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REVIEW

# Toward Personalized Treatment of Urogenital Cancers: The Role of Patient-Derived Organoids

Serena Sagliocchi · Michele Musone · Stefano Chianese · Annunziata Gaetana Cicatiello · Silvia Del Mastro · Francesco Del Giudice · Monica Dentice · Felice Crocetto

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## ABSTRACT

Urogenital cancers, including prostate, kidney, and bladder cancer, remain a significant clinical challenge due to their high incidence, molecular heterogeneity, and frequent resistance to standard therapies. Despite progress in genomic profiling and precision oncology, the translation of molecular data into effective therapeutic decisions remains limited by the lack of functional models capable of capturing tumor complexity. Patient-derived organoids (PDOs) have emerged as transformative tools in this context, offering the unique advantage of preserving the genetic, phenotypic, and functional features of individual tumors ex vivo. Beyond their well-established applications in drug screening and resistance studies, PDOs contribute to personalized treatment strategies by enabling functional molecular stratification, modeling tumor–microenvironment interactions, and predicting the efficacy of targeted and immunotherapeutic approaches. When integrated with liquid biopsy analyses, PDOs also allow real-time tracking of clonal evolution and can be repeatedly generated during the disease course, providing dynamic insights that guide longitudinal treatment decisions. As organoid biobanking and multi-omic integration advance, PDOs are poised to evolve into clinically actionable avatars that complement genomic profiling and help tailor therapeutic strategies for patients with urogenital cancers. Nevertheless, the clinical integration of PDOs still faces important barriers, including variability in culture protocols, incomplete representation of the native tumor microenvironment, and the time required for organoid establishment. Moreover, the predictive value of PDO-based drug screening—although promising—needs rigorous prospective validation in large patient cohorts. This review highlights the pivotal role of PDOs in bridging the gap between laboratory research and clinical oncology, emphasizing their application in guiding personalized therapeutic strategies. As organoid biobanking and genomic profiling expand, the integration of PDOs into precision oncology pipelines holds promise for reshaping the

S. Sagliocchi · A. G. Cicatiello · S. Del Mastro · M. Dentice
Department of Clinical Medicine and Surgery, University of Naples "Federico II", 80131 Naples, Italy

M. Musone · S. Chianese · F. Crocetto (✉)
Unit of Urology, Department of Neurosciences, Reproductive Sciences, and Odontostomatology, University of Naples "Federico II", 80131 Naples, Italy
e-mail: felice.crocetto@unina.it

F. Del Giudice
Unit Department of Maternal Infant and Urologic Sciences, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy

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clinical management of urogenital malignancies and advancing toward truly individualized cancer treatment.

**Keywords:** Patient-derived organoids; Urogenital tumors; Tumor heterogeneity; Drug response prediction; Cancer precision medicine

| **Key Summary Points** |
| --- |
| Urogenital cancers, particularly prostate, kidney, and bladder cancer, remain major clinical challenges due to their molecular heterogeneity and frequent resistance to therapy. |
| Patient-derived organoids (PDOs) faithfully replicate the genetic, phenotypic, and functional complexity of individual tumors, offering superior predictive value compared to traditional 2D cultures or animal models. |
| PDOs enable real-time assessment of drug sensitivity, resistance mechanisms, and clonal evolution, supporting precision oncology approaches in both research and clinical settings. |
| The integration of PDOs with liquid biopsy (ctDNA, CTCs, urine biomarkers) offers a minimally invasive and dynamic platform to monitor tumor evolution and adapt treatment strategies over time. |
| The implementation of organoid biobanks and bioinformatic integration pipelines will be pivotal to establishing PDOs as functional avatars for personalized cancer therapy. |

## INTRODUCTION

Cancer has long represented one of the greatest and most complex challenges for the global medical and scientific communities [1]. In addition, it remains a major burden on healthcare systems worldwide, posing a persistent threat to public health and societal progress [2]. Consequently, cancer research must prioritize a deeper understanding of tumor biology, the identification of novel biomarkers, and the development of more effective therapeutic strategies. Despite substantial progress in cancer genomics, immuno-oncology, and targeted therapy, advances have not been uniformly translated into improved outcomes for many tumor types. This is particularly evident in urogenital malignancies, where biological heterogeneity, clonal evolution, and treatment resistance continue to undermine therapeutic effectiveness. Although traditional tumor models have played a crucial role in advancing our understanding of cancer biology, they possess inherent limitations that impact the predictive accuracy and translational success of preclinical findings. These models often fail to fully replicate the complex tumor microenvironment, including cellular heterogeneity, stromal interactions, immune system components, and the extracellular matrix, which are essential factors influencing tumor growth, metastasis, and therapeutic response. Moreover, many traditional models lack the ability to mimic the dynamic and adaptive nature of tumors in patients, leading to discrepancies between drug efficacy observed in preclinical studies and outcomes in human subjects. As a result, these limitations contribute to the high rate of failure in clinical trials and highlight the need for more sophisticated and physiologically relevant cancer models to improve drug development and personalized treatment strategies. Collectively, these constraints contribute to the low predictive value of preclinical studies and the persistent gap between experimental observations and clinical outcomes.

These challenges are particularly evident in urinary tract tumors, such as prostate, kidney, and bladder cancers, which together account for a substantial proportion of global cancer morbidity and mortality.

Patient-derived organoids (PDOs) represent an innovative and promising strategy in cancer treatment, enabling personalized therapy by closely mimicking the unique biological and genetic features of individual tumors. Indeed, the principal advantage of organoids resides in their capacity to faithfully preserve the genetic heterogeneity and phenotypic complexity characteristic of in vivo tumors. This fidelity enables

organoids to serve as highly representative in vitro models for investigating the molecular mechanisms underlying tumorigenesis and cancer progression. However, while organoid technology holds immense promise, its application in precision oncology is still maturing. Critical issues—including the standardization of culture methods, integration with multi-omics data, scalability for clinical workflows, and the incomplete recapitulation of stromal and immune components—must be addressed before PDOs can be fully embedded in personalized treatment pathways. This review aims to critically evaluate the potential and limitations of PDOs in urogenital oncology, highlighting their current applications, technological constraints, and future directions necessary to transform them into reliable clinical decision-making tools.

### Purpose

This review provides a comprehensive overview of the current knowledge on urogenital cancers, highlighting recent advances in PDO technology and its role in improving diagnosis, guiding personalized therapies, and advancing precision oncology.

## OVERVIEW OF UROGENITAL CANCERS

Urogenital tumors comprise a heterogeneous group of tumors which, sharing a common anatomical start, are distinctly characteristic in their clinical, biological, and prognostic aspects [3, 4]. Much progress was made, particularly throughout the last century, in the field of diagnosis and treatment; however, the management of malignant diseases continues to become more and more complicated [5–7]. Tumor heterogeneity on every scale, the almost invariable acquired resistance to treatment, and the relative lack of tools able to predict outcomes make for an often ill-defined, complicated treatment pathway [6, 7]. A further complicating factor is that current clinical pathways often rely on static and fragmented assessments—limited biopsies, intermittent imaging, and delayed molecular testing—which fail to capture the dynamic evolution of the disease under therapeutic pressure. This discrepancy is magnified by the inadequacy of standard preclinical models, which rarely reflect the full biological spectrum of urogenital malignancies. Consequently, although molecular oncology has uncovered numerous actionable alterations, only a limited fraction have been successfully translated into practice, highlighting the gap between genomic knowledge and functional application. In this context, urogenital cancers exemplify how conventional diagnostic and therapeutic tools remain insufficient for precision oncology.

PDOs offer a unique opportunity to overcome several of the limitations inherent to current diagnostic and preclinical approaches. By preserving the clonal architecture and molecular heterogeneity of individual tumors, PDOs allow functional modeling of key biological processes that drive therapeutic failure, including lineage plasticity, androgen-receptor reprogramming, immune evasion, and emergence of neuroendocrine or basal-like resistant subclones. Importantly, PDOs enable real-time assessment of treatment-induced adaptations—such as activation of bypass pathways or acquisition of DNA-repair defects—providing a dynamic and patient-specific platform to investigate resistance mechanisms in both prostate and bladder cancer. This functional dimension directly complements molecular profiling and offers an avenue to anticipate resistance early, refine therapeutic choices, and guide more personalized interventions.

### Prostate Cancer

Prostate cancer is the most common solid tumor found in men; many cases are fairly indolent; however, high-risk and metastatic types still challenge the clinician greatly [8, 9]. The cancer begins as and remains largely dependent on androgen signaling, thereby making androgen deprivation therapy (ADT) initially effective, but almost all patients with advanced disease will eventually transition to castration-resistant prostate cancer (CRPC) [10]. This transition is an important phase in the tumor's evolution

and is subsequently accompanied by the activation of very complex biological processes such as amplification or mutation of the androgen receptor (AR), activation of alternate signaling pathways such as PI3K/AKT and WNT, the very aggressive neuroendocrine variants, and the beginning of alterations in DNA repair genes [11–13]. While these changes support the progression of the tumor, they may also allow for potential therapeutic interventions [14]. Indeed, the identification of actionable alterations in DNA repair genes has already opened the way to the clinical use of poly(ADP-ribose) polymerase (PARP) inhibitors in selected patients, exemplifying how a better understanding of tumor biology can translate into targeted treatments. At the same time, the heterogeneity of resistance mechanisms underscores the necessity for combinatorial therapeutic strategies that address multiple pathways simultaneously [15–18].

The conventional methods of preclinical models have made valuable contributions in these areas, although they come with a range of disadvantages [19, 20].

Liquid biopsy approaches, including circulating miRNAs and urine-based testing, have shown promise in predicting treatment response and monitoring disease evolution [21–24]. In particular, the analysis of extracellular vesicles and other non-coding RNAs is emerging as an attractive strategy to obtain real-time information on tumor biology, with the potential to complement conventional imaging and tissue biopsies. These technologies are also being evaluated as tools for early detection, risk stratification, and longitudinal follow-up, raising the possibility of more personalized and adaptive treatment strategies. Moreover, liquid biopsies hold the advantage of being minimally invasive and repeatable over time, which makes them suitable for monitoring clonal evolution and therapy-induced selective pressures, aspects that are otherwise difficult to capture in routine clinical practice [22].

Furthermore, studies have highlighted the role of androgen-thyroid hormone crosstalk in prostate cancer progression, which can be investigated in organoid models [25] and integrated with liquid biopsy monitoring [26–29]. The interplay between these hormonal signals and the tumor microenvironment has been shown to influence tumor aggressiveness and therapy resistance [30–33]. Recent data also suggest that hormonal crosstalk interacts with metabolic reprogramming and immune evasion pathways, further complicating the biological landscape of advanced prostate cancer. A deeper understanding of these interactions may reveal novel therapeutic targets and contribute to the development of multimodal approaches that combine systemic therapies, targeted agents, and innovative biomarkers to improve patient outcomes.

Recent work has demonstrated the value of prostate cancer PDOs as functional models to investigate AR signaling and treatment response. Gao et al. first generated organoids from metastatic prostate tumors and showed that they retained AR expression and faithfully reproduced ligand-dependent transcriptional programs, enabling direct interrogation of AR pathway activity under different hormonal conditions [34]. More recent studies have used PDOs to model adaptive AR reprogramming and the emergence of AR-splice variants associated with resistance to androgen-receptor pathway inhibitors (ARPIs). For example, organoid models derived from CRPC have been used to evaluate the efficacy of next-generation ARPIs, demonstrating concordance between organoid drug sensitivity and clinical response. PDOs have also supported high-throughput drug testing: assays using CRPC organoids revealed selective vulnerability to PARP inhibitors in tumors with homologous recombination repair defects and identified actionable sensitivities to PI3K/AKT pathway inhibitors in organoids harboring PTEN loss [35]. Collectively, these findings illustrate how prostate cancer PDOs serve not only as faithful AR-signaling models but also as practical tools to test therapeutic strategies and anticipate mechanisms of resistance (Table 1).

Collectively, prostate cancer illustrates the urgent need for integrated platforms that combine molecular characterization with functional assessment, enabling real-time evaluation of treatment sensitivity and resistance. PDOs represent a promising solution, particularly for studying AR signaling dynamics, CRPC evolution, and response to targeted therapies [36].

**Table 1** Epidemiological, biological, and therapeutic characteristics of urogenital cancers and their modeling through PDOs

| Cancer type | Global incidence/mortality | 5-year survival | Main biological features | Standard therapy | Major limitations | PDO applications |
|---|---|---|---|---|---|---|
| Prostate | Approx.1.4 million new cases/year; 375,000 deaths/year; 2nd most common malignancy in men (GLOBOCAN 2024) | Approx. 98% (localized), 30% (metastatic) | Androgen-dependent; progression to castration-resistant phase (CRPC); frequent AR, PI3K/AKT, WNT alterations; DNA repair defects (BRCA1/2, ATM) | ADT; next-generation AR inhibitors; chemotherapy; PARP inhibitors (selected cases) | Inevitable ADT resistance; molecular heterogeneity; emergence of neuroendocrine variants | PDOs replicate androgen sensitivity and CRPC; enable study of AR signaling, hormonal crosstalk, and drug screening for PARP inhibitors and radioligands |
| Bladder | Approx. 600,000 new cases/year; 220,000 deaths/year; 10th most common cancer globally | Approx. 77% (NMIBC), 35% (MIBC) | Two main forms: NMIBC (superficial, recurrent) and MIBC (aggressive, invasive); luminal/basal/double-negative molecular subtypes | NMIBC: TURB + intravesical BCG; MIBC: neoadjuvant chemotherapy + radical cystectomy ± immunotherapy (PD-1/PD-L1 inhibitors) | BCG and systemic therapy resistance; frequent recurrences; lack of predictive biomarkers | PDOs preserve histopathology and subtype features; used to model BCG resistance, test chemotherapy/immunotherapy response, and validate molecular stratification |
| Testicular | Approx. 75,000 new cases/year; 9000 deaths/year; most common solid tumor in men < 40 years | Approx. 95% overall | Germ cell tumor origin (seminoma and non-seminoma); high chemosensitivity; cisplatin resistance in few cases | Radical orchiectomy + platinum-based chemotherapy ± radiotherapy | Relapse and long-term toxicity in resistant or refractory cases | Emerging PDO models from germ cell tumors to study chemoresistance and fertility-preserving strategies |
| Ovarian | Approx. 313,000 new cases/year; 207,000 deaths/year; leading cause of death among gynecologic cancers | Approx. 47% overall | Late-stage diagnosis; high-grade serous carcinoma predominant; BRCA1/2 and TP53 mutations frequent | Cytoreductive surgery + platinum-taxane chemotherapy ± PARP inhibitors (BRCA-mutated) | Chemoresistance and recurrence in advanced disease; limited early detection tools | PDOs reproduce histotypes (serous, endometrioid, clear cell); used for PARP inhibitor testing and biomarker discovery |

*ADT* androgen deprivation therapy, *AR* androgen receptor, *CRPC* castration-resistant prostate cancer, *NMIBC* non-muscle-invasive bladder cancer, *MIBC* muscle-invasive bladder cancer, *PDO* patient-derived organoid, *TURB* transurethral resection of the bladder

## Bladder Cancer

Bladder cancer is the second most common urological malignancy and has remarkable clinical and biological diversity [37, 38]. Bladder cancer is mostly presented as non-muscle invasive disease (NMIBC), which has a low chance of being lethal but some likelihood of recurrence and variable progression risk. A small, but clinically much more significant, portion of muscle-invasive disease (MIBC) is often poorly prognosed and requires multimodal therapy [39, 40].

The current approach (for non-muscle invasive disease, complete endoscopic resection followed by intravesical BCG instillations, and for muscle-invasive disease, neoadjuvant chemotherapy followed by radical cystectomy) has certainly increased survival but represents nothing more than palliation [41, 42]. Resistance to BCG is a significant clinical challenge, and the efficacy of chemotherapy and immunotherapies in advanced cases is seen only in a minority of patients [43–45]. New treatment options for bladder cancer have long been hindered by the lack of adequate preclinical models [46]. Traditional 2D cell lines do not capture the complex urothelium architecture or its genetic heterogeneity; moreover, mouse models fail to capture the molecular heterogeneity typically found in human tumors [47].

Liquid biopsy approaches for bladder cancer, including urine-based biomarkers, have emerged as complementary tools to organoids, offering minimally invasive monitoring and guiding precision therapy [21, 23, 24, 48]. This integration of PDOs and liquid biopsy represents a promising step toward personalized oncology in bladder cancer [49, 50]. Analyses of cell-free DNA, exosomal RNA, and extracellular vesicles offer minimally invasive approaches for early detection and disease monitoring [51]. Yet, similar to prostate cancer, liquid biopsy provides molecular snapshots but lacks functional predictive power. Moreover, differential outcomes between NMIBC and MIBC underscore unresolved biological questions, such as (1) which molecular alterations drive progression from non-muscle-invasive to muscle-invasive disease? (2) How do tumor–immune interactions contribute to BCG resistance? (3) To what extent do early clonal events determine therapeutic response? These gaps highlight the need for experimental systems that preserve patient-specific tumor architecture and molecular features, support high-throughput drug testing, and allow interrogation of tumor evolution. Bladder cancer PDOs respond precisely to this need, although challenges remain regarding culture standardization, representation of immune and stromal components, and predictive accuracy [45, 46].

Moreover, integrating PDOs with liquid biopsy technologies offers a powerful framework for personalized therapeutic prediction. While urine- and blood-based assays provide dynamic, minimally invasive access to evolving tumor clones, PDOs enable functional testing of how these molecular changes translate into treatment responses. This combined approach is particularly promising for BCG therapy, where response depends on complex interactions between tumor cells and the immune microenvironment. For example, urinary cell-free DNA or extracellular vesicles can identify emerging molecular signatures of BCG resistance, which can then be functionally validated in matched bladder cancer organoids to assess susceptibility to BCG or alternative intravesical agents. Similarly, integrating serial liquid biopsy profiles with PDO-based drug testing may help identify which patients are likely to benefit from immunotherapy, FGFR3 inhibitors, or combination strategies. Together, this synergistic platform strengthens patient-specific prediction and enables earlier therapeutic redirection in cases of impending treatment failure (Table 1).

PDOs present significant value, not only because they amalgamate molecular and functional data within a single model but also because they enable prediction of tumor response and resistance in vitro over time, track clonal evolution, and anticipate mechanisms of resistance-bridging preclinical findings and real-world clinical practice [34, 50, 52].

## Renal Cancer

Renal cell carcinoma (RCC) represents one of the most biologically and clinically heterogeneous

malignancies within urogenital oncology. The most common subtype is clear cell carcinoma, but others, including papillary, chromophobe, collecting duct carcinoma, and translocation-associated tumors, also show different molecular features that result in different clinical behavior and treatment responsiveness [53]. The main oncogenic driver of the clear cell type is loss of VHL function and subsequent activation of the HIF pathway [54], but besides this, there are also mutations in chromatin remodeling genes, radical metabolic changes, and a very interactive stromal and immune microenvironment that add to the complexity.

The development of targeted therapies and immune checkpoint inhibitors has brought about significant changes in treatment options, but the challenge of treatment resistance (whether primary or acquired) persists in advanced RCC cases [55, 56]. The introduction of PDOs has sped up the process of finding a functional model which can connect molecular profiling to clinically relevant therapeutic decision-making within this complex situation [57]. The creation of RCC organoids was very hard in the past because of the characteristics of the tumor cells, which are very lipid-rich, the strong need for hypoxic signaling, and the lack of microenvironmental support. However, currently available optimized culture conditions allow labs to create organoid systems that are stable and reproducible from surgical specimens, biopsies, and metastatic lesions, whilst keeping the histological and genetic identity of the original tumor intact. The most important clinical factor regarding renal cancer PDOs is their capability to uphold the intratumor heterogeneity that is a hallmark of RCC. This allows the dynamic observation of clonal competition and adaptation under the pressure of therapy, thus really capturing the mechanisms that mostly lead to the failure of treatment in vivo. The accuracy with which organoids mimic the molecular state of the VHL/HIF pathway, epigenetic changes, and metabolic programming makes them extremely useful for the real-time assessment of drug sensitivity within a functional setting that comes very close to the patient's disease. In the clinic, RCC PDOs facilitate quick evaluation of single and individualized responses to existing medically approved therapies, which include VEGFR-targeted agents, HIF-2α inhibitors, mTOR pathway inhibitors, ICI–TKI combinations, etc. RCC PDOs also provide a platform to test new approaches to fighting disease that are envisioned in targeting metabolic weaknesses, epigenetic disorders, or immune system reprogramming [58]. Importantly, organoids made from metastatic spots have already shown quite different therapeutic sensitivities from the primary tumor, thus implying that the selection of treatment might need to be customized to the character of each metastatic site rather than just depending on the primary tumor profile. The creation of co-culture systems with autologous immune components is the major breakthrough in the clinical application of PDOs. Since RCC has a very strong immunological influence, the possibility of rebuilding tumor–immune interactions in vitro opens numerous possibilities to study immune evasion routes, discover predictive biomarkers, and even test immune checkpoint inhibitors. Tumor microenvironment reconstruction based on more complex models that consist of myeloid cells, fibroblasts, and endothelial components facilitates a more physiological representation of the tumor microenvironment which in turn gives functional insights, especially in the case of patients who progress on immunotherapy. The detection of circulating tumor DNA (ctDNA) [59] and PDO platform integration is what gives them even more clinical significance [60]. Tracking of ctDNA changes alongside PDO changes may reveal early signs of the formation of resistant clones which would then allow therapy to be altered in advance and thus support a more personalized, response-guided treatment strategy. This combined approach is increasingly considered to be among the most promising ways to reach truly individualized precision oncology in RCC.

To sum up, PDOs in renal cancer represent a clinically relevant functional model that can not only predict treatment response but also uncover resistance mechanisms, infer clonal evolution, and inform drug selection [61]. With the continuous standardization of culturing methods and the growing integration with genomic, immunological, and computational

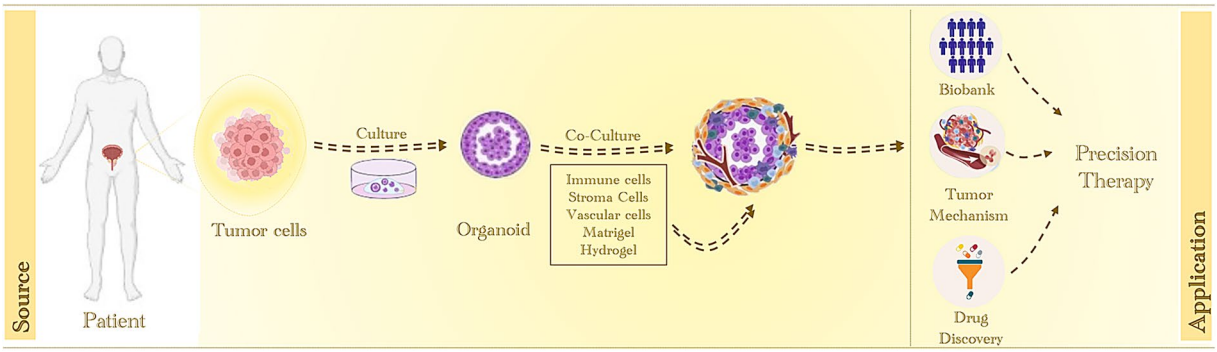


**Fig. 1** Patient-derived organoids (PDOs) from urogenital tumors are established and cultured in conditions that mimic the native tumor microenviroment. These models serve as functional platforms for personalized drug screening, biomarker identification, and mechanistic studies, aiming to translate patient-specific tumor biology into tailored therapeutic strategies

techniques, RCC organoids are anticipated to be avatars of the respective patient's tumor, thus providing an effective and robust tool for the personalized management of RCC.

### Current Limitations of Diagnostic and Therapeutic Approaches

Despite advances, limitations remain in both diagnosis and treatment of prostate and bladder cancer, largely due to relatively static and oversimplified assessments [2, 3, 37]. Moreover, standard imaging modalities lack the sensitivity to detect micrometastatic disease or subtle patterns of clonal selection occurring during or after therapy [3, 33, 36]. From a therapeutic standpoint, resistance remains a major clinical obstacle [4, 5, 20]. While novel targeted agents, immunotherapies, and combination regimens have been introduced over the past years, their efficacy is often short-lived and benefits only a subset of patients [19, 20, 46]. Mechanisms of resistance—whether driven by genomic instability, lineage plasticity, or paracrine interactions within the tumor microenvironment—are highly diverse and frequently patient-specific.

## INSIGHT INTO ORGANOID-DERIVED SYSTEMS

Over the past decade, three-dimensional organoid technology has rapidly emerged as a groundbreaking platform, opening unprecedented avenues for the development of innovative models that closely mimic human physiological and pathological processes (Fig. 1). Organoids originate from pluripotent stem cells (PSCs) or from organ-specific adult stem cells (ASCs), which are tissue-specific resident stem cells [62]; these in turn undergo differentiation to generate organ-like structures composed of multiple cell types that self-organize, closely mimicking the architecture and function of the corresponding organ in vivo. However, stem cell self-organization can be difficult to control without external guidance, leading to a general lack of reproducibility in most organoids. Thus, culture methods that can produce uniform and stable organoid models for better application in clinical research are constantly being explored by researchers.

Therefore, these intricate structures offer a valuable platform to replicate human organ development in a system that closely mimics in vivo conditions. While the complete degree of similarity has yet to be fully established in many cases, organoids are already being utilized to address human-specific biological questions. Additionally, organoid technology has

significant potential for evaluating efficacy and toxicity of drugs [63], regenerative medicine [64], and precision treatment [65].

Organoids play a crucial role in advancing new drug discovery efforts [66]. Their use in the early phases of drug development enables the identification of compounds that are broadly effective across patient populations, as well as those targeting tumors with specific genetic alterations. Moreover, organoids derived from healthy tissues also offer a valuable tool for evaluating potential drug-induced side effects on specific organs [67–69]. The use of organoid drug sensitivity screening to guide clinical treatment is still in its initial stages, and it remains to be confirmed whether it is reliable and safe despite its promising applications.

In the field of regenerative medicine, organoids are increasingly being recognized as a valuable and versatile source of transplantable tissues and functional cell types. Their ability to mimic native tissue architecture and function makes them highly promising tools for advancing cell-based therapies aimed at repairing or replacing damaged organs. Several proof-of-concept studies have already been conducted in animal models. For instance, using a modified optic cup organoid protocol, researchers have successfully generated retinal tissue from mouse embryonic stem cells (ESCs) or induced PSCs (iPSCs). When transplanted into mice with retinal degeneration, these retinal sheets developed into mature photoreceptors. In some cases, they even formed synaptic connections with host retinal cells and restored sensitivity to light stimuli [70]. In vitro genetic correction strategies can be combined with organoids to enable the autologous replacement of tissues affected by genetic disorders. The most common CFTR mutation that leads to cystic fibrosis (CF), which is phenylalanine deletion at position 508, was corrected in patient-derived ISCs using CRISPR–Cas9-mediated gene editing, which then led to functional organoids [71]. While these results are preliminary, they show great promise and illustrate that clinical transplantation of organoid-derived cells and tissues may be feasible.

Another major advantage of exploiting organoid technology is that PDOs from iPSCs are of great interest for the study of pathologies for which no genetic causes have been identified. These studies could prove suitable for patients suffering from complex pathologies that present a high degree of variability.

Finally, this advanced technology serves as a bridge between traditional 2D in vitro systems and in vivo models, offering significant potential for clinical applications, particularly in the field of cancer research [72–74]. Indeed, the shift from basic cancer research to clinical practice is facilitated by organoids as an excellent preclinical model for human cancers.

## Use of Organoid Models in Cancer Studies

Recent studies provide compelling evidence that prostate and bladder PDOs can directly contribute to the development of new therapeutic strategies. In prostate cancer, a landmark investigation by Puca et al. [75] demonstrated that PDOs derived from castration-resistant and neuroendocrine tumors could faithfully model resistance to AR-targeted therapies and were instrumental in identifying Aurora kinase inhibitors as a promising treatment option for aggressive neuroendocrine subtypes. Similarly, organoids derived from tumors harboring DNA damage–repair deficiencies have been used to validate selective sensitivity to PARP inhibitors, providing functional proof-of-concept that anticipated clinical benefit and was consistent with patient outcomes. In a separate study, high-throughput drug screening performed on CRPC PDOs revealed actionable vulnerabilities to PI3K/AKT inhibitors in organoids with PTEN loss, supporting the rationale for dual AR and PI3K pathway inhibition.

In bladder cancer, PDO-based drug screening has also produced clinically relevant findings. The study by Lee et al. [49] established a living biobank of bladder cancer organoids representing multiple molecular subtypes and demonstrated that organoid drug responses closely mirrored individual patient outcomes. Notably, organoids carrying FGFR3 mutations showed pronounced sensitivity to FGFR inhibitors such as erdafitinib, validating the molecular dependency observed in vivo and helping refine

subtype-specific therapeutic strategies. Additionally, PDOs have recently been used to investigate mechanisms of BCG failure: organoids derived from BCG-unresponsive tumors exhibited impaired cytokine signaling and altered interferon pathways, enabling the identification of alternative intravesical agents—including oncolytic viruses and STING agonists—that restored anti-tumor activity ex vivo. These examples underscore the capacity of PDOs not only to reproduce complex tumor biology but also to accelerate the discovery of new, patient-tailored treatment avenues in urogenital oncology.

The integration of PDO platforms with advanced molecular profiling technologies—particularly single-cell RNA sequencing (scRNA-seq)—is further expanding their utility in urogenital oncology [76]. Single-cell resolution allows the dissection of intratumoral heterogeneity within organoids, enabling the identification of rare cellular subpopulations that may drive disease progression or therapeutic resistance [77]. In both prostate and bladder cancer, scRNA-seq applied to PDOs has revealed treatment-tolerant cell states, alternative lineage programs, and transcriptional rewiring associated with AR bypass mechanisms, neuroendocrine differentiation, or BCG resistance. Importantly, coupling functional drug screening in PDOs with scRNA-seq-derived transcriptional signatures enables direct mapping of therapeutic responses to specific cellular phenotypes, providing a mechanistic framework to explain why only certain clones respond to targeted therapies or immunomodulatory agents [78, 79]. This combined approach increases the precision and interpretability of PDO-based assays and underscores their translational value as platforms capable of linking molecular diversity to actionable therapeutic vulnerabilities.

A significant breakthrough in modeling prostate cancer came from the work of Gao et al., who were the first to demonstrate that organoids could be successfully derived from human prostate tumors and expanded in vitro. Their study, published in *Cell* in 2014, reported the generation of six prostate cancer organoid lines and one derived from circulating tumor cells (CTCs), all of which retained structural and histological similarities to the original metastatic tissues [34]. Building on this advancement, Hans Clevers published a protocol in 2016 for establishing 3D prostate organoids within 2 weeks. These organoids closely mimic the in vivo tumor characteristics, making them powerful tools for studying prostate cancer biology and for high-throughput drug screening [80]. Moreover, Sawyers et al. utilized mouse prostate organoids to investigate the biological roles of both wild-type and mutant forms of forkhead box protein A1 (FOXA1). The study demonstrated that FOXA1 mutations significantly alter its transcriptional function, disrupt normal luminal epithelial differentiation, and contribute to the progression of prostate cancer [81]. Therefore, the genomic fidelity of the original tumor is maintained by these organoids while also providing a reproducible and scalable platform for functional assays. The genetic manipulation of organoids allows for the study of specific tumor-driving mutations, which is not feasible for PDX models or standard 2D cultures [80].

Moreover, organoid models of prostate cancer have played a crucial role in studying AR signaling, a key driver in the development and progression of the disease. While ADT remains a standard treatment approach, the emergence of resistance—especially in the form of CRPC—continues to pose a significant therapeutic challenge [82, 83]. Looking ahead, prostate cancer organoid models hold great promise for advancing our understanding of disease mechanisms and may lead to novel strategies for diagnosis and targeted therapy.

In bladder cancer, early-stage detection is relatively common, particularly in cases of NMIBC. These patients often undergo repeated surgical resections and intravesical therapies in an effort to manage disease progression and delay or avoid radical cystectomy, a procedure associated with significant morbidity and a profound impact on quality of life. Given this clinical context, the use of PDOs offers a promising platform for the ex vivo screening of therapeutic agents tailored to individual tumors.

Multiple lines of evidence indicate that the differing clinical outcomes between MIBC and NMIBC are largely driven by their distinct molecular characteristics [84, 85]. This underscores the need for robust models representing

both subtypes, in order to investigate the biological roles of recurrent somatic mutations and understand how they contribute to malignant transformation and disease progression.

In particular, the differentiation of PSCs into bladder urothelial cells reported by Kang et al. and Shin et al. has provided new insights into bladder cancer development and progression [86, 87]. Moreover, Lee et al. established a biobank of organoids derived from 22 patients with bladder cancer, and it now contains 53 samples [88]. The original tumors' histopathological and genetic characteristics are preserved in these organoids, making them a valuable resource for personalized medicine and drug testing. Thus, to study drug responses and tumor evolution, bladder cancer organoid biobanks have been set up to offer a diverse array of models. Finally, the use of bladder cancer organoids has been further expanded by recent technological advances, such as microfluidic biochips and 3D bioprinting. The creation of models that are more physiologically relevant and include immune cells and endothelial cells, enabling drug screening efforts to be more accurate, is made possible by these innovations. Despite the significant advancements in organoid models for urological cancers in recent years, there are still some limitations.

## PERSONALIZED CANCER RESEARCH AND THERAPY

Currently, precision medicine is one of the major unresolved issues of contemporary oncology, as well as one of the most exciting possibilities for transforming the therapeutic paradigm for cancer [89, 90]. The aim is, therefore, to convert decisions from applying standardized and uniform protocols to clinical decisions that take the specific molecularly and genetically informed treatment approach for each tumor into consideration, as well as the dynamics of how the disease continues to evolve under the pressure of therapies [91, 92].

A major obstacle in implementing precision medicine for urogenital cancers is the profound molecular heterogeneity that characterizes them, as well as their dynamic evolution under therapeutic pressure. PDOs offer a unique way to overcome these limitations by serving as functional avatars of individual tumors [93]. Unlike genomic profiling alone, PDOs capture the full spectrum of clonal diversity, enabling direct observation of how distinct subpopulations respond to therapeutic agents. This is particularly relevant in prostate cancer, where PDOs can model divergent AR signaling states, lineage plasticity, and the emergence of resistant subclones typical of castration-resistant or neuroendocrine disease. Similarly, bladder cancer PDOs retain luminal, basal, and neuroendocrine transcriptional programs, allowing precise assessment of subtype-specific vulnerabilities—including sensitivity to FGFR3 inhibitors, platinum-based regimens, and immunomodulatory agents. By integrating PDO functional data with liquid biopsy-derived molecular profiles, clinicians gain a dynamic and patient-specific framework for anticipating treatment failure, identifying alternative therapeutic strategies, and guiding real-time therapeutic decisions. Collectively, PDOs help translate molecular heterogeneity into actionable insights, offering a powerful tool to refine personalized treatment approaches and improve clinical outcomes in both prostate and bladder cancer [94]. They take the assessment from simple compendia of molecular description to an actual site for assessing drug response, meaning these dynamic tools can indeed evolve along with the disease [95].

### Patient-Derived Organoids as a Platform for Precision Cancer Research and Treatment

PDOs preserve some of the architecture and molecular complexity of the tumor in vitro and retain the clonal heterogeneity of real patients with disease [6, 12, 30, 36, 38–40]. In the lab, these 3D models afford the ability to directly observe adaptation processes to therapeutic pressure, the relatively rapid evaluation of hundreds of drugs or combinations of therapies, the validation of predictive biomarkers, and the study of emerging resistance mechanisms [96, 97].

By co-culturing PDOs with fibroblasts, immune cells, or ECM components, we are

increasingly understanding the impacts of the tumor microenvironment, which is now recognized as a crucial component of mediating response to treatment [98]. From a clinical lens, PDOs offer entirely new scenarios: it is conceivable to take a tumor resequencing sample, generate organoids, and evaluate, in vitro, the sensitivity of the disease to different therapeutic options, providing timely information to the clinician [99, 100].

Collaborative efforts optimize therapy approaches, as functional analysis of organoids can always be repeated whenever the disease progresses, recreating updated models that reflect tumor evolution and allow new therapeutic strategies to be implemented in real time. These features increase the probability of therapeutic success and limit the risk of exposing patients to ineffective or toxic drugs.

In prostate cancer, PDOs have been shown to recreate all stages of the disease, from androgen-sensitive to CRPC to neuroendocrine variants, and to allow the study of mechanisms regulating the transition to resistance. They are also used to assess response to targeted therapies such as PARP inhibitors in patients with DNA repair alterations and to explore new therapeutic strategies including radioligand targeting of prostate-specific membrane antigen (PSMA) [101]. Functional data from organoids can also be correlated with liquid biopsy data, such as ctDNA and CTCs, effectively constructing dynamic therapeutic profiles that evolve with disease progression [102, 103].

Similarly, in bladder cancer, PDOs have enabled validation of molecular classifications into luminal, basal, and double-negative subtypes, and assessment of differential responses to chemotherapy, immunotherapy, and targeted therapies (e.g., FGFR3 inhibitors). PDOs have also allowed the study of BCG resistance mechanisms and development of new combination strategies for refractory patients [104].

The ability to generate PDOs from exfoliated cells in urine is particularly promising, providing a minimally invasive means of monitoring disease while avoiding costly and invasive procedures [76]. Nevertheless, significant obstacles remain, including standardization of organoid isolation and culture protocols, reduction of time to generate PDOs, and organization of sophisticated bioinformatics platforms to integrate molecular, functional, and clinical data meaningfully. As these obstacles are addressed, PDOs are expected to become avatars of patients' tumors, enabling increasingly precise and personalized therapeutic decisions.

## CONCLUSION

Nevertheless, significant limitations persist, including the absence of stromal, vascular, and immune components, which are essential to fully recapitulate the native tumor microenvironment. Ongoing technological innovations—such as CRISPR/Cas9-based gene editing, high-throughput drug screening, and multi-lineage co-culture systems—are progressively enhancing the physiological relevance of organoid platforms. With continued advancements, organoid-based platforms are evolving from research tools into clinically relevant systems that can guide individualized therapy and accelerate drug development in the field of urological oncology. Thus, as research progresses, organoid technology is expected to play a central role in narrowing the gap between laboratory discoveries and clinical application, ultimately improving outcomes for patients with urologic malignancies. A key future objective will be incorporating these models into routine clinical practice, enabling the seamless translation of experimental discoveries into meaningful therapeutic outcomes for patients.

### The Critical Path Forward

As both prostate and bladder cancer organoid platforms continue to evolve, key priorities include: (1) Establishing standardized protocols for sample processing, culture, and drug testing. (2) Developing immune-competent organoid co-cultures, essential for immunotherapy evaluation. (3) Linking organoid drug responses with longitudinal liquid biopsy data to track tumor evolution. (4) Creating interoperable biobanks and computational pipelines for multicenter research and clinical integration. (5) Reducing

the time needed for organoid generation to make PDO-guided decisions clinically actionable. Although progress has been substantial, routine use of urogenital PDOs in clinical decision-making will require systematic validation in prospective clinical trials and integration with multidisciplinary oncology workflows.

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### *Declarations*

***Conflict of Interest.*** The authors declare that they have no competing interests. All authors (Serena Sagliocchi, Michele Musone, Stefano Chianese, Annunziata Gaetana Cicatiello, Silvia Del Mastro, Francesco Del Giudice, Monica Dentice and Felice Crocetto) have nothing to declare.

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