intervention (58). Nevertheless, radiation therapy may be associated with significant adverse effects, including rectal bleeding and urinary complications (44). In certain cases, prolonged radiation exposure has also been linked to an elevated risk of secondary malignancies (45). Despite these concerns, hypofractionated radiation therapy employs fewer treatment sessions and demonstrates comparable efficacy to conventional fractionation, while offering additional benefits such as reduced overall treatment duration (21).

Cryotherapy, although less frequently utilized than surgical or radiation-based interventions, represents a minimally invasive therapeutic alternative, particularly for patients experiencing recurrence following radiation therapy or for those who are poor candidates for surgery (46). However, the long-term oncologic outcomes of cryotherapy, in comparison with surgery and radiation, remain insufficiently well defined (30, 46). Additionally, patients undergoing cryotherapy may face an increased risk of adverse effects, including sexual dysfunction and injury to adjacent tissues (46).

Overall, radical prostatectomy and radiation therapy remain the cornerstone treatment modalities for the management of early-stage disease. Surgical intervention provides a more definitive therapeutic approach but is associated with a higher risk of treatment-related morbidity, whereas radiation therapy offers a less invasive alternative that typically requires a longer treatment course (41, 47, 48). Selection between these modalities should be individualized, taking into account patient clinical characteristics, anticipated side effects, and patient preferences (41, 49).

5. Optimal therapeutic strategies for intermediate and locally advanced prostate cancer (Stage III)

In intermediate-risk or locally advanced prostate cancer, the malignancy extends beyond the confines of the prostate gland into adjacent tissues or structures. Management at this stage typically involves a multimodal approach, incorporating surgery, radiation therapy, and hormonal treatment, such as ADT (10,11). The primary objectives of this combined strategy are to limit disease dissemination, reduce tumor burden, and delay further disease progression (50,51).

Surgical intervention may still be considered at this stage, particularly in younger patients with good overall health status. Radical prostatectomy can aid in reducing tumor burden; however, it is unlikely to be curative when the malignancy has extended beyond the prostate gland (10, 41). In selected cases, pelvic lymph node dissection is also performed to decrease the risk of further metastatic spread. Surgery is frequently combined with adjuvant or salvage radiation therapy—most commonly external beam radiation therapy—to eradicate residual disease (51). Advances in radiation delivery, including IMRT and SBRT, allow for greater precision, thereby enhancing treatment efficacy while minimizing treatment-related toxicity (22,44).

Hormonal therapy plays a pivotal role in the management of more advanced prostate cancer. By reducing androgen levels, particularly testosterone, this therapeutic approach can effectively slow or arrest the proliferation of androgen-dependent cancer cells (31,45). Although hormone therapy is not curative, it can provide sustained disease control in many patients. Notable adverse effects include fatigue, vasomotor symptoms such as hot flashes, decreased bone mineral density, and loss of libido (45, 52). Clinical outcomes may be further enhanced when hormone therapy is combined with radiation therapy or surgery, particularly in cases involving extension into surrounding tissues (50,51).

Consequently, the management of locally advanced prostate cancer most commonly necessitates a multimodal treatment strategy that integrates surgery, radiation therapy, and hormonal therapy. This comprehensive approach aims to maximize tumor control and prolong survival, albeit at the expense of increased treatment-related toxicity and a more prolonged recovery period.

6. Optimal treatment strategies for advanced-stage prostate cancer (Stage IV)

Advanced prostate cancer presents substantial therapeutic challenges, as the malignancy has typically metastasized to distant organs or osseous structures, rendering curative treatment unlikely. At this stage, the primary goals of care shift toward symptom palliation,

deceleration of disease progression, and preservation or improvement of quality of life (9,31). Standard treatment strategies for stage IV prostate cancer commonly include hormonal therapy, chemotherapy, immunotherapy, and targeted therapeutic agents (31,36,50,53).

Hormone therapy remains a cornerstone for the treatment of metastatic prostate cancer. Newer drugs, such as Abiraterone and Enzalutamide, when administered in combination with conventional hormone treatments, have been shown to extend life and alleviate symptoms, as demonstrated in large randomized trials of treatment intensification in metastatic hormone-sensitive disease (54, 55, 56). The ENZAMET trial (55) demonstrated that adding enzalutamide to ADT significantly improved overall survival in metastatic hormone-sensitive prostate cancer. Similarly, the TITAN trial (54) demonstrated that apalutamide added to ADT improved both radiographic progression-free survival and overall survival in metastatic castration-sensitive prostate cancer. The PEACE-1 trial (56) further demonstrated that adding abiraterone to standard therapy improved overall survival in *de novo* metastatic disease. These medications act by blocking the production of androgens or the androgen receptor, thereby reducing the fuel required by these prostate cancer cells for growth (31, 32). Hormone treatment can be continuous or intermittent to provide breaks from side effects (31). However, most cancers that initially respond to hormone therapy eventually become resistant, and additional treatments must be considered due to what is now termed castration-resistant prostate cancer (31). These treatments are generally reserved for cases in which tumor growth has become unresponsive to hormone treatment (31). Drugs used in this setting include Docetaxel and Cabazitaxel (36,37).

Chemotherapy using these compounds can diminish tumor size, reduce symptoms, and prolong life, but it is not a cure (36, 37). General side effects include fatigue, nausea, and immune suppression, which significantly affect the quality of a patient's life (37).

Immunotherapy has emerged as a novel therapeutic approach for select patients with metastatic prostate cancer (57). In particular, sipuleucel-T (Provenge®) does not directly reduce tumor burden or PSA levels; rather, it functions by stimulating the patient’s immune system to mount a targeted response against malignant cells (57). This mechanism has been associated with a modest but clinically meaningful improvement in overall survival, typically on the order of several months (57). Sipuleucel-T is generally well tolerated; however, its use is limited to carefully selected patients and is not universally applicable (57).

In addition to immunotherapy, targeted therapies have expanded the treatment landscape for advanced prostate cancer. Notably, PARP inhibitors are effective in tumors harboring specific genetic alterations, particularly mutations in BRCA1 and BRCA2 (43). Germline and somatic defects in DNA repair genes—including BRCA2, ATM, and CHEK2—are enriched in advanced prostate cancer and have been shown to predict sensitivity to PARP inhibition (42). These agents exploit deficiencies in tumor DNA repair pathways, leading to selective cancer cell death (42, 43). Targeted therapies are typically employed in cases of disease progression despite hormone therapy and represent an

important therapeutic option in advanced-stage disease (43).

An additional critical consideration in advanced prostate cancer management is the alleviation of bone pain and the prevention of skeletal-related events in patients with bone metastases (58). Agents used to enhance bone integrity, such as bisphosphonates and denosumab, have been shown to reduce the incidence of complications associated with metastatic bone disease, including fractures and spinal cord compression (58).

At this stage of disease, no single therapeutic modality is curative. Consequently, hormonal therapy is almost invariably combined with chemotherapy and targeted agents in an effort to achieve sustained disease control for the longest possible duration (59). Although these interventions have demonstrated survival benefits, they are often accompanied by substantial adverse effects. As a result, increasing emphasis is placed on optimizing symptom management and preserving quality of life for affected patients (45).

6.1. Genomic stratification and Homologous Recombination Repair-directed therapy

Genomic stratification has become a critical component of therapeutic decision-making in advanced prostate cancer. The prevalence of pathogenic alterations in BRCA1, BRCA2, ATM, and other homologous recombination repair (HRR) genes was first systematically characterized by Pritchard and colleagues (42) in 2016, thereby establishing the biological and clinical rationale for the use of PARP inhibitors in this disease context. Patients harboring BRCA1 or BRCA2 mutations demonstrate markedly increased sensitivity to PARP inhibition and may derive substantial benefit from the earlier integration of agents such as olaparib or rucaparib into their treatment regimen.

The PROfound Trial demonstrated improved radiographic progression-free survival and overall survival in men with metastatic castration-resistant prostate cancer harboring BRCA1, BRCA2, or ATM mutations who were treated with PARP inhibitors compared with standard physician-selected therapy (42, 43). Based on these findings, major guidelines now recommend both germline and somatic genomic testing for all patients with metastatic prostate cancer. Testing helps identify candidates who may respond to PARP inhibition, informs the selection of combination strategies, and enables appropriate hereditary cancer risk counseling for affected families. As treatment options continue to expand, choosing the appropriate therapy depends on accurate staging, risk classification, and disease biology. The following section summarizes treatment recommendations by stage to contextualize how these systemic options can be applied across the clinical spectrum.

7. Treatment recommendations by stage

Ultimately, the optimal management of prostate cancer is highly individualized, taking into account disease stage, patient health status, and personal preferences, particularly in light of the varying side effect profiles associated with different therapies (41). For localized disease, effective treatment options include surgical intervention, such as radical prostatectomy, and radiation therapy, including external beam radiation or brachytherapy. In intermediate-risk disease, the addition of ADT to radiation is frequently employed to enhance therapeutic

efficacy (38,50). Among older patients or those with significant comorbidities, active surveillance is often favored to minimize exposure to treatment-related adverse effects while maintaining careful disease monitoring.

In advanced and metastatic prostate cancer, a diverse array of therapeutic strategies is employed. ADT may be combined with chemotherapy, such as docetaxel, or with novel androgen-signaling inhibitors, including enzalutamide or abiraterone, to more effectively suppress tumor growth (54,55,59,60). Immunotherapy and radiopharmaceutical approaches are also utilized in select metastatic contexts (57,61).

Concurrently, Prostate-Specific Membrane Antigen (PSMA) imaging has transformed contemporary staging paradigms. The proPSMA randomized trial (62) demonstrated that PSMA Positron Emission Tomography (PET) provides substantially greater accuracy than conventional computed tomography and bone scans in detecting nodal and distant metastases among high-risk patients. Beyond its diagnostic utility, PSMA-targeted radioligand therapy has emerged as a potent systemic treatment option. The VISION (53) and TheraP (61) trials established that ^177Lu-PSMA-617 significantly improves radiographic progression-free survival and overall survival in metastatic castration-resistant prostate cancer, thereby validating PSMA-directed therapy as a clinically meaningful intervention. Collectively, these approaches can substantially prolong survival while maintaining or improving quality of life.

Across all stages of disease, proactive management of treatment-related adverse effects is essential to preserving patient well-being. Therapeutic strategies should be individualized based on clinical characteristics and patient-centered goals (47). In early-stage, pre-biopsy triage for low- and intermediate-risk presentations, a malignancy-weighted glycan index may complement magnetic resonance imaging and reflex testing to refine biopsy decisions. For patients with Grade Group 1–2 disease under active surveillance, validated biomarkers—such as a rising α2,3/α2,6 sialylation ratio or altered core-fucosylated/non-fucosylated PSA ratio—could justify earlier confirmatory biopsy or shortened surveillance intervals. Similarly, in cases of biochemical recurrence with inconclusive imaging, an unfavorable glycan shift may prompt earlier restaging or escalation of therapy. While these applications require standardized cut points and external validation, they represent feasible integration points into contemporary clinical pathways (13,16,17).

8. Limitations of current decision models

Many existing treatment guidelines for prostate cancer rely predominantly on the Gleason score and PSA levels. While these metrics provide valuable clinical information, they often fail to capture critical biological and molecular heterogeneity among patients. For instance, two individuals with similar PSA levels and Gleason scores may exhibit markedly different responses to the same therapy due to underlying genetic or molecular differences. This highlights a key limitation of current models, which tend to treat patients as a homogeneous group rather than accounting for individual variations in disease biology.

Moreover, contemporary decision-making frameworks are often static and do not adapt

effectively over time. Changes in PSA levels, emergence of treatment resistance, or disease progression are frequently addressed in a reactive manner rather than through a proactive, structured model. There is a clear need for more dynamic and adaptive treatment models that can respond in real time to the evolving clinical and molecular profile of each patient.

8.1 Limitations of PSA glycosylation as a clinical decision tool

PSA glycosylation shows biologically plausible associations with malignancy, but current evidence comes from small, single-center discovery studies that use a wide variety of analytical methods. Glycan signatures overlap extensively between clinical stages and reflect cellular phenotypes rather than true anatomic T, N, or M extent. For this reason, they cannot function as staging tools and should be interpreted as probability-shifting markers rather than fixed diagnostic cutoffs. Many existing studies rely on highly selected research populations or controlled laboratory samples that do not reflect real-world variability, including the effects of BPH, prostatitis, metabolic conditions, and other factors that influence glycan patterns. Differences in sample preparation, lectin specificity, enrichment techniques, and mass-spectrometry workflows create additional analytical variation and make it difficult to compare results across studies or to derive universal thresholds. Larger prospective and multicenter studies with standardized assays and clearly defined clinical endpoints, such as discrimination of clinically significant cancer, prediction of adverse pathology, biochemical recurrence, or metastasis-free survival, are needed to determine whether PSA glycan indices add meaningful value beyond PSA density, the Prostate Health Index, multiparametric MRI, and genomic classifiers. Until such evidence becomes available, PSA glycosylation should be regarded as an emerging investigational biomarker rather than a validated tool for treatment selection or anatomical staging. Meaningful clinical adoption will require standardized analytical workflows and external calibration across laboratories, as current variability in lectin specificity and mass-spectrometry protocols limits reproducibility.

8.2 Shared decision-making, toxicity profiles, and patient-reported outcomes

A significant limitation of current prostate-cancer decision frameworks is the insufficient incorporation of real-world toxicity data and Patient-Reported Outcomes (PROs). Although staging systems, PSA kinetics, and genomic classifiers guide the selection of therapy, they do not fully capture the wide variation in urinary, bowel, sexual, metabolic, and fatigue-related toxicities that patients experience across different treatments (45, 63, 64). Radical prostatectomy, EBRT, brachytherapy, ADT, PARP inhibitors, and radioligand therapy each influence functional outcomes in distinct ways. These patterns vary considerably between patients, yet most contemporary risk-stratification approaches do not integrate validated toxicity predictors or long-term functional trajectories (45, 49).

Due of these limitations, shared decision-making has become a crucial element of management. Many patients prioritize continence, sexual function, bowel control, and preservation of physical and emotional well-being as strongly as they prioritize oncologic control. Several studies demonstrate that

toxicities reported in clinical trials often underestimate those seen in routine practice, particularly among older adults, individuals with comorbidities, and populations affected by socioeconomic or racial disparities (49). Without routine discussions of treatment trade-offs and expected functional outcomes, clinical recommendations may diverge from patient values and long-term preferences.

Validated PRO instruments, including the Expanded Prostate Cancer Index Composite (EPIC), the International Prostate Symptom Score (IPSS), the Functional Assessment of Cancer Therapy–Prostate (FACT-P), and the PROMIS quality-of-life domains, provide reliable methods for tracking symptoms and function over time (63,64). Incorporating these measures into clinical practice enables clinicians to identify early toxicity signals, intervene proactively, and modify treatment when necessary to maintain quality of life. PRO-based monitoring is especially important during ADT because mood changes, fatigue, metabolic alterations, bone loss, and sexual dysfunction often remain unreported unless assessed directly (45,65).

As prostate-cancer therapy increasingly shifts toward multimodal approaches, including combinations of ADT, radiotherapy, docetaxel, next-generation androgen-receptor inhibitors, PARP inhibitors, and PSMA-targeted radioligand therapy, the integration of toxicity data and PROs becomes essential. These measures complement molecular and imaging-based tools by ensuring that treatment decisions reflect both disease biology and the daily lived experience of the patient.

9. Re-framing the risk classification system

Static tools centered on PSA concentration and Gleason grading do not capture interpatient biological heterogeneity or within patient temporal evolution. Response adapted frameworks should integrate PSA kinetics, radiographic findings, and molecular diagnostics, including PSA glycosylation. In such models, glycan-based variables; α2,3/α2,6 sialylation, corefucosylated /non-fucosylated PSA, branched/non-branched N-glycans, and truncated/extended O-glycans; enter as continuous predictors that recalibrate risk at predefined checkpoints. Machine-learning approaches trained on harmonized glycomics, imaging, and outcomes can identify early inflection points that presage resistance or metastatic spread and thereby inform timely intensification while balancing toxicity and quality of life (12– 16).

Additionally, treatment response itself should be used as a marker of risk. For example, if a patient on ADT shows increasing PSA within six months, that should trigger automatic reclassification and treatment escalation. A feedback-based model could enable timely interventions before the cancer becomes resistant or metastatic.

9.1 Glycan-informed decision diagram for risk stratification and response monitoring

PSA glycan indices do not function as independent staging tools; instead, they modify risk probabilities when integrated with MRI, PSA kinetics, and Grade Group. Because these metrics act as probabilistic modifiers, they should refine existing variables such as MRI findings, PSA kinetics, and Grade Group rather than function as standalone determinants. Figure 2 outlines a conceptual decision

diagram that integrates glycan-aware indices into existing prostate cancer pathways. These glycan indices function as probability-modifying biomarkers that refine, rather than replace, conventional risk markers such as MRI findings, PSA kinetics, and Grade Group.

9.1.1 *Step 1 – Initial evaluation (elevated PSA or abnormal DRE)*
Standard tools—total PSA, age, DRE, family history, MRI, and reflex tests (percent-free PSA, PHI, 4Kscore)—are used to estimate baseline risk. If this assessment clearly indicates very low risk or very high risk, patients follow guideline-based pathways (observation vs biopsy vs immediate treatment). If the risk estimate is equivocal, the clinician may order a PSA glycosylation panel.

9.1.2 *Step 2 – Glycan-based malignancy triage (benign vs malignant)*
Composite glycan indices and simple ratios (e.g., α2,3/α2,6-sialylation, core-fucosylated /non-fucosylated PSA) are interpreted as probabilistic modifiers of malignancy risk. "Benign-like" profiles—lower glycan index values and less malignant glycoform enrichment—shift the post-test probability toward benign conditions (BPH, prostatitis) and may support biopsy deferral in otherwise low-risk men after shared decision-making. "Malignant-like" profiles shift probability toward clinically significant prostate cancer and support proceeding to biopsy in borderline cases.

9.1.3 *Step 3 – Biologic aggressiveness layer (indolent vs aggressive)*
Among biopsy-proven cancers, glycan metrics are integrated with Gleason Grade Group, PSA density, MRI PI-RADS, and tumor volume. Glycan profiles closer to benign controls (lower composite scores, less truncated O-glycans, and lower α2,3/α2,6 ratios) favor active surveillance in suitable Grade Group 1–2 patients. More malignant-like glycan profiles (higher composite scores and greater malignant glycoform burden) tilt borderline cases toward definitive local therapy or multimodal treatment, especially in intermediate-risk disease.

9.1.4 *Step 4 – Serial monitoring and response assessment (responders vs non-responders)*
During active surveillance or systemic therapy, longitudinal changes in PSA glycan indices can be followed alongside PSA kinetics and imaging. Stable or improving glycan profiles may reinforce continued surveillance or maintenance therapy, whereas worsening profiles (e.g., rising α2,3/α2,6 ratio, increasing core fucosylation index, or increasing heterogeneity) could signal biologic progression and justify earlier restaging or treatment escalation.

At every step, glycan-aware metrics serve as adjunctive probabilistic tools rather than stand-alone decision-makers, and all cut-points and weightings in this conceptual diagram require formal derivation and prospective validation before clinical use.

Figure 2 shows a qualitative schematic illustrating how reported PSA glycosylation features, including α2,3/α2,6 sialylation, core fucosylation, N-glycan branching, truncated O-glycans, and glycan heterogeneity, may be integrated into a composite glycan index ($G_{composite}$) to probabilistically inform clinical decision-making. Lower composite scores are associated with benign-like or

indolent phenotypes, whereas higher scores align with malignant or aggressive disease biology and may support consideration of earlier or intensified intervention. The schematic summarizes directional trends reported across studies and does not represent stage-specific quantitative measurements, diagnostic cutoffs, or non-overlapping clinical categories. Numerical ranges, normalization, weighting, and stage-wise composite index calculations are provided separately in Supplementary Table S1 and Figure 3.

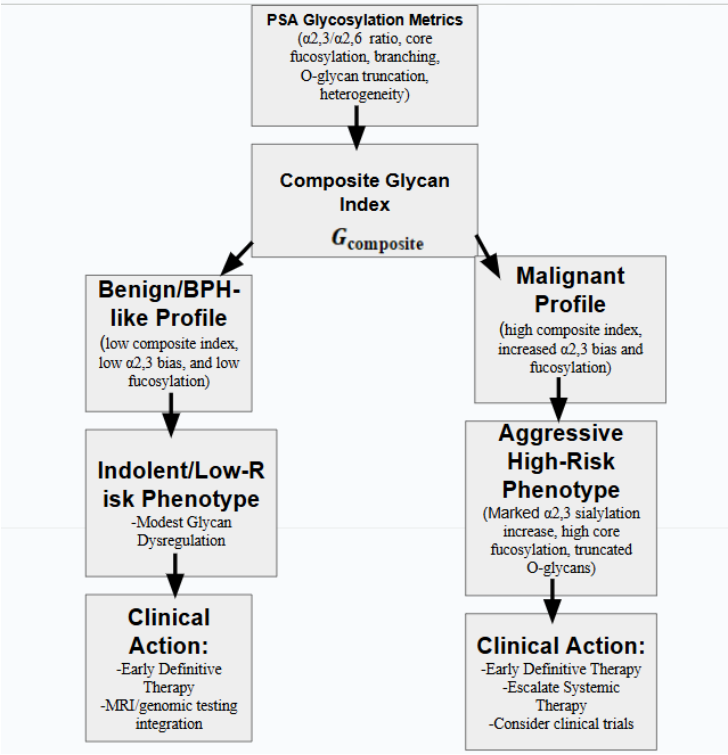

Figure 2. A conceptual decision diagram that integrates glycan-aware indices into existing prostate cancer pathways

10. Emerging tools for adaptive prostate cancer management

10.1 Proposal: Integrated molecular treatment mapping

Building on patterns observed in treatment resistance and disease relapse, an integrated molecular–treatment mapping model can be proposed. This framework would correlate tumor characteristics—including PSA kinetics, Gleason patterns, and timelines of therapeutic resistance—with optimized sequences of intervention. For instance, a patient exhibiting a rapid PSA rise following initial hormone therapy could be guided toward early chemotherapy or second-line hormonal agents based on the mapped response pathways. The model would incorporate predefined checkpoints for reassessment, such as every six months, allowing treatment strategies to be adjusted in response to changes in disease progression. By aligning observed patterns with clinical outcomes, this approach minimizes reliance on trial-and-error methods

and supports more evidence-informed decision-making. It extends the principles of traditional staging and treatment research by integrating a predictive component grounded in individual patient response data.

10.2 Integration of Artificial Intelligence and Machine Learning

Additionally, a promising advancement in prostate cancer management could involve the integration of artificial intelligence (AI) and machine learning (ML) to improve clinical decision-making. These technologies enable the real-time analysis of complex datasets, including PSA kinetics, Gleason patterns, imaging, and molecular profiles, to identify predictive patterns associated with treatment resistance and progression. For instance, ML models can anticipate transitions to castration-resistant prostate cancer by evaluating subtle trends in biomarker behavior, allowing for earlier therapeutic adjustments. AI assisted platforms may also guide the selection and sequencing of therapies by matching patient specific characteristics with historical outcome data. Integrating these tools into electronic medical records could streamline care, reduce diagnostic error, and support more timely interventions. These approaches have the potential to shift treatment planning from reactive to adaptive, which enhances precision and improves long-term outcomes through continuous learning and model refinement.

Platforms like the open-source DeepSurv model and IBM Watson® for oncology have already demonstrated the feasibility of outcome prediction and treatment optimization in oncology. Integrating such tools into prostate cancer care could enable real-time, data-informed decisions tailored to each patient's evolving disease profile.

10.3 Potential of gene editing technologies (CRISPR)

Gene editing tools such as CRISPR show great promise for precision medicine in prostate cancer. These technologies enable the direct modification of genomic sequences, which could be essential to help correct oncogenic mutations and even deactivate genes responsible for treatment resistance. In the context of prostate cancer, this could mean selectively targeting androgen receptor signaling pathways, which could enhance sensitivity to hormone therapies, or even prevent the progression to castration-resistant states. Although CRISPR is still in preclinical stages for prostate cancer, combining CRISPR with conventional treatments (Chemotherapy or Androgen deprivation) could potentially enhance the treatment efficacy by targeting resistance mechanisms. Future studies should prioritize safety, delivery mechanisms, and combination approaches to harness the full potential of gene editing in clinical settings.

10.4 Roadmap for clinical translation of PSA glycosylation

Clinical translation requires assay harmonization across platforms, external calibrators, and inter-laboratory reproducibility studies. Cut-off points for a glycan index and for ratios of α2,3/α2,6 sialylation, core fucosylation, branching, and truncated O-glycans should be derived in training cohorts and validated in prospective, stage-stratified studies that include BPH and prostatitis controls. Prespecified endpoints should include discrimination at biopsy, prediction of clinically significant cancer, adverse pathology

at prostatectomy, biochemical recurrence–free survival, metastasis-free survival, treatment decision impact, and downstream resource use. Trials should test whether glycan-guided strategies safely reduce biopsies or imaging, reclassify surveillance candidates, or trigger earlier intensification, with embedded patient reported outcomes to measure functional trade-offs (13,16,17).

Future validation should employ multicenter cohorts that include men with BPH, prostatitis, and low-grade cancers to determine specificity under real-world conditions. Derived metrics—such as α2,3/α2,6-sialylation ratios, fucosylation indices, and truncated O-glycan frequency—should be correlated with clinical outcomes including Gleason upgrading, metastasis-free survival, and therapy resistance. Statistical modeling (e.g., ROC analysis, logistic regression, and multivariate Cox models) will be essential to establish robust cutoffs and to translate these biochemical measures into actionable clinical tools.

Beyond single-parameter ratios, future work should focus on algebraic composite indices that integrate multiple aspects of PSA glycosylation. Candidate components include: (i) malignant-favoring ratios (such as α2,3/α2,6-sialylation, core-fucosylated/non-fucosylated PSA, branched/non-branched N-glycans, truncated/extended O-glycans), (ii) overall malignant glycoform burden, and (iii) intra-sample heterogeneity measures such as variance or entropy of the glycan distribution. Conceptually, such an index could be expressed as,

$$G_{composite} = w_1 + [W_2 \times R_{core\text{-}fuc}] + [W_3 \times R_{branching}] + [W_4 \times R_{O\text{-}glycan\ truncation}] + [W_5 \times H_{heterogeneity}]$$

where each weight w_i estimated in a training cohort and validated independently, and $H_{heterogeneity}$ summarizes dispersion or clonal diversity in the PSA glycoform profile. When examined across clinical stages, a well-calibrated $G_{composite}$ would be expected to show higher average values in more advanced or aggressive disease, but with broad, overlapping distributions rather than discrete, non-overlapping clusters. Figure 3 provides a literature-derived quantitative illustration of the composite index behavior across stages based on the numbers in Supplementary Table S1.

Composite index values were calculated for each clinical stage using literature-derived glycosylation feature ranges combined according to the data in Supplementary Table S1(1-4) (section 18). Bars indicate index values computed from normalized feature midpoints using fixed weights applied uniformly across stages. Error bars represent the minimum–maximum index values obtained by propagating reported feature ranges through normalization and weighting. Negative error-bar extents reflect propagated uncertainty in normalized composite values and do not imply negative biological quantities.

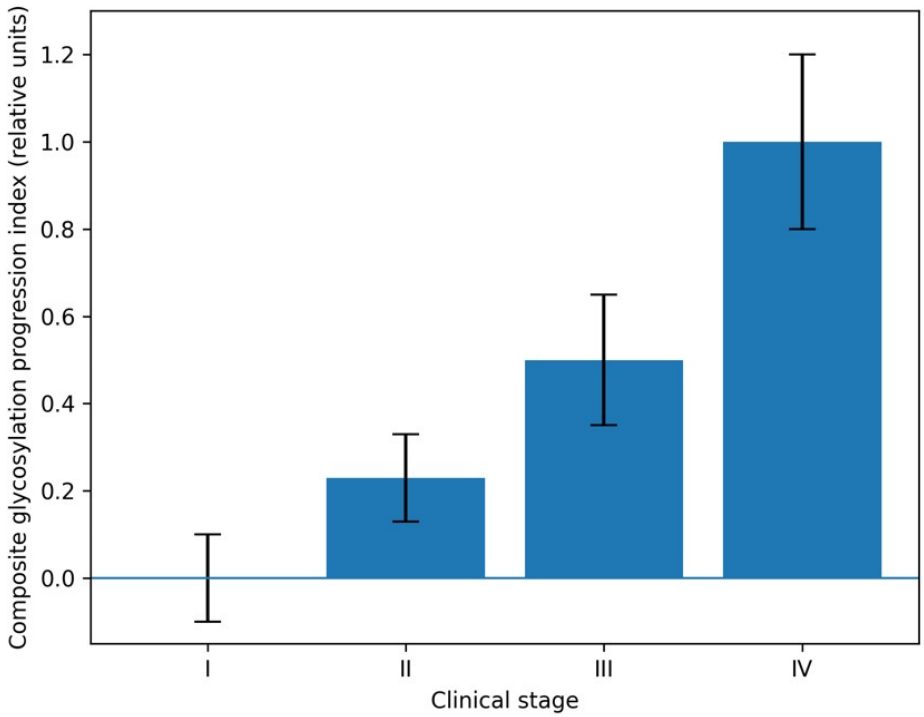

Figure 3. Composite glycosylation progression index across stages, from Supplementary Table S1(1-4)

11. Addressing underrepresented data in treatment outcomes

In addition to biochemical validation, patient experience and functional outcomes remain essential components of any future diagnostic framework. Many existing studies emphasize survival statistics but do not focus enough on quality of life. Important data such as long-term urinary, bowel, sexual, and emotional effects of treatment are often overlooked or underreported, especially in younger patients. For instance, two treatments may yield similar survival outcomes, but one may lead to significant incontinence or erectile dysfunction.

Long-term PROs should be systematically collected across all treatment types and stages. These include validated questionnaires administered annually after treatment. Collecting and comparing these data can help guide treatment recommendations not just for longevity, but for life satisfaction. This data should be incorporated into future guidelines.

12. Diagnostic precision and research design

12.1 Advancing non-invasive diagnostics

Emerging technologies, including liquid biopsies, AI-enhanced imaging, and urine-based genomic assays, have demonstrated potential to improve the accuracy of disease staging and the monitoring of treatment response while minimizing invasiveness. Consequently, these tools may reduce dependence on traditional tissue biopsies and facilitate real-time, individualized clinical decision-making based on disease progression.

12.2 The need for stage-specific research studies

Many clinical trials enroll broad groups of prostate cancer patients without focusing on stage-specific effectiveness. As a result, data often do not differentiate which treatment works best at any one particular stage. This makes it difficult for physicians to make precise recommendations for a patient with, for example, Stage IIB cancer versus a patient with a Stage IIIB cancer. Future studies should be stratified by stage and by relevant variables such as PSA levels and Gleason grade. Trials should also examine how treatment combinations work differently in early versus late-stage disease. Only through targeted research will more accurate, stage-appropriate treatment pathways be developed. A key limitation in current prostate cancer research is the underrepresentation of stage stratified treatment outcomes in clinical trials. Studies that group patients across diverse clinical stages often fail to capture the differential responses to treatment, which limits the applicability of the findings in the real-world. Future research should prioritize stage-specific trial designs, which integrates variables like PSA, doubling time, tumor genomics, and treatment resistance timelines to guide more tailored interventions.

13. Limitations

Several important limitations should be recognized when interpreting PSA glycosylation patterns and considering their potential integration into clinical decision pathways. As mentioned earlier, Glycan alterations, including shifts in sialylation linkages, increases in core fucosylation, modifications in N-glycan branching, and the presence of truncated O-glycans, reflect cellular phenotype rather than the anatomical extent of disease. For this reason, glycosylation features cannot determine T, N, or M stage. Any association between glycan measures and cancer stage are better viewed as probability-shifting signals, since the distributions of glycan values overlap substantially across clinical groups.

A second limitation involves the nature of the existing evidence base. Much of what is known about PSA glycosylation comes from small, discovery-phase studies performed at single centers, often using highly controlled laboratory conditions. These studies do not fully represent real-world populations that include individuals with BPH, prostatitis, metabolic conditions, or other sources of biological variation. As a result, the effect sizes in early glycomics reports may be larger than those observed in routine clinical settings.

Analytical variability presents a third challenge. Differences in sample preparation, lectin specificity, enrichment protocols, derivatization chemistry, ionization efficiency, and glycopeptide coverage can lead to inconsistent measurements across platforms. Even though advances in mass-spectrometry-based glycomics allow detailed structural characterization of complex glycan mixtures (66), without standardized workflows, it is difficult to define cut-points or composite indices that can be reproduced across laboratories.

Longitudinal stability is another area that requires further study. It remains unclear whether changes in PSA glycan signatures over time represent true biological evolution of the tumor or whether they reflect pre-analytical

variation and measurement noise. Large prospective studies with repeated sampling and standardized analysis methods are needed to clarify intra-patient variability.

Finally, even when glycosylation features correlate with adverse pathology, biochemical recurrence, upgrading, or metastatic progression, this does not establish clinical utility. To determine whether glycan-based markers add value beyond current tools, they must be compared directly with established diagnostics such as PSA density, the Prostate Health Index, multiparametric MRI, and genomic classifiers. Until such comparative evidence becomes available, PSA glycosylation patterns should be considered emerging investigational biomarkers rather than a validated instrument for treatment selection or staging.

14. Using existing patterns to improve future treatment

Patients who receive aggressive combination therapy early in advanced-stage disease often experience better outcomes than those treated in a sequential manner. This suggests that early identification of non-response and treatment intensification may improve both survival and quality of life.

More work is needed to formalize these patterns into clinical guidelines. For instance, patients showing any type of PSA resistance within 6–12 months of ADT should be considered for early combination therapy. Similarly, monitoring PSA trends and side effect profiles in real time should become standard practice. By implementing response-based treatment adjustments, physicians can better manage disease progression.

15. Future research and equity in care

Several underrepresented domains in prostate cancer care warrant focused investigation to advance equity and patient centered outcomes. Disparities in access to advanced treatments, particularly among socioeconomically disadvantaged and racially marginalized populations, continue to be a significant barrier to optimal care and should be addressed through inclusive research design and health policy reform. Moreover, the long-term psychological and functional consequences of prostate cancer treatment such as depression, anxiety, and sexual dysfunction require systematic evaluation through validated patient reported outcomes. In addition, lifestyle related factors, including physical activity, nutrition, and inflammation-modulating behaviors, suggest further study for their potential to improve prognosis and reduce recurrence. For example, physical activity may improve immune surveillance and hormone regulation, while dietary changes could support metabolic health and treatment tolerance. Clinical care teams should include these components in survivorship plans and evaluate them using standardized metrics.

In addition to various biomedical treatment strategies, lifestyle and behavioral interventions could also have the potential to influence prostate cancer outcomes. Physical activity, plant-based or anti-inflammatory diets, and weight management have been shown to decrease disease progression and improve the quality of life. Furthermore, activities like mindfulness meditation, acupuncture, and yoga have shown efficacy in reducing fatigue that occurs due to treatment. These approaches can enhance overall treatment tolerability and patient satisfaction and should be evaluated

through well-designed clinical studies. Moreover, PROs should be standardized across care centers and collected at regular intervals. These metrics should be embedded into clinical guidelines, serving as benchmarks for assessing functional recovery, psychological health, and satisfaction with care.

16. Conclusion

To improve prostate care, it is vital to address key gaps in staging accuracy, treatment personalization, and patient reported outcomes. Additionally, there is a need for a model that integrates clinical indicators with treatment response and patient-specific patterns.

There should also be emphasis on the importance of long-term outcome tracking, especially for a good and functional quality of life. Future research should focus on building adaptive, stage-specific, and feedback-driven treatment models. Clinical trials must better reflect real-world variability by stratifying patients based on stage and biologic features. Ultimately, treatment success should be measured not only in years of survival but in the preserved quality of life.

Glycosylation of PSA provides mechanistic specificity that bulk PSA cannot. Cancer-associated remodeling—particularly α2,3-biased sialylation, core fucosylation, increased branching, and O-glycan truncation—is biologically plausible and consistent with pathways that promote invasion, immune evasion, and metastatic seeding. A composite glycan index aggregating malignant glycoforms into a single score has already demonstrated strong rule-in performance in discovery-phase work and in differentiating BPH from cancer, indicating immediate diagnostic potential while motivating larger validation (13,16,17).

If supported prospectively, glycan-aware metrics could influence clinical decision-making at three junctures: pre-biopsy triage; selection between surveillance and definitive therapy in Grade Group 1–2 disease; and timing of escalation in biochemical recurrence or oligometastatic states. Priority areas include multi-center harmonization, transparent reporting of analytical variability, and clear, stage-specific clinical endpoints such that glycan-guided algorithms can be compared against established risk tools and integrated into response-adapted pathways (12–16).

Moving forward, prostate cancer management must evolve toward a model that is not only personalized but also predictive and proactive. Integrating AI tools, lifestyle interventions, and state specific data into clinical practice will enable more precise, timely, and patient centered care. Ultimately, success should be measured not only in survival rates, but also in preserved function, psychological wellbeing, and quality of life.

Acknowledgments

The author would like to thank Ngozi Akingbesote for their guidance, technical feedback, and mentorship throughout the research and manuscript preparation process. Their insights substantially improved the clarity and rigor of this review.

17. References

1. CDC. (2021, June). USCS data visualizations. Gis.cdc.gov. https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/

2. Doyle-Lindrud, S. (2007). Prostate cancer: a chronic illness. *Clinical Journal of Oncology Nursing*, 11(6), 857–861. https://doi.org/10.1188/07.CJON.857-861

3. Wong, R. S. (2011). Apoptosis in cancer: from pathogenesis to treatment. *Journal of Experimental & Clinical Cancer Research*, 30(1). https://doi.org/10.1186/1756-9966-30-87

4. Gerstberger, S., Jiang, Q., Ganesh, K. (2023). Metastasis. *Cell*, 186(8), 1564–1579. https://doi.org/10.1016/j.cell.2023.03.003

5. Schiliro, C., Firestein, B. L. (2021). Mechanisms of Metabolic Reprogramming in Cancer Cells Supporting Enhanced Growth and Proliferation. *Cells*, 10(5), 1056. https://doi.org/10.3390/cells10051056

6. Kim, S. K., Cho, S. W. (2022). The evasion mechanisms of cancer immunity and drug intervention in the tumor microenvironment. *Frontiers in Pharmacology*, 13, Article 868695. https://doi.org/10.3389/fphar.2022.868695

7. Yao, Y., Dai, W. (2014). Genomic Instability and Cancer. *Journal of Carcinogenesis & Mutagenesis*, 5, Article 1000165. https://doi.org/10.4172/2157-2518.1000165

8. Munjal, A., Leslie, S. W. (2023). *Gleason score*. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK553178/

9. Raychaudhuri, R., Lin, D. W., Montgomery, R. B. (2025). Prostate Cancer, A review. *JAMA*, 333(16), 1433-1446. https://doi.org/10.1001/jama.2025.0228

10. Cheng, L., Montironi, R., Bostwick, D. G., Lopez-Beltran, A.,Berney, D. M. (2012). Staging of Prostate Cancer. *Histopathology*, 60(1),87-117. https://doi.org/10.1111/j.1365-2559.2011.04025.x

11. Lee, H., Lee, M., Byun, S.-S., Lee, S. E., Hong, S. K. (2019). Evaluation of Prostate Cancer Stage Groups Updated in the 8th Edition of the American Joint Committee on Cancer Tumor–Node–Metastasis Staging Manual. *Clinical Genitourinary Cancer*, 17(1), e221–e226. https://doi.org/10.1016/j.clgc.2018.10.015

12. Liu, Y., Hatano, K., Nonomura, N. (2024). Liquid Biomarkers in Prostate Cancer Diagnosis: Current Status and Emerging Prospects. *World Journal of Men's Health*, 43(1), 8-27. https://doi.org/10.5534/wjmh.230386

13. Saldova, R., Fan, Y., Fitzpatrick, J. M., Watson, R. W. G., Rudd, P. M. (2011). Core fucosylation and 2-3 sialylation in serum N-glycome is significantly increased in prostate cancer comparing to benign prostate hyperplasia. *Glycobiology*, 21(2), 195–205. https://doi.org/10.1093/glycob/cwq147

14. Pinho, S. S., Reis, C. A. (2015). Glycosylation in cancer: mechanisms and clinical implications. *Nature Reviews. Cancer*, 15(9), 540–555. https://doi.org/10.1038/nrc3982

15. Fujita, K., Hatano, K., Tomiyama, E., Hayashi, Y., Matsushita, M., Tsuchiya, M., et al. (2021). Serum core-type fucosylated prostate-specific antigen index for the detection of high-risk prostate cancer. *International Journal of Cancer*, 148(12), 3111–3118. https://doi.org/10.1002/ijc.33517

16. Hatano, K., Yoneyama, T., Hatakeyama, S., Tomiyama, E., Tsuchiya, M., Nishimoto, M., et al. (2022). Simultaneous analysis of serum α2,3-linked sialylation and core-type fucosylation of prostate-specific antigen for the detection of high-grade prostate cancer. *British Journal of Cancer*, 126(5), 764–770. https://doi.org/10.1038/s41416-021-01637-x

17. Bertok, T., Jane, E., Bertokova, A., Lorencova, L., Zvara, P., Smolkova, B. et al. (2020). Validating fPSA Glycoprofile as a Prostate Cancer Biomarker to Avoid Unnecessary Biopsies and Re-Biopsies. *Cancers*, 12(10), 2988.https://doi.org/10.3390/cancers12102988

18. Varki, A. (2017). Biological roles of glycans. *Glycobiology*, 27(1), 3–49. https://doi.org/10.1093/glycob/cww086

19. Slevin, F., Zattoni, F., Checcucci, E., Cumberbatch, M. G. K., Nacchia, A., Cornford, P., Briers, E., et al. (2024). A Systematic Review of the Efficacy and Toxicity of Brachytherapy Boost Combined with External Beam Radiotherapy for Nonmetastatic Prostate Cancer. *European Urology Oncology*, 7(4), 677–696.https://doi.org/10.1016/j.euo.2023.11.018

20. Tseng, Y. D. (2023). Radiation Therapy for Painful Bone Metastases: Fractionation, Recalcification, and Symptom Control. *Seminars in Radiation Oncology*, 33(2), 139–147. https://doi.org/10.1016/j.semradonc.2022.11.004

21. Akimoto, T., Aoyama, H., Chua M. L. K., Song, S. Y., , Zeidan, Y. H., Sharma, R. A., et al. (2023). Challenges and Opportunities With the Use of Hypofractionated Radiation Therapy in Cancer Care: Regional Perspectives From South Korea, Japan, Singapore,

and Australia. *Advances in Radiation Oncology*, 8(6), 101291. https://doi.org/10.1016/j.adro.2023.101291

22. Fischer-Valuck, B. W., Rao, Y. J., Michalski, J. M. (2018). Intensity-modulated radiotherapy for prostate cancer. *Translational Andrology and Urology*, 7(3), 297–307. https://doi.org/10.21037/tau.2017.12.16

23. Morris, W. J., Tyldesley, S., Rodda, S., Morton, G., Hamm, J., Murray, N., et al. (2017). Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. *International Journal of Radiation Oncology, Biology, Physics*, 98(2), 275–285. https://doi.org/10.1016/j.ijrobp.2016.11.026

24. American Cancer Society. (2023, November 22). *Radiation Therapy for Prostate Cancer.* Www.cancer.org. https://www.cancer.org/cancer/types/prostate-cancer/treating/radiation-therapy.html

25. Osman, S. O. S., Jeevanandam, P., Kanakavelu, N., Irvine, D. M., Lyons, C. A., Jain, S., Hounsell, A. R., McGarry, C. K. (2016). Class solutions for SABR-VMAT for high-risk prostate cancer with and without elective nodal irradiation. Radiation Oncology, 11, Article 155. https://doi.org/10.1186/s13014-016-0730-7

26. Pan, H. Y., Jiang, J., Hoffman, K. E., Tang, C., Choi, S. L., Nguyen, Q.-N., Frank, S. J., Anscher, M. S., Shih, Y.-C. T., Smith, B. D. (2018). Comparative Toxicities and Cost of Intensity-Modulated Radiotherapy, Proton Radiation, and Stereotactic Body Radiotherapy Among Younger Men With Prostate Cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *36*(18), 1823–1830. https://doi.org/10.1200/JCO.2017.75.5371

27. Secin, F. P., Bianco, F. J., Cronin, A., Eastham, J. A., Scardino, P. T., Bertrand Guillonneau, Vickers, A. J. (2009). Is it Necessary to Remove the Seminal Vesicles Completely at Radical Prostatectomy? Decision Curve Analysis of European Society of Urologic Oncology Criteria. *the Journal of Urology/the Journal of Urology*, *181*(2), 609–614. https://doi.org/10.1016/j.juro.2008.10.035

28. Ma, J., Xu, W., Chen, R., Zhu, Y., Wang, Y., Cao, W., et al. (2023). Robotic-assisted versus laparoscopic radical prostatectomy for prostate cancer: the first separate systematic review and meta-analysis of randomised controlled trials and non-randomised studies. *International Journal of Surgery*, 109(5), 1350–1359. https://doi.org/10.1097/js9.0000000000000193

29. Haglind, E., Carlsson, S., Stranne, J., Wallerstedt, A., Wilderäng, U., Thorsteinsdottir, T., et al. (2015). Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. *European Urology*, 68(2), 216–225. https://doi.org/10.1016/j.eururo.2015.02.029

30. Bahn, D. K., Lee, F., Badalament, R., Kumar, A., Greski, J., Chernick, M. (2002). Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. *Urology*, 60(2 Suppl 1), 3–11. https://doi.org/10.1016/s0090-4295(02)01678-3

31. Kassab, J., Meeks, R., de Riese, W. (2024). Current Clinical Aspects of Androgen Deprivation Therapy for Locally Advanced and Metastatic Prostate Cancer: A Scoping Review for Urologists and Medical Providers. *Research and Reports in Urology*, 16, 187–193. https://doi.org/10.2147/rru.s467344

32. Armandari, I., Hamid, A. R., Verhaegh, G., Schalken, J. (2014). Intratumoral steroidogenesis in castration-resistant prostate cancer: a target for therapy. *Prostate International*, 2(3), 105–113. https://doi.org/10.12954/pi.14063

33. Atta, M. A., Elabbady, A., Sameh, W., Sharafeldeen, M., Elsaqa, M. (2020). Is there still a role for bilateral orchidectomy in androgen-deprivation therapy for metastatic prostate cancer? *Arab Journal of Urology*, 18(1), 9–13. https://doi.org/10.1080/2090598x.2019.1690270

34. Stein, M. N., Vinceneux, A., Robbrecht, D., Doger, B., Autio, K. A., Schweizer, M. T., et al. (2025). Pasritamig, a First-in-Class, Bispecific T-Cell Engager Targeting Human Kallikrein 2, in Metastatic Castration-Resistant Prostate Cancer: A Phase 1 Study. *Journal of Clinical Oncology*, 43(22), 2515-2526. https://doi.org/10.1200/jco-25-00678

35. Antonarakis, E. S., Subudhi, S. K., Pieczonka, C. M., Karsh, L. I., Quinn, D. I., Hafron, J. M., et al. (2023). Combination Treatment with Sipuleucel-T and Abiraterone Acetate or Enzalutamide for Metastatic Castration-Resistant Prostate Cancer: STAMP and STRIDE Trials. *Clinical Cancer Research*, 29(13), 2426–2434. https://doi.org/10.1158/1078-0432.ccr-22-3832

36. de Wit, R., de Bono, J., Sternberg, C. N., Fizazi, K., Tombal, B., Wülfing, C., et al. (2019). Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. *New England Journal of Medicine*, 381(26), 2506-2518. https://doi.org/10.1056/nejmoa1911206

37. Tannock, I. F., de Wit, R., Berry, W. R., Horti, J., Pluzanska, A., Chi, K. N., et al. (2004). Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. *New England Journal of Medicine*, 351(15), 1502–1512. https://doi.org/10.1056/nejmoa040720

38. Payton, S. (2011). Intermediate-risk patients on radiotherapy benefit from addition of short-term ADT. *Nature Reviews Urology*, 8(9), 469. https://doi.org/10.1038/nrurol.2011.121

39. Zuur, L. G., deBarros, H. A., van der Mijn, K. J. C.,Vis, A. N., Bergman, A. M., Pos, F. J., van Moorselaar, J. A., et al. (2023). Treating Primary Node-Positive Prostate Cancer: A Scoping Review of Available Treatment Options. *Cancers*, 15(11), 2962. https://doi.org/10.3390/cancers15112962

40. Crain, D. S., Amling, C. L., Kane, C. J. (2004). Palliative Transurethral Prostate Resection for Bladder Outlet Obstruction in Patients With Locally Advanced Prostate Cancer. *Journal of Urology*, 171(2), 668–671. https://doi.org/10.1097/01.ju.0000104845.24632.92

41. Hamdy, F. C., Donovan, J. L., Lane, J. A., Metcalfe, C., Davis, M., Turner, E. L., et al. (2023). Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *New England Journal of Medicine*, 388(17), 1547-1558. https://doi.org/10.1056/nejmoa2214122

42. Pritchard, C. C., Mateo, J., Walsh, M. F., De Sarkar, N., Abida, W., Beltran, H., et al. (2016). Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. *New England Journal of Medicine*, 375(5), 443–453. https://doi.org/10.1056/nejmoa1603144

43. Hussain, M., Mateo, J., Fizazi, K., Saad, F., Shore, N., Sandhu, S., et al. (2020). Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. *New England Journal of Medicine*, 383(24), 2345–2357. https://doi.org/10.1056/nejmoa2022485

44. Viani, G. A., Viana, B. S., Martin, J. E. C., MedPhys, B. T. R., Zuliani, G., Stefano, E. J. (2016). Intensity-modulated radiotherapy reduces toxicity with similar biochemical control compared with 3-dimensional conformal radiotherapy for prostate cancer: A randomized clinical trial. *Cancer*, 122(13), 2004–2011. https://doi.org/10.1002/cncr.29983

45. Nguyen, P. L., Alibhai, S. M. H., Basaria, S., D'Amico, A. V., Kantoff, P. W., Keating, N. L., et al. (2015). Adverse Effects of Androgen Deprivation Therapy and Strategies to Mitigate Them. *European Urology*, 67(5), 825–836. https://doi.org/10.1016/j.eururo.2014.07.010

46. Chin, Y. F., Lynn, N. (2022). Systematic Review of Focal and Salvage Cryotherapy for Prostate Cancer. *Cureus*, 14(6), e26400. https://doi.org/10.7759/cureus.26400

47. Chen, R. C., Basak, R., Meyer, A.-M., Kuo, T.-M., Carpenter, W. R., Agans, R. P., et al. (2017). Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. *JAMA*, 317(11), 1141-1150. https://doi.org/10.1001/jama.2017.1652

48. Jones, C. U., Hunt, D., McGowan, D. G., Amin, M. B., Chetner, M. P., Bruner, D. W., et al. (2011). Radiotherapy and Short-Term Androgen Deprivation for Localized Prostate Cancer. *New England Journal of Medicine*, 365(2), 107–118. https://doi.org/10.1056/nejmoa1012348

49. Donovan, J. L., Hamdy, F. C., Lane, J. A., Mason, M., Metcalfe, C., Walsh, E., et al. (2016). Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *New England Journal of Medicine*, 375(15), 1425–1437. https://doi.org/10.1056/nejmoa1606221

50. Wallis, C. J. D., Zhao, Z., Huang, L.-C., Penson, D. F., Koyama, T., Kaplan, S. H., et al. (2022). Association of Treatment Modality, Functional Outcomes, and Baseline Characteristics With Treatment-Related Regret Among Men With Localized Prostate Cancer. *JAMA Oncology*, 8(1), 50–59. https://doi.org/10.1001/jamaoncol.2021.5160

51. Vale, C. L., Fisher, D., Kneebone, A., Parker, C., Pearse, M., Richaud, P., et al. (2020). Adjuvant or early salvage radiotherapy for the treatment of localized and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *The Lancet*, 396(10260), 1422–1431. https://doi.org/10.1016/S0140-6736(20)31952-8

52. Smith, M. R., Egerdie, B., Toriz, N. H., Feldman, R., Tammela, T. L. J., Saad, F., et al. (2009). Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer. *New England Journal of Medicine*, 361(8), 745–755. https://doi.org/10.1056/NEJMoa0809003

53. Sartor, O., de Bono, J., Chi, K. N., Fizazi, K., Herrmann, K., Rahbar, K., et al. (2021). Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *New England Journal of Medicine*, 385(12), 1091–1103. https://doi.org/10.1056/nejmoa2107322

54. Chi, K. N., Agarwal, N., Bjartell, A., Chung, B. H., Pereira de Santana Gomes, A. J., Given, R., et al. (2019). Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *New England Journal of Medicine*, 381(1), 13–24. https://doi.org/10.1056/nejmoa1903307

55. Davis, I. D., Martin, A. J., Stockler, M. R., Begbie, S., Chi, K. N., Chowdhury, S., et al. (2019). Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *New England Journal of Medicine*, 381(2), 121–131. https://doi.org/10.1056/NEJMoa1903835

56. Fizazi, K., Foulon, S., Carles, J., Roubaud, G., McDermott, R., Fléchon, A., et al. (2022). Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet (London, England)*, *399*(10336), 1695–1707. https://doi.org/10.1016/S0140-6736(22)00367-1

57. Garcia, J. A. (2011). Sipuleucel-T in patients with metastatic castration-resistant prostate cancer: an insight for oncologists. *Therapeutic Advances in Medical Oncology*, 3(2), 101–108. https://doi.org/10.1177/1758834010397692

58. Fizazi, K., Carducci, M., Smith, M., Damião, R., Brown, J., Karsh, L., et al. (2011). Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *The Lancet*, 377(9768), 813–822. https://doi.org/10.1016/s0140-6736(10)62344-6

59. Sweeney, C. J., Chen, Y.-H., Carducci, M., Liu, G., Jarrard, D. F., Eisenberger, M., et al. (2015). Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *New England Journal of Medicine*, 373(8), 737–746. https://doi.org/10.1056/nejmoa1503747

60. Fizazi, K., Tran, N., Fein, L., Matsubara, N., Rodriguez-Antolin, A., Alekseev, B. Y., et al. (2017). Abiraterone plus Prednisone in Metastatic, CastrationSensitive Prostate Cancer. *New England Journal of Medicine*, 377(4), 352–360. https://doi.org/10.1056/nejmoa1704174

61. Hofman, M. S., Emmett, L., Sandhu, S., Iravani, A., Joshua, A. M., Goh, J. C., et al. (2021). [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *The Lancet*, 397(10276), 797–804. https://doi.org/10.1016/s0140-6736(21)00237-3

62. Hofman, M. S., Lawrentschuk, N., Francis, R. J., Tang, C., Vela, I., Thomas, P., et al. "Prostate-Specific Membrane Antigen PET-CT in Patients with High-Risk Prostate Cancer before Curative-Intent Surgery or Radiotherapy (ProPSMA): A Prospective, Randomised, Multicentre Study." *The Lancet*, 395(10231), 1208–1216. https://doi.org/10.1016/S0140-6736(20)30314-7

63. Sanda, M. G., Dunn, R. L., Michalski, J., Sandler, H. M., Northouse, L., Hembroff, L., et al. (2008). Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors. *New England Journal of Medicine*, 358(12), 1250–1261. https://doi.org/10.1056/nejmoa074311

64. Szymanski, K. M., Wei, J. T., Dunn, R. L., Sanda, M. G. (2010). Development and Validation of an Abbreviated Version of the Expanded Prostate Cancer Index Composite Instrument for Measuring Health-related Quality of Life Among Prostate Cancer Survivors. *Urology*, 76(5), 1245–1250. https://doi.org/10.1016/j.urology.2010.01.027

65. Koskderelioglu, A., Gedizlioglu, M., Ceylan, Y., Gunlusoy, B., Kahyaoglu, N. (2017). Quality of sleep in patients receiving androgen deprivation therapy for prostate cancer. *Neurol. Sci*., 38(8), 1445-1451.https://doi.org/10.1007/s10072-017-2989-3

66. Zaia, J. (2010). Mass Spectrometry and Glycomics. *OMICS: A Journal of Integrative Biology*, 14(4), 401–418. https://doi.org/10.1089/omi.2009.0146

67. Wang, X., Chen, J., Li, Q. K., Peskoe, S. B., Zhang, B., Choi, C., et al. (2014). Overexpression of α (1,6) fucosyltransferase associated with aggressive prostate cancer. *Glycobiology*, 24(10), 935–944. https://doi.org/10.1093/glycob/cwu051

68. Llop, E., Ferrer-Batallé, M., Barrabés, S., Guerrero, P. E., Ramírez, M., Saldova, R., et al. (2016). Improvement of Prostate Cancer Diagnosis by Detecting PSA Glycosylation-Specific Changes. *Theranostics*, 6(8), 1190–1204. https://doi.org/10.7150/thno.15226

69. Wong, N., Major, P., Kapoor, A., Wei, F., Yan, J., Aziz, T., et al. (2016). Amplification of MUC1 in prostate cancer metastasis and CRPC development. *Oncotarget*, 7, 83115–83133. https://doi.org/10.18632/oncotarget.13073

18. Supplementary Materials

Feature-level literature ranges, representative midpoints, normalization, weights, weighted contributions, and composite glycosylation index values across clinical stages are presented in Supplementary Table S1(1-4). These concepts are quantitatively explored across clinical stages using a composite glycosylation index (Figure 2).

Supplementary Table S1(1-4) presents the full stage-wise dataset used to construct the composite glycosylation progression index. For each clinical stage and substage, literature-derived ranges are reported for individual glycosylation features along with representative midpoints. Where stage-specific quantitative values were not directly available, estimates were generated by linear interpolation within biologically plausible bounds. All features were normalized on a 0–1 scale across stages, weighted using fixed coefficients, and combined to compute the composite index shown in Figure 2. Normalized values of 0 or 1 indicate minimum or maximum observed midpoints following min–max scaling. Composite index totals represent the sum of weighted normalized feature values and are not intended to imply non-overlapping stage-specific thresholds.

Feature values were derived from published figures and tables (16, 67-68). Where specific stage values were unavailable, linear interpolation between adjacent stages was applied. Midpoints were min–max normalized across stages for each feature. Normalized values were derived using min–max scaling across all stages; therefore, Stage I values normalize to zero by construction and Stage IV values normalize to one. Fixed heuristic weights were applied uniformly across stages. Composite index scores were computed as the sum of weighted normalized feature values. For each feature and stage, the cited reference corresponds to the primary source from which the numerical range was extracted; when stage-specific values were not explicitly reported, ranges were estimated by linear interpolation between adjacent stages and are labeled accordingly. Moreover, Interpolated indicates that stage-specific quantitative values were not

explicitly reported in the source study and were adjacent stage anchors within biologically estimated by linear interpolation between plausible bounds.

Supplementary Table S1-1. Glycan feature values for Stage I

Feature	Literature range	Reference	Midpoint	Normalized value	Weight (w)	Weighted contribution
α2,3/α2,6 sialylation	0.65–0.75	Hatano et al., (16), Fig. 2a–b	0.7	0	0.35	0
Core fucosylation	0.25–0.35	Wang et al.,(67),Wong et al.,(69), interpolated	0.3	0	0.25	0
Glycan branching	0.10–0.20	Wang et al.,(67), Fig. 4, interpolated	0.15	0	0.2	0
Truncated O-glycans (Peak 4)	0.02–0.05	Llop et al.,(68), Wong et al.,(70), interpolated	0.035	0	0.1	0
Glycan heterogeneity	0.05–0.15	Hatano et al.,(16), interpolated	0.1	0	0.1	0
Composite index	--	--	--	--	--	0

Supplementary Table S1-2. Glycan feature values for Stage II

Feature	Literature range	Reference	Midpoint	Normalized value	Weight (w)	Weighted contribution
α2,3/α2,6 sialylation	0.75–0.95	Hatano et al.,(16), interpolated	0.85	0.23	0.35	0.081
Core fucosylation	0.30–0.45	Wang et al.,(67), Wong et al.,(69), interpolated	0.375	0.23	0.25	0.058
Glycan branching	0.20–0.40	Wang et al.,(67), interpolated	0.3	0.23	0.2	0.046
Truncated O-glycans (Peak 4)	0.04–0.08	Llop et al.,(69), Wong et al., 69), interpolated	0.06	0.23	0.1	0.023
Glycan heterogeneity	0.15–0.35	Hatano et al.,(16), interpolated	0.25	0.23	0.1	0.023
Composite index	--	---	--	--	--	0.23

Supplementary Table S1-3. Glycan feature values for Stage III

Feature	Literature range	Reference	Midpoint	Normalized value	Weight (w)	Weighted contribution
α2,3/α2,6 sialylation	1.05–1.30	Hatano et al.,(16)	1.175	0.5	0.35	0.175
Core fucosylation	0.45–0.55	Wang et al.,(67), Wong et al.,(69)	0.5	0.5	0.25	0.125
Glycan branching	0.50–0.65	Wang et al.,(67), Fig. 4	0.575	0.5	0.2	0.1
Truncated O-glycans (Peak 4)	0.08–0.10	Llop et al.,(68), Wong et al.,(69)	0.09	0.5	0.1	0.05
Glycan heterogeneity	0.45–0.65	Hatano et al.,(16)	0.55	0.5	0.1	0.05
Composite index	--	--	--	--	--	0.5

Supplementary Table S1-4. Glycan feature values for Stage IV

Feature	Literature range	Reference	Midpoint	Normalized value	Weight (w)	Weighted contribution
α2,3/α2,6 sialylation	1.60–2.00	Hatano et al.(16)	1.8	1	0.35	0.35
Core fucosylation	0.75–0.90	Wang et al.,(67), Wong et al.,(69)	0.825	1	0.25	0.25
Glycan branching	0.85–1.20	Wang et al.,(67)	1.025	1	0.2	0.2
Truncated O-glycans (Peak 4)	0.18–0.25	Llop et al.,(68), Wong et al.,(69)	0.215	1	0.1	0.1
Glycan heterogeneity	0.75–1.00	Hatano et al.,(16)	0.875	1	0.1	0.1
Composite index	--	--	--	--	--	1.00

Appendix 1. Data sources and derivation of conceptual figures

Figure 1 presents a conceptual summary of reported PSA glycosylation trends, while Figure 2 presents a quantitative, literature-derived composite index, constructed from the values in Supplementary Table S1(1-4). Figure 1 was constructed as a qualitative integration of published literature, while Figure 2 was quantitatively derived from literature-reported feature ranges rather than from a single consolidated patient dataset. Trend orientations, mean shifts, and overlap patterns were based on findings from Saldova et al. (13), Fujita et al. (15), Hatano et al. (16), Bertok et al. (17), Pinho et al. (14), and related glycomics investigations that examined α2,3- and α2,6-linked sialylation, core fucosylation, N-glycan branching, and O-glycan truncation in prostate cancer.

Since available studies differ in patient populations, analytical platforms, and reporting formats, no unified stage-specific numeric dataset exists from which standardized values, error bars, or distributional parameters can be calculated. As stated, Figure 1 is a conceptual schematic summarizing qualitative trends reported across studies. Figure 2 is quantitatively derived from literature-based feature ranges using the procedure described in Section 1.3 and detailed in Supplementary Table S1.

For each clinical stage group (I–IV), literature-derived ranges were compiled for each glycosylation feature, with individual feature ranges traced to specific figures or tables in the cited references and recorded directly in Supplementary Table S1. A representative midpoint was recorded for each feature, and where direct stage-specific quantitative data were unavailable, values were estimated within stage bounds to preserve continuity across stages. Midpoints were normalized using min–max scaling across all stages for each feature independently. Fixed weights ($w_1 = 0.35$, $w_2 = 0.25$, $w_3 = 0.20$, $w_4 = 0.10$, $w_5 = 0.10$) were applied uniformly across all stages. Weighted contributions were calculated as the product of the normalized value and its corresponding weight, and the composite index total for each stage was computed as the sum of the five weighted contributions. Full numerical details are provided in Supplementary Table S1.