

Review

The Role of Genitourinary Microbiome in Male Cancer Etiology and Progression: Insights from Next-Generation Sequencing and Meta-Omics

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Abstract

Male genitourinary (mGU) malignancies, including prostate, bladder, kidney, testicular, and penile cancers, represent a clinically and epidemiologically significant subset of global cancer burden. Although well-established etiological factors such as genetic mutations, androgen signaling, and environmental exposures contribute to tumorigenesis, the underlying mechanisms remain ill-defined. Recent advances in next-generation sequencing and metagenomics technologies have facilitated a deeper understanding of the human microbiome, revealing its potential role in carcinogenesis. While the gut microbiome has been extensively studied, emerging evidence indicates that site-specific microbial communities within the genitourinary (GU) tract may significantly influence cancer susceptibility, progression, and therapeutic outcomes. Accordingly, this review aims to comprehensively summarize the current evidence examining the relationship between the GU microbiome and the development, progression, and treatment of mGU cancers. To provide the specific context, relevant publications were collected from Google Scholar, PubMed, Science Direct, Dimension AI, and EBSCO Host using specific keywords such as “bladder cancer”, “dysbiosis”, “genitourinary”, “genitourinary cancer”, “microbiome”, “pathogens”, “penile cancer”, “prostate cancer”, “renal cancer”, “testicular cancer”, “urogenital microbiome”. We did not add any limits to the publication date during the inclusion of papers. However, it is noteworthy that the initial reports, including the aforementioned keywords, have been published since 2015. Emerging evidence highlights a significant association between the dysbiosis of the GU microbiome and the development of mGU cancers. Notably, an increase in bacterial richness and species diversity has been correlated with a rapid progression of these cancers, suggesting that such features may be explored as potential candidate biomarkers. Advanced sequencing and meta-omics technologies have enabled the identification of distinct microbial signatures with emerging diagnostic, prognostic, and therapeutic potential. Despite these advancements, the understanding of the functional and mechanistic roles of microbiota, particularly within the penile and seminal environments, remains limited.

Keywords: bladder cancer; dysbiosis; genitourinary; genitourinary cancer; microbiome; pathogens; penile cancer; prostate cancer; renal cancer; testicular cancer; urogenital microbiome



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1. Introduction

Globally, cancer remains one of the most formidable health challenges, posing a significant threat to millions of lives every year. According to the latest global cancer statistics, GLOBOCAN 2020 projected a remarkable increase in cancer cases to 28.4 million in 2040 from 19.3 million in 2020 [1]. Among this growing global burden, cancers affecting the male genitourinary (mGU) system represent a significant and alarming subset [2]. These include prostate, bladder, kidney, testicular, and penile malignancies, which collectively contribute to a substantial proportion of cancer-related morbidity and mortality in men.

Among these, prostate cancer (PC) is the most prominent genitourinary (GU) malignancy in men, with an estimated 288,300 new cases in 2023 [3,4], and global case numbers projected to surpass 2.3 million worldwide by 2040 [1,5,6] due to demographic shifts and global population growth and aging. In addition to PC, the global burden of other mGU malignancies is substantial and escalating progressively. According to the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), approximately 431,000 new cases of renal cancer were reported in 2020 alone [7]. Bladder cancer (BCa), with a global prevalence of 2.9 million cases in 2019, is also expected to increase, with projected annual incidence rates approaching 600,000–650,000 by 2040 [1,8,9]. Furthermore, testicular cancer, although relatively rare, is the most frequently diagnosed cancer in young adult males aged 15–35 years, with a global incidence of approximately 0.4% [1]. Additionally, penile cancer, although less common, is on an upward trend in several European countries. A global epidemiological study on penile cancer estimated 36,068 new cases reported in 2020, with an age-standardized incidence rate (ASIR) of 0.80 per 100,000 individuals [10]. Notably, recent analyses using data from the Global Cancer Observatory also suggest a rising incidence of penile cancer in younger male populations [11]. These epidemiological trends highlight the growing and heterogeneous burden of mGU cancers and the challenges associated with their prevention, diagnosis, and management.

Etiological risk factors, such as male sex, environmental exposures, hormonal influences, and genetic alterations, including X-chromosome gene mutations and androgen receptor signaling, are well documented [12,13]. However, the precise mechanisms underlying tumorigenesis remain incompletely elucidated, complicating efforts in risk stratification, early detection, prevention, and prognosis [13]. Although the role of environmental endocrine disruptors in hormone-related malignancies (e.g., prostate, testicular, and bladder cancers) is gaining recognition, the specific molecular pathways involved and their population-level implications are still not fully delineated [14]. These persistent gaps in the mechanistic understanding of GU cancers have catalyzed a growing interest in investigating novel biological contributors to cancer development.

Over the previous decade, the human microbiome has emerged as a promising area of investigation. Advances in high-throughput sequencing technologies have revolutionized our understanding of microbial ecosystems and their complex interactions with the host [15,16]. Alterations in microbial composition and function, referred to as dysbiosis, have been implicated in the pathogenesis of several cancers, suggesting that the microbiome may serve not only as a predictive, diagnostic and prognostic biomarker but also as a novel therapeutic target [17,18]. The gut microbiome, in particular, has been extensively studied and is strongly associated with malignancies, such as colorectal, liver, and pancreatic cancers. In parallel, a two-sample Mendelian randomization study further established a significant association between the gut microbiome and prostate cancer, highlighting an inverse relationship with bacterial taxa, such as *Alphaproteobacteria* [19]. Moreover, microbial dysbiosis influences cancer susceptibility and progression through multiple pathways, including genomic instability, chronic inflammation, and immune modulation [20].

Beyond the gut, emerging evidence links microbiome disruptions to GU malignancies, each characterized by distinct bacterial signatures. Specifically, the mGU microbiota has been implicated as a contributory factor in the development of urological malignancies, particularly prostate, testicular, and penile cancers [21]. Studies have identified specific bacterial taxa within the prostate, bladder, and renal microbiomes that may potentially contribute to their pathogenesis, as discussed in detail in subsequent sections [22–25]. While research on the testicular and penile microbiomes remains limited, further characterization of these microbial communities in the male genitourinary tract may provide valuable insights into disease biology and could inform future efforts toward personalized and targeted therapeutic strategies [26,27]. This review aims to comprehensively summarize the current body of evidence on the relationship between the GU microbiome and the development, progression, and treatment of mGU cancers. It also seeks to elucidate the potential mechanisms through which microbial communities may influence testicular and penile tumor biology and underscore emerging microbiome-based diagnostic and therapeutic approaches. Moreover, it addresses current challenges, knowledge gaps, and future directions in leveraging the microbiome for improved management of mGU malignancies.

2. Association of Human Microbiome with Genitourinary Cancer

The terms “human microbiota” and “human microbiome” are often used interchangeably; however, they have distinct meanings. The human microbiota refers to the taxonomy of microbes, such as bacteria, viruses, and fungi, that inhabit the human body [28]. In contrast, the human microbiome encompasses a broader ecosystem that includes both microbiota and genetic makeup [28]. The microbial species are localized to various bodily sites, including the gut, oral cavity, and skin, and the GU tract is no exception. Notably, the gut microbiome harbors nearly 100 trillion microbes, with bacteria being the dominant taxa [29–31]. Widely considered a virtual organ, the gut microbiota maintains a symbiotic relationship with the host and performs crucial physiological functions, thus maintaining homeostasis. Although a detailed exploration of the physiological roles of human microbiota is beyond the purview of this review, readers are encouraged to consult the works of Valdes et al. [32] and Hou et al. [33] for a comprehensive overview of the topic.

Principally, perturbations in gut microbial diversity and functionality can often lead to pathogenic colonization, shifting the balance from eubiosis (a state of healthy microbial balance) to dysbiosis (an imbalance in gut microbes). This dysbiosis of commensal microbes is increasingly linked to the development of various diseases (as illustrated in Figure 1) [34]. Among these diseases, cancer has hogged the limelight of biomedical research in recent years owing to its profound impact on public health worldwide [35]. In particular, PC stands out as the most frequently diagnosed cancer in the male population, with approximately 313,780 cases and 35,770 deaths in the US by 2025 [36]. Despite advancements in treatment strategies, the management of PC remains cumbersome due to issues such as drug resistance, disease recurrence, and poor survival rates, especially in advanced stages [37]. While prostate cancer accounts for the largest proportion of mGU malignancies, this review adopts a comparative perspective across multiple mGU cancers to examine shared and distinct microbiome-related associations. These challenges call for an urgent need to improve the risk assessment as well as to identify new biological factors that could serve as targets for innovative therapeutic options in advanced and metastatic cancer [38].

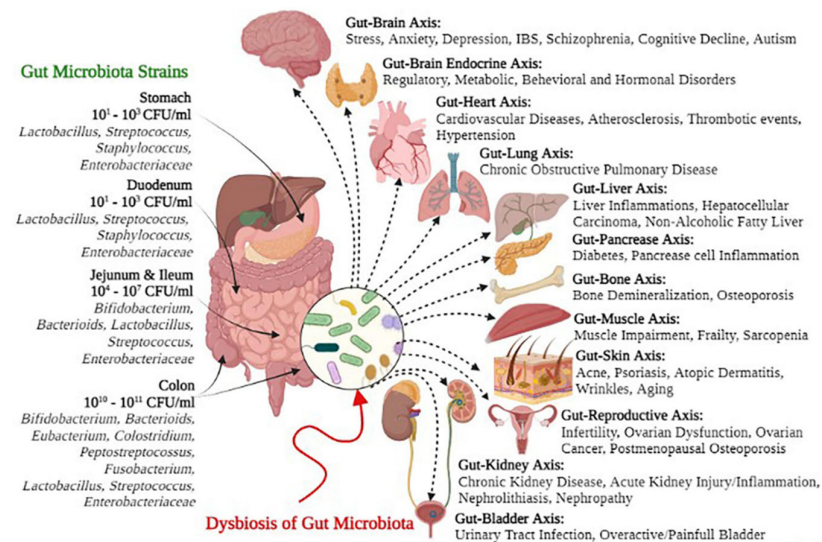


Figure 1. Gut microbial strains and adverse health effects associated with gut microbiota dysbiosis (see red arrow in the figure). Reproduced from Afzaal et al. [34], under the terms of the Creative Commons Attribution License (CC BY). IBS: irritable bowel syndrome. CFU: colony forming unit.

Emerging shreds of evidence suggest a mechanistic link between gut microbial dysbiosis and the pathogenesis of PC. Importantly, the development and progression of PC is a complex interplay of various factors that negatively impact the gut microbiota. Several exposures such as high-fat diet (HFD), obesity [39], and antibiotic (ABX) consumption [40,41] have been associated with alterations in gut microbiota composition; however, evidence linking these factors causally to prostate cancer development or progression remains inconsistent. To briefly explain, an HFD downregulates tight junction molecules, such as zonula occludens-1 (ZO-1), which in turn increases gut permeability and allows lipoteichoic acids (LTA) or lipopolysaccharides (LPS) to enter the systemic circulation [42,43]. Furthermore, an Intratumoral LPS reportedly elevates histamine decarboxylase (*Hdc*) expression, a gene involved in histamine production. Elevated histamine secretion within the prostate gland upregulates interleukin (IL) 6/signal transducer and activator of transcription 3 (STAT3) signaling and myeloid-derived suppressor cells (MDSCs), which promote PC growth [44]. Moreover, short-chain fatty acids (SCFAs) are pivotal for regulating both systemic and local insulin-like growth factor-1 (IGF1). Dysbiosis caused by HFD often leads to the production of gut microbiota-derived SCFAs, which effectively induces IGF1 expression. This process activates the local mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) signaling pathways, driving PC progression [45]. In addition, ABX exposure has been associated with increased intestinal permeability (“leaky gut”) in experimental settings, which may facilitate greater systemic exposure to microbial components such as lipopolysaccharide (LPS). These processes have been hypothesized to activate pro-inflammatory signaling pathways, including the nuclear factor κ B (NF- κ B)–IL-6–STAT3 axis, with potential implications for prostate cancer progression and response to docetaxel chemotherapy [46].

Furthermore, commensal gut microbes play an essential role in the metabolism and production of estrogen, a phenomenon referred to as the estrobolome. Gut microbes can synthesize beta-glucuronidase, an enzyme that converts estrogen to its functional form, which is necessary for normal human health. When gut dysbiosis occurs, this process can be disrupted, leading to decreased levels of bioavailable and circulating estrogen. Such disruptions precipitate DNA damage, genetic mutations, or chronic inflammation, all of which can contribute to the pathogenesis of PC [47]. In a study, the microbial composition differed substantially between the control and PC groups. Significant ($p < 0.05$) variations

at the genus level included *Prevotella*, *Faecalibacterium*, *Megasphaera*, *Bacteroides*, *Escherichia-Shigella*, and *Veillonella* [48]. Research has identified a higher abundance of *Prevotella* in the gut microbiome of patients diagnosed with colorectal cancer [49], and this enrichment has also been observed in patients with PC, suggesting a potential link [48]. However, further research is required to fully elucidate this association between them.

Moreover, the relationship between gut microbes and PC development can be explained through the concept of the “gut-prostate axis.” For instance, Liu et al. [50] conducted a study in which they transferred gut microbes from patients with castration-resistant prostate cancer (CRPC) to the transgenic adenocarcinoma of the mouse prostate (TRAMP) using fecal microbiota transplantation (FMT). The researchers found that TRAMP mice developed PC, which was associated with an increased abundance of the gut bacterium *Ruminococcus*. This increase was linked to elevated levels of lysophosphatidylcholine acyltransferase 1 (LPCAT1), an enzyme implicated in several malignancies [50]. Additionally, analyses of the gut microbiome in patients with PC show an enrichment of phyla, including *Proteobacteria* and genera such as *Faecalibacterium*, *Prevotella*, *Escherichia-Shigella*, and *Bacteroides*. In contrast, there are noticeably lower abundances of phyla, such as *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*, along with genera, such as *Megasphaera* and *Veillonella* [48]. These studies underscore the important role of the gut microbiota in the development and progression of PC.

These promising, albeit preclinical, findings highlight the potential role of the gut microbiota in the development of PC, thereby providing a strong foundation for exploring the effects of other human microbiomes, particularly the oral and skin microbiomes, on PC pathogenesis. Currently, limited research has examined the relationship between the oral microbiome and PC. With advancements in technologies such as next-generation sequencing [16] and multi-omics technologies [51,52], future studies are expected to uncover the specific microbes and molecular mechanisms through which the oral microbiome may influence the carcinogenesis of PC. In contrast, growing evidence suggests a link between the skin microbiome and the risk of developing PC. For instance, Chen et al. [53] demonstrated that skin-associated *Neisseriaceae* might modulate the immune system, trigger inflammatory responses, influence the endocrine system, and have pro-carcinogenic effects related to PC. However, further preclinical and clinical studies are pivotal to validate these findings.

Apart from PC, BCa is the second most prevalent GU cancer in men, with an estimated annual incidence of 65,080 cases and 12,640 deaths predicted in the US in 2025 alone [36]. Recent scientific advancements have spurred research to identify novel risk factors for BCa that could serve as potential biomarkers and inform future therapeutic decisions. For instance, a study by Mingdong et al. [54] reported significant associations between the *Ruminococcus torques* group, *Bifidobacterium*, and *Actinobacteria* with an increased risk of BCa. Another study identified the genus *Bilophila* ($p = 0.019$) as a potential factor in BCa development [55]. Additionally, alterations in nicotinamide adenine dinucleotide (NAD) and amino acid metabolism have been implicated in BCa pathogenesis [55]. Moreover, a considerable reduction in *Prevotella* and *Clostridium cluster XI*, along with lower butyric acid levels, was observed in patients with BCa. Elevated levels of D-lactic acid and LPS further indicate an incidence of leaky gut in these patients [56]. Furthermore, reductions in the abundance of *Lactobacillus* and *Bifidobacterium*, as well as lower butyric acid levels, were observed in patients with BCa. These findings suggest that gut dysbiosis may contribute to BCa pathogenesis [57]. However, further comprehensive studies, including multicenter trials, are necessary to establish a clear mechanistic link between the gut microbiota and BCa progression. Taken together, these findings indicate that the gut microbiome is a significant factor in GU cancer development. These insights underscore the need to explore

the role of localized microbial communities in GU cancers, a topic briefly discussed in the subsequent sections.

3. Factors Affecting the Genitourinary Microbiome

The composition of the local mGU microbiome is influenced by a complex interplay of factors, including host genetics, hygiene practices, circumcision status, and sexual behavior [58]. Personal hygiene directly impacts the stability and diversity of the local microbiota, potentially altering host–microbe interactions in ways that increase susceptibility to urological disorders, oncogenic microbial colonization, and sexually transmitted infections (STIs) [58,59]. Furthermore, the GU microbiome is not isolated; it can be modulated by sexual activity, including the microbiome of one's partner, condom use, sexual practices, and penile hygiene [60].

Circumcision status is another key determinant of microbial diversity, particularly in the penile microbiome. Studies have shown that uncircumcised men harbor a higher bacterial richness, notably with a greater relative abundance of anaerobic taxa, such as *Corynebacterium*, *Prevotella*, *Peptoniphilus*, and *Anaerococcus* [61]. The sub-preputial space in uncircumcised individuals provides an environment conducive to the proliferation of pro-inflammatory anaerobes, including *Prevotellaceae* and members of *Clostridiales* Family XI, which may contribute to local inflammation and increase the risk of genital infections [61]. These microbial drifts have also been associated with a higher prevalence of bacterial vaginosis in female partners and a significantly elevated risk of human papillomavirus (HPV) infection. Additionally, the prevalence of HPV has been reported to be substantially higher among uncircumcised men (46%) than among circumcised men (29%) (odds ratio: 1.96) [62]. Several studies have conclusively identified that circumcision has a significant impact on male microbiota, resulting in a marked decrease in alpha diversity [58,59,63–65]. Furthermore, circumcision is associated with a reduction in the genital anaerobic bacterial load, which may have important implications for the risk of human immunodeficiency virus (HIV) acquisition, penile cancer development, and STIs. An extensive study conducted on the pediatric population by Mishra et al. [66] demonstrated that circumcision significantly alters the microbial landscape, leading to a marked reduction in fungal taxa, such as *Saccharomycetales* and *Pleosporales*, as well as bacterial orders, including *Clostridiales*, *Bacteroidales*, *Campylobacteriales*, and *Enterobacteriales*. This shift in microbial composition is believed to mitigate local inflammation and lower the risk of cancer [67]. Despite these endorsements, further research is necessary to elucidate the immune-mediated mechanisms underlying microbiome modulation post-circumcision.

Sex hormones, particularly androgens such as testosterone and dihydrotestosterone, play pivotal roles in modulating the male genitourinary microbiome [68]. Androgens have been shown to impair neutrophil maturation and function within the urinary tract, potentially facilitating abscess formation and infection persistence. Distinct microbial community profiles have been observed in androgen-rich environments compared to those in females or castrated males, underscoring the influence of hormones on microbial composition of these environments. Furthermore, animal studies have underscored the role of estrogen receptor alpha in shaping the seminal plasma microbiome, including the regulation of specific bacterial taxa, such as *Propionibacterium acnes* [69]. However, the modulatory effects of estrogens in males appear less prominent than those of androgens. These intrinsic and extrinsic factors together shape the composition and function of the mGU microbiome, laying a foundation for its potential role in health, disease susceptibility, and tumorigenesis, which are now gaining increasing attention in urological cancer research.

4. Impact of Specific Microbiome in Genitourinary Cancer

The concept of a “specific microbiome” highlights the unique microbial populations that inhabit a specific anatomical site or niche in the body. Unlike gut microbes that are dispersed throughout the gastrointestinal system, specific microbiomes represent site-specific ecosystems shaped by distinct environmental and physiological conditions [39,70]. Some notable examples include the prostatic microbiome (of the prostate gland) [71], urinary microbiome (of the bladder) [72], renal microbiome (of the kidneys) [73], seminal and testicular microbiome (of the testicles) [74,75], and penile microbiome (of the penile tissue) [76]. These microbiomes play an essential role in maintaining homeostasis. However, in a dysbiotic state, they can significantly contribute to the pathogenesis of GU diseases, and GU cancers are no exception [39].

Despite their theoretical importance, the precise characterization of these microbiomes remains inadequately explored, largely due to technical limitations such as low microbial biomass and a high risk of contamination [77]. Moreover, while preliminary evidence suggests a potential overlap between the urinary and prostatic microbiomes, the absence of robust and reproducible data hinders definitive conclusions [39]. Nevertheless, a deeper understanding of the composition and function of local microbiomes is necessary. This knowledge may provide critical insights into disease pathophysiology, facilitate early diagnosis, and pave the way for innovative microbiome-targeted therapeutic interventions for mGU cancers. This section consolidates emerging shreds of evidence on the complex relationship between the local microbiome and the risk of mGU cancers.

4.1. Prostate Cancer

Salachan et al. [78] explored the relationship between microbial dysbiosis and the progression of PC by comparing the microbiomes of PC patients to those of a healthy cohort. They reported a decrease in microbial species diversity among patients with cancer, specifically noting a significant reduction in *Staphylococcus saprophyticus* and *Vibrio parahaemolyticus*, alongside a notable increase in *Shewanella* in the cancer group. Additionally, when comparing tumor samples that had low levels of *Vibrio parahaemolyticus* to those with high levels, researchers found differences in the activity of certain biological pathways, especially those involved in olfactory transduction and drug metabolism. Furthermore, malignant samples categorized by high versus low *Shewanella* counts showed decreased Toll-like receptor (TLR) signaling and reduced dendritic cell enrichment (Figure 2). These findings underscore the connection between the prostate microbiome and the development and progression of PC by suppressing the immune system.

In addition, researchers have found that the abundance of *Propionibacterium* is significantly higher in PC patients than in healthy participants [79]. In concordance to these findings, a systematic review revealed substantial increase in *Propionibacterium acnes* (*P. acnes*) in PC tissues in three of nine studies [80]. Although a direct link between *P. acnes* and PC development remains unclear, an indirect relationship can be suggested, indicating that *P. acnes* has the potential to enhance proinflammatory cytokine signaling and promote neutrophil mobilization. This may yield an immunosuppressive environment that facilitates cancer growth and progression [81–83].

In another recent systematic review and meta-analysis, the number of microbial genera, phyla, and species were found to be greater in individuals with PC than in healthy individuals. Notably, an enrichment of specific microbes, such as *Porphyromonas* sp. Nov, *Alloscardovia omnicolens*, *Varibaculum* sp. Nov, *Streptococcus*, and *Ureaplasma urealyticum*, was observed in patients with high-grade PC. Intriguingly, the meta-analysis indicated no statistically significant association between urinary microbiota and the risk of PC (pooled odds ratio: 1.35; 95% confidence interval: 0.70–2.59) [84]. However, it is of paramount

importance to note that only two studies contributed to this meta-analysis because of a lack of quantitative data in the majority of the included studies [84].

Moreover, there is a scarcity of data delineating the mechanisms linking the prostate microbiome to the risk of PC. Most studies reported in the literature fail to establish a functional connection with cancer, which limits our understanding of how microbes may contribute to prostate tumorigenesis. Consequently, future research should focus on conducting extensive longitudinal studies and detailed mechanistic investigations to clarify these microbial influences.

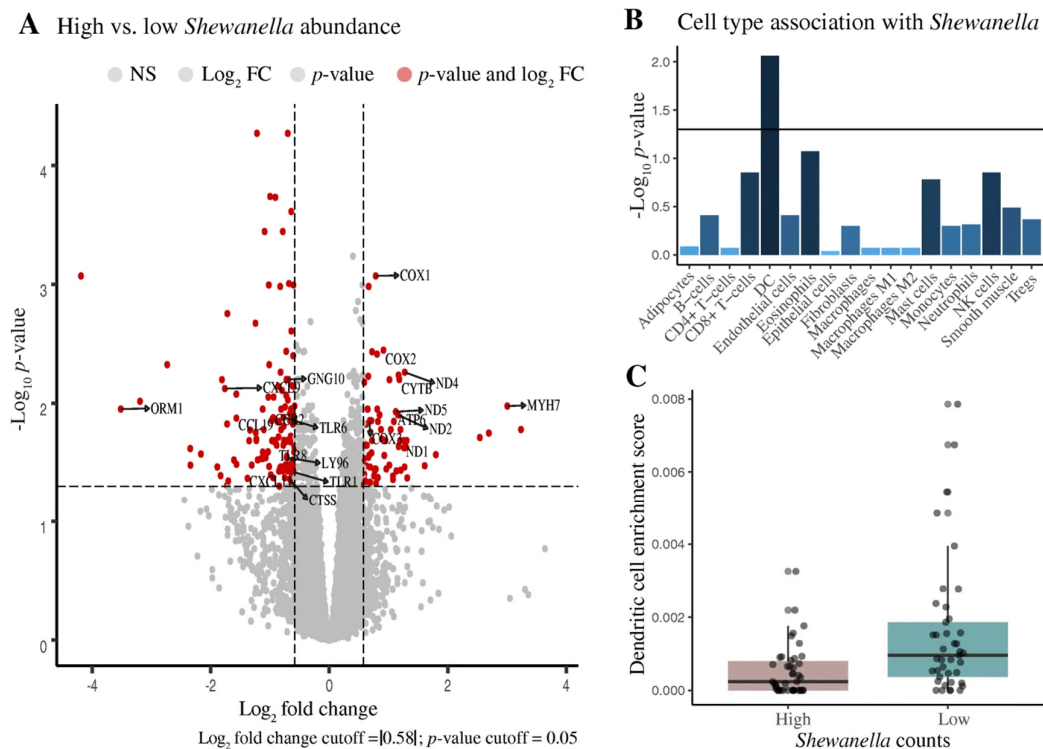


Figure 2. Host gene expression and cell type associations with *Shewanella*. (A) Volcano plot of differentially expressed genes between high and low *Shewanella* groups, highlighting genes in significant Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. (B) Bar chart showing cell type associations with *Shewanella*; dendritic cells (DC) are significantly associated. (C) Boxplot comparing DC enrichment scores between high and low *Shewanella* groups. Reproduced from Salachan et al. [85], under the terms of the Creative Commons CC BY license. NS: not significant; FC: fold change; NK: natural killer.

4.2. Bladder Cancer

In a study conducted by Popović et al. [86], the urinary microbiome of healthy individuals was compared with that of BCa patients to explore the potential association between the microbiome and BCa. Bacterial populations were sampled from age-matched individuals, including healthy participants (n = 11) and BCa (n = 12) patients. The researchers identified indistinguishable microbial diversity and overall microbiome composition between the two cohorts ($p < 0.05$) (Figure 3). However, significant differences were observed in the operational taxonomic units (OTUs). Notably, patients with BCa showed a substantial increase in the abundance of *Fusobacterium*, a potentially oncogenic pathogen. Additionally, higher abundances of the genera *Actinobaculum*, *Fusobacterium*, *Campylobacter*, and *Facklamia* were reported in the BCa group, whereas *Corynebacterium* species were predominant in the urinary microbiome of healthy individuals [86].

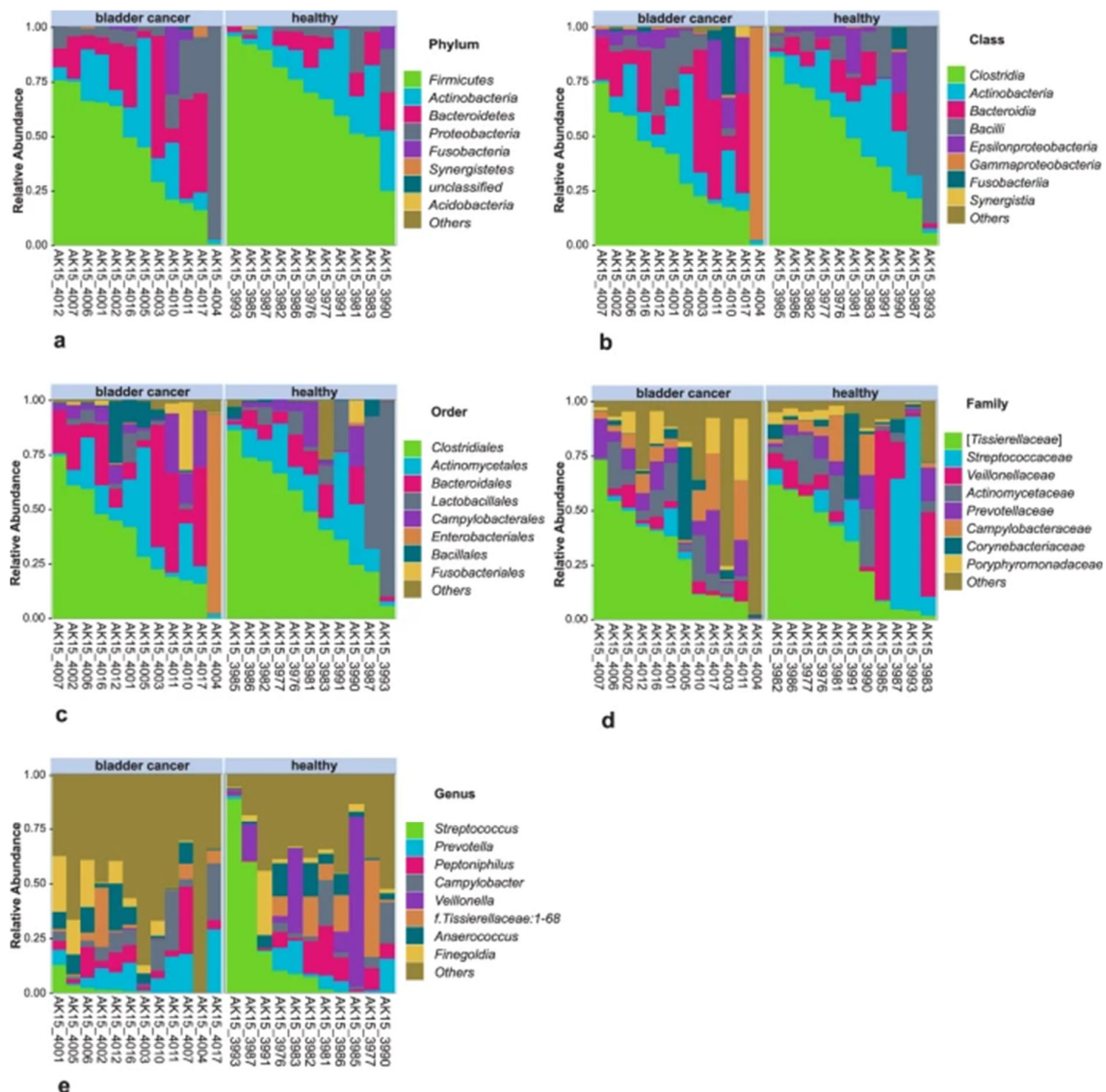


Figure 3. Urinary microbiota composition in male bladder cancer patients and healthy controls, highlighting the most prevalent taxa at the phylum (a), class (b), order (c), family (d), and genus (e) levels. Reproduced from Popović et al. [86], under the terms of the Creative Commons CC BY license.

Another study analyzed the urinary microbiome of male BCa patients ($n = 31$) and non-neoplastic populations ($n = 18$) [87]. Compared to the control group, patients with BCa exhibited a significant elevation in bacterial richness, as indicated by higher values of Observed Species (120.0 vs. 56.0), Chao1 (134.5 vs. 68.3), and abundance-based coverage estimator (ACE) (139.6 vs. 72.9) indices. Furthermore, specific genera, such as *Acinetobacter*, *Sphingobacterium*, and *Anaerococcus*, were more abundant in the cancer group. Moreover, substantial differences in beta diversity have been reported between the two cohorts. The cancer population also demonstrated enrichment of functional pathways related to glycerolipid metabolism, *Staphylococcus aureus* infection, and retinol metabolism, suggesting a potential link between the urinary microbiome and BCa development [87].

Emerging body of evidence suggests several mechanisms through which the intratumoral microbiota of BCa may influence its progression. For instance, *Cupriavidus* bacteria may increase the abundance of various toxic chemicals and exhibit persistent metabolic capabilities within the bladder, leading to oxidative DNA damage in human urothelial cells. Additionally, biofilm formation enhances the secretion of extracellular proteases, disrupts

intercellular junctions, and induces mutagenic DNA damage. Furthermore, *Staphylococcus* spp. have been linked to the persistence of chronic urinary tract infections, which elevates the risk of bladder carcinogenesis [88].

Ma et al. [89] assessed the impact of smoking, a recognized risk factor for dysbiosis, on the urinary microbiome of patients with BCa. Urine samples from 15 men with BCa and 11 healthy men were analyzed. Among smokers, there was a notable enrichment of the bacterial families *Bacteroidaceae*, *Lachnospiraceae*, and *Erysipelotrichales*. Additionally, smokers showed significantly higher alpha diversity (a measure of microbial variety within a sample) compared to non-smokers ($p < 0.05$) (Figure 4). The smokers displayed altered metabolic signaling and increased immune activity, which together may create an environment conducive to cancer growth. In addition, Bukavina et al. [90] investigated and compared the urinary microbiome of BCa patients ($n = 129$) with that of healthy individuals ($n = 60$) on a global scale. They reported a higher abundance of several genera in the cancer group ($n = 97$ out of 548 bacterial genera) than in the non-cancer cohort. Notably, there was an enrichment of polycyclic aromatic hydrocarbon (PAH)-degrading bacteria, such as *Acinetobacter*, *Sphingomonas*, *Pseudomonas*, *Micrococcus*, and *Ralstonia*, in the cancer group, illustrating a correlation between the urinary microbiome and BCa [90].

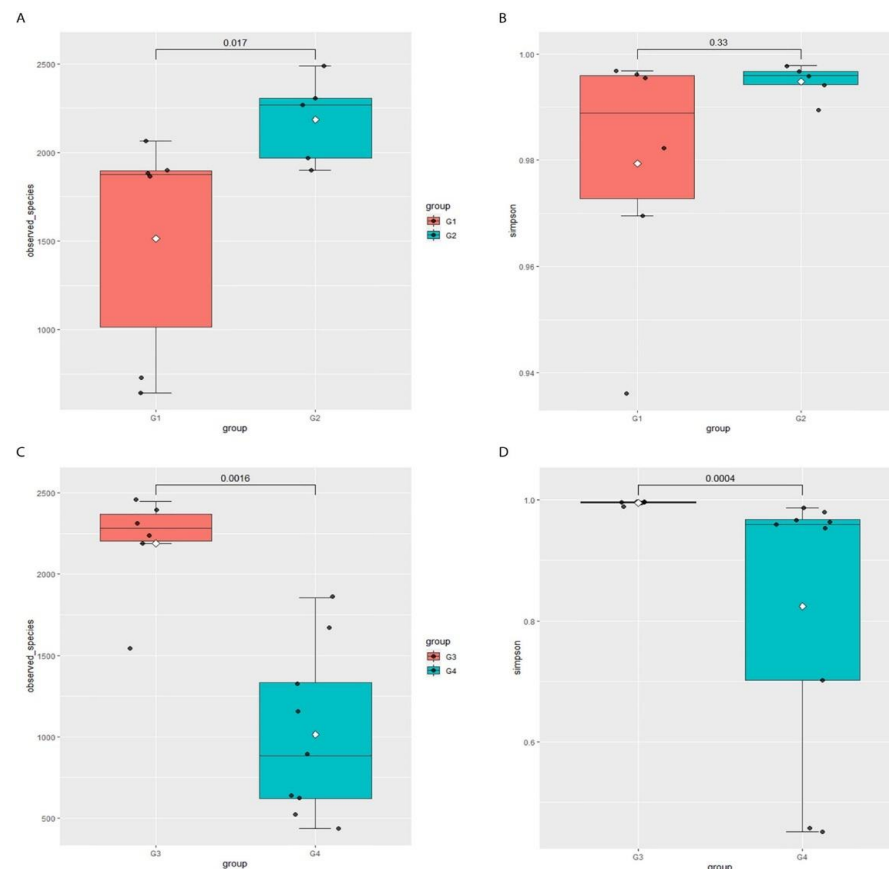


Figure 4. Microbial alpha diversity in urine samples: (A) Number of observed species in healthy men; (B) Simpson Index in healthy men; (C) Number of observed species in men with bladder cancer; (D) Simpson Index in men with bladder cancer. Reproduced from Ma et al. [89], under the terms of the Creative Commons Attribution License (CC BY). Black dots represent individual samples, while the white diamond indicates the group mean.

Recently, Wu et al. [87] demonstrated significant increases in IL-6 ($p < 0.01$), IL-8, and IL-10 levels ($p < 0.05$) in patients with BCa. Additionally, the cancer group exhibited substantially greater alpha diversity ($p < 0.01$) and elevated levels of fatty acids and fatty acylcarnitines. Following tumor resection in the BCa group, there was a significant re-

duction in the levels of fatty acylcarnitine ($p < 0.05$). Pathway enrichment analysis also indicated a notable involvement of fatty acid β -oxidation ($p < 0.001$). Moreover, receiver operating characteristic (ROC) curves revealed that a biomarker panel consisting of *Actinomycetaceae*, arachidonic acid, and IL-6 demonstrated excellent diagnostic performance, achieving a sensitivity of 0.94 and specificity of 1.00. These findings indicate that microbiome dysbiosis, inflammation, and altered fatty acid metabolism are involved in bladder cancer progression.

4.3. Kidney Cancer

The role of the microbiome in renal carcinogenesis is an emerging field; however, the specific association between bacterial colonization and renal cells remains largely uncharacterized. Nevertheless, multiple studies have identified distinct bacterial taxa in patients with renal cancer compared to healthy controls, implying their potential contribution to tumor development and progression [91]. In a comprehensive analysis of renal cell carcinoma (RCC) tissues, researchers observed a significant shift in microbial composition relative to adjacent normal tissues (Simpson index, $p = 0.0340$) [92]. A comparative analysis of microbial communities between RCC tissues and adjacent normal tissues (ANT) was performed. The study identified ten differentially abundant taxa, including *Pseudomonas*, *Klebsiella*, *Carludovica*, *Phyllobacterium*, *Rhodoplanes*, *Allobaculum*, *Chloroplast*, *Streptophyta*, *Rickettsiales*, and *Deinococcus*. Among these, eight taxa were more prevalent in normal tissues. Notably, *Klebsiella* (area under the curve [AUC] = 0.86, $p < 0.0001$), *Chloroplast* (AUC = 0.91, $p < 0.0001$), and *Streptophyta* (AUC = 0.89, $p < 0.0001$) showed significantly reduced relative abundance in RCC tissues. Conversely, *Deinococcus* (AUC = 0.72, $p = 0.0081$) and *Phyllobacterium* (AUC = 0.71, $p = 0.0115$) were enriched in RCC tissues and showed moderate predictive power for RCC diagnosis. In addition, *Rhodoplanes* were significantly more abundant in grade I RCC samples than in grade II samples, suggesting a potential role in tumor grade differentiation.

Perturbations in microbial balance induced by antibiotic exposure have been shown to influence therapeutic outcomes in RCC, particularly in patients undergoing immune checkpoint inhibitor (ICI) therapy. Moreover, antibiotic administration significantly alters gut microbial diversity, which may affect ICI efficacy [93]. Furthermore, emerging evidence has linked RCC-associated microbiota with immunomodulatory markers, such as programmed cell death ligand 1 (PD-L1). A study demonstrated elevated abundance of *Fusobacterium nucleatum*, *Corynebacterium diphtheriae*, *Micrococcus luteus*, and *Streptococcus agalactiae* in tumor tissues compared to venous tumor thrombi and adjacent normal kidneys, implicating microbial influence on immune checkpoint regulation (Figure 5) [94]. Additionally, a pilot investigation involving patients undergoing laparoscopic nephrectomy revealed diverse microbial populations residing in malignant renal tissues. Notably, species such as *Phaeocystis antarctica*, *Euglena mutabilis*, *Cyanophora paradoxa*, *Mycoplasma vulturii*, and *Spirosoma navajo* were consistently detected in RCC samples [95]. These findings provide compelling evidence for the presence of a distinct renal microbiome in malignancies, potentially implicated in immune modulation and tumor progression. However, the precise mechanisms underlying microbial dysbiosis in RCC remain elusive, warranting further in-depth investigation.

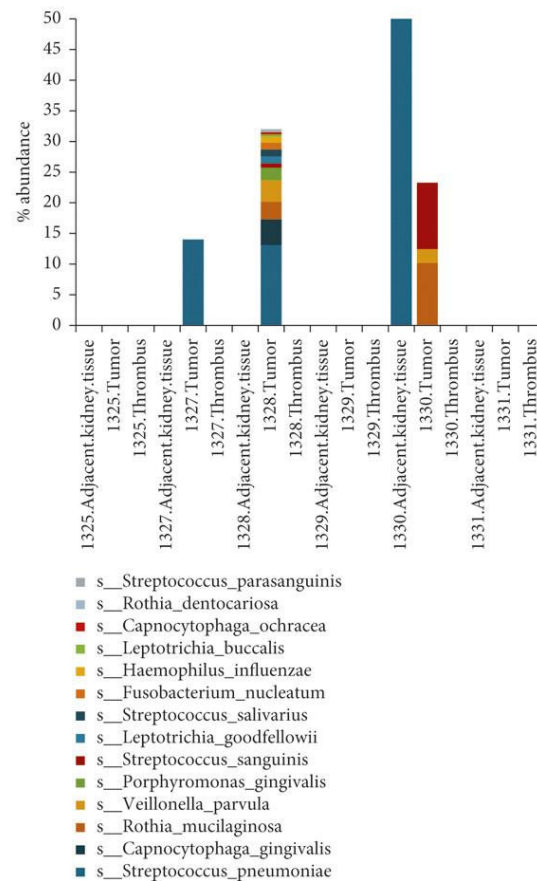


Figure 5. Programmed cell death ligand 1 (PD-L1) expression and oral microbiome abundance in renal tumor thrombus. Bar graphs show (**top**) PD-L1 expression in tumor thrombus versus adjacent normal tissue, with a red line indicating a two-fold difference, and (**bottom**) the relative abundance of oral microbiome taxa in the same tumor specimen. Reproduced from Liss et al. [94] under the terms and conditions of CC BY 4.0.

4.4. Testicular Cancer

Although the role of the testicular and seminal plasma microbiomes in testicular cancer remains an emerging area of investigation, recent findings suggest a potential association. Mørup et al. [96] conducted a high-throughput 16S rRNA sequencing analysis and identified significant microbial differences in the seminal plasma of patients diagnosed with germ cell neoplasia in situ (GCNIS) and testicular germ cell tumors (TGCT) compared to healthy controls. Furthermore, six microbial species, *Halovirus HGTV-1*, *Thioalkalivibrio* sp. K90 mix, *Desulfurivibrio alkaliphilus*, *Burkholderia* sp. YI23, *Acaryochloris marina*, and *Thermaerobacter marianensis* were significantly elevated in GCNIS and TGCT cases (q -value < 0.05), suggesting a possible link between microbial dysbiosis and tumorigenesis. The distribution of microbial reads among the studied groups is illustrated in Figure 6 [96]. While causality remains to be firmly established, the consistent microbial signatures observed in patients with neoplasia indicate a plausible contributory role of the seminal microbiome in the early stages of testicular carcinogenesis.

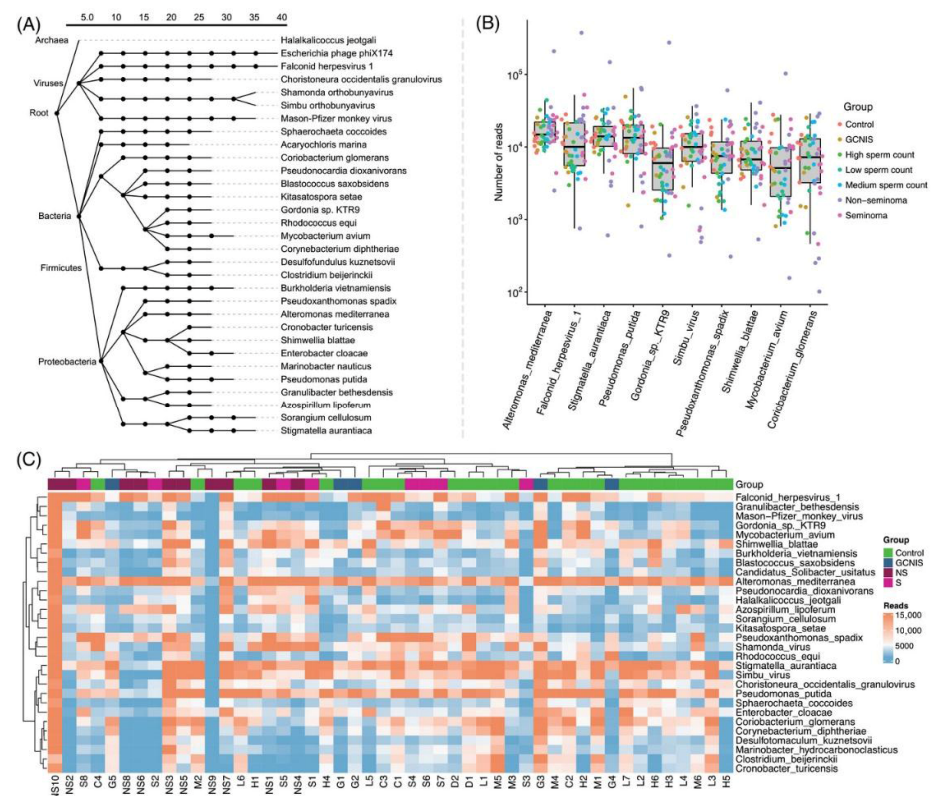


Figure 6. Distribution of Microbiome Reads. (A) Phylogenetic tree of the 30 most common species. (B) Boxplots of the 10 most prevalent species across all groups. (C) Heatmap showing sample group clustering by the top 30 species, with color indicating read counts and group labels shown below the sample tree. Reproduced from Mørup et al. [96], under the terms and conditions of CC BY-NC-ND 4.0. GCNIS: germ cell neoplasia in situ.

Complementary to this, Neto et al. [97] emphasized the fundamental role of a balanced seminal microbiome in maintaining the male reproductive health. Their study highlighted that dysbiosis within the seminal environment not only contributes to male infertility but may also disrupt local immunological and inflammatory homeostasis, which are conditions known to facilitate oncogenesis. Although direct mechanistic pathways between seminal microbiome disruption and testicular cancer have yet to be fully delineated, emerging evidence strongly supports the hypothesis that microbiome imbalances may influence the initiation and progression of testicular malignancies. These findings underscore the need for further research to validate the microbiome as both a biomarker and potential therapeutic target in testicular cancer, with an emphasis on longitudinal and mechanistic studies that can unravel the causative pathways.

4.5. Penile Cancer

The current body of literature exploring the relationship between the penile microbiome and male genital malignancies is limited, with most studies focusing primarily on STIs and the impact of circumcision [98]. However, recent evidence highlights the more intricate role of the penile microbiota in influencing susceptibility to viral oncogenesis and potentially contributing to carcinogenesis. Research has identified the presence of HPV in the penile microbiome and specific microbial communities that may enhance susceptibility to HPV infection [98,99]. HPV is a well-established oncogenic virus known to express E6 and E7 viral proteins, which inactivate key tumor suppressor genes, such as p53 and Rb, thereby disrupting normal cell cycle regulation and promoting oncogenesis. Several extrinsic and intrinsic factors, including sexual practices, circumcision status, and the mi-

crobiome of sexual partners, have been shown to influence the composition and diversity of the penile microbiome [62,64].

Onywera et al. [98] conducted a comprehensive study on the penile microbiota of Black South African men to explore the relationship between HPV, HIV, and their associated immune status. This study evaluated the alpha diversity indices of penile bacterial communities in relation to HPV infection status (including high-risk HPV or HR-HPV), HIV infection status, and CD4+ T-cell count (Figure 7). Results revealed no statistically significant difference in alpha diversity between men with and without HR-HPV infection (Shannon index: 1.6 [1.3–2.0] vs. 1.5 [1.1–1.9], $p = 0.149$), nor between HIV-positive and HIV-negative individuals (Shannon: 1.6 [1.4–2.0] vs. 1.6 [1.1–1.9], $p = 0.050$). However, men co-infected with HIV and HPV exhibited significantly higher alpha diversity (Shannon: 1.7 [1.4–2.1]) than those with only HIV (Shannon: 1.6 [1.1–1.9], $p = 0.037$) or only HPV (Shannon: 1.6 [1.1–1.9], $p = 0.045$). Importantly, HIV-positive men with HR-HPV infections also demonstrated significantly greater alpha diversity than HIV-negative men with HR-HPV (Shannon: 1.7 [1.5–2.1] vs. 1.6 [1.1–1.9], $p = 0.025$). No significant difference in microbial diversity was observed between HIV-positive individuals with CD4+ T-cell counts above or below 350 cells/ μL ($p = 0.873$).

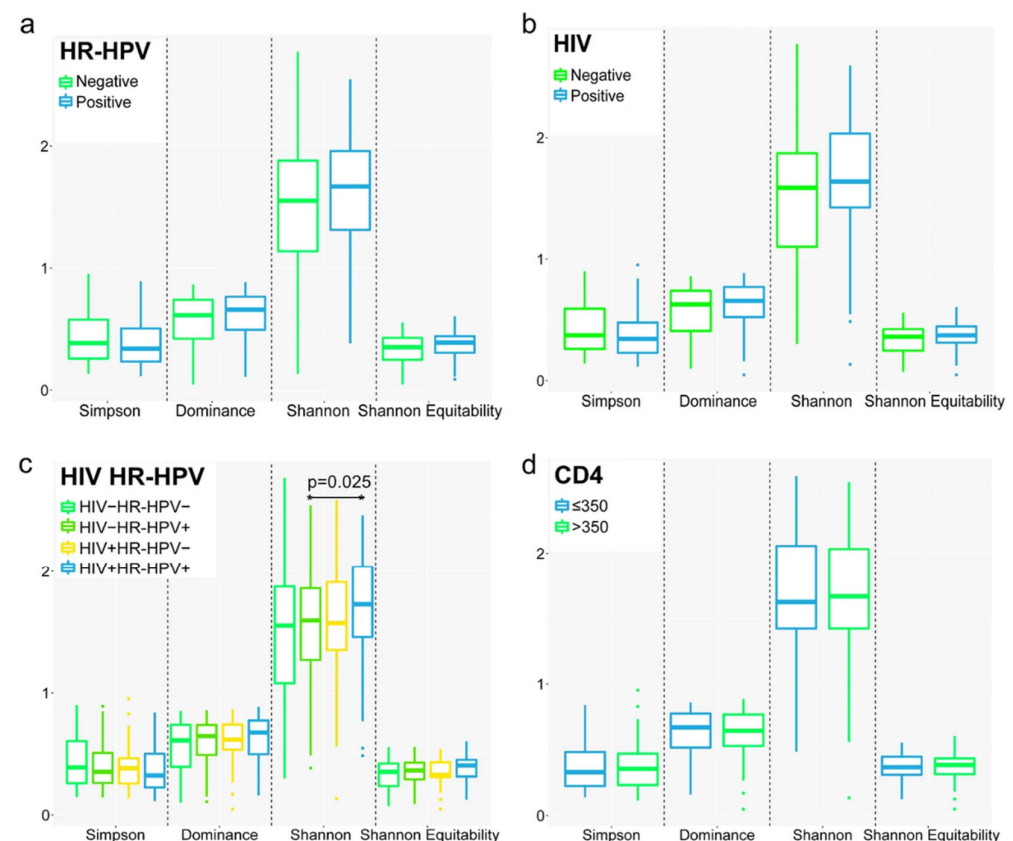


Figure 7. Alpha diversity of penile microbiota compared by. (a) high-risk human papillomavirus (HPV) infection, (b) Human immunodeficiency virus (HIV) infection, (c) combined high-risk human papillomavirus (HR-HPV) and HIV status, (d) CD4+ T-cell count. Reproduced from Onywera et al. [98], under the terms of the Creative Commons CC BY license.

Beta diversity analyses further supported the differences in microbial community composition (Figure 8). A significant separation in beta diversity was observed between HR-HPV-positive and HR-HPV-negative men (Figure 8a, $R^2 = 0.0123$, $p = 0.011$). Although no clear separation was observed based on HIV infection alone (Figure 8b, $R^2 = 0.0061$, $p = 0.189$), distinct clustering was observed in men co-infected with both HIV

and HR-HPV (Figure 8c, $R^2 = 0.0231$, $p = 0.049$). CD4+ T-cell count did not contribute to significant beta diversity differences among HIV-positive individuals (Figure 8d, $R^2 = 0.0077$, $p = 0.129$). Moreover, taxonomic profiling revealed that members of the *Corynebacteriaceae* family and the genus *Corynebacterium* were predominant in the penile microbiota of circumcised men. Additionally, *Prevotella*, *Dialister*, *Peptoniphilus*, and unclassified *Clostridiales* were significantly enriched in HR-HPV-positive individuals, suggesting a possible association between these anaerobic taxa and HPV persistence [98]. Given the established link between persistent HR-HPV infection, anaerobic microbial colonization, and penile carcinogenesis, these findings underscore the need for further studies to elucidate the role of penile microbial communities in penile cancer pathogenesis.

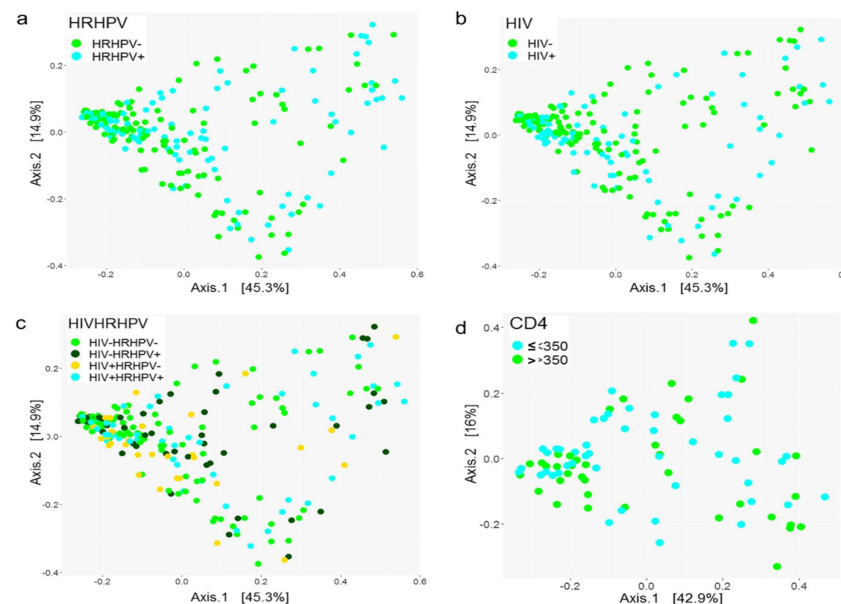


Figure 8. Beta diversity of penile microbiota: Principal Coordinates Analysis (PCoA) plots of weighted UniFrac distances, colored by (a) high-risk human papillomavirus (HR-HPV) infection, (b) Human immunodeficiency virus (HIV) infection, (c) combined HIV and HR-HPV status, and (d) CD4+ T-cell count. The first two axes and their explained variation are shown; each point represents a bacterial community. Reproduced from Onywera et al. [98], under the terms of the Creative Commons CC BY license.

Importantly, circumcision is associated with a reduction in anaerobic bacterial load, which may contribute to a lower risk of HPV infection and subsequent malignancies. Despite these findings, a direct causal link between penile cancer and specific microbial dysbiosis remains to be definitively established. Nevertheless, the potential oncogenic role of dysbiotic penile microbiomes warrants further investigation. Therefore, future research should aim to elucidate the mechanistic pathways by which the penile microbiome influences the initiation and progression of penile cancer. Establishing this link could provide novel insights into microbiome-based preventive, diagnostic, and therapeutic strategies for penile malignancies.

5. Studies

We conducted a comprehensive review of the existing literature investigating the association between the male GU microbiome and the development of GU cancer. The key findings of these studies are systematically summarized in Table 1.

Table 1. Overview of genitourinary (GU) microbiome in different GU cancers Clinical Trials and Translational Studies. (Summary of associations between bacterial species diversity and cancer, with “+” representing increased diversity, “−” representing decreased diversity, and “0” indicating no significant association).

Study Number	Microbiome	Associated Cancer	Techniques Used/Evaluation Parameter	Key Results	Remarks	Utility	Advantages	Limitations	Model	Reference
1	Urinary (<i>Bacteroidetes</i> , <i>Alphaproteobacteria</i> , <i>Firmicutes</i> , <i>Lachnospiraceae</i> , <i>Propioniceimon</i>)	Prostate Cancer	Polymerase chain reaction-denaturing gradient gel electrophoresis (PCR-DGGE), quantitative real-time polymerase chain reaction (PCR)	Difference in the bacterial flora in expressed prostatic secretion (EPS) of prostate cancer and benign prostatic hyperplasia (BPH) Increase in <i>Bacteroidetes</i> , <i>Alphaproteobacteria</i> , <i>Firmicutes</i> , <i>Lachnospiraceae</i> , <i>Propioniceimon</i> , decrease in <i>Eubacterium</i> and <i>Defluviicoccus</i> Significant decrease in <i>Escherichia coli</i> (<i>E. coli</i>) in prostate cancer patients.	+	Early detection and therapeutic intervention	Establishes the role of ecological dysbiosis in pathophysiology of prostate cancer	Culture-independent method, no study of the function role of identified bacteria in prostate cancer	In vitro	[100]
2	Urinary and Prostate (<i>Porphyromonas</i> sp. nov., <i>Varibaculum</i> sp. nov., <i>Peptoniphilus</i> sp. nov., and <i>Fenollaria</i> sp. Nov)	Prostate Cancer	16S ribosomal amplicon DNA sequencing, quantitative polymerase chain reaction (qPCR), metagenomics, RNA-seq meta transcriptomics	Presence of bacteria and bacterial aggregates were associated with high risk of prostate cancer	+	Prognostic potential	Complete characterization of urinary and prostate microbiome	Potential mechanism for cancer development is not established	In vitro	[84]
3	Prostate tumor (<i>Escherichia</i> , <i>Propionibacterium</i> , and <i>Pseudomonas</i> and <i>proteobacteria</i>)	Prostate Cancer	Metagenomic analysis of host-derived whole-genome sequencing data	23 common bacterial general in prostate tissue of patients from three continents with an abundance of proteobacteria No link with clinical presentation of prostate cancer	0	Detection of bacterial richness	Experimentally controlled data generated from cancerous prostate tissue derived from patients from geographically distinct continent	Fecal contamination	In vitro	[101]

Table 1. Cont.

Study Number	Microbiome	Associated Cancer	Techniques Used/Evaluation Parameter	Key Results	Remarks	Utility	Advantages	Limitations	Model	Reference
4	Prostate adenocarcinoma	Prostate Cancer	PathoChip Design, Probe-capture and next-generation sequencing, PCR validations	Three distinct prostate cancer-specific microbiome Viral—Poxviridae, Reoviridae, Pappilomaviridae, Herpesviridae Bacterial— <i>Proteobacteria</i> (55%), <i>Firmicutes</i> (19%), <i>Actinobacteria</i> (11%), <i>Bacteroides</i> (7%) Fungal—dermatophytes (31%), yeasts (15%), Zygomycetes (15%), and Microsporidia (12%)	+	Diagnostic and prognostic potential	Integration discovery and comprehensive microbial analysis	-	In vitro	[102]
5	Prostate tumor microenvironment	Prostate Cancer	Prostate ultradeep pyrosequencing, Friedman's test, Wilcoxon rank-sum test, and beta-diversity analysis	Predominant <i>Actinobacteria</i> followed by <i>Firmicutes</i> and <i>Proteobacteria</i>	+	Potential Biomarker	Novel therapeutic approaches based on prostate specific microbiome population	Contamination with bacteria from trans-rectal biopsy procedure	In vitro	[77]
6	Urinary and fecal	Prostate Cancer	DNA amplification, 16S rRNA	Urinary microbiome—Increased abundance of <i>Veillonella</i> , <i>Streptococcus</i> , and <i>Bacteroides</i> Decreased abundance of <i>faecalibacterium</i> , <i>lactobacilli</i> , and <i>Acinetobacter</i> Fecal microbiome—increased <i>Bacteroides</i> species	+	Potential Biomarker	Potential of urinary microbiome as a biomarker in early detection of prostate cancer	Small sample size, limited geographic location, homogeneity in study population	In vitro	[103]

Table 1. Cont.

Study Number	Microbiome	Associated Cancer	Techniques Used/Evaluation Parameter	Key Results	Remarks	Utility	Advantages	Limitations	Model	Reference
7	Prostate cancer tissue	Prostate Cancer	Massively Parallel Sequencing (MPS), 16S rRNA gene amplicon sequencing	<i>Propionibacterium acnes</i> (<i>P. acnes</i>) in 95% of the samples <i>Enterobacteriaceae</i> common to all samples V4 region— <i>Actinobacter</i> , <i>Pseudomonas</i> , and <i>Streptococcus</i> in 95% prostate sample	0	Diagnosis	Detection of potential pathogen involved in high-grade prostate tumor with targeted 16S rRNA and total RNA sequencing	Small sample size, presence of multiple 16S rRNA gene copies, extraction methods, experimental controls, library preparation, and bioinformatics approach posed inherent limitations	In vitro	[79]
8	Commensal bacteria in BPH and prostate cancer (PCa)	Prostate Cancer	16S rRNA amplicon sequencing and qPCR analyses	<i>Propionibacterium acne</i> abundance in BPH and Prostate cancer including <i>Prevotella</i> , <i>P. copri</i> , and <i>Corynebacterium</i> indicating potential involvement with gastrointestinal (GI) microbiota with PCA development Revealed association of oncogenic virus (Epstein–Barr virus and high-risk human papillomaviruses) with PCa	+	Dysbiotic microbiota as novel biomarker and therapeutic target	Early diagnosis and prognosis with the identified microbiome	Limited sample size and focus on Indian patients only, lack of analysis on functional role of identified microbial species in PCa development	In vitro	[104]
9	Prostate tumor microenvironment	Prostate Cancer	Metatranscriptomic	Reduced species diversity in malignant as compared to benign tissue sample	+	Diagnostic and prognostic potential	Revealed microbial dysbiosis associated with PCa providing insights into potential biomarkers	Lack of test for possible source of contamination, missing microbial taxa of low level of transcription, lack of non-PCa control sample, lack of microbial read counts	In vitro	[85]

Table 1. Cont.

Study Number	Microbiome	Associated Cancer	Techniques Used/Evaluation Parameter	Key Results	Remarks	Utility	Advantages	Limitations	Model	Reference
10	Urinary microbiome	Prostate Cancer	16S rDNA Illumina® sequencing and 16S rDNA quantitative polymerase chain reaction.	Diverse urine species in urinary tract of men with PCa, no significant difference in α or β diversity, and no clear hierarchical clustering of benign or cancer samples	0	Detection of associated inflammation and therapeutic modalities	Identified potential link between urinary microbiome and chronic inflammation in the prostate	Limited sample size, biased study population	In vitro	[105]
11	Prostate microbiota	Prostate Cancer	Metagenomics, Metatranscriptomic, and Kaplan–Meier (KM) survival analysis	No change in alpha or beta diversity. Abundance of <i>Escherichia</i> , <i>Propionibacterium</i> , <i>Acinetobacter</i> and <i>Pseudomonas</i>	0				In vitro	[106]
12	Bladder tissue microbiome	Bladder Cancer	16S rRNA gene sequencing, MiSeq Sequencing, Defensin Expression Assays, Enzyme-Linked Immunosorbent Assay (ELISA)	Significant difference in the alpha and beta diversity of BPH and bladder cancer. High abundance of <i>Staphylococcus</i> , <i>Corynebacterium</i> , and <i>Oxyphotobacteria</i> genera in bladder cancer (BCa)	—	Diagnostic and therapeutic potential	Understanding of microbiome composition and difference in bacterial diversity of bladder cancer and prostatic hyperplasia tissue	Small sample size, lack of assessment on the functional activity of identified microbiome	In vitro	[107]
13	Urinary microbiota	Non-muscle invasive Bladder Cancer	Metagenome sequencing, RNA sequencing, Western blotting, qPCR	Identification of potential non-invasive biomarker <i>Eubacterium</i> sp. CAG:581 for non-muscle invasive bladder cancer (NMIBC)	+	Diagnostic biomarker	Highlights the role of ECM1/MMP9 pathway in bladder cancer development	-	In vitro	[108]
14	Urine microbiome (<i>Bacteroidaceae</i> , <i>Erysipelotrichales</i> , <i>Lachnospiraceae</i> , <i>Bacteroides</i>)	Bladder Cancer	Alpha diversity, principal component analysis (PCA), Adonis analysis, linear discriminant analysis (LDA)	Elevated alpha diversity and higher abundance of bacteria in smokers with bladder cancer	+	Prognosis potential	Insights into the correlation between bladder cancer and smoking. Understanding of differences in the microbiome of smokers and non-smokers	Retrospective study, small sample size, single-center study	In vitro	[89]

Table 1. Cont.

Study Number	Microbiome	Associated Cancer	Techniques Used/Evaluation Parameter	Key Results	Remarks	Utility	Advantages	Limitations	Model	Reference
15	Urinary and tissue (Urinary-bacterial phyla <i>Proteobacteria</i> , <i>Firmicutes</i> , and <i>Bacteroidetes</i> Tissue— <i>Betaproteobacteria</i> and subordinate order <i>Burkholderiales</i> family <i>Burkholderiaceae</i> down to genus <i>Burkholderia</i>)	Urothelial bladder cancer	16 s rDNA sequencing	No clinically relevant bacteria were found in men Genus <i>Burkholderia</i> was significant in neoplastic tissue	0		Identification of sex-specific differences in urinary and tissue microbiome of therapy naïve urothelial bladder cancer patients	Lack of generalizability in selected patient population, lack of study in the longitudinal change in microbiome during bladder cancer treatment	In vitro	[109]
16	Urobiome	Bladder Cancer	16S rRNA gene sequencing	Increased bacterial richness in the cancer group High alpha diversity in recurrence group	+	Diagnostic potential	Highlights the association of urobiome with bladder cancer and clinical outcomes in patients with NMIBC after transurethral resection of bladder tumor (TURBT)	Lack of precision due to limited sample size	In vitro	[110]
17	Urogenital microbiota	Bladder Cancer	16S rRNA gene sequencing	Increase in bacterial richness (<i>Leptotrichia</i> , <i>Roseomonas</i> , and <i>Propionibacterium</i>) with increase in programmed death-ligand 1 (PD-L1) positive cells Decreased abundance of <i>Prevotella</i> and <i>Massilia</i>	+	Diagnostic potential	Provides an association between non-muscle invasive bladder cancer and PD-L1 expression	Small sample size, lack of mechanism through which urogenital microbiota affects PD-L1 expression	In vitro	[111]

Table 1. Cont.

Study Number	Microbiome	Associated Cancer	Techniques Used/Evaluation Parameter	Key Results	Remarks	Utility	Advantages	Limitations	Model	Reference
18	Bladder cancer tissue	Bladder Cancer	16S rRNA gene sequencing, PCR amplification, Illumina MiSeq platform	Lower species richness and diversity in cancerous tissue Relatively higher abundance of <i>Cupriavidus</i> , <i>Acinetobacter</i> , <i>Anoxybacillus</i> , <i>Escherichia-Shigella</i> , <i>Geobacillus</i> , <i>Pelomonas</i> , <i>Ralstonia</i> , and <i>Sphingomonas</i>	+	Biomarker potential	Association of dysbiotic microbiome with bladder cancer may serve as biomarker in assisting disease screening and monitoring	Lack of analysis between the composition of bacterial flora with bladder cancer and clinical indicators	In vitro	[112]
19	Urinary microbiome	Bladder Cancer	16S rRNA gene sequencing and PCR	No significant difference in microbial diversity in newly diagnosed bladder cancer or with tobacco smoking history	0		Establish the association between effect of tobacco exposure on human microbiome and risk of bladder cancer	Single-center study, small sample size, possible contamination of mid-stream urine sample	In vitro	[113]
20	Urinary microbiota	Bladder Cancer	16S rRNA gene sequencing and DNA isolation	Higher bacterial richness (<i>Acinetobacter</i> , <i>Anaerococcus</i> , and <i>Sphingobacterium</i>) in urine samples <i>Herbaspirillum</i> , <i>Porphyrobacter</i> , and <i>Bacteroides</i> were associated with higher risk of recurrence and progression Significant difference in beta diversity between cancer and non-cancer group at risk level	+	Biomarker potential	Retrospective study, lower number of cases, possible contamination of mid-stream urine with microbiota surrounding urethral orifice		In vitro	[24]
21	Primary tumor tissue from Renal cell carcinoma	Kidney Cancer	RNA sequencing	No statistical difference in the alpha diversity Abundance of <i>Micrococcus luteus</i> , <i>Fusobacterium nucleatum</i> , <i>Streptococcus agalactiae</i> , and <i>Corynebacterium diphtheriae</i> in tumor specimens	+	Biomarker potential	Reveals microbiome analysis in different tissue and PD-L1 expression in tumor thrombus	Small sample size	In vitro	[94]

Table 1. Cont.

Study Number	Microbiome	Associated Cancer	Techniques Used/Evaluation Parameter	Key Results	Remarks	Utility	Advantages	Limitations	Model	Reference
22	Microbiota in renal cell carcinoma	Kidney Cancer	Illumina Mi Sequencing, quantitative insights into microbial ecology (QIIME), linear discriminant effect size (LEfSe), phylogenetic investigation of communities by reconstruction of unobserved states (PICRUST)	Distinct and decreased species diversity in patients with renal cell carcinoma (RCC) Nine altered pathways were identified to reveal potential microbial function	—	Diagnostic potential	Identification of intratumoral microbiome in RCC	Small sample size, Retrospective study	In vitro	[92]
23	Seminal Plasma microbiome	Testicular and Penile Cancer	RNA isolation using Trizol LS Reagent protocol, small RNA sequencing	High abundance of <i>Acaryochloris marina</i> , <i>Halovirus HGTV-1</i> , <i>Thermaerobacter marianensis</i> , <i>Thioalkalivibrio</i> sp. K90mix, <i>Burkholderia</i> sp. Y123, and <i>Desulfurivibrio alkaliphilus</i> of testicular germ cell tumor (TGCT) and germ cell neoplasia in situ (GCNIS)	+	Biomarker potential	Potential of early detection of TGCT and GCNIS	Smaller RNA reads, principal different methodology	In vitro	[64]

This review included data from seven clinical trials (Table 2). Among them, three trials investigated and characterized the microbiome in both male and female populations, focusing on a range of conditions, including genital microbiota composition, genital lichen sclerosus, vaginal and seminal microbiomes, HPV status, fertility outcomes, and the influence of reproductive and gastrointestinal tract microbiota on pregnancy.

The remaining four studies exclusively focused on the GU tract, examining its microbiome in relation to conditions such as the penile microbiome and its association with bacterial vaginosis, seminal microbiota and fertility, microbiome–metabolomic profiles in non-obstructive azoospermia, and the role of the urinary and gut microbiome in organ recovery following radiation therapy. Male genital cancers represent a complex and heterogeneous group of diseases, with several obstacles hindering the clinical translation of microbiome-related findings. A primary challenge is the multifaceted interaction between the microbiome and host immunity. Dysbiosis of the genital microbiota may contribute to carcinogenesis; however, the precise mechanisms underlying these interactions remain poorly understood. In addition, the relative rarity of these cancers, specifically testicular and penile cancers, and their often-overlooked clinical burden limit the feasibility of large-scale, statistically powered clinical trials. This scarcity of patient data hinders a comprehensive understanding of disease progression and therapeutic responses. Compounding this challenge is the absence of standardized protocols for microbiome sampling and analysis in the GU tract, leading to variability in microbial identification and inconsistent results across different studies. Although infections and chronic inflammatory states have been implicated in carcinogenesis across multiple organ systems, direct evidence linking infection-driven dysbiosis to male genital cancers remains sparse, underscoring the need for focused mechanistic and longitudinal studies. These limitations underscore the urgent need for methodological harmonization and deeper mechanistic studies to elucidate the role of the microbiome in genital cancer in males.

The investigation of the GU microbiome in the context of GU cancers is an emerging and rapidly evolving research area. Our comprehensive literature review revealed a growing body of evidence linking microbial dysbiosis to the onset and progression of bladder, prostate, kidney, testicular, and penile cancers. Notably, increased microbial richness and diversity are associated with a heightened cancer risk and accelerated disease progression. These findings underscore the potential utility of microbiome profiling for enhancing diagnostic accuracy, refining disease staging, and informing prognosis. Despite these promising correlations, the precise molecular mechanisms underlying microbe–host interactions and their roles in carcinogenesis remain largely undefined. The field currently lags behind the well-established studies of the gut microbiome; however, advances in GU microbiome research are anticipated to parallel those in gastrointestinal oncology. As sequencing technologies and bioinformatics tools continue to evolve, a deeper understanding of the GU microbiome may open new avenues for microbiome-targeted therapy. Several innovative approaches are being explored to restore microbiome balance and harness its therapeutic potential. These include probiotic engineering, antimicrobial peptides, and hybrid systems combining probiotics with biomaterials, which show promise in modulating local microbial ecosystems to support anti-cancer interventions.

Table 2. Summary of clinical studies investigating the association between the male genitourinary microbiome to genitourinary cancer. Conclusion and Outlook.

NCT Number	Study Title	Study Status	Number of Patients	Brief Summary	Conditions	Interventions	Primary Outcome	Secondary Outcome	Sex	Study Type
NCT05963711	The Genital Microbiome of Male Partners of Women With Recurrent bacterial vaginosis (BV) Undergoing Vaginal Microbiome Transplantation	Recruiting	100	This study aims to assess the role of male partner's genital microbiome in the recurrence of BV in women undergoing vaginal microbiota transplantation, as sexual activity is associated with the acquisition and recurrence of Bacterial Vaginosis.	Bacterial Vaginosis Microbial Colonization	chlorhexidine gluconate 4%	To characterize the penile microbiota and its resemblance to vaginal microbiota of their sexual partner.	N/A	MALE	Interventional
NCT05671263	Genital Lichen Sclerosus—Epidemiology, Comorbidities and the Role of Vulvar and Penile Microbiome	Recruiting	200	This study analyzes the genital microbiome pre- and post-therapy, and determines the correlation between genital lichen sclerosis (LSc) and other diseases.	Lichen Sclerosus	N/A	To determine quality of life (QoL) of genital LSc patients To analyze the role of genital microbiome in genital LSc treatment resistance To determine genital LSc comorbidity.	N/A	ALL	Observational
NCT05328999	Fertility and the Microbiome	Recruiting	300	This study aims to investigate the microbiome and human papillomavirus (HPV) status of subfertile couples and its relationship with fertility, sperm quality, and probiotic intake through a randomized placebo controlled double blind pilot study.	Subfertility Asthenozoospermia	Dietary Supplement: Probiotics [Omnibiotic (R)]	To characterize seminal microbiome, vaginal microbiome, and uterine microbiome	To determine status of various male and female hormones such as Testosterone, free testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEAS), luteinizing hormone, follicle-stimulating hormone, Anti-Müllerian hormone (AMH), thyroid-stimulating hormone, free T3, free T4, and 25 (OH) Vitamin D To determine the HPV status and to characterize stool, oral microbiome	ALL	Observational
NCT04784260	Microbiome Influence on Seminal Quality	Completed	40	The role of microbiome in seminal quality and its relationship with male fertility is being studied using bioinformatics and next-gen sequencing.	Infertility, Male	Microbiome analysis	To characterize seminal microbiome and identify its associations with seminal quality	To evaluate the impact of the microbiome on the seminal quality of an individual and to identify whether it can serve as fertility marker	MALE	Observational

Table 2. Cont.

NCT Number	Study Title	Study Status	Number of Patients	Brief Summary	Conditions	Interventions	Primary Outcome	Secondary Outcome	Sex	Study Type
NCT06181851	2015-Metabolomics & Microbiome-infertility	Recruiting	45	The objective of this study is to analyze the microbiome and metabolomics in non-obstructive azoospermia patients to evaluate the prognostic factors which can predict the presence of sperm post extracting testicular pulp, and determine the underlying etiopathology, in comparison to fertile individuals.	Azoospermia, Nonobstructive	Analysis of microbiome and metabolomics	To compare blood and semen levels of certain substances of individuals undergoing testicular pulp extraction with fertile men.	N/A	MALE	Observational
NCT03637777	The Human Microbiome and IVF Outcomes	Completed	332	The aim of this study is to analyze the microbiome of the gastrointestinal tract, male reproductive system, and female reproductive system in patients and their partners who are undergoing in-vitro fertilization (IVF).	Infertility	Diagnostic Test: 16S rRNA gene sequencing	To identify whether microbiome has any impact of delivery of live birth of infants	-	ALL	Observational
NCT04775355	Study to Detect Changes in Urinary and Gut Microbiome During Androgen Deprivation Therapy and Radiation Therapy in Patients With Prostate Cancer	Recruiting	30	The objective of this study is to identify whether the microbiome helps in organ healing post radiation.	Stage I Prostate Cancer American Joint Committee on Cancer (AJCC) v7 Stage II Prostate Cancer AJCC v7 Stage IIA Prostate Cancer AJCC v7 Stage IIB Prostate Cancer AJCC v7 Stage III Prostate Cancer AJCC v7 Stage IV Prostate Cancer AJCC v7	Procedure: Biospecimen Collection Others: Electronic Health Record Review Quality-of-Life Assessment Questionnaire Administration	To identify and analyze urinary and gut microbiota	To detect any changes in the microbiome population and to identify its associations with toxicity	MALE	Observational

High-throughput techniques, such as amplicon sequencing (e.g., 16S rRNA gene sequencing), along with meta-omics approaches, including metagenomics, metatranscriptomics, metaproteomics, and metabolomics, are increasingly being applied to decipher the biology of the human microbiome. These advanced methodologies have proven instrumental in identifying dysbiotic microbial communities, particularly those associated with prostate cancer. However, a critical gap remains in the comprehensive analysis of the penile and seminal microbiomes, specifically regarding their taxonomic composition, functional activity, and mechanistic links to male genital cancers. These technologies pave the way for precision medicine by enabling patient-specific microbiome characterization and therapeutic customizations. In particular, metaproteomic platforms such as MetaLab provide automated, in-depth analyses of protein expression profiles within microbial communities, offering critical insights into their role in prostate cancer biology. This area warrants deeper exploration, as uncovering the role of microbiome dysbiosis in cancers such as penile, testicular, and prostate cancers could profoundly impact our understanding of their pathogenesis. Moreover, it holds promise for optimizing therapeutic strategies, enabling the development of personalized medicine, improving patient outcomes, and enhancing the quality of life.

Additionally, FMT, a strategy already proven valuable in gastrointestinal disorders, is being investigated for its potential to modulate immune responses and enhance cancer immunotherapy, particularly when used alongside narrow-spectrum antibiotics and immune checkpoint inhibitors [114]. While current research on the urogenital microbiome and its link to genitourinary malignancies remains in its infancy, the prospects for future breakthroughs are substantial. Continued interdisciplinary efforts and high-resolution omics-based investigations are essential to fully elucidate the clinical relevance of the GU microbiome and to translate these findings into innovative diagnostic and therapeutic strategies in genitourinary oncology.

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