



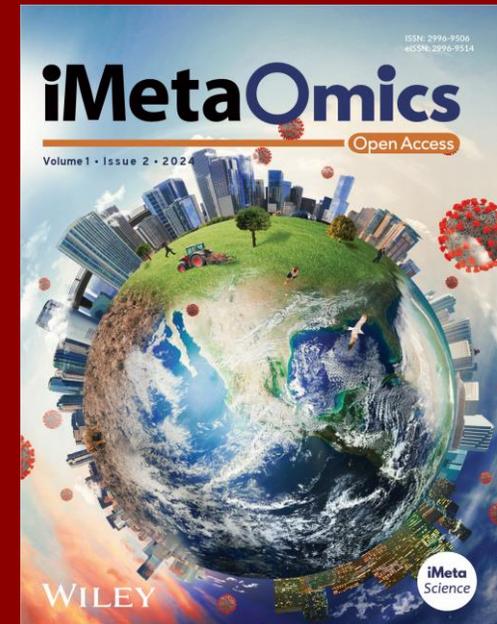
Microbiome-urothelium crosstalk in bladder cancer: From dysbiosis to clinical translation

Haoxiang Xu^{1#}, Zhibiao Li^{1#}, Lin Yang¹, Jun Zheng¹, Weijia Li¹, Rulin Liao¹,
Wenxue Huang¹, Boyuan Sun¹, Zhuohang Li¹, Cunzhen Ma¹, Xunguo Yang¹,
Zongwei Wang^{2*}, Jie Zhao^{3*}, Bisheng Cheng^{1,2*}, Peng Wu^{1*}

¹Department of Urology, Nanfang Hospital, Southern Medical University, Guangzhou, China

²Department of Surgery, Division of Urology, Beth Israel Deaconess Medical Center,
Harvard Medical School, Boston, USA

³NMPA Key Laboratory for Research and Evaluation of Drug Metabolism,
Guangdong Provincial Key Laboratory of New Drug Screening,
School of Pharmaceutical Sciences, Southern Medical University, Guangzhou, China



Haoxiang Xu, Zhibiao Li, Lin Yang, Jun Zheng, Weijia Li, Rulin Liao, Wenxue Huang, et al. 2026.
Microbiome-urothelium crosstalk in bladder cancer: From dysbiosis to clinical translation.
iMetaOmics 3:e70081. <https://doi.org/10.1002/imo2.70081>



Introduction

Bladder Cancer & Urobiome

- ❑ **Paradigm Shift:** Advanced sequencing confirms the "Urobiome" exists, overturning the "sterile urine" dogma.
- ❑ **Microbial Dysbiosis:** BCa is characterized by pathogen enrichment and beneficial bacteria depletion.
- ❑ **Tumorigenesis:** Driven by chronic inflammation, bacterial genotoxins, and metabolic reprogramming.



Clinical Challenges & Translation

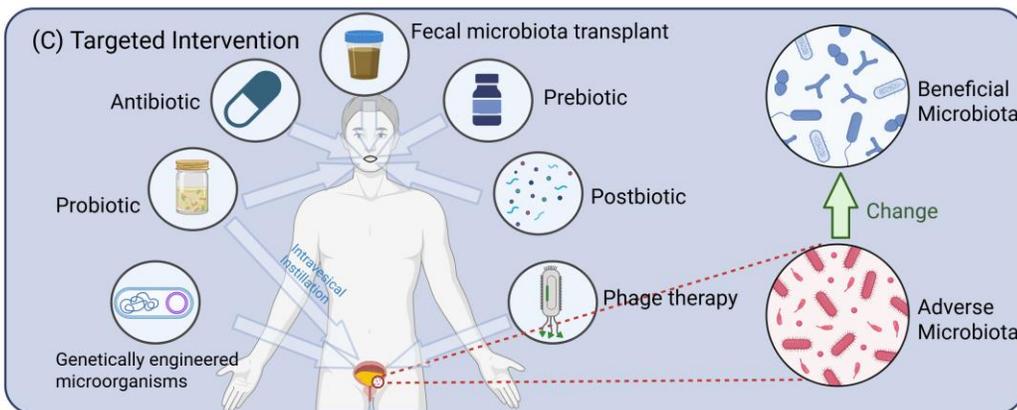
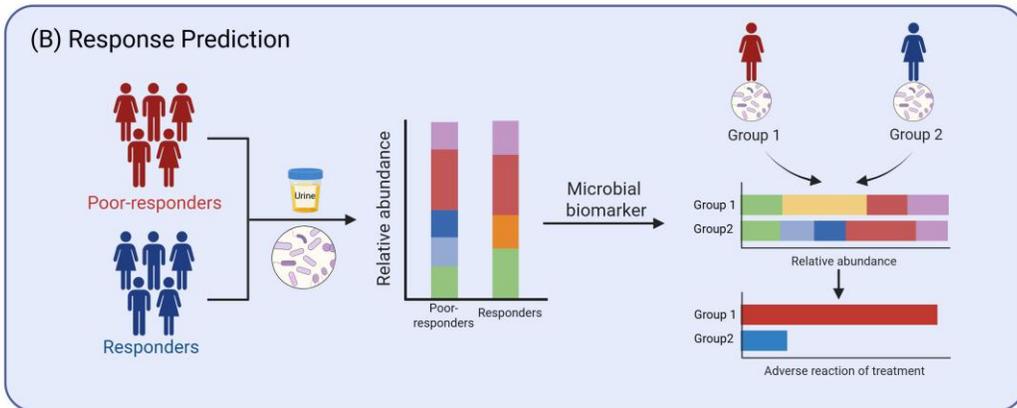
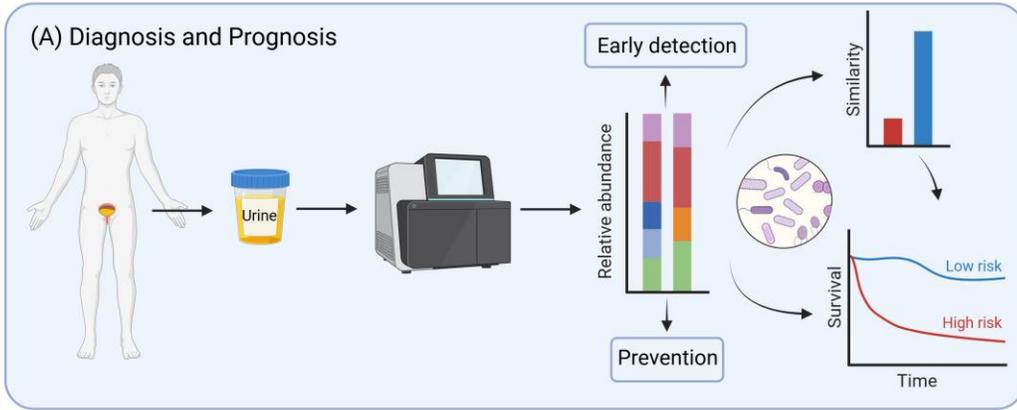
- ❑ **Current Limitations:** Invasive diagnostics (cystoscopy) and variable treatment responses (BCG/ICIs).
- ❑ **Liquid Biopsy:** Urobiome serves as a non-invasive biomarker for diagnosis and risk stratification.
- ❑ **Precision Intervention:** Enables response prediction and novel therapies like probiotics and FMT.

Core Contributions

Systematically integrating urobiomics with clinical translation. We map the path from dysbiosis and mechanisms to precision medicine, highlighting the microbiome's role in diagnosis, prognosis, and therapeutic modulation.



Highlights



- ✓ The urinary microbiome exhibits distinct dysbiosis in bladder cancer, providing specific microbial signatures for non-invasive diagnosis and risk stratification.
- ✓ Mechanistic crosstalk drives tumorigenesis through chronic inflammation, bacterial genotoxins, and metabolic reprogramming via the gut-bladder axis.
- ✓ Microbial profiles serve as robust predictors of therapeutic efficacy for both intravesical BCG immunotherapy and systemic ICIs.
- ✓ Personalized strategies, including microbiome-conscious antibiotic stewardship and probiotic interventions, offer novel avenues to enhance bladder cancer treatment outcomes.



Sampling Strategy & Microbial Dysbiosis

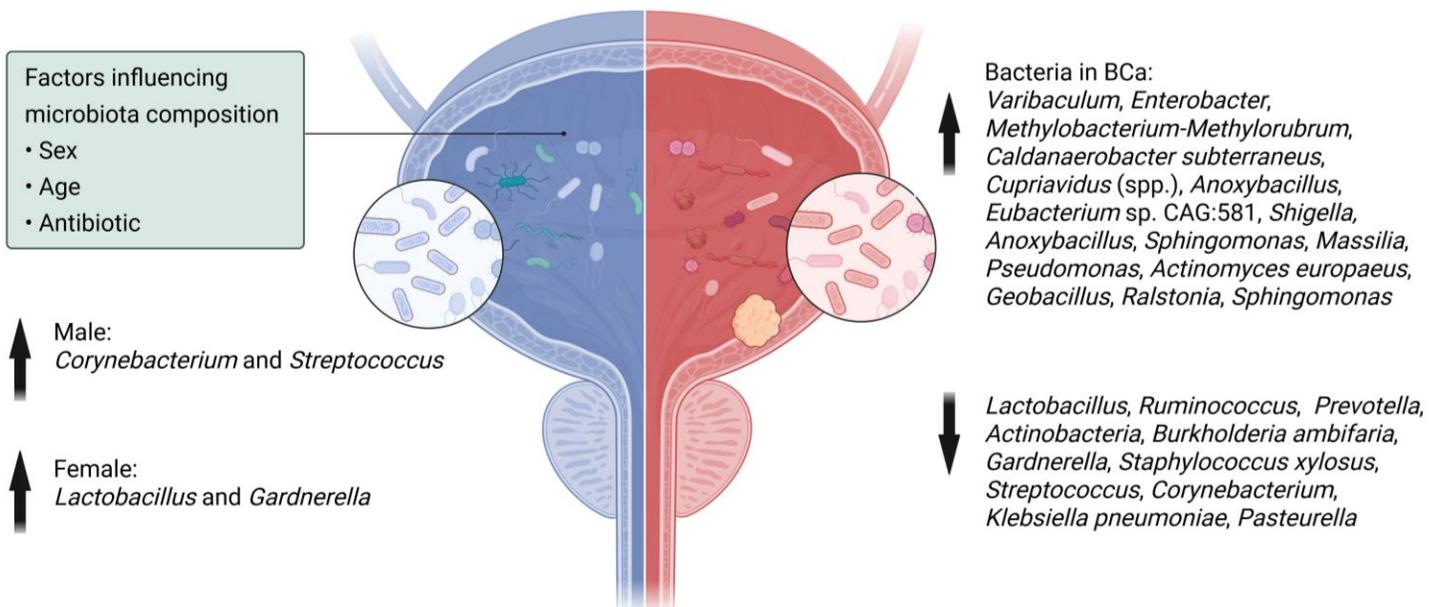
(A)

Characteristic	Midstream clean-catch urine (CC)	Transurethral catheter (TUC)	Suprapubic Aspiration (SPA)
Contamination Risk	High	Moderate	Low
Invasiveness	None	Moderate	High

Sampling Method Evaluation

- Midstream Urine (CC): High contamination risk; reflects "urogenital" microbiota.
- Catheterized (TUC) / Suprapubic (SPA): Accurately reflects the "bladder" niche; ideal for cancer research.

(B) Healthy Individual Microbiome Bladder Cancer Microbiome



Homeostasis

- Females: Dominated by *Lactobacillus*.
- Males: Dominated by *Corynebacterium* & *Streptococcus*.

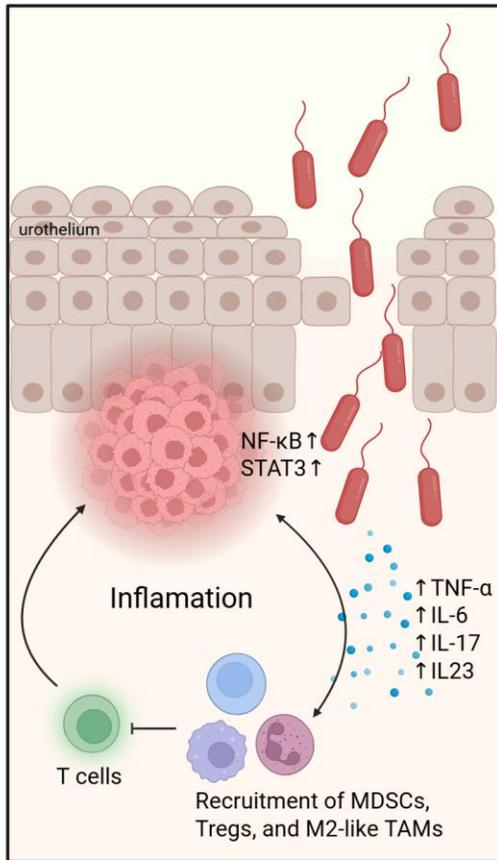
Dysbiosis in BCa

- Enriched: Potential pathogens (e.g., *Enterobacter*, *Streptococcus*).
- Depleted: Beneficial commensals (e.g., *Lactobacillus*, *Bifidobacterium*).

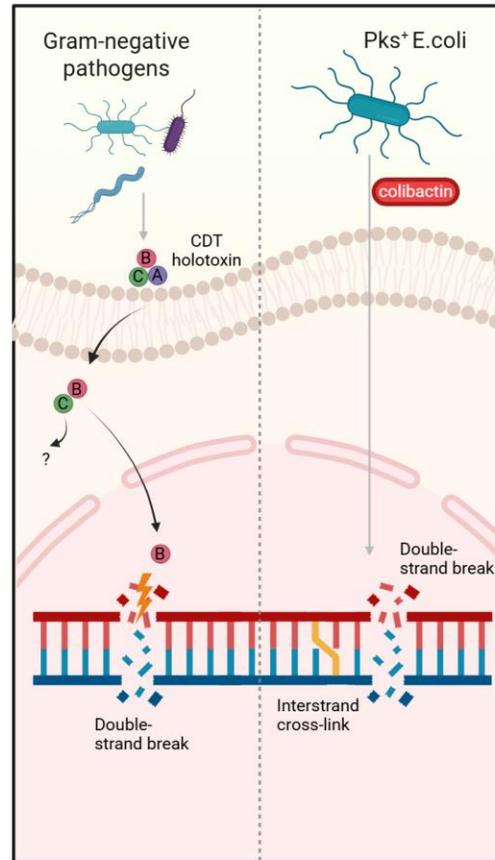
Figure 1 Comparison of the urinary microbiome in health versus cancer and implications of sampling methodologies.

Mechanisms of Microbial Carcinogenesis

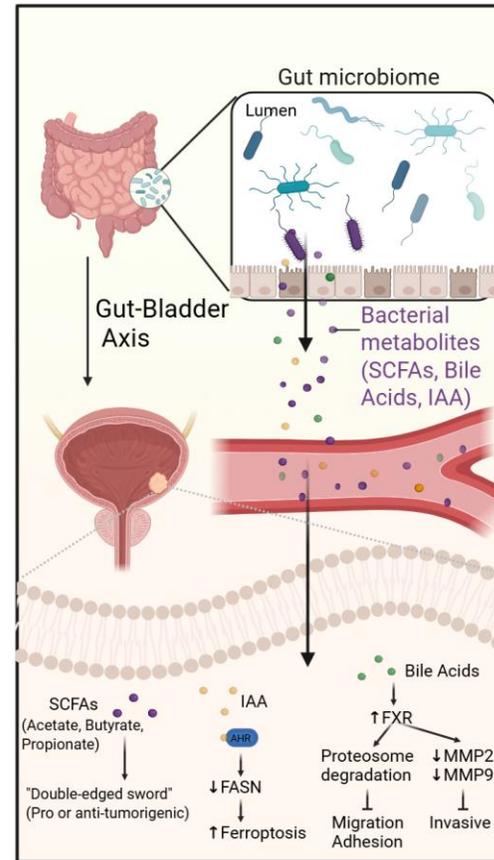
(A) Chronic inflammation and immune modulation



(B) Genotoxin-producing bacteria and DNA damage



(C) Metabolic reprogramming



(D) Tumor-promoting pathways

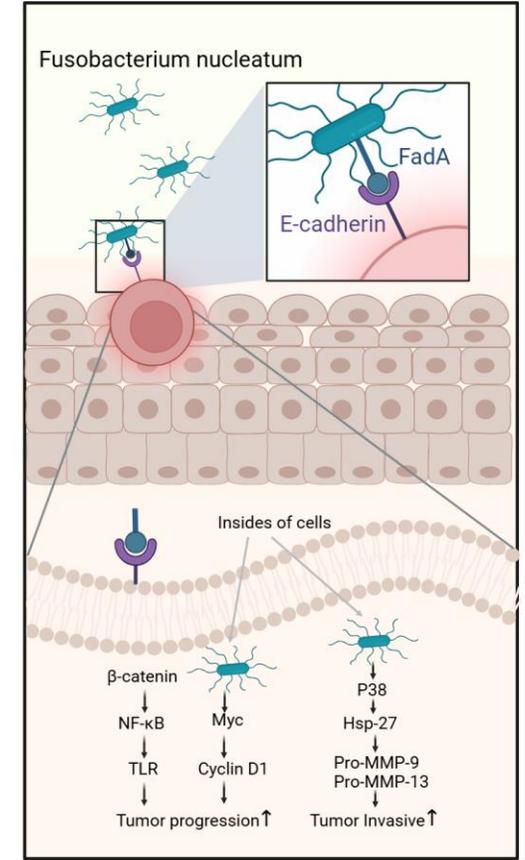
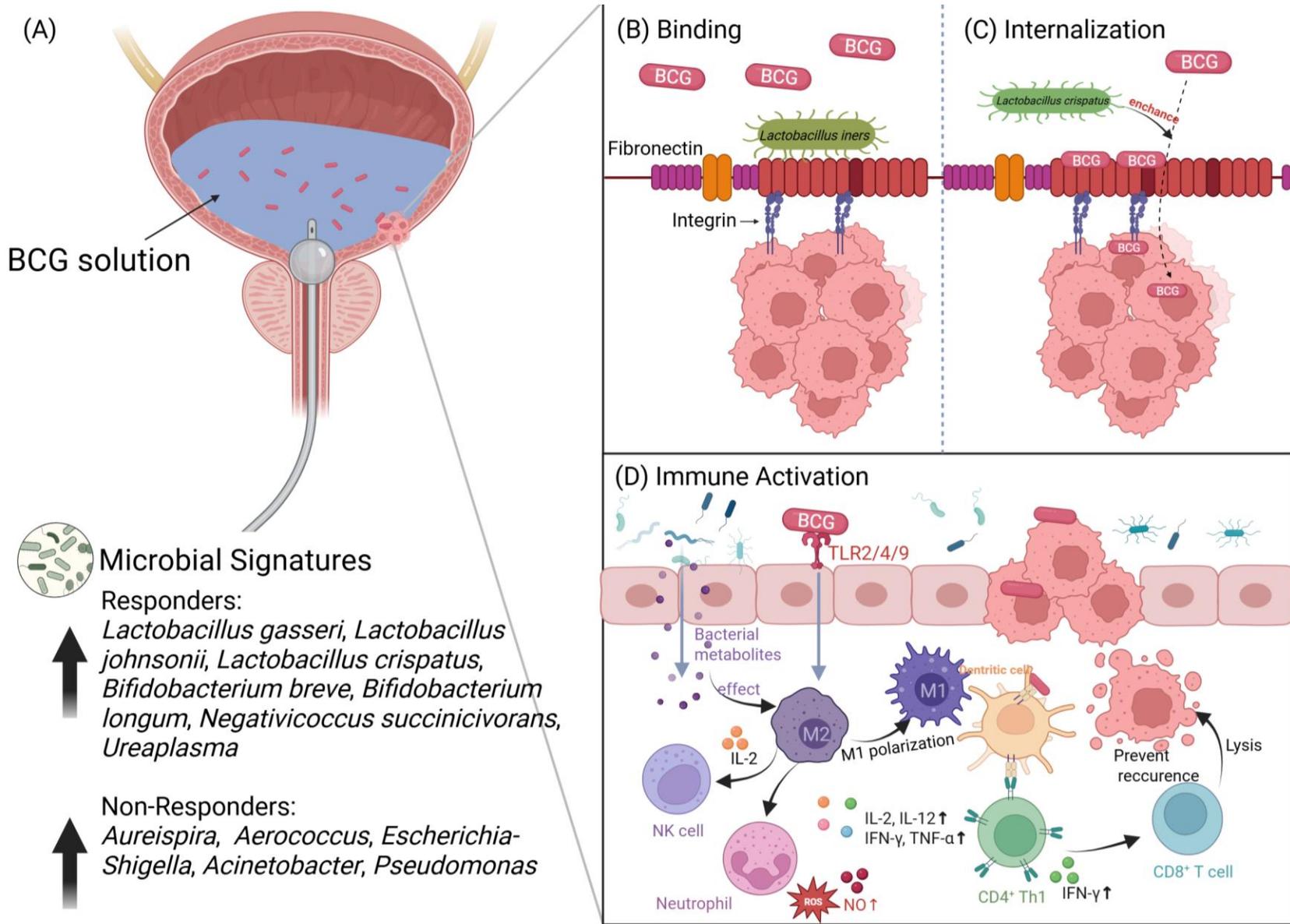


Figure 2 Putative mechanisms by which the microbiome promotes bladder carcinogenesis.

Microbial Modulation of BCG Efficacy



Physical Blocking (Competitive Adhesion)

- Mechanism: *Lactobacillus iners* competitively binds to fibronectin on the urothelium.
- Impact: Reduces BCG attachment and effective therapeutic load.

Enhanced Internalization

- Mechanism: *Lactobacillus crispatus* promotes BCG uptake by bladder cancer cells.
- Impact: Triggers crucial antigen presentation processes.

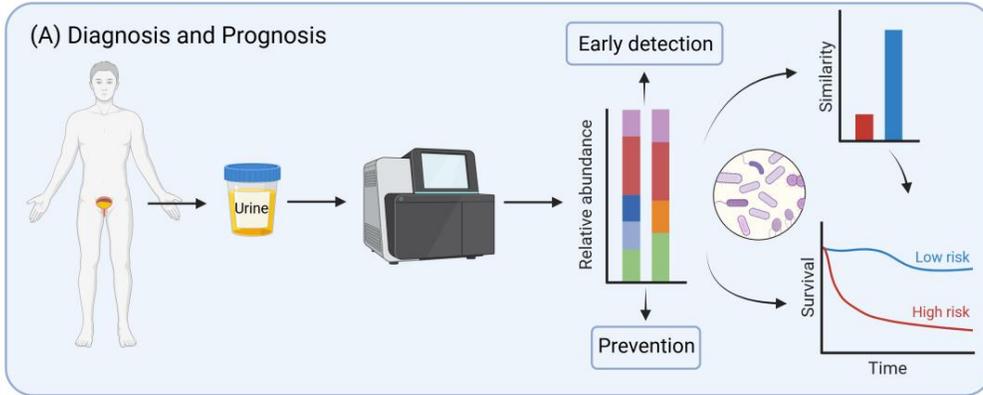
Synergistic Immune Activation

- Signaling: Beneficial bacteria activate TLR2/4/9 pathways.
- Response: Induces M1 macrophage polarization and cytokine release (IL-12, IFN- γ).
- Outcome: Activates CD8⁺ T cells for tumor cytotoxicity.

Figure 3 Proposed mechanisms modulating BCG immunotherapy efficacy via the urinary microbiome.

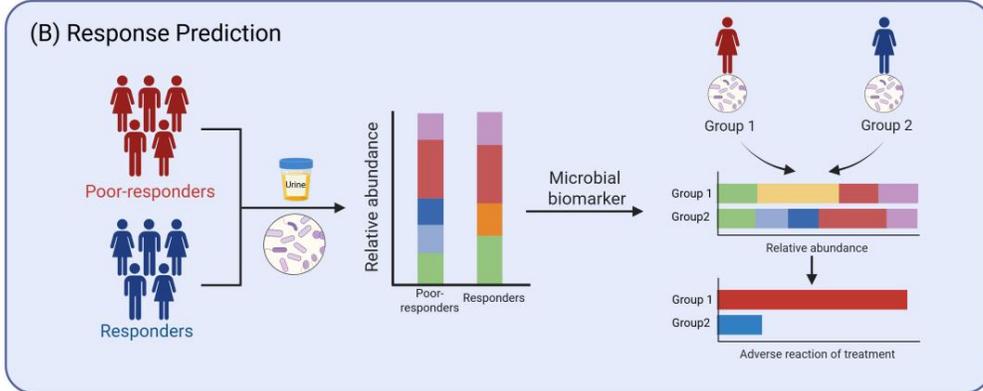


Clinical Translational Applications



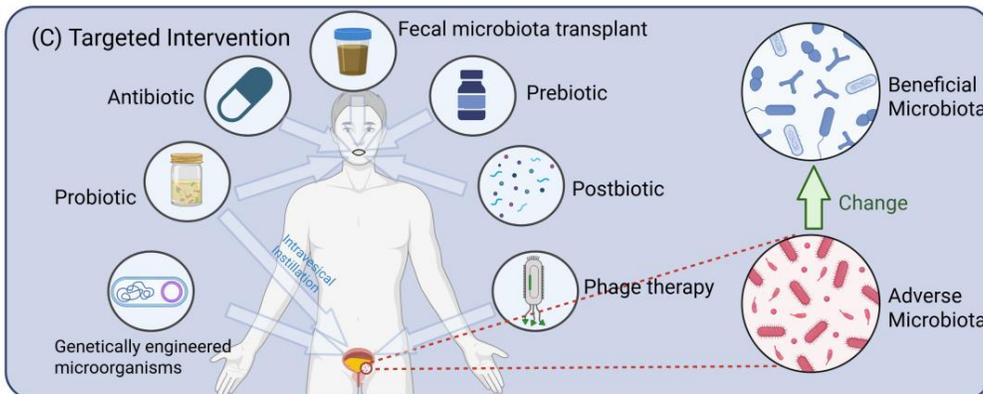
Diagnosis & Prognosis (Liquid Biopsy)

- Early Detection: Utilization of the urinary microbiome as non-invasive biomarkers.
- Risk Stratification: Distinguishes high-risk vs. low-risk groups to predict survival outcomes.



Response Prediction

- Signature Identification: Pre-treatment differentiation of Responders vs. Non-Responders.
- Precision Selection: Screens potential beneficiaries to maximize immunotherapy efficacy and minimize adverse events.



Targeted Intervention (Microbiome Reshaping)

- Goal: Reverses pro-tumor dysbiosis into a beneficial state.
- Strategies: Probiotics, FMT (Fecal Microbiota Transplant), prebiotics, postbiotics, and phage therapy.

Figure 4 Clinical applications of the microbiome in bladder cancer management.



Summary & Perspectives

- **Dysbiosis Landscape:** Constructed a bladder cancer-specific microbial map, integrating microbiomics with clinical translation beyond the "sterile urine" dogma.
- **Mechanistic Insights:** Elucidated host-microbe crosstalk driving tumorigenesis via chronic inflammation, bacterial genotoxicity, and the gut-bladder metabolic axis.
- **Clinical Utility (Liquid Biopsy):** Established the microbiome as a non-invasive tool for early diagnosis, risk stratification, and predicting immunotherapy response (BCG/ICIs).
- **Methodological Standardization:** Addressed challenges in low-biomass samples by proposing standardized sampling and contamination control workflows.
- **Precision Intervention:** Proposed a shift from "observation" to "action," targeting the microbiome (e.g., probiotics, FMT) for personalized precision oncology.

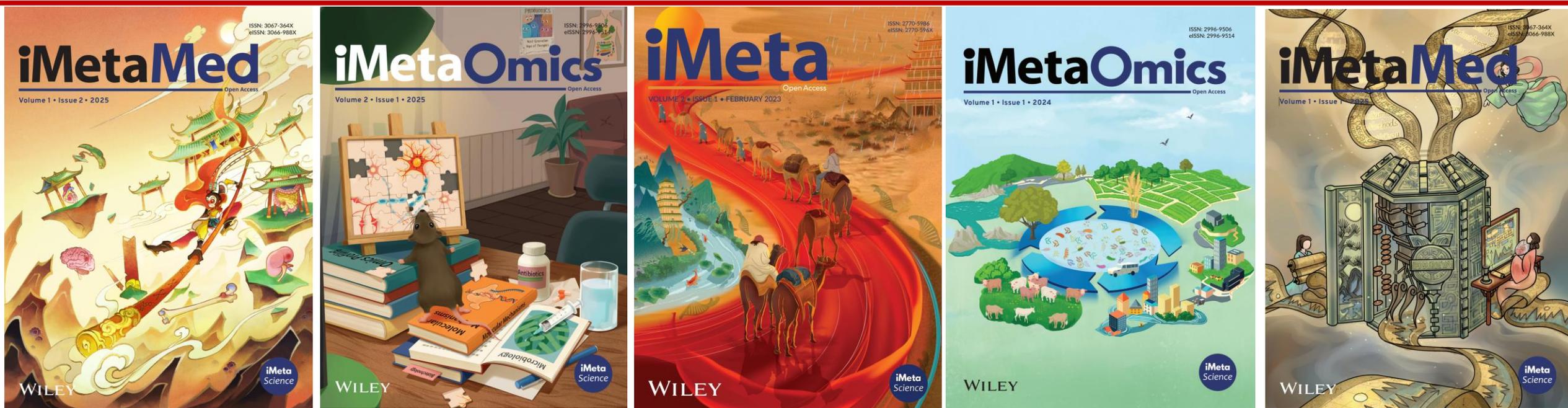
Haoxiang Xu, Zhibiao Li, Lin Yang, Jun Zheng, Weijia Li, Rulin Liao, Wenxue Huang, et al. 2026.

Microbiome-urothelium crosstalk in bladder cancer: From dysbiosis to clinical translation.

iMetaOmics 3:e70081. <https://doi.org/10.1002/imo2.70081>

iMeta: To be top journals in biology and medicine

WILEY



“**iMeta**” launched in 2022 by iMeta Science Society, **impact factor (IF) 33.2**, ranking **top 65/22249 in world and 2/161 in the microbiology**. It aims to publish innovative and high-quality papers with broad and diverse audiences. **Its scope is similar to Cell, Nature Biotechnology/Methods/Microbiology/Medicine/Food**. Its unique features include video abstract, bilingual publication, and social media with 600,000 followers. Indexed by **SCIE/ESI, PubMed, Google Scholar** etc.

“**iMetaOmics**” launched in 2024, with a **target IF>10**, and its scope is similar to **Nature Communications, Cell Reports, Microbiome, ISME J, Nucleic Acids Research, Briefings in Bioinformatics**, etc.

“**iMetaMed**” launched in 2025, with a **target IF>15**, similar to **Med, Cell Reports Medicine, eBioMedicine, eClinicalMedicine** etc.



Society: <http://www.imeta.science>

Publisher: <https://wileyonlinelibrary.com/journal/imeta>

iMeta: <https://wiley.atyponrex.com/journal/IMT2>

Submission: iMetaOmics: <https://wiley.atyponrex.com/journal/IMO2>

iMetaMed: <https://wiley.atyponrex.com/journal/IMM3>



[iMetaScience](#)



[iMetaScience](#)



office@imeta.science
imetaomics@imeta.science



[Promotion Video](#)

Update
2025/7/6