Topic Brief

Comparative Effectiveness of Treatments for Non-Muscle-Invasive Bladder Cancer

PCORI Scientific Program Area:
Assessment of Prevention, Diagnosis and Treatment Options

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Topic: Comparative Effectiveness of Treatments and Evaluation Strategies for Non Muscle-Invasive Bladder Cancer

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION Bladder cancer is the 4th most commonly diagnosed cancer in men and the 10th most commonly diagnosed cancer in women in the United States.[1] The most common risk factor for bladder cancer is cigarette smoking; other risk factors include occupational exposures and family history.[2] Bladder cancer is staged based on the extent of penetration or invasion into the bladder wall and adjacent structures.[3] Bladder cancers that have not invaded the bladder smooth muscle layer are grouped as non-muscle-invasive bladder cancer (NMIBC), and include stage classifications Tis (carcinoma in situ), Ta (noninvasive papillary carcinoma), and T1 (cancer that invades the subepithelial connective tissue). Approximately 75% of newly diagnosed bladder cancers are NMIBC.[4] Individuals with NMIBC have 5-year survival rates higher than 88%.[5] Prognosis is poorer for patients with muscle-invasive bladder cancers (MIBC), with 5-year survival rates from 63% to 15%.[5] As many as 70% of NMIBC tumors recur after initial treatment, with a 10% to 20% risk of progression to MIBC.[4] The likelihood of recurrence or progression to MIBC depends on a number of factors. These include cancer stage, tumor grade, whether the tumor is an initial tumor or a recurrence, number and size of tumors, and patient's age and general health. These factors may also affect treatment options. The main treatment for NMIBC is local resection with transurethral resection of the bladder tumor (TURBT), often with adjuvant intravesical therapy (i.e., the treatment solution is put inside the bladder) to destroy residual tumor cells using bacillus Calmette-Guérin (BCG), various chemotherapy agents (e.g., mitomycin C [MMC], apaziquone, paclitaxel, gemcitabine, thiotepa, valrubicin, doxorubicin, epirubicin), or interferon immunotherapy.[6] Post-TURBT adjuvant intravesical therapy is associated with potential local side effects (e.g., dysuria, urinary frequency, or hematuria) and systemic side effects (e.g., fever, chills, rash, or fatigue). However, not using adjuvant intravesical therapy may increase the risk of bladder cancer recurrence or progression, particularly in patients with higher risk NMIBC. Radical cystectomy is a treatment option in patients with NMIBC who are at

	high risk for progression to MIBC. In one recent study, approximately 10% of patients with high-risk bladder cancer underwent cystectomy.[7] Various tools using clinical and pathologic variables have been developed for risk stratification and predicting bladder cancer recurrence and/or progression in persons with NMIBC. These include the European Organization for Research and Treatment of Cancer (EORTC) risk calculator,[8] and a tool developed by the Spanish Urological Club for Oncological Treatment/Club Urologico Espanol de Tratamiento Oncologico (CUETO).[9] In eight retrospective cohort studies of these two tools that were included in a recent systematic review,[10] discrimination (how well a risk assessment method separates persons with from those without an outcome) was poor to fair for recurrence (C-index scores ranged from 0.52 to 0.66) and fair to good for progression (C-index scores ranged from 0.62 to 0.81). No study evaluated clinical outcomes associated with use of a formal risk assessment tool in a risk-adapted approach to management of NMIBC versus other approaches.[11] Recently, an expert panel of the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) created the AUA/SUO Guideline Risk Stratification System.[12] This system categorizes the risk of recurrence and/or progression of NMIBC as 'low', 'intermediate', and 'high,' and is meant for use in clinical practice for guiding patient counseling and treatment decisions. Unlike previous instruments, this system includes consideration of a patient's prior treatment with BCG. Intermediate risk patients who have persistent or recurrent bladder cancer after intravesical therapy with BCG are reclassified as high risk. The risk categories in this system are based on the panel members' consensus, not on meta-analyses or original data, and the panel recognized the need for validation of the model's performance.[12] The AUA guideline recommends that patients with low-risk NMIBC receive a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin). In patients with intermediate-risk NMIBC, the AUA guideline recommends a six-week course chemotherapy (e.g., mitomycin C, epirubicin) or immunotherapy (BCG), with an option to continue for up to 1 year in responders to initial treatment. In high-risk patients, the AUA recommends intravesical BCG therapy for six-weeks, with continued therapy for three years in responders. Radical cystectomy is an option for patients with higher-risk NMIBC who have failed intravesical therapies (in some cases, including repeat treatment with BCG) or have features that put them at very high risk for progression.

	METHODS This Topic Brief is based on a review of a recent systematic review funded by the Agency for Health Research and Quality on NMIBC[11] and a subsequent supplement funded by the American Urological Association,[10] searches on ClinicalTrials.gov and selected databases from groups funding bladder cancer research (EORTC and SWOG), and consultation with experts (John Gore, M.D., M.S., University of Washington, and Sam Chang, M.D., Vanderbilt University).
Relevance to patient-centered outcomes	SYMPTOMS[3] • The most common symptom of bladder cancer is painless hematuria (blood in the urine). • Other symptoms include: increased frequency of urination, dysuria (pain or burning when urinating), urgency (feeling the need to urinate immediately, even though the bladder is not full), or difficulty urinating. However, each of these symptoms is more likely to be caused by problems other than bladder cancer. • Bladder cancer that is far advanced may also cause a variety of other symptoms, such as: being unable to urinate, lower back pain, loss of appetite, weight loss, tiredness or weakness, swelling in the feet, or bone pain. PATIENT-CENTERED OUTCOMES • Mortality • Need for cystectomy • Progression to muscle-invasive bladder cancer • Bladder cancer recurrence • Quality of life <u>Possible adverse effects of treatment include</u>: cystitis, urinary urgency, urinary frequency, incontinence, hematuria, pain, flu-like symptoms, surgical complications, urosepsis, and myelosuppression.
Burden on Society	
Recent prevalence in populations and subpopulations	INCIDENCE AND PREVALENCE[2] The American Cancer Society estimates 76,960 new cases of bladder cancer in the United States in 2016 (58,950 in men and 18,010 in women) and about 16,390 deaths (11,820 in men and 4,570 in women). Bladder cancer represents ~5% of all incident cancers in the U.S. The lifetime probability of developing bladder cancer is approximately 3.8% in men and 1.2% in women. Bladder cancer occurs primarily in people age 55 and older, and is roughly twice as common in whites compared with African Americans or Hispanic Americans.

Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	• Aside from the mortality rates cited above, NMIBC and treatments for NMIBC may have various effects on patients' quality of life, functional capacity, and use of health care services. • TURBT may cause dysuria and/or hematuria lasting for one or two weeks after the procedure; repeated TURBT may cause scarring of the bladder leading to urinary frequency and/or incontinence. • Intravesical immunotherapy or chemotherapy may cause cystitis, urinary frequency, dysuria, hematuria, bladder pain, or flu-like symptoms, such as fever, chills, and fatigue. • Patients with low-risk NMIBC often receive a single dose of intravesical therapy during TURBT; patients with higher-risk NMIBC typically receive at least an induction course. • An induction course of intravesical therapy usually requires the patient to receive a treatment once per week for 6 consecutive weeks, beginning a few weeks after the TURBT. Each treatment requires the patient to hold the solution inside the bladder for approximately one to two hours. Additional induction courses and/or maintenance therapy may be utilized. The duration of maintenance therapy varies, commonly lasting for 1 year or longer. The frequency of maintenance therapy also varies, with treatments commonly given once per month (MMC) or every 3 to 6 months (BCG). • After initial treatment for NMIBC, surveillance with cystoscopy is typically conducted every 3 to 6 months for at least a couple of years. • Radical cystectomy may be an option in patients who have high-risk NMIBC and recurrent and/or progressive disease. Radical cystectomy may have profound adverse effects on a patient's functional capacity and quality of life. Some of these effects are due to the surgical urinary diversion and urostomy, including the need to empty the urostomy bag or drain the urine pouch with a catheter. In addition, urinary diversion and urostomy may also lead to infections, urine leaks, pouch stones, and/or blockage of urine flow.[13] • Radical cystectomy and/or urostomy may also have adverse sexual effects for both men and women.
How strongly does this overall societal burden suggest that CER on alternative approaches to this	• Bladder cancer is a common cancer, accounting for approximately 5% of all incident cancers in the U.S. It is an important health problem, with no substantial improvement in associated mortality since 1975.[2,14] • Economic analyses have shown bladder cancer to be the costliest cancer to treat in the United States on a per capita basis, taking into account diagnostic testing,

problem should be given high priority?	management, and long-term followup.[15] • Given the overall societal burden of bladder cancer, CER to identify more effective and/or safer approaches to the treatment of NMIBC should be a high priority.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	A recent systematic review commissioned by the Agency for Healthcare Research and Quality and an associated supplement commissioned by the American Urological Association addressed various active questions related to the comparative effectiveness of treatments for NMIBC,[10,11] including: the comparative effectiveness of various intravesical chemotherapeutic or immunotherapeutic agents; the effectiveness of fluorescent cystoscopy versus white light cystoscopy on risk of recurrence, progression and/or mortality; and the effectiveness of various treatments (intravesical immunotherapy/ chemotherapy or surgical) in patients with persistent or recurrent disease after intravesical therapy with BCG or other agents. <u>Intravesical immunotherapy/chemotherapy</u> • Intravesical therapy with any of several different agents was associated with reduced risk for bladder cancer ***recurrence*** versus no intravesical therapy (strength of evidence [SOE]: low for BCG; moderate for others).[11] These agents were BCG (3 trials; RR 0.56; 95% CI, 0.43 to 0.71), MMC (8 trials; RR 0.71; 95% CI, 0.57 to 0.89), doxorubicin (10 trials; RR 0.80; 95% CI, 0.72 to 0.88), and epirubicin (9 trials; RR 0.63; 95% CI, 0.53 to 0.75). • BCG was the only agent associated with reduced risk for bladder cancer ***progression*** versus no intravesical therapy (4 trials; RR 0.39; 95% CI, 0.24 to 0.64; SOE: low).[11] (For BCG and risk of recurrence and progression, the SOE was rated low due to methodological limitations in the studies; in addition, there were relatively few studies). • No intravesical agent was associated with decreased risk of all-cause or bladder cancer specific ***mortality*** versus no intravesical therapy.[11] • Evidence on gemcitabine, interferon alpha, and thiotepa was sparse, and the investigators found no randomized trials of valrubicin, paclitaxel, or apaziquone.[11] • Head-to-head trials of intravesical therapy using different drugs showed few clear differences. For BCG versus MMC, the most well-studied comparison, there was no difference on any outcome, including bladder cancer recurrence, progression, or mortality (SOE: moderate). However, BCG was associated with decreased risk of bladder cancer recurrence in the subgroup of trials that evaluated maintenance regimens (SOE: low). Other head-to-head comparisons were evaluated in fewer

	trials, and showed few differences.[11] • Four trials of BCG versus no intravesical therapy found that local and systemic adverse events were relatively common (granulomatous cystitis or irritative symptoms in 27% to 84% of patients, macroscopic hematuria in 21% to 72%, and fever in 27% to 44%) (SOE: low). BCG was also associated with an increased risk of local adverse events and fever versus MMC (SOE: low). Few trials reported harms of intravesical agents other than BCG versus no intravesical therapy, or against another intravesical agent.[11] • Biomarkers such as FISH appear to predict response to intravesical therapies, but have not been evaluated for effects on clinical outcomes.[11] *Treatment frequency and duration:* • A single instillation of intravesical therapy for NMIBC plus TURBT was more effective than TURBT without intravesical therapy for reducing risk of recurrence, based on 15 RCTs (RR 0.74; 95% CI 0.64 to 0.86; SOE: moderate); evidence was strongest for epirubicin and MMC. There were no clear effects of single instillation intravesical therapy on risk of progression or mortality and estimates were imprecise.[10] • Limited evidence suggested that BCG maintenance regimens (>6 weeks) are more effective than induction regimens (≤6 weeks) at reducing risk of bladder cancer recurrence in responders to induction therapy or in patients with higher risk tumors (2 trials; RR, 0.54; 95% CI, 0.31 to 0.95; SOE: low).[11] • Evidence on the effectiveness of induction (multiple instillations over 4 to 8 weeks) versus maintenance (induction therapy plus additional instillations beyond 8 weeks) intravesical chemotherapy is limited (SOE: low). One trial that excluded patients with low-risk tumors (primary, solitary TaG1) found MMC maintenance therapy (6 weekly instillation followed by monthly instillations for 3 years) associated with decreased risk of recurrence vs. induction therapy (6 weekly instillations) (10% vs. 26%, RR 0.41, 95% CI 0.24 to 0.69), but there were no differences in 3 trials of patients not selected for being at higher risk. Three of four trials (none focused on patients with higher risk tumors) found no difference between longer (1 year) versus shorter (3 to 6 months) maintenance chemotherapy.[10] *Patient and tumor characteristics:* • No trial evaluated how effectiveness of intravesical therapy may vary in subgroups defined by patient characteristics such as age, sex, race/ethnicity, performance status, and comorbidities.[11]

	• Based on limited evidence, there were no clear differences in estimates of effectiveness of intravesical therapies in subgroups defined by tumor stage, grade, size, multiplicity, recurrence status, or DNA ploidy (SOE: low).[11] <u>Fluorescent cystoscopy</u> Fluorescent cystoscopy is a method for enhancing the visualization of tumors that may improve the likelihood of complete resection. It uses ultraviolet light (versus the traditional white light) and a dye injected into the bladder. • Fluorescent cystoscopy was associated with decreased risk of bladder cancer ***recurrence*** versus white light cystoscopy at short-term follow-up (<3 months; 9 trials, RR 0.58; 95% CI 0.36 to 0.94; SOE: moderate), intermediate-term follow-up (3 months to <1 year; 6 trials; RR 0.70, 95% CI 0.56 to 0.88; SOE: moderate), and long-term follow-up (≥1 year; 12 trials, RR 0.82, 95% CI 0.69 to 0.97; SOE: moderate).[10] However, findings were inconsistent and potentially susceptible to publication and performance bias (surgeons cannot easily be blinded to use of fluorescent cystoscopy). • There were no differences between fluorescent cystoscopy versus white light cystoscopy in risk of ***progression*** or ***mortality***, although fewer studies looked at these outcomes (SOE: low).[10] <u>Treatment for recurrence or persistence after intravesical therapy</u> • One trial of patients with high-risk Ta or T1 NMIBC who failed BCG therapy found gemcitabine maintenance associated with decreased risk of recurrence versus BCG (53% vs. 88%; RR 0.60; 95% CI 0.44 to 0.82), though there was no difference in risk of progression (33% vs. 38%).[16] • One trial of patients with recurrent NMIBC after intravesical therapy who primarily received BCG (83% BCG) found a MMC maintenance regimen associated with increased risk for recurrence (40% vs. 28%; RR 1.44; 95% CI 0.84 to 2.47) and progression (18% vs. 11%; RR 1.64; 95% CI 0.64 to 4.19) versus gemcitabine, though neither finding was statistically significant.[17] • An additional 9 trials assessed intravesical therapies in patients with recurrent bladder cancer, but none specified whether patients had received prior intravesical therapy or the type of intravesical therapy that was received.[10]

What could new research contribute to achieving better patient-centered outcomes?	• Although various risk stratification tools have been developed to inform treatment decisions, no study has evaluated clinical outcomes associated with use of a formal risk assessment tool versus other approaches. New research that evaluates and validates the accuracy of risk-adapted approaches in predicting recurrence and progression of NMIBC could help to achieve better patient-centered outcomes. • Research on the effects of biomarkers on clinical outcomes for predicting response to intravesical therapy could help inform treatment choices, and guide decisions in patients who fail BCG. • Additional head-to-head trials of intravesical therapies that use more standardized instillation regimens and doses, report outcomes in subgroups stratified by patient and tumor characteristics, and include more long-term outcomes related to progression and mortality would help clarify optimal treatment strategies, including optimal dosing and duration. • Fluorescent cystoscopy may decrease risk of recurrent NMIBC, but more research is needed to determine its effects on risk of bladder cancer progression and mortality. RCTs that adequately safeguard against performance bias associated with the use of photosensitizers for fluorescent cystoscopy are needed to better define its utility. • Evidence on the management of patients with recurrence or progression of bladder cancer after induction intravesical therapy with BCG or other agents is sparse. New research into the comparative effectiveness of various treatments after failure of first-line intravesical therapy could help to improve patient outcomes. This research should assess the comparative effectiveness of various intravesical agents, cystectomy or bladder-preserving alternatives to cystectomy, and/or novel agents (e.g., immune checkpoint inhibitors). • The effectiveness of intravesical therapy in reducing the risk of progression in high risk patients is uncertain, and recent guidelines recommend considering initial radical cystectomy for such patients.[12] However, these guidelines are based on limited evidence (grade C) that does not compare initial radical cystectomy with other treatments. New randomized trials that compare initial cystectomy with intravesical therapy or other bladder-preserving therapies for high risk NMIBC could provide needed information to inform treatment decisions. • Cystoscopy, bladder tumor resection, intravesical therapy, and cystectomy are each associated with discomfort and possible adverse effects. New research into approaches that might reduce discomfort and/or adverse effects could improve patient-centered outcomes. This research could look into optimal dosing of

	intravesical agents that considers adverse effects; supplemental agents to reduce local or systemic side effects; and new technologies designed to reduce adverse effects and/or improve patient recovery time, such as PlasmaKinetic (PK) button vaporization in TURBT or robotic cystectomy. • New research into the comparative effectiveness of novel or understudied approaches to treatment of NMIBC (e.g., enhanced cystoscopy with narrow band imaging, electromotive intravesical chemotherapy, chemohyperthermia, and external beam radiation therapy) could improve patient-centered outcomes.
Have recent innovations made research on this topic especially compelling?	• As part of The Cancer Genome Atlas project, molecular alterations in 131 muscle-invasive bladder cancers have been characterized, with potential for the development of molecularly-targeted agents for treating NMIBC, as well as muscle-invasive bladder cancer.[18] • Newer immunotherapeutic agents – immune checkpoint inhibitors – have been developed and may hold promise for the treatment of NMIBC. • Device assisted approaches to intravesical therapy (e.g., electromotive drug administration [EMDA] or hyperthermic intravesical chemotherapy [HIVEC]) may hold promise for increasing the absorption of chemotherapeutic agents and, thereby, improving outcomes. • New technologies designed to reduce adverse effects and/or improve patient recovery time, such as PlasmaKinetic (PK) button vaporization in TURBT or robotic cystectomy hold promise. • Use of these innovations in clinical practice and evidence on their effectiveness from well-conducted RCT's appear to be limited at this time.
How widely does care now vary?	• Women with bladder cancer have worse survival than men, likely due to delays in diagnosis and consequent diagnosis at later stages.[19] In one study of a university-affiliated managed care organization, women received fewer referrals to urologists for evaluation of hematuria than did men (28% versus 47%).[20] These disparities may be due to higher rates of urinary tract infections (which may have similar symptoms as bladder cancer) and the lower incidence of bladder cancer in women. • African Americans are more likely to be diagnosed with bladder cancer of higher grades and stages and have worse survival rates compared with whites.[19,21] They are also less likely to undergo radical cystectomy for localized muscle-invasive bladder cancer. However, there is less information on disparities in care specifically for NMIBC. One study of early stage bladder cancer that used SEER-Medicare data from 1992 through 2002, found differences in initial treatment between African Americans and whites. African Americans were more likely to undergo restaging

	resection (12% versus 6.5%) and urine cytology (37% versus 30%), and received fewer endoscopic examinations (4 versus 5).[22] However, these differences "did not appear to be systematic and had unclear clinical significance". There was no difference in "aggressive therapy" between African American and white patients. • Intravesical chemotherapy to reduce risk of recurrence is underutilized, with analyses of claims data showing fewer than 5% of patients with NMIBC receiving an installation of intravesical chemotherapy after TURBT.[19,23,24] Similarly, less than one third of patients with NMIBC receive induction courses of intravesical BCG according to NCCN guidelines, and fewer still receive maintenance BCG.[19,24]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	ClinicalTrials.gov On October 3, 2016, we searched ClinicalTrials.gov using the search term "non-muscle invasive bladder cancer" and identified 88 studies, of which 72 studies (30 RCTs identified below in bold) were of known status and related to treatment of NMIBC. Results were available for 6 of these studies; however, in 4 of those studies no actual results were reported due to inadequate enrollment or inadequate outcome events. • Thirty-two of these studies (14 RCTs) evaluate various agents for intravesical therapy for primary and/or recurrent NMIBC. Most are of induction therapy and a few are of maintenance therapy. Most are not restricted to patients with intermediate- and/or high-risk tumors. Studies include: NCT02371447, **NCT02138734**, NCT02891460, NCT01458847, NCT02316171, **NCT02214602**, NCT01314664, NCT01498172, **NCT01469221**, **NCT01410565**, **NCT01438112**, **NCT00974818**, NCT02808143, **NCT02075060**, NCT02365818, NCT01731652, NCT02720367, NCT00782587, **NCT01475266**, NCT02307487, **NCT01803295**, NCT01373398, **NCT02716961**, **NCT02563561**, **NCT01310803**, NCT01648010, **NCT02202772**, **NCT02695771**, NCT01162785, NCT01304173, NCT02311101, NCT00794950. • An additional 10 studies (2 RCTs) evaluate various agents administered via other routes (oral, intravenous, intradermal, or percutaneous), including: NCT02343614, **NCT02753309**, NCT02605863, NCT02197897, NCT02657486, NCT01373294, NCT02792192, NCT02009332, **NCT02010203**, NCT02326168. • Eleven studies evaluate treatments specifically for patients who have failed BCG therapy. Most (n = 8 [3 RCTs]) of these trials are of various intravesical treatments (NCT01625260, **NCT02015104**, NCT02773849, **NCT01200992**, NCT02449239, NCT02143804, NCT00406068, **NCT01687244**), while two trials are of intravenous agents (NCT02625961 [pembrolizumab] and NCT02451423 [an anti-PD-L1 antibody]) and one (NCT02844816) is of an orally-administered agent (atezolizumab). • Studies also evaluate various other therapies and treatment approaches, including

	electromotive drug administration (3 RCTs) (**NCT01149174**, **NCT01920269**, NCT02202044, **NCT01442519**), hyperthermic chemotherapy (3 RCTs) (NCT02471495, **NCT01094964**, **NCT02254915**, **NCT00384891**), photodynamic therapy (NCT00322699), narrow band imaging (2 RCTs) (**NCT01004211**, **NCT01180478**). One study (NCT01166230) of fluorescent cystoscopy (n = 255) versus white light cystoscopy (n = 261) reported results and found improved recurrence-free survival for fluorescent cystoscopy (16.4 months versus 9.6 months). • Three studies evaluate differences in quality of life related to treatment with different intravesical agents (**NCT01697306** [RCT]) or possible benefits of interventions for reducing local side effects of BCG (1 RCT) (**NCT02207608**, NCT01939756). One of these studies (NCT02207608) reported results and found no effect of hyaluronic acid in reducing serious side effects. • One study (**NCT02070120** [RCT]) compares chemo-resection (i.e., not adjuvant therapy) with intravesical MMC versus surgical intervention (TURBT or ablation, according to local practice), and another study (NCT02113501) evaluates the effectiveness of treatment based on sub-staging with a 2nd TURBT after BCG induction therapy. <u>Other databases</u> • A search of the European Organisation for Research and Treatment of Cancer (EORTC) clinical trials database found 19 trials of treatments for NMIBC. The majority (n = 16) of these trials evaluate various intravesical agents and/or various doses or timings of treatment. Two studies are of chemo-resection and one is of treatment with YAG-laser versus TURBT.
How likely it is that new CER on this topic would provide better information to guide clinical decision making?	It is very likely that a new CER on this topic would provide better information to guide clinical decision making. A recent systematic review and associated supplement identified numerous gaps and methodological limitations in the research related to various aspects of treatment for NMIBC.[10,11] Many of the recent AUA/SUO guidelines are based on limited evidence (grade C).[12] New research could provide a better evidence base particularly related to: the accuracy and value of formal risk-adapted approaches to treatment decisions; the comparative effectiveness of enhanced cystoscopy techniques such as fluorescent cystoscopy; the effectiveness of various treatments for persistent or recurrent disease after intravesical therapy with BCG or other agents; the comparative effectiveness of initial cystectomy in patients with high-risk NMIBC; and approaches for reducing discomfort and adverse effects associated with treatments for NMIBC.

Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS: • There exists considerable uncertainty about various aspects of treatment for patients with NMIBC and urologists are eager to have better evidence to guide treatment decisions. • Groups such as the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) have a great interest in the topic and are active in synthesizing and disseminating research findings among urologists. The Bladder Cancer Advocacy Network (BCAN) also has a great interest in the topic and includes patient stakeholders. • New treatments have historically faced difficulty in gaining FDA approval. A recent approval of a drug for treating metastatic bladder cancer (atezolizumab) may open doors for additional approval for treatment of NMIBC. • Formal risk stratification tools would be clinically useful and potentially effective in refining treatment for improved outcomes. • Patients would be interested in using interventions that have been shown to reduce the discomfort and/or adverse effects associated with treatments for NMIBC. BARRIERS: • The cost of newer techniques (e.g., enhanced cystoscopy, EMDA, HIVEC, PlasmaKinetic button vaporization, robotic cystectomy) or novel agents may be a barrier to their implementation. Cost-benefit analyses could be useful for guiding policies regarding certain treatments. • New findings might provide evidence in support of particular treatment options (e.g., initial radical cystectomy over intravesical therapy) that could be less acceptable or attractive to patients. In such circumstances, it would be important to develop appropriate and effective tools for shared decision making.

How likely is it that the results of new research on this topic would be implemented in practice right away?	• Results of new research that addresses limitations in the current evidence and clarifies some of the uncertainty around treatment questions for NMIBC are likely to be implemented in practice right away. • Research that validates the accuracy and utility of formal risk-adapted approaches to treatment would likely be implemented right away. • The best management of patients with intermediate- or high-risk NMIBC that have failed induction intravesical therapy with BCG remains uncertain.[12] Results of new research that helps to clarify the comparative effectiveness of various chemotherapeutic, immunotherapeutic, and/or surgical treatments would likely be implemented in practice right away. • Similarly, the results of CER examining initial cystectomy versus intravesical therapy in patients with high risk NMIBC would likely be implemented in practice right away.
Would new information from CER on this topic remain current for several years?	• New information related to formal risk-adapted approaches and/or the influence of patient and tumor characteristics on the effectiveness of intravesical therapy would likely remain current for several years. This information would likely be adaptable and relevant for use with new chemotherapeutic or immunotherapeutic agents, and thereby remain current for years. • Given the moderate number of ongoing clinical trials (and some comparative effectiveness studies) evaluating various intravesical agents for NMIBC, to remain current for several years it would be important for new CER of intravesical agents to anticipate and avoid possible overlap with current ongoing studies. • Similarly, there are a number of ongoing trials of various types of enhanced cystoscopy, particularly of blue light cystoscopy, and efforts should be made avoid possible overlap with current ongoing studies. • Well-done RCTs of initial cystectomy versus intravesical therapy in patients with high risk NMIBC would likely to remain current for several years. • New information on methods to reduce discomfort and/or adverse effects of various treatments is likely to remain current for several years.
Conclusions	• NMIBC is a common cancer for which there are a number of important research gaps that could be addressed in comparative effectiveness research. • Research is needed to validate the accuracy and utility of risk-adapted approaches to treatment, understand optimal approaches to management of patients with intermediate- or high-risk NMIBC who fail BCG, and determine the role of cystectomy for high-risk or recurrent NMIBC, the effects of fluorescent cystoscopy on clinical outcomes, and the use of biomarkers to predict response to treatments. • Research is needed to understand effects of management strategies for NMIBC on patient-centered outcomes such as quality of life and on methods for reducing adverse effects associated with intravesical therapy and cystectomy.

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