Clinical Policy Title: Enhanced cystoscopy for bladder cancer

Clinical Policy Number: CCP.1295

Effective Date:	**April 1 2017**
Initial Review Date:	February 15 2017
Most Recent Review Date:	March 5, 2019
Next Review Date:	March 2020

Policy contains:

- Non-muscle invasive bladder cancer.
- Blue light or fluorescent cystoscopy.
- Photodynamic diagnosis.
- Hexaminolevulinate.

Related policies:

None.

ABOUT THIS POLICY: *AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas' clinical policies are not guarantees of payment.*

Coverage policy

AmeriHealth Caritas consider the use of photodynamic diagnosis (also called blue light or fluorescent cystoscopy) to be clinically proven and, therefore, medically necessary for the cystoscopic detection of non-muscle invasive bladder cancer when the following criteria are met (Chang, 2016; European Association of Urology, 2017; National Comprehensive Cancer Network, 2019; National Institute for Health and Care Excellence, 2015; U.S. Food and Drug Administration, 2010b):

- Performed after or concurrent with white light cystoscopy.
- Use of the fluorescence agent hexaminolevulinate, marketed in the United States as Cysview® (Cato Research Ltd., Durham, North Carolina) in combination with the Karl Storz D-Light C Photodynamic Diagnostic system (Karl Storz Endoscopy-America Inc., El Segundo, California).
- For the following clinical indications:
  - At the time of the first three-month cystoscopy in all patients with a history of intermediate- to high-risk non-muscle invasive bladder cancer.

        - Exception: patients with low-risk single small non-recurrent low-grade papillary cancers (stage ta), as the expected three-month recurrence rate is less than 15 percent.
    - To guide transurethral resection.

Limitations:

Contraindications to hexaminolevulinate include porphyria, gross hematuria, intravesical immunotherapy, or chemotherapy within 90 days, or known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives (U.S. Food and Drug Administration, 2010b).

Repetitive administrations of hexaminolevulinate are not medically necessary (U.S. Food and Drug Administration, 2010b).

Photodynamic diagnosis using 5-aminolevulinic acid is considered an off-label use and not medically necessary.

Alternative covered services:

- Cytology with urinalysis.
- White light cystoscopy.
- Upper urinary tract imaging.
- Random bladder biopsies.

Background

Bladder cancer accounts for approximately 5 percent of all new cancers in the United States. It is the fourth most common cancer in men, but it is less common in women (American Cancer Society, 2017). About half of all bladder cancers are found while the cancer is non-invasive or in situ and still confined to the inner layer of the urothelium. About one in three bladder cancers have invaded into deeper layers but are still only in the bladder. High recurrence rates are associated with bladder cancer, often requiring repeat treatment and lifelong surveillance (Zlatev, 2015).

The most common tests used to detect bladder cancer are cytology with urinalysis and transurethral intravesical illumination using white light cystoscopy with biopsy. Cytology detects morphological changes in intact, exfoliated cells. It can identify high-risk disease reliably but tends to miss low-grade or early-stage tumors. White light cystoscopy is unreliable for determining low- and high-grade cancer, assessing level of invasion, differentiating non-papillary and flat malignant lesions (e.g., carcinoma in situ) from inflammation, detecting smaller or satellite tumors, and visualizing submucosal tumor margins during transurethral resection. These limitations can lead to incomplete tumor resection and

under-staging, which can increase the risk of cancer persistence, recurrence, and progression (of high-grade cancer) to more lethal disease (Lopez, 2014; Zlatev, 2015).

Photodynamic diagnosis in urology:

Photodynamic diagnosis in urology applies the principle of fluorescence under ultraviolet light to distinguish suspicious lesions from non-cancerous mucosa. Innovations in transurethral intravesical illumination using fluorescent markers, which show selective absorption by malignant cells, provide additional contrast enhancement. The goal of these modifications is to improve optical diagnosis beyond standard white light cystoscopy, resulting in more effective use of both bladder sparing management for low-grade cancer and more aggressive treatment for high-grade cancer (Lopez, 2014; Zlatev, 2015).

Clinical application of photodynamic diagnosis of bladder cancer involves two agents: the heme precursor 5-aminolevulinic acid and its derivative hexaminolevulinate. The U.S. Food and Drug Administration (1999) has approved 5-aminolevulinic acid for topical use in dermatology; intravesical evaluation of the bladder is an off-label use. Hexaminolevulinate is available in the United States as Cysview performed in combination with the Karl Storz D-Light C Photodynamic Diagnostic system for the cystoscopic detection of non-muscle invasive bladder cancer in patients suspected or known to have lesion(s) on the basis of a prior white light cystoscopy (U.S. Food and Drug Administration, 2010a, 2010b). Approval highlights the importance of performing a thorough white light examination first, as some lesions may be missed with Cysview/blue light. Cysview/blue light cystoscopy may be used during an endoscopic examination of the bladder and during resection of bladder cancer.

Searches

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.
- The Cochrane Library.

We conducted searches on January 15, 2019. Search terms were: “urinary bladder neoplasms” (MeSH), “cystoscopy” (MeSH), “hexaminolevulinate,” “blue light cystoscopy,” and “enhanced cystoscopy.”

We included:

- Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- Guidelines based on systematic reviews.

- Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

We found five systematic reviews/meta-analyses, three evidence-based guidelines, and no cost-effectiveness analyses for this policy. Moderate quality evidence from randomized controlled trials, nonrandomized controlled trials, and cross-sectional studies comprised the majority of the evidence in the secondary analyses (Burger, 2013; Chou, 2015; Di Stasi, 2015; Gakis, 2016; Lee, 2015). Studies enrolled persons with known or suspected bladder cancer. They compared photodynamic diagnosis using hexaminolevulinate and, to a lesser extent, 5-aminolevulinic acid as an adjunct to white light cystoscopy during initial diagnosis and transurethral resection. The role of photodynamic diagnosis as a replacement for white light cystoscopy has not been evaluated.

Most studies reported data by lesion, which may hyperinflate estimates of diagnostic accuracy, as opposed to analysis by patient (i.e., intention-to-treat analyses) that is generally more relevant to assess clinical effectiveness. Cystoscopies were performed in a hospital inpatient setting. Since applying photodynamic diagnosis with 5-aminolevulinic acid during cystoscopy is considered an off label use, this policy will restrict discussion to photodynamic diagnosis using hexaminolevulinate.

Photodynamic diagnosis is a reasonably safe procedure, as no serious side effects were noted. The harms associated with any cystoscopy procedure are discomfort, subsequent dysuria and bleeding, and the possibility of urinary tract infection or acute retention. Hexaminolevulinate is contraindicated in patients with porphyria, gross hematuria, intravesical immunotherapy or chemotherapy within 90 days, or known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives, as false-positive results may occur from inflammatory lesions, previous biopsy sites, or in patients previously treated with bacillus Calmette-Guérin (U.S. Food and Drug Administration, 2010b).

Although repetitive use of hexaminolevulinate has not been evaluated in prospective clinical trials, one retrospective study with 180 patients and another study that summarized data from six controlled trials (4,324 total patients) and a European registry found no statistically significant differences in the frequency or grade of adverse events between single- and repeat-use of blue light cystoscopy with hexaminolevulinate (Lane, 2017; Witjes, 2014). A registry study that will address the safety and efficacy of repetitive use of hexaminolevulinate in urologists' practices in the United States is underway (Clinicaltrials.gov identifier: NCT02660645).

There is consistent evidence that a single application of photodynamic diagnosis added to white light cystoscopy improves the detection and resection of non-muscle invasive bladder cancer. Photodynamic diagnosis detects significantly more Ta, T1, and carcinoma in situ tumors than white light cystoscopy alone. This benefit extends to most subgroups, including more aggressive, higher risk primary and recurrent bladder cancer. However, the benefits must be weighed against the higher false positive rate

(corresponding to lower specificity) of photodynamic diagnosis plus white light cystoscopy, which may result in an increase in unnecessary biopsies.

The added value of enhanced detection with respect to the risk of recurrence, recurrence-free survival, mortality, progression to muscle-invasive bladder cancer, or cost-effectiveness has not been established. Limited evidence with a high potential for bias suggests photodynamic diagnosis with white light cystoscopy may reduce recurrence rates up to one year, and possibly longer, but the findings were conflicting across studies (Burger, 2013; Chou, 2015; Di Stasi, 2015; Gakis, 2016; Lee, 2015).

Photodynamic diagnosis can miss some high grade lesions found on white light cystoscopy. Use of single-dose adjuvant chemotherapy following transurethral resection of bladder tumor , which alone can reduce recurrence rates, was inconsistently reported or accounted for across studies. Most studies reported a relatively short follow-up period (up to 12 months), which is insufficient to detect changes to invasive cancer, and used various definitions for disease progression. More comparative prospective studies are needed to define the optimum use of photodynamic diagnosis relative to white light cystoscopy.

Evidence-based guidelines by the American Urological Association/ Society of Urologic Oncology (Chang, 2016), National Institute for Health and Care Excellence (2015), and the European Association of Urology (2015) recommend photodynamic diagnosis-guided transurethral resection for persons with suspected bladder cancer, when available, based on the ability of photodynamic diagnosis to enhance detection and lower recurrence. There is general agreement, based on expert opinion, that photodynamic diagnosis is one of several diagnostic options for patients with a history of non-muscle invasive bladder cancer with normal white light cystoscopy and positive cytology.

Other diagnostic options include prostatic urethral biopsies, upper tract imaging, ureteroscopy, and random bladder biopsies. The European Association of Urology (2015) recommends photodynamic diagnosis-guided biopsy instead of random biopsies when carcinoma in situ or high-grade tumor is suspected (e.g., positive cytology or recurrent tumor with previous history of a high-grade lesion) based on moderate quality evidence, and either random biopsies or photodynamic diagnosis-guided biopsies after intravesical treatment (at three or six months) in patients with carcinoma in situ based on expert opinion.

Policy updates:

In 2018, we added two guideline updates on management of bladder cancer: one by the National Comprehensive Cancer Network (2018) and the other by the European Association of Urology (2017). Their recommendations for blue light cystoscopy are consistent with the previous findings, and no policy changes are warranted.

In 2019, we identified no newly published, relevant literature to add to the policy. The policy ID was changed from CP# 13.01.04 to CCP.1295.

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Peer-reviewed references:

Burger M, Grossman HB, Droller M, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. *Eur Urol.* 2013;64(5):846-854. Doi: 10.1016/j.eururo.2013.03.059.

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Centers for Medicare & Medicaid Services National Coverage Determinations:

No National Coverage Determinations identified as of the writing of this policy.

Local Coverage Determinations:

No Local Coverage Determinations identified as of the writing of this policy.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

CPT Code	Description	Comments
52204	Cystourethroscopy, with biopsy(s)	
52214	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) of trigone, bladder neck, prostatic fossa, urethra, or periurethral glands	
52224	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) or treatment of MINOR (less than 0.5 cm) lesion(s) with or without biopsy	
52234	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) and/or resection of SMALL bladder tumor(s) (0.5 to 2.0 cm)	
52235	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) and/or resection of MEDUIUM bladder tumor(s) (2.0 to 5.0 cm)	
52240	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) and/or resection of LARGE bladder tumor(s)	

ICD-10 Code	Description	Comments
C67.0-C67.9	Neoplasm of bladder	

HCPCS Level II Code	Description	Comments
C9275	Injection, hexaminolevulinate hydrochloride, 100 mg, per study	
C9738	Adjunctive blue light cystoscopy with fluorescent imaging agent (list separately in addition to code for primary procedure)	