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DISCOVERY SCIENTIFIC SOCIETY

A review of contemporary therapeutic strategies for the management of bladder cancer

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ABSTRACT

Introduction: Bladder cancer has become a noteworthy worldwide wellbeing issue, being one of the most frequently analyzed cancers around the world and appearing high rates of recurrence and metastasis. Traditional management strategies, including transurethral resection, intravesical Bacillus Calmette-Guérin (BCG) immunotherapy, and radical cystectomy, have long formed the cornerstone of treatment. *Results*: Recent developments have significantly changed the treatment landscape for bladder cancer. Recent advances have transformed the therapeutic landscape of bladder cancer. Moreover, inventive sedative conveyance frameworks and consecutive intravesical chemotherapy regimens have tended to neglect the needs in local treatment. In spite of advances, obstacles continue, including treatment resistance, distinguishing reliable biomarkers, long-term security issues, and reasonable access to novel treatments. *Conclusions*: Recently, how we treat bladder cancer has changed significantly. Our treatment plans now use immunotherapy, targeted therapy, and advanced distribution methods. Proceeding with the investigation is urgent to move forward with quiet determination methods and guarantee impartial access to modern medicines.

Keywords: bladder cancer; immunotherapy; gene therapy; targeted therapy

1. INTRODUCTION

Bladder cancer is a malignancy originating from the urothelial cells lining the bladder, with significant clinical and molecular heterogeneity that influences prognosis and treatment strategies. Ranking as the sixth most prevalent cancer in the United States, it is anticipated that there will be around 84,870 new diagnoses and 17,420 fatalities in 2025, indicating an ongoing global health challenge. The disease predominantly affects males, with a 3:1 male-to-female incidence ratio, mainly attributable to higher rates of tobacco use and occupational exposure to aromatic amines in industries such as painting and chemical manufacturing (Siegel et al., 2025)

Bladder cancer is anatomically classified into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). NMIBC, representing 75% of initial diagnoses, is confined to the mucosal or submucosal layers (Ta, T1, or

carcinoma in situ) and is characterized by high recurrence rates (50–70%) but low progression risk (10–15%). In contrast, MIBC (T2+) invades the detrusor muscle and carries a poorer prognosis, with five-year survival rates declining to 35–50% due to metastatic spread to lymph nodes, lungs, or bones. Histologically, urothelial carcinoma constitutes 90% of cases, while rare variants include squamous cell carcinoma (associated with chronic schistosomiasis infection) and adenocarcinoma (Chen et al., 2023). Diagnosis begins with urinalysis and cytology to detect hematuria or malignant cells in urine. Positive findings typically prompt cystoscopy, the gold standard for visualizing bladder lesions, followed by transurethral resection of bladder tumor (TURBT) for histopathological confirmation. Advanced imaging modalities, such as CT urography or MRI, assess local invasion and distant metastasis, while an intravenous pyelogram evaluates upper urinary tract involvement. Emerging biomarkers, including urinary FGFR3 mutations and circulating tumor DNA (ctDNA), are increasingly integrated into diagnostic algorithms to predict recurrence and guide therapy (Black et al., 2023).

Distinct pathways in NMIBC and MIBC drive the molecular landscape of bladder cancer. NMIBC is frequently associated with activating mutations in FGFR3 (in approximately 80% of cases) and dysregulation of the PI3K/AKT/mTOR pathway, often via PIK3CA mutations or loss of TSC1, which promotes cell proliferation and survival. Conversely, MIBC exhibits inactivation of tumor suppressors TP53 (in 49% of cases) and RB1, alongside chromosomal instability (e.g., loss of chromosome 9), which enables unchecked cell cycle progression and metastasis (Bogale, 2024).

Carcinogenesis is potentiated by chronic exposure to aryl amines (e.g., benzidine) and tobacco smoke, which induce DNA adducts and oxidative stress, disrupting apoptotic mechanisms. Schistosomiasis infection in Africa drives the development of squamous cell carcinoma through chronic inflammation and HRAS mutations. The tumor microenvironment further facilitates progression via immunosuppressive cytokines (e.g., TGF-β) and angiogenesis mediated by VEGF overexpression. Bladder cancer is anatomically and molecularly heterogeneous, classified broadly into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). NMIBC, constituting 75% of initial diagnoses, is characterized by tumors confined to the mucosal or submucosal layers (Ta, T1, or carcinoma in situ). In spite of tall repeat rates of 50–70%, as it were, 10–15% of cases advance to intrusive illness, requiring careful observation. In contrast, MIBC (T2+), though less common at diagnosis, carries a dire prognosis, with five-year survival rates plummeting to 35–50% due to rapid metastasis to lymph nodes, bones, and lungs. Molecularly, NMIBC is frequently associated with activating mutations in FGFR3 and dysregulated PI3K/AKT pathways, whereas MIBC often involves the inactivation of TP53 and RB1, contributing to treatment resistance and aggressive behavior (Lenis et al., 2020).

Historically, management relied on transurethral resection of bladder tumors (TURBT) for NMIBC, followed by intravesical Bacillus Calmette-Guérin (BCG) immunotherapy or chemotherapy to reduce recurrence. BCG, introduced in the 1990s, became the gold standard for high-risk NMIBC, achieving remission in 70% of cases. Worldwide BCG deficiencies, coupled with inherent resistance in 30–40% of patients, highlighted basic holes in care. For MIBC, radical cystectomy with neoadjuvant cisplatin-based chemotherapy was the cornerstone, yet nearly half of the patients experienced metastatic relapse within two years, underscoring the limitations of conventional approaches (Dudani et al., 2024).

The way we treat diseases has undergone significant changes since 2020. This change is primarily due to advancements in immunotherapy, targeted therapies, and gene-based treatments. Immune checkpoint inhibitors (ICIs), such as pembrolizumab and atezolizumab, have redefined the first-line treatment for metastatic urothelial carcinoma, offering durable responses in PD-L1–positive patients who were previously deemed ineligible for cisplatin. The 2023 approval of enfortumab vedotin—an antibody-drug conjugate targeting nectin-4—combined with pembrolizumab marked a watershed moment, demonstrating a 55% reduction in progression risk and establishing a new standard of care. For BCG-unresponsive NMIBC, intravesical gene therapy with nadofaragene firadenovec, which delivers interferon alfa via a viral vector, has emerged as a bladder-preserving option, achieving 47% complete response rates at six months (Gupta et al., 2023; Chen et al., 2023).

Concurrently, the integration of biomarker-driven strategies has enabled the development of personalized therapies. Erdafitinib, a selective FGFR3 inhibitor, benefits 20–30% of patients with actionable FGFR alterations, while ctDNA monitoring guides adjuvant decisions, minimizing overtreatment. Innovations such as TAR-200, a gemcitabine-releasing intravesical system, and cretostimogene grenadenorepvec, an oncolytic virus that stimulates GM-CSF production, exemplify the shift toward minimally invasive, precision-oriented regimens (Facchinetti et al., 2023).

Despite these advances, challenges persist. Financial aberrations constrain access to novel treatments in low-resource settings, where schistosomiasis-related squamous cell carcinoma remains predominant. Furthermore, the long-term toxicities of combination therapies and mechanisms of acquired resistance necessitate ongoing research. International collaboration and equitable resource

allocation will translate scientific breakthroughs into universal benefits for survival as the field advances toward bladder preservation and molecular stratification. This survey aims to comprehensively analyze novel bladder cancer treatment modalities, with a focus on resistant checkpoint inhibitors, targeted treatments, gene-based interventions, and innovative delivery frameworks. By integrating the latest findings, we aim to provide clinicians and researchers with a comprehensive framework to help them navigate the rapidly evolving therapeutic landscape and identify the most effective strategies for individualized patient care (Gupta et al., 2023).

2. METHODOLOGY

Databases: PubMed, Google Scholar.

Inclusion criteria:

- RCTs, systematic reviews, meta-analyses, and phase II/III clinical trials (Jan 2020–Mar 2025).
- Studies evaluating novel therapeutic approaches for non-muscle invasive (NMIBC) and muscle-invasive bladder cancer (MIBC).
- English language publications reporting on primary outcomes: overall survival, progression-free survival, complete response rate, or disease-free survival.
- Studies examining FDA/EMA-approved therapies or treatments in late-stage clinical development.

Exclusion criteria:

- Non-English studies, animal models, in vitro studies, and case reports.
- Conference abstracts without full-text publication.
- Studies focused exclusively on conventional treatments (TURBT, radical cystectomy, traditional chemotherapy).
- Articles without transparent methodology or outcome measures.

Screening:

2,143 studies were identified; 87 met the criteria after deduplication and relevance assessment (Chen et al., 2023; Dudani et al., 2024).

3. RESULTS AND DISCUSSION

Advances in immunotherapy

Immune checkpoint inhibitors (ICIs) have revolutionized treatment paradigms for bladder cancer, particularly for patients with advanced or metastatic disease. Targeting the PD-1/PD-L1 and CTLA-4 pathways, these agents reinvigorate exhausted T cells and restore anti-tumor immunity (Khan et al., 2025).

Pembrolizumab, a PD-1 inhibitor, received FDA approval in January 2020 for BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS), based on the KEYNOTE-057 trial, which demonstrated a 41% complete response rate, with 46% of responses lasting 12 months or longer (Lenis et al., 2020). For patients with advanced urothelial carcinoma ineligible for cisplatin chemotherapy, pembrolizumab monotherapy showed durable responses in those with PD-L1 expression (Combined Positive Score ≥10).

The FDA approval of avelumab maintenance therapy in 2020 marked another milestone, following the JAVELIN Bladder 100 trial, which demonstrated a 7.1-month improvement in median overall survival compared to best supportive care (21.4 vs. 14.3 months) for patients who had not progressed on platinum-based chemotherapy (Liu et al., 2023).

Combination strategies have further enhanced therapeutic efficacy. The LEAP-011 and KEYNOTE-866 trials evaluated pembrolizumab with chemotherapy in the neoadjuvant setting for MIBC, showing pathological complete response rates of 42% and 36.0%, respectively (Gupta et al., 2023). These developments have driven worldview shifts in preoperative administration, possibly saving patients from radical cystectomy through total obsessive reactions.

Despite these advances, primary and acquired resistance to ICIs remains a significant challenge. Ongoing trials explore novel combinations with targeted agents, including anti-CTLA-4 therapies (ipilimumab, tremelimumab) and anti-TIGIT antibodies, to overcome resistance mechanisms and expand the proportion of responding patients (Li et al., 2023).

Gene and viral therapies

The approval of nadofaragene firadenovec (Adstiladrin) in December 2022 marked a watershed moment, as it represented the first gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC). This non-replicating adenoviral vector delivers interferon alfa-2b directly to urothelial cells, enhancing local anti-tumor immune responses while minimizing systemic exposure (Black

et al., 2023). In the pivotal phase III trial, nadofaragene firadenovec achieved a 53.4% complete response rate at three months and a 47% response rate at six months in patients with CIS ± Ta/T1 disease. Notably, 46% of complete responders maintained their response through 12 months, with a favorable safety profile characterized predominantly by transient local symptoms (irritative voiding, fatigue, hematuria) (Liu et al., 2023).

Cretostimogene grenadenorepvec (CG0070), an oncolytic adenovirus engineered to replicate selectively in retinoblastoma (Rb) pathway-deficient cells and express granulocyte-macrophage colony-stimulating factor (GM-CSF), has shown promising results in the phase II BOND-002 trial. Among 45 patients with high-risk NMIBC CIS and a history of BCG failure, CG0070 achieved a 47% overall complete response rate at six months, with 50% of CIS patients demonstrating complete responses (Gupta et al., 2023).

These gene and viral therapies represent a significant advance in bladder preservation strategies for patients who would otherwise face radical cystectomy. Ongoing research focuses on identifying predictive biomarkers of response and evaluating combinatorial approaches with immune checkpoint inhibitors to enhance the efficacy and durability of response.

Novel drug delivery systems

Innovative drug delivery systems have emerged to overcome the limitations of conventional intravesical therapy, including limited dwell time, poor tissue penetration, and frequent instillations. TAR-200 (GemRIS), a silicone-based drug delivery system that continuously releases gemcitabine within the bladder over a seven-day period, has demonstrated promising efficacy in early-phase trials. By maintaining therapeutic drug concentrations while minimizing systemic exposure, TAR-200 represents a paradigm shift in local therapy administration (Liu et al., 2023). The SunRISe-1 phase 2b study evaluating TAR-200 in patients with BCG-unresponsive NMIBC showed the highest complete response rates at 12 months, maintained in patients with high-risk NMIBC (Li et al., 2023).

UGN-102, a mitomycin-containing reverse thermal gel that solidifies at body temperature to enhance drug retention, has shown efficacy in intermediate-risk NMIBC. The Optima II trial evaluated six weekly instillations in patients with low-grade, intermediate-risk NMIBC, achieving a 65% complete response rate at three months, with 61% remaining disease-free at 12 months (Gupta et al., 2023). The ENVISION phase III trial demonstrated a 79.6% complete response rate at three months.

Sequential intravesical gemcitabine and docetaxel (Gem/Doce) have emerged as effective alternatives during BCG shortages. A multi-institutional retrospective analysis reported a 46% two-year recurrence-free survival and 52% high-grade recurrence-free survival rate with minimal toxicity (3.3% discontinuation rate) (Chen et al., 2023). The ongoing BRIDGE phase III randomized trial comparing Gem/Doce with BCG in 870 patients will provide definitive evidence regarding the comparative efficacy of this regimen.

These novel delivery systems address unmet critical needs of NMIBC management by enhancing drug delivery, reducing treatment burden, and improving quality of life through fewer clinic visits and procedures.

Targeted therapies

Molecular profiling has unveiled actionable genetic alterations in bladder cancer, catalyzing the development of precision medicine approaches tailored to specific tumor biology. Erdafitinib (Balversa), a fibroblast growth factor receptor (FGFR) inhibitor targeting FGFR2/3 alterations present in approximately 20% of bladder cancers, received accelerated FDA approval in 2019 for locally advanced or metastatic urothelial carcinoma with susceptible FGFR alterations (Dudani et al., 2024). The THOR-2 phase II randomized trial comparing erdafitinib with intravesical chemotherapy in high-risk NMIBC with FGFR alterations demonstrated superior efficacy, with 6-month recurrence-free survival rates of 96% versus 73% and 12-month rates of 77% versus 41% (Gupta et al., 2023).

Enfortumab vedotin (Padcev), an antibody-drug conjugate targeting Nectin-4 (expressed in >90% of urothelial carcinomas), received accelerated approval in 2019 for advanced urothelial carcinoma after platinum-based chemotherapy and immunotherapy. The corroborative EV-301 trial demonstrated a 30% reduction in the likelihood of progression compared to chemotherapy, supporting its efficacy in pretreated patients (Liu et al., 2023).

The landscape of targeted therapy expanded dramatically with the FDA approval of enfortumab vedotin in combination with pembrolizumab in December 2023, based on the EV-302/KEYNOTE-A39 trial. This combination demonstrated a 55% reduction in the risk of disease progression or death compared to platinum-based chemotherapy, establishing a new first-line standard for metastatic urothelial carcinoma (Dudani et al., 2024).

Other promising approaches focused on incorporating inhibitors of CDKN2A/B deletions, PARP inhibitors for improving DNA damage repair quality, and specialists targeting the PI3K/AKT/mTOR pathway. These precision medicine strategies represent a

paradigm shift toward biomarker-driven treatment selection, potentially improving outcomes while minimizing toxicity in molecularly defined patient subsets.

Advances in Radical and Bladder-Preserving Approaches for MIBC

While radical cystectomy remains the standard of care for MIBC, significant advances have emerged in perioperative management and bladder preservation strategies. Neoadjuvant immunotherapy, either as monotherapy or in combination with chemotherapy, has demonstrated promising pathological complete response rates (pCR) in several phase II trials. The PURE-01 study evaluating neoadjuvant pembrolizumab reported a 42% pCR rate, while the BLASST-1 trial of nivolumab plus gemcitabine-cisplatin achieved a 49% pCR rate (Liu et al., 2023). The KEYNOTE-866 trial evaluating pembrolizumab plus cisplatin-based chemotherapy showed a pCR rate of 36.0% versus 23.3% with chemotherapy alone, potentially expanding eligibility for bladder preservation (Dudani et al., 2024).

Trimodality therapy (TMT), consisting of maximal TURBT followed by concurrent chemoradiotherapy, has emerged as a viable bladder-preserving alternative for select patients with MIBC. The addition of immunotherapy to TMT is being evaluated in the Phase III SWOG/NRG 1806 trial, which examines concurrent chemoradiotherapy with or without atezolizumab. Preliminary data are promising, suggesting enhanced complete response rates and potentially improved local control (Li et al., 2023).

Robot-assisted radical cystectomy (RARC) has gained traction, with improved perioperative outcomes, including reduced blood loss, shorter length of stay, and faster recovery compared to open procedures. Recent innovations include enhanced recovery protocols, intracorporeal urinary diversion techniques, and novel approaches to nerve-sparing procedures that preserve sexual and urinary function (Chen et al., 2023). These advances in surgical and bladder-preserving approaches reflect a growing emphasis on quality-of-life considerations alongside oncologic outcomes. They may possibly change the administration's worldview for MIBC by saving select patients from radical cystectomy and its related horror.

Future directions and emerging technologies

Several innovative approaches are in early-phase development, potentially representing the next wave of therapeutic breakthroughs. Nanorobot technology, particularly mRNA-based urea-powered nanomotors, has shown remarkable efficacy in preclinical models, reducing tumor mass by 90% after a single dose through preferential accumulation in bladder tumors (Liu et al., 2023). This minimally invasive approach could revolutionize drug delivery while minimizing systemic toxicity. Cell-based therapies, including chimeric antigen receptor (CAR) T cells targeting bladder cancer-specific antigens such as EGFR and HER2, are advancing through preclinical and early clinical evaluation. These "living drugs" offer the potential for durable responses through persistent immune surveillance (Li et al., 2023).

Manufactured insights and machine learning calculations are being created to anticipate treatment reactions and optimize therapeutic choices based on clinical, operative, and molecular parameters. These personalized back apparatuses may enhance targeted pharmaceutical approaches by identifying patients most likely to benefit from specific medications (Gupta et al., 2023). Novel combination strategies, including triplet regimens that incorporate immune checkpoint inhibitors (ICIs), targeted agents, and antibody-drug conjugates, are being evaluated to overcome resistance mechanisms and enhance therapeutic efficacy. The EV-103 trial combining enfortumab vedotin, pembrolizumab, and chemotherapy in advanced urothelial carcinoma exemplifies this approach (Dudani et al., 2024).

Biomarker development remains a critical focus, with liquid biopsy techniques (circulating tumor DNA, extracellular vesicles) offering non-invasive methods for monitoring treatment response, detecting minimal residual disease, and identifying resistance mechanisms early in the treatment course (Black et al., 2023). These emerging technologies and approaches promise to further transform bladder cancer management in the coming years, potentially leading to more precise, effective, and patient-centered treatment paradigms (Table 1).

Table 1. Synthesis of findings: New Methods of Bladder Cancer Treatment (2020-2024)

Treatment Approach	Agent/System	Mechanism of Action	Key Clinical Findings	Trial Information	Current Status
Immunotherapy	Pembrolizumab	PD-1 inhibitor	41% complete response rate; 46% responses lasting ≥12 months	KEYNOTE-057: single-arm study (n=96) in BCG-unresponsive NMIBC	FDA approved (Jan 2020) for high-risk BCG-unresponsive NMIBC with CIS
	Atezolizumab	PD-L1 inhibitor	Enhanced efficacy in tumors with high expression of PD-L1 or high levels of tumor-infiltrating lymphocytes	Multiple trials evaluating use in various settings	FDA approved for advanced UC
	Avelumab	PD-L1 inhibitor	Improved survival as maintenance therapy	Referenced in NCCN guidelines	Recommended as maintenance therapy per NCCN guidelines
Gene/Viral Therapy	Nadofaragene firadenovec	Viral vector delivering interferon alfa to urothelial cells	First gene therapy for BCG-unresponsive NMIBC	Mentioned as a clinical advancement	First approved gene therapy for bladder cancer
	Cretostimogene grenadenorepvec (CG0070)	Modified adenovirus expressing GM-CSF	47% overall CR rate at 6 months; 50% CR in CIS patients	BOND-002: phase II trial (n=45) in HR NMIBC CIS BCG-unresponsive	In clinical development
Novel Delivery Systems	TAR-200 (GemRIS)	Flexible device for continuous intravesical gemcitabine delivery	Maintains therapeutic drug concentrations while minimizing systemic exposure	Early-phase trials showing enhanced therapeutic efficacy	In clinical development
	UGN-102	Mitomycin-containing reverse thermal gel	65% CR at 3 months; 61% remained disease-free at 12 months	Optima II trial: 6 weekly instillations in LG IR NMIBC; ATLAS phase III trial;	In clinical development

				ENVISION phase III trial (79.6% CR at 3 months)	
	Gemcitabine/Docetaxel (Gem/Doce)	Sequential intravesical chemotherapy	46% 2-year recurrence-free survival; 52% HG RFS rate; minimal toxicity (3.3% discontinuation)	Multi-institutional retrospective analysis; BRIDGE phase III randomized trial comparing BCG (n=870) with ongoing	Alternative during BCG shortages
Targeted Therapy	Erdafitinib (Balversa)	FGFR inhibitor targeting FGFR2/3 alterations	6-month RFS: 96% vs. 73% for chemotherapy; 12-month RFS: 77% vs. 41%	THOR-2: phase II randomized trial comparing intravesical chemotherapy	FDA approved for locally advanced/metastatic UC with FGFR alterations
	Enfortumab vedotin (Padcev)	Antibody-drug conjugate targeting Nectin-4	Referenced as an important advancement	Mentioned in multiple sources	FDA approved for advanced UC
Combination Approaches	Various combinations	Multiple mechanisms	Enhanced efficacy through synergistic effects	Multiple ongoing trials	Research focuses on overcoming resistance and improving responses

Abbreviations: BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; CR = complete response; FDA = Food and Drug Administration; FGFR = fibroblast growth factor receptor; GM-CSF = granulocyte-macrophage colony-stimulating factor; HG = high-grade; HR = high-risk; IR = intermediate-risk; LG = low-grade; NCCN = National Comprehensive Cancer Network; NMIBC = non-muscle invasive bladder cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; RFS = recurrence-free survival; UC = urothelial carcinoma

4. CONCLUSIONS

This review critically examines the latest developments in bladder cancer management, with a focus on the transformative impact of novel therapeutic modalities introduced in 2020. Incorporating immune checkpoint inhibitors, targeted treatments, gene and viral therapies, and advanced drug delivery systems has greatly broadened the treatment choices for non-muscle-invasive and muscle-invasive bladder cancer. New medical technology has improved patient care and outcomes. These advancements focus on personalized treatments that help preserve organs and meet individual needs.

Moreover, several important considerations must be acknowledged. Numerous key studies that advise current homes are limited by moderately brief follow-up periods, small sample sizes, or a focus on particular populations, which may constrain the generalizability of their findings. Besides, the high costs and limited accessibility of particular inventive drugs pose noteworthy deterrents to a wide range, particularly in scenarios with restricted assets. Moreover, the nonappearance of strong, affirmed biomarkers for deciding treatment response and resistance may be a basic difficulty, emphasizing the require for persistent translational examination.

The implications of these findings are substantial. While these later restorative advances hold the potential to significantly improve survival and quality of life for patients with bladder cancer, their full benefits can, in effect, be realized through ongoing efforts to

refine treatment strategies, optimize treatment plans, and address barriers to care access. The subsequent research should prioritize large-scale, prospective studies that include diverse patient populations, the development of predictive biomarkers, and strategies to overcome the financial and logistical challenges associated with novel therapies.

In conclusion, the advancing scene of bladder cancer treatment reflects a broader drift toward precision oncology and individualized patient care.

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Justyna Gręda - Conceptualization; writing - rough preparation; supervision
Bartosz Zieliński - Writing - rough preparation
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Conflict of interest
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Data and materials availability
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